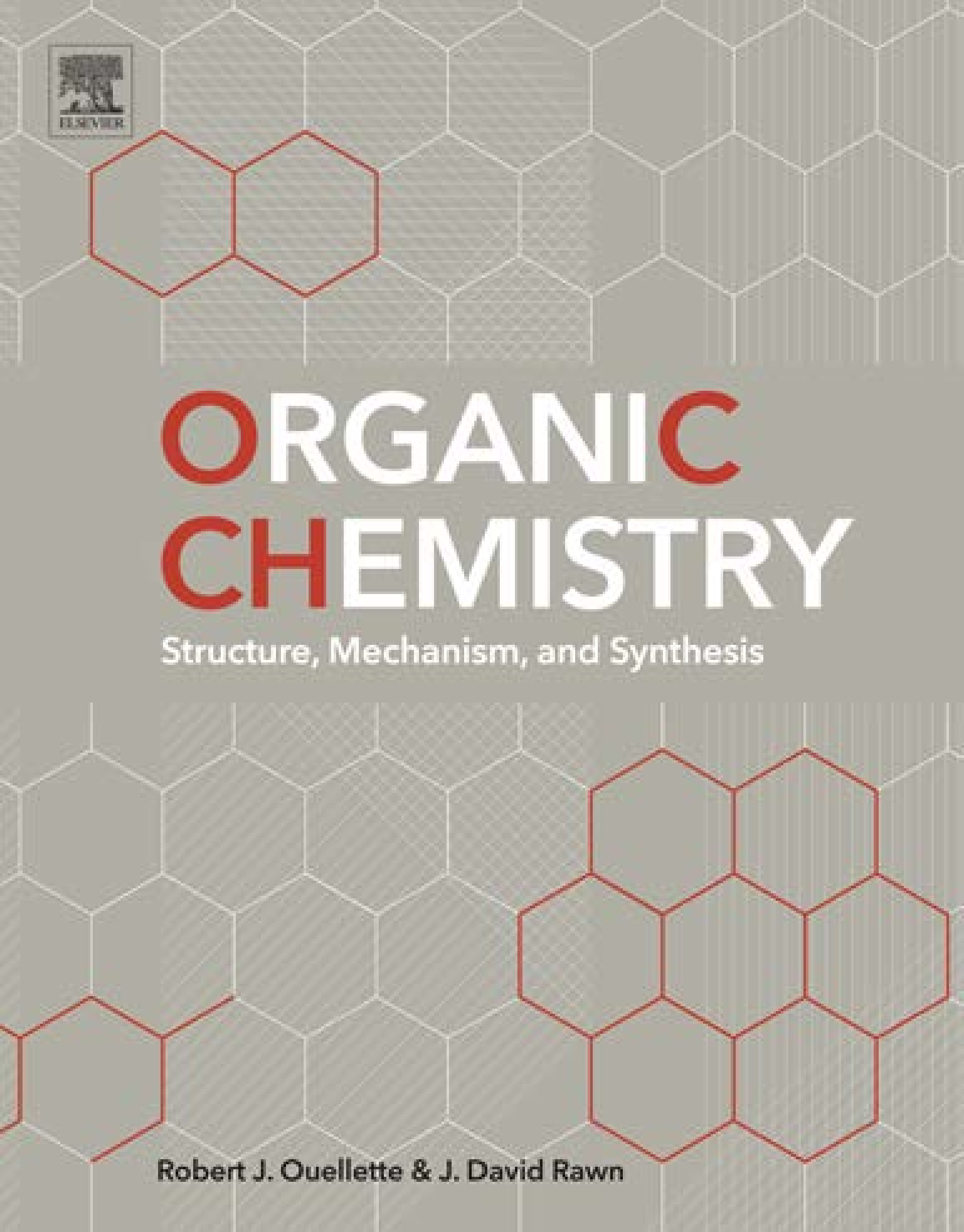
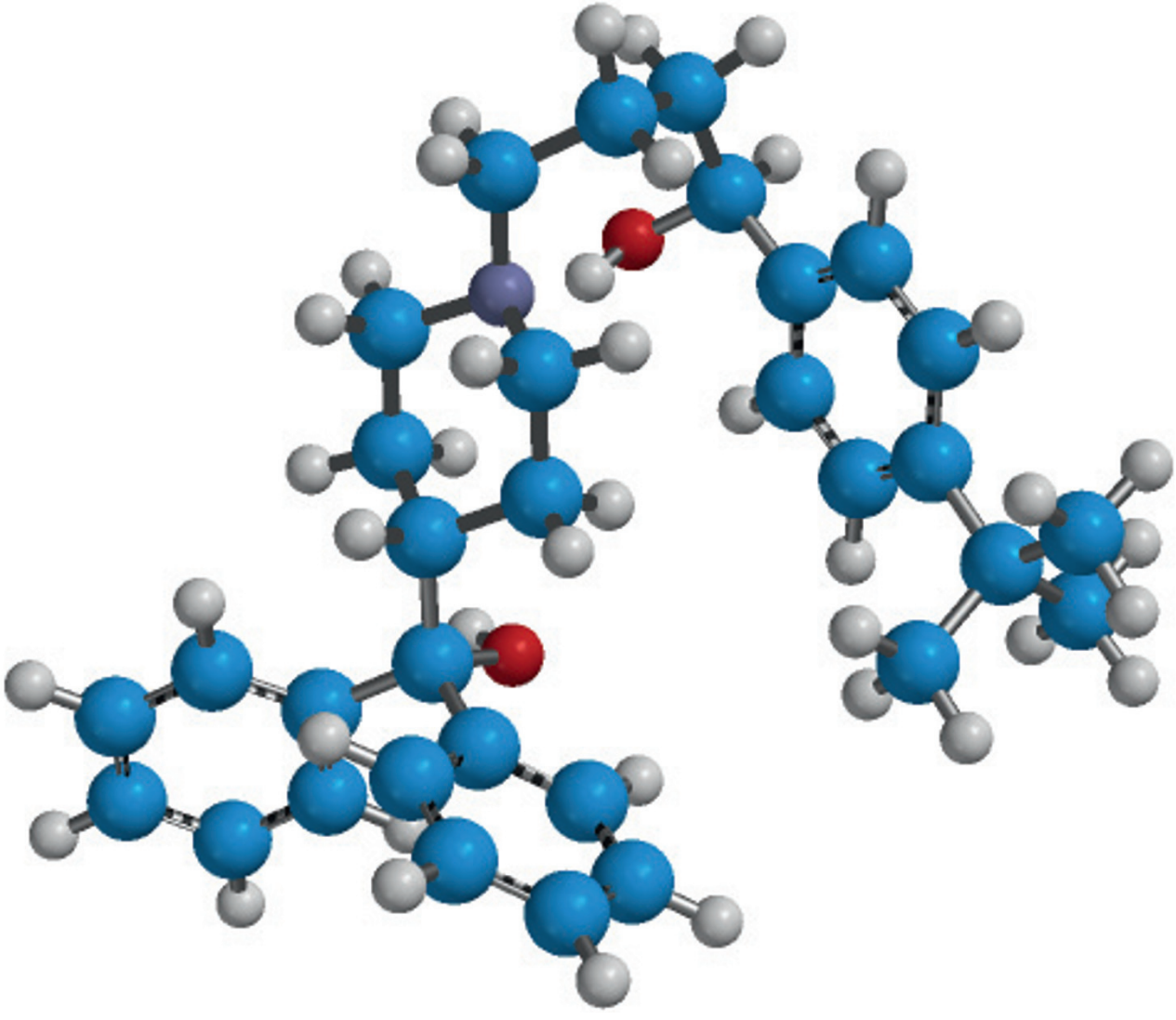

ORGANIC
CHEMISTRY
Structure, Mechanism, and Synthesis
Robert J. Ouellette & J. David Rawn

Organic Chemistry:
Structure, Mechanism, and Synthesis

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Organic Chemistry:
Structure, Mechanism, and Synthesis



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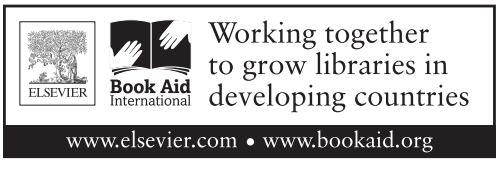
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To our families

Verweile doch, du bist so schön.

—Johann Wolfgang von Goethe, *Faust*

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PREFACE

The subject matter of organic chemistry revolves around a single element, carbon. It occupies an inauspicious place in the periodic table, half way across the second period. Why is carbon so important? The answer is that carbon is the most chemically versatile atom. Carbon forms chemical bonds to most of the elements in the periodic table; even more importantly, it forms bonds to itself. As a result, immensely complex structures that can contain tens of thousands of atoms have been synthesized in the laboratory and made by living cells. The purpose of this book is to provide a structure for learning organic chemistry. How are we going to approach as vast and at first glance impenetrable subject? The subtitle of this text tells us: we will link molecular structure to the step-by-step processes, called mechanisms, by which reactions occur. Then, we will use these reactions to make new compounds; that is, we will explore organic synthesis.

To learn is in some deep sense to see, and this clarity emerges in part because organic compounds can be divided into classes based on their "functional groups." A functional group is a constellation of atoms— for example, a carbon bonded to a halogen, such as a $—CH_2Cl$ group, that is the site of characteristic chemical reactions. Then, we will find that the reactions of functional groups can be divided into classes of common reaction mechanisms. The close interplay between the "class of compound" and "class of mechanism" provides an overall unity to organic chemistry. The unifying principles that underlie reaction mechanisms provide "keys" that open many doors. By analogy, we can say that functional groups are the anatomy of organic chemistry, and that reaction mechanisms and their associated energy changes constitute its "physiology."

To the unity of structure in the form of functional groups, and function in the form of reaction mechanisms, we have added many biochemical applications. These are integrated into the structure of the text from beginning to end, in every chapter, in every problem set. They are not mere artifacts, as if we were putting a hat on a horse; they illustrate basic structural and mechanistic principles, and provide a background against which organic chemistry can be seen as one of the foundation stones of modern biological chemistry.

We can say, without too much exaggeration, that you won't have to memorize in this course. On the other hand, you will have a lot to remember! These slightly contradictory assertions summarize an essential part of learning any subject, especially one as complex as organic chemistry. It might seem tempting to seek refuge from intellectual difficulty by memorizing a seemingly infinite number of facts. However, even if it were possible to memorize the known facts of organic chemistry (it isn't), that feat would avail nothing unless the facts were understood in terms of underlying general principles. Understanding mechanisms of organic reactions is the key to understanding organic chemistry.

How are you going to learn organic chemistry? The answer is surprisingly simple: work the problems! There are problems at the end of most sections, including a sample problem with a worked answer. Do that one first and then do the adjacent problems. In that way, you will have reviewed each section of each chapter as you proceed. There are many more problems at the end of each chapter. They are organized by section and graded in difficulty. Do some of these problems for each section until you are satisfied that you understand the material. Finally, don't study organic chemistry as a Burmese python eats its monthly lunch, by trying to digest an immense amount at one sitting (followed by some weeks of indigestion). Instead, study systematically every day. That way you will not fall behind. There is too much material, it goes too fast, and it is too complicated to learn on the night before an exam. If you study systematically, you can be confident that you will succeed in organic chemistry.

Success in any endeavor is contagious: once one has learned how to master one thing, that template provides the foundation for continued success in new ventures.

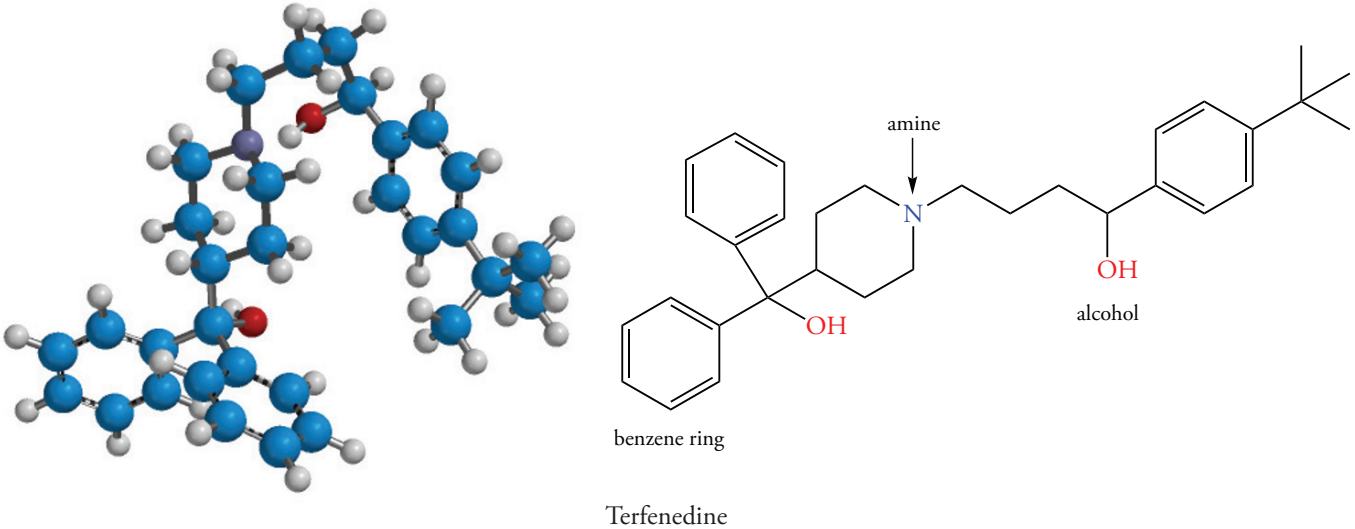
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1 Structure and Bonding in Organic Compounds

Organic chemistry began to emerge as a science about 200 years ago. By the late eighteenth century, substances had been divided into inorganic and organic compounds. In those days, early in the history of organic chemistry, inorganic compounds were isolated from mineral sources, and organic compounds were obtained only from plants or animals. Organic compounds were more difficult to study in the laboratory and decomposed more easily than inorganic compounds. The differences between inorganic and organic compounds were attributed to a "vital force" that was required for the synthesis of organic compounds. It was believed that organic compounds could not be synthesized in the laboratory without the vital force. However, by the middle of the nineteenth century, chemists had learned how to work with organic compounds in the laboratory and how to synthesize them.

The organic compounds we will discuss throughout this text contain carbon and a few other elements, such as hydrogen, oxygen, and nitrogen. We will also examine compounds containing sulfur, phosphorus, and halogens. Many, more exotic, organic compounds are also known, and organic compounds have been made that contain virtually every element in the periodic table.

The molecule shown below is terfenedine, an antihistamine whose formula is $C_{32}H_{41}NO_2$. The structure of terfenedine is an example of the amazing variety of structures of organic compounds. They are everywhere in nature, including interstellar space. No known living organism can exist without organic compounds, and synthetic organic compounds are an integral part of the objects we use every day. Their importance cannot easily be exaggerated.



Terfenedine

1.1 BRIEF REVIEW OF ATOMIC STRUCTURE

The physical and chemical properties of a molecule depend on the bonds that hold it together. And these bonds depend on the electron configurations of its atoms. Therefore, we will review some of the electronic features of atoms and the periodic properties of the elements before describing bonding and its relation to structure in organic compounds.

Atomic Structure

Each atom has a central, small, dense **nucleus** that contains protons and neutrons, which are embedded in a sea of electrons. The **atomic number**, which equals the number of protons in the nucleus, determines the identity of an atom. Since atoms have an equal number of protons and electrons and are electrically neutral, the atomic number also equals the number of electrons in an atom.

The elements in the periodic table are arranged by atomic number. The elements are arrayed in horizontal rows called **periods** and vertical columns called **groups**. In this text, we will emphasize hydrogen in the first period and the elements carbon, nitrogen, and oxygen in the second period. The electronic structure of an atom determines its chemical reactivity.

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Atomic Orbitals

The electrons in an atom occupy **atomic orbitals**, which are designated by the letters s, p, d, and f. Each orbital can contain a maximum of two electrons. An atomic orbital is a mathematical equation that describes the energy of an electron. The *square* of the equation for the atomic orbital defines the probability of finding an electron within a given region of space.

Orbitals are grouped in shells of increasing energy, designated by the integers 1, 2, 3, 4, . . . , *n*. These integers are called **principal quantum numbers**. Each shell contains a unique number and type of orbitals. The first shell contains a single 1s orbital. The second shell contains one 2s orbital and three 2p orbitals. Each orbital can contain no more than two electrons, and two electrons in *any* orbital must have opposite spin. We need to consider only the orbitals of the first three shells for the elements commonly found in organic compounds.

All s orbitals are spherically symmetrical (Figure 1.1a). The 2s orbital is larger than the 1s orbital. A 2s orbital is farther from the nucleus, and it has a higher energy than a 1s orbital. The three p orbitals in a shell are not spherically symmetrical. Electron density in each p orbital is concentrated in two regions or lobes—one on each side of the nucleus. The two lobes together are the orbital. The shapes of the p orbitals are shown in Figure 1.1b. The p orbitals are often designated as p_x, p_y, and p_z. They are mutually perpendicular to one another, and they are aligned along the *x*, *y*, and *z* axes. Although the orientations of the p_x, p_y, and p_z orbitals differ, the electrons in each p orbital have equal energies.

Orbitals of the same type within a shell constitute a group called a **subshell**. For example, an s subshell has one orbital and can contain only two electrons. In contrast, a p subshell, which begins in period two, contains three p orbitals and can contain a total of six electrons.

Electrons are distributed in subshells to give an electron configuration that has the lowest energy. The order of increasing energy of subshells is 1s < 2s < 2p < 3s < 3p for elements of atomic number less than 18. For any subshell, the lowest energy state is the arrangement that maximizes the number of electrons having the same spin. This generalization is **Hund's Rule**. This means that electrons first occupy orbitals one at a time within subshells before pairing in a common orbital. Table 1.1 shows the atomic numbers and electron configurations for the first two periods in the periodic table.

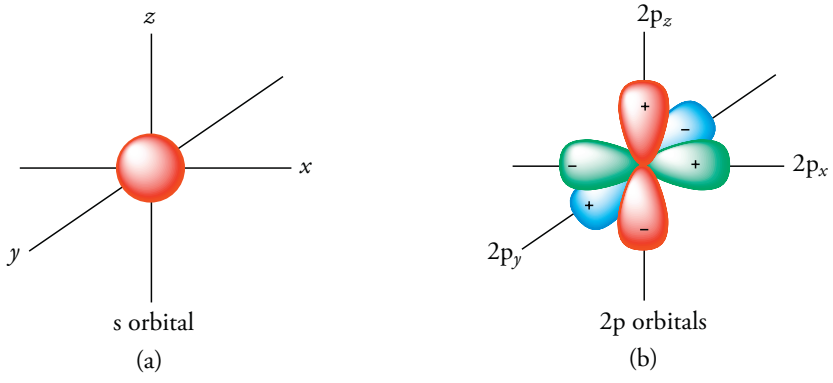


Figure 1.1 Shapes of 2s and 2p Orbitals
(a) An orbital is a boundary surface enclosing a volume where electrons can be located with 90% probability. An s orbital has a spherical boundary surface. (b) Boundary surfaces of the three mutually perpendicular 2p orbitals. Each orbital can hold a maximum of two electrons. The + and – signs on the orbitals refer to the phase of the orbital, *not* to the charge of the orbital.

Table 1.1
Electron Configurations of First and Second Period Elements

Element	*Atomic Number*	*1s*	*2s*	*2p$_x$*	*2p$_y$*	*2p$_z$*	*Electron Configuration*
H	1	1					$1s^1$
He	2	2					$1s^2$
Li	3	2	1				$1s^2\,2s^1$
Be	4	2	2				$1s^2\,2s^2$
B	5	2	2	1(↑)			$1s^2\,2s^2\,2p^1$
C	6	2	2	1 (↑)	1 (↑)		$1s^2\,2s^2\,2p^2$
N	7	2	2	1 (↑)	1 (↑)	1 (↑)	$1s^2\,2s^2\,2p^3$
O	8	2	2	2(↑↓)	1 (↑)	1 (↑)	$1s^2\,2s^2\,2p^4$
F	9	2	2	2 (↑↓)	2 (↑↓)	1 (↑)	$1s^2\,2s^2\,2p^5$
Ne	10	2	2	2 (↑↓)	2 (↑↓)	2 (↑↓)	$1s^2\,2s^2\,2p^6$

Valence Shell Electrons

Electrons in filled, lower energy shells of atoms have no role in determining the structure of molecules, and they do not participate in chemical reactions because they are held too tightly to the nucleus. Only the higher energy electrons, which are located in the outermost shell, called the **valence shell**, participate in chemical bonding. These are the **valence electrons**. For example, the single electron of the hydrogen atom is a valence electron. The number of valence electrons for the common atoms contained in organic molecules is given by their group number in the periodic table. Thus, carbon, nitrogen, and oxygen atoms have four, five, and six valence electrons, respectively. With this information we can understand how these elements combine to form organic compounds.

1.2 ATOMIC PROPERTIES

The elements in the periodic table are arranged by atomic number. The elements are arranged in horizontal rows called **periods** and vertical columns called **groups**. The physical and chemical properties of an element can be estimated from its position in the periodic table. Two properties that help us explain the properties of organic compounds are the **atomic radius** and **electronegativity**.

Atomic Radius

The overall shape of an atom is spherical, and its volume depends both on the number of electrons and on the energies of the orbitals the electrons occupy. The sizes of some atoms, expressed as the atomic radius, in picometers (pm,10^{-12} m), are given in Figure 1.2 in a greatly abbreviated periodic table that shows the atoms we will most commonly encounter in our discussion of organic compounds. Atomic radii increase from top to bottom in a group of the periodic table because the electrons in each new shell are located at greater distances from the nucleus. Thus, the atomic radius of sulfur is greater than that of oxygen, and the radii of the halogens increase in the order F < Cl < Br < I.

The atomic radius decreases from left to right across a period. Although electrons are located in the same energy level within the s and p orbitals of the elements, the nuclear charge increases from left to right within a period. These electrons are not shielded very well from the nuclear charge, and the atomic radius decreases. The radii of the common elements in organic compounds decrease in the order C > N > O.

Figure 1.2
Atomic Radii in Picometers, pm (10^{-12} m)

H						
37						
Li	**Be**	**B**	**C**	**N**	**O**	**F**
152	111	88	77	70	66	64
Na	**Mg**	**Al**	**Si**	**P**	**S**	**Cl**
186	160	143	117	110	104	99
						Br
						114
						I
						133

Electronegativity

Electronegativity is an index of the tendency of an atom to attract electrons. It is proportional to the difference between an atom's ionization potential and its electron affinity. Linus Pauling placed electronegativity values on a scale of slightly less than 1.0 for alkali metals to a maximum of 4.0 for fluorine (Figure 1.3). The alkali metals and alkaline earth metals tend to lose an electron to gain an inert gas configuration. Thus, groups I and II contain the least electronegative atoms. In fact they are electropositive. On the other end of the scale, halogens, in group VII, tend to gain an electron to give an inert gas configuration. Thus, we find that electronegativity increases from left to right across the periodic table. Electronegativity values increase in period 2 in the order C < N < O < F. Electronegativity values decrease from top to bottom within a group of elements. We will often use these periodic trends to interpret the chemical and physical properties of organic compounds.

Figure 1.3
Electronegativity

H						
2.1						
Li	Be	B	C	N	O	F
1.0	1.5	2.0	2.5	3.0	3.5	4.0
Na	Mg	Al	Si	P	S	Cl
0.9	1.2	1.5	1.8	2.1	2.5	3.0
						Br
						2.8
						I
						2.5

Problem 1.1

A few proteins contain selenocysteine, which contains a selenium atom in place of the sulfur atom of the amino acid cysteine. Selenium is in the fourth period, just below sulfur. Is sulfur or selenium more electronegative?

1.3 IONIC AND COVALENT BONDS

In 1916, the American chemist G. N. Lewis proposed that elements react to obtain the electron configurations of the inert gases. This hypothesis is summarized in the Lewis **octet rule** for second period atoms: *Atoms tend to combine and form bonds by transferring or "sharing" electrons until each atom contains eight electrons in its valence shell.* Note that hydrogen requires only two electrons to complete its valence shell because it has only a 1s orbital.

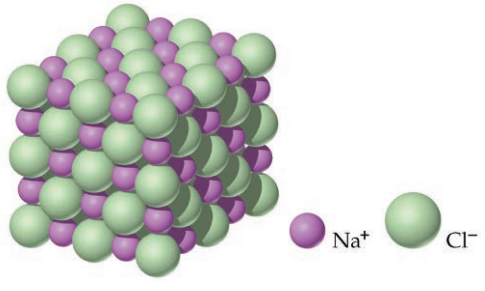
Ionic Bonds

Ionic bonds are formed between two or more atoms by the transfer of one or more electrons between atoms. Electron transfer produces negative ions called **anions** and positive ions called **cations**. Ionic substances exist as crystalline solids. When the solid dissolves, the ions dissociate and can diffuse freely in solution.

Sodium chloride is an example of an ionic solid. A sodium atom, which has 11 protons and 11 electrons, has a single valence electron in its 3s subshell. A chlorine atom, which has 17 protons and 17 electrons, has seven valence electrons in its third shell, represented as $3s^2 3p^5$. In forming an ionic bond, the sodium atom, which is electropositive, loses its valence electron to chlorine. The resulting sodium ion has the same electron configuration as neon ($1s^2\ 2s^2 2p^6$). It has a +1 charge, because there are 11 protons in the nucleus, but only 10 electrons around the nucleus of the ion. The chlorine atom, which has a high electronegativity, gains an electron and is converted into a chloride ion that has the same electron configuration as argon ($1s^2\ 2s^2 2p^6\ 3s^2 3p^5$). The chloride ion has a –1 charge because there are 17 protons in the nucleus, but there are 18 electrons around the nucleus of the ion.

In the crystal structure, each sodium ion is surrounded by six chloride ions and each chloride ion is surrounded by six sodium ions. Each ion has a complete electron shell that corresponds to the nearest inert gas; neon for a sodium ion, argon for a chloride ion (Figure 1.4).

Figure 1.4 Sodium Chloride Crystal
In the ionic solid, sodium chloride, each sodium ion is surrounded by 6 chloride ions and each chloride ion is surrounded by 6 sodium ions.



Covalent Bonds

Covalent bonds are much more common in organic chemistry than ionic bonds. *A covalent bond consists of the simultaneous attraction of two nuclei for one or more pairs of electrons.* The electrons located between the two nuclei are **bonding electrons**. Covalent bonds occur between identical atoms or between different atoms whose difference in electronegativity is insufficient to allow transfer of electrons to form ions.

Let's consider the covalent bond in the hydrogen molecule. A hydrogen molecule forms from two hydrogen atoms, each with one electron in a 1s orbital. The two hydrogen atoms are attracted to the same pair of electrons in the covalent bond. The bond is represented either as a pair of "dots" or as a solid line. Each hydrogen atom acquires a helium-like electron configuration.

$$H\bullet + H\bullet \longrightarrow H\bullet\bullet H \quad \text{or} \quad H{-}H$$

Energy is released when the electrons associated with the two hydrogen atoms form a covalent bond. The process releases heat; therefore, it is **exothermic**. The heat released when one molecule of a compound forms at 298K is the **standard enthalpy change** ($\Delta H°$) for the process. $\Delta H°$ for forming a mole of hydrogen from two hydrogen atoms is –435 kJ mole^{-1}. Since energy is released in the reaction, the hydrogen molecule is more stable than the two hydrogen atoms. The reverse process, pulling the two bonded hydrogen atoms apart, requires 435 kJ mole^{-1}, a quantity called the bond strength of the H—H bond.

The two hydrogen nuclei are separated by a distance called the **bond length**. This distance results from a balance between attractive and repulsive forces. There is an attraction between the nuclei and the bonding electrons, but there is also a repulsion between the two nuclei as well as between the two electrons. Figure 1.5 is a schematic diagram of these attractive and repulsive forces. It provides a starting point for our discussion of bonding.

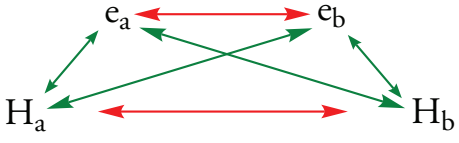
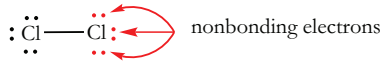


Figure 1.5 Bonding Forces in a Hydrogen Molecule

When a covalent bond forms between two hydrogen atoms, there are two sets of electrostatic repulsions (nuclear–nuclear and electron–electron, red), but four sets of electrostatic attractions (green). The attractive forces are equal in magnitude, but opposite in sign. Each hydrogen nucleus attracts both electrons. The net result is that the energy of the system decreases when the bond forms. This simple electrostatic model for bonding does not adequately describe chemical bonds. For that we will need to expand our analysis, and we will do that in the following sections.

A covalent bond also occurs in Cl_2. In the chlorine molecule, the two chlorine atoms are attracted to the same pair of electrons. Each chlorine atom has seven valence electrons in the third energy level and requires one more electron to form an electron core with an argon electron configuration. Each chlorine atom contributes one electron to the bonded pair shared by the two atoms. The remaining six valence electrons of each chlorine atom are not involved in bonding. They are variously called **nonbonding electrons**, **lone pair electrons**, or **unshared electron pairs**.



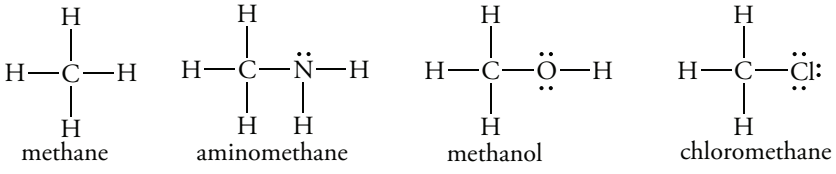
As we noted earlier, a covalent bond is drawn as a dash in a Lewis structure. Also, in a Lewis structure, nonbonding electron pairs are shown as "dots." The Lewis structures of four simple organic compounds: methane, aminomethane, methanol, and chloromethane are shown below with both bonding and nonbonding electrons.

Table 1.2

Valences of Common Elements[1]

Atom	*Valence*
Hydrogen	1
Fluorine	1
Bromine	1
Chlorine	1
Iodine	1
Oxygen	2
Sulfur	2
Nitrogen	3
Carbon	4

[1]The valence is the usual number of bonds formed by the atom in neutral compounds.



The hydrogen atom and the halogen atoms form only one covalent bond to other atoms in stable neutral compounds. However, the carbon, oxygen, and nitrogen atoms can bond to more than one atom. The number of covalent bonds an atom can form is called the **valence** of the atom. The **valence** of a given atom is the same in most stable neutral organic compounds. Table 1.2 lists the valences of some common elements contained in organic compounds.

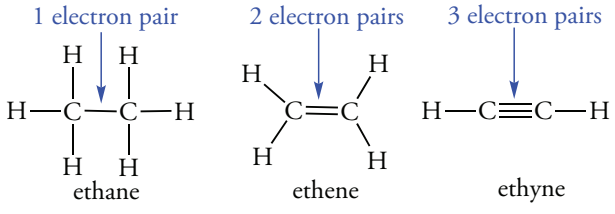
Structural Formulas

A molecular formula tells us the composition of a molecule. A **structural formula** shows the arrangement of atoms and bonds in a molecule. The structural formulas for methane, aminomethane, methanol, and chloromethane show all of the bonds connecting the constituent atoms. Structural formulas are often drawn in abbreviated or condensed versions to save time and space. **Condensed structural formulas** show only specific bonds; other bonds are implied, but not shown. The degree of condensation depends on which bonds are shown and which are only implied. For example, because hydrogen forms only a single bond to carbon, the C—H bond need not be shown in the condensed structure. Similarly, the two nitrogen–hydrogen bonds in aminomethane and the oxygen–hydrogen bond in methanol need not be shown. Condensed structural formulas showing only the bond from carbon to atoms other than hydrogen are written as follows.

CH_4	$CH_3—NH_2$	$CH_3—OH$	$CH_3—Cl$
methane	aminomethane	methanol	chloromethane

Multiple Covalent Bonds

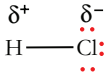
A carbon atom forms four bonds in stable organic compounds such as ethane, ethene (ethylene), and ethyne (acetylene).



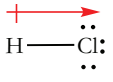
Each carbon atom in ethane forms four single bonds, one to each of three hydrogen atoms and one to the neighboring carbon atom. However, in some organic molecules, a carbon atom shares two or three pairs of electrons with another bonded atom. If two electron pairs are shared, a double bond exists. For example, ethene has a carbon–carbon double bond. Each carbon atom in ethene forms two single bonds to hydrogen atoms and one double bond to the neighboring carbon atom. If two bonded atoms share three electron pairs, a triple bond exists. For example, each carbon atom in ethyne forms a single bond to a hydrogen atom, and the two carbon atoms share a triple bond. This triple bond contains six electrons. In ethane, ethene, and ethyne, each carbon atom makes a total of four bonds.

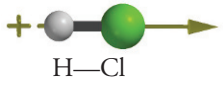
Polar Covalent Bonds

When the atoms in a covalent bond have different electronegativities, the bond is polar. For example, the covalent bond in an HCl molecule is polar. In HCl each atom requires one more electron to form an inert gas electron configuration. Chlorine is more electronegative than hydrogen, but the chlorine atom does not attract electrons strongly enough to remove an electron from hydrogen. Even though the shared electron pair is associated to a larger extent with chlorine than with hydrogen, the molecule is represented by a Lewis structure. Because the bonded pair is shared unequally, there is a partial negative charge on the chlorine atom and a partial positive charge on the hydrogen atom. These fractional charges are denoted by the symbol δ (Greek lowercase delta).



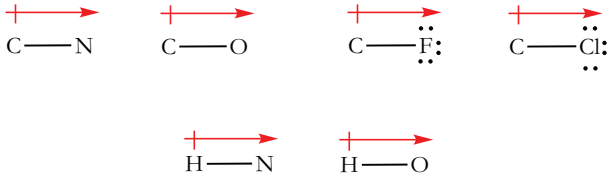
The hydrogen chloride molecule has a **dipole** (two poles), which consists of a pair of opposite charges separated from each other. The dipole is shown by an arrow with a cross at one end. The cross indicates the partially positive end of the molecule, and the arrowhead indicates the partially negative end of the molecule. Since the dipole has both a magnitude and a direction, it is a vector called the dipole moment. We discuss dipole moments in Section 1.9.





Unlike the polar bond in HCl, single or multiple bonds between carbon atoms are nonpolar. Hydrogen and carbon have similar electronegativity values, and the C—H bond is not normally considered a polar covalent bond. Ethane, ethene, and ethyne have nonpolar covalent bonds, and these compounds are nonpolar.

The polarity of a bond depends upon the difference in the electronegativities of the bonded atoms. As the difference between the electronegativities of the bonded atoms increases, the bond polarity also increases. Hence, the direction of the polarity of common bonds found in organic molecules is easily predicted. The common nonmetals are more electronegative than carbon. Therefore, when a carbon atom is bonded to common nonmetal atoms, it has a partial positive charge. Bond polarity plays a huge role in the chemistry of organic compounds.



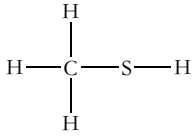
Hydrogen is less electronegative than the common nonmetals. Therefore, when a hydrogen atom is bonded to a common nonmetal, the resulting polar bond has a partial positive charge on the hydrogen atom.

Problem 1.2

Unlike methanol, which is a nearly odorless liquid, methanethiol (CH_3SH) is a gas with an appalling odor reminiscent of skunks. It is one of the compounds added to natural gas as a warning for gas leaks. Write the Lewis structure of methanethiol.

Sample Solution

The molecular formula for methanol (CH_3OH) resembles that of methanethiol. Sulfur is in the same family as oxygen. Sulfur and oxygen have the same number of valence electrons and can form the same number and type of bonds. Thus, we write a structure similar to methanol and simply substitute sulfur for oxygen. The structure is shown below.

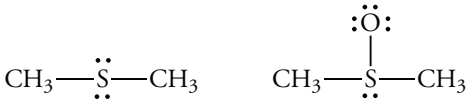


Problem 1.3

Chloroethane (CH_3CH_2Cl) is a topical anesthetic that boils at 12°C. When liquid chloroethane is released from a pressurized spray can, it expands and cools rapidly, numbing the skin. Describe the bonding in this compound. (Refer to the structure of ethane.)

Problem 1.4

Dimethyl sulfoxide is a liquid that is readily absorbed through the skin. It was once considered as a possible solvent to deliver drugs by direct application to the skin, but turned out to be too toxic for this use. Compare its structure to dimethyl sulfide and describe the sulfur–oxygen bond.

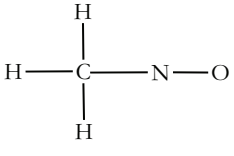


1.4 STRATEGIES FOR WRITING LEWIS STRUCTURES

When we write the Lewis structure of a molecule, we show all valence electrons. Hydrogen shares two electrons in a covalent bond. The second-row elements carbon through fluorine have octets of electrons either as nonbonded or bonded pairs. The electrons may participate in single, double, or triple bonds. We can use the following strategy to write Lewis structures.

1. Determine the total number of valence electrons by adding the valence electrons in the constituent atoms.
2. Write a skeletal structure linking the necessary atoms with single covalent bonds. This structure has the minimum number of bonding electrons.
3. For each bond, subtract two electrons from the total number of valence electrons to give the number of electrons that can exist as nonbonded electrons or form multiple bonds.
4. Determine the number of electrons required to complete the octet around each atom (except hydrogen, which only requires two electrons). If this number equals the number calculated in step 3, place the electrons as nonbonded electron pairs around the appropriate atoms to complete the structure.
5. If the number of electrons determined in step 3 does not provide all atoms with octets, we must use multiple bonds. If the deficiency is 2, a double bond must be used. If the deficiency is 4, either two double bonds or a triple bond must be used.
6. Modify the structure with the appropriate number of multiple bonds. The remaining electrons are nonbonded electrons that satisfy the electronic requirements of each atom.

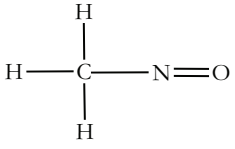
We'll apply these rules to nitrosomethane (CH_3NO), which has the following arrangement of atoms.



The total number of valence electrons is 3(1) + 4 + 5 + 6 = 18 for the hydrogen, carbon, nitrogen, and oxygen atoms. A total of 10 electrons is shown in the skeletal structure. The number of "unused" electrons is 18 – 10 = 8. Now find out the number of electrons needed by each atom to complete its octet (remember, hydrogen needs only two).

Atom	Electrons present	Electrons needed
Hydrogen	2 for each one	0
Carbon	4 × 2= 8	0
Nitrogen	2 × 2= 4	4
Oxygen	2	6

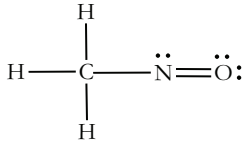
Because the 10 electrons required to form octets exceed the 8 electrons available after forming the single bonds, we need a double bond in the structure. The carbon atom has its required octet, so the double bond can be placed only between nitrogen and oxygen.



Based on this structure, calculate the number of electrons needed by each atom.

Atom	Electrons present	Electrons needed
Hydrogen	2 for each one	0
Carbon	4 × 2= 8	0
Nitrogen	2 + 4= 6	2
Oxygen	4	4

The number of electrons present in the structure is now 12, and 6 more electrons are required to complete the necessary octets. Six electrons remain available after using 8 for single bonds and 4 for a double bond. The 2 electrons required by nitrogen are added as a lone pair, the 4 needed by oxygen are added as two lone pairs. The structure is shown below.



Problem 1.5

Sodium borohydride ($NaBH_4$) is a reducing agent used in organic chemistry. This ionic compound contains the borohydride ion BH_4^-. Write its Lewis structure.

Problem 1.6

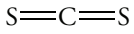
Write the Lewis structure for carbon disulfide (CS_2), a solvent used in some organic reactions. The sulfur atoms are bonded to the central carbon atom, but not to each other.

Sample Solution

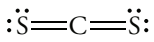
First write the connection of atoms in a molecular framework using only single covalent bonds between atoms.

C—S —C

Now calculate the total number of valence electrons for one carbon atom and two sulfur atoms, which is 4 + 2(6) = 16. Four electrons are placed in the two covalent bonds, leaving 12 electrons to complete octets around each atom using either lone pairs or multiple bonds. Each sulfur atom requires an additional 6 electrons and carbon requires 4 electrons. The total of 16 electrons is 4 more than are available. This deficiency is made up by using two double bonds—one between each sulfur atom and the central carbon atom.

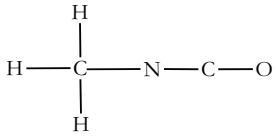


Now we have used 8 electrons of the original 16 valence electrons to form the molecular framework. Each sulfur atom now requires 4 more electrons, and carbon does not require any because it already has an octet of electrons. The remaining 8 electrons are distributed as two lone pairs of electrons on each sulfur atom, giving each an octet.



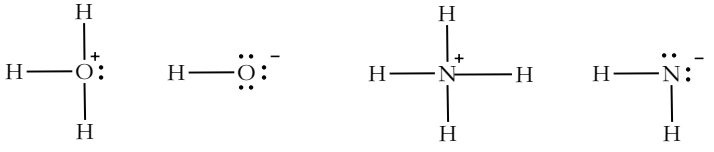
Problem 1.7

Methyl isocyanate is an important industrial intermediate used to synthesize compounds such as Sevin, an insecticide. A massive leak of this compound occurred in Bhopal, India, in 1984 that caused the deaths of nearly 4000 people almost immediately. Thousands more died later from gas-related causes. Using the following molecular framework, write a Lewis structure for methyl isocyanate.



1.5 FORMAL CHARGE

Although most organic molecules are represented by Lewis structures containing the "normal" number of bonds, some organic ions—and even molecules—do not have the customary number of bonds. First, let's recall the structures of some inorganic ions. The valence of the oxygen atom is two: it normally forms two bonds. However, oxygen has one bond in hydroxide ion and three in hydronium ion. Similarly, the nitrogen atom, whose valence is three, has four bonds in an ammonium ion and two bonds in an amide ion.



Two questions arise when atoms in polyatomic ions contain more or fewer bonds than expected from the valence of the central atom.

1. First, what is the net charge of the ion?
2. Second, what atom bears that charge?

We answer these questions by assigning to each atom a formal charge determined by a bookkeeping method. The method is also used for neutral molecules that have unusual numbers of bonds. In such cases, centers of both positive and negative charge are located at specific atoms.

The formal charge of an atom equals the number of its valence electrons as a free atom minus the number of electrons that it "owns" in the Lewis structure.

$$\text{formal charge} = \begin{pmatrix}\text{number of valence}\\ \text{electrons in free atom}\end{pmatrix} - \begin{pmatrix}\text{number of valence}\\ \text{electrons in bonded atom}\end{pmatrix}$$

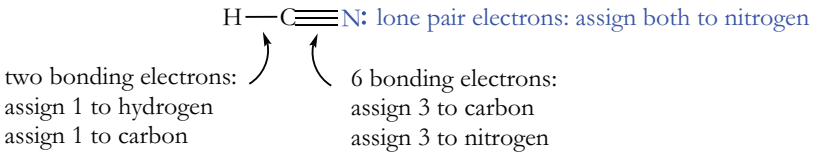
Two simple rules decide the question of "ownership."

1. Unshared electrons belong exclusively to the parent atom.
2. One half of the bonded electrons between a pair of atoms is assigned to each atom.

Thus, the total number of electrons "owned" by an atom in the Lewis structure equals the number of nonbonded electrons plus half the number of bonded electrons. Therefore, we may write the following equation.

$$\text{formal charge} = \left(\begin{array}{l}\text{number of valence}\\ \text{electrons in free atom}\end{array}\right) - \left(\begin{array}{l}\text{number of valence}\\ \text{electrons in bonded atom}\end{array}\right) - 1/2\left(\text{number of bonded electrons}\right)$$

The formal charge of an atom may be zero, negative, or positive. The sum of the formal charges of each atom in a molecule equals zero. The sum of the formal charges of each atom in an ion equals the charge of the ion. We'll use these rules to determine the formal charge of each atom in HCN.



The formal charge of each atom is calculated by substitution into the formula.

$$\begin{aligned}\text{formal charge of hydrogen} &= 1 - 0 - 1/2(2) = 0\\ \text{formal charge of carbon} &= 4 - 0 - 1/2(8) = 0\\ \text{formal charge of nitrogen} &= 5 - 2 - 1/2(6) = 0\end{aligned}$$

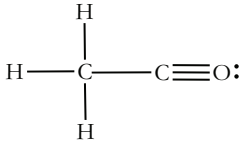
The formal charge of carbon is −1 and the formal charge of nitrogen is + 1. However, the *sum* of the formal charges of these atoms equals the net charge of the species, which in this case is zero.

Problem 1.8

Consider the structure of dimethyl sulfoxide given in Problem 1.4 and calculate the formal charges of sulfur and oxygen.

Problem 1.9

The acylium ion is an intermediate in one of the substitution reactions of aromatic compounds (Chapter 14). Calculate the formal charges of the carbon and oxygen atoms connected by a triple bond in the following structure. What is the charge of the ion?



1.6 MOLECULAR GEOMETRY

Until now we have shown organic compounds as two-dimensional structures. But molecules are three-dimensional. The three-dimensional structure of a molecule is defined by its bond lengths, the distance between the nuclei of two bonded atoms, and bond angles, the angle between two bonds to the same atom.

Bond Lengths

The length of a bond depends on the properties of the bonded atoms. Table 1.3 lists some representative bond lengths. The following generalizations are based on these data.

1. Bond lengths increase as the sizes of the bonded atoms increase. For example, chlorine is larger than fluorine, and the C—Cl bond is longer than the C—F bond.
2. Bond lengths between a given atom and a series of other atoms decrease from left to right within a period of the periodic table. For example, the C—F bond is shorter than the C—C bond. Part of the decrease of the bond length results from the smaller size of atoms toward the right in a period. However, the decrease is also partly due to the greater attraction for the bonding electrons, which are "pulled" closer by these electronegative atoms.
3. Bond lengths between atoms of the same element decrease as the number of bonds increase. For example, the bond lengths for carbon–carbon bonds decrease in the order C—C > C=C > C≡C. We will explain the reasons for this trend in Section 1.18.

Table 1.3

Average Bond Lengths

Structural Unit	*Bond Length (pm)*
H—C	110
H—N	98
H—O	94
H—F	92
H—S	132
H—Cl	127
H—Br	142
H—I	161
C—C	154
C—N	147
C—O	143
C—F	141
C—Cl	176
C—Br	191
C—I	210
C=C	134
C=O	122
Alkyne C≡C	121
Cyano (C≡N)	115

Drawing Structures

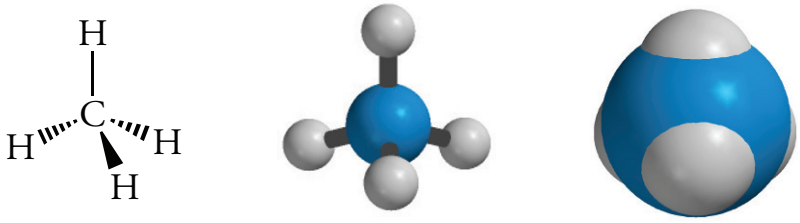
We will use the following conventions to draw the three-dimensional structures of molecules and their bonds.

1. Solid lines represent bonds in the plane of the page.
2. Wedge-shaped lines represent bonds projecting forward out of the plane of the page.
3. Dashed lines represent bonds projecting back out of the plane of the page.

Let's apply these conventions to the structure of methane (CH_4). The four hydrogen atoms in methane are located at the corners of a regular tetrahedron with the carbon atom in the center of the tetrahedron and in the plane of the page (Figure 1.6a). Each H—C—H bond angle is 109.5°, the "tetrahedral" angle. One hydrogen atom is also in the plane of the page. Its bond is shown with a solid line. Two hydrogen atoms, shown with dashed bond lines, lie behind the plane of the page, and one hydrogen atom, shown with a wedge-shaped bond line, lies in front of the plane.

Two types of molecular models are ball-and-stick models and space-filling models. Each has certain advantages and disadvantages. Ball-and-stick models show the molecular framework and bond angles: the balls represent the atoms; the sticks represent bonds (Figure 1.6b). Ball-and-stick models do not show the actual volume occupied by the molecule, however. Space-filling models represent the volume occupied by the electrons surrounding each atom, but the carbon skeleton and its bond angles are obscured (Figure 1.6c).

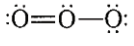
Figure 1.6 Perspective Structural Formulas and Molecular Models



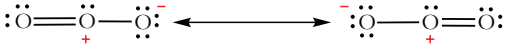
(a) Perspective Structure (b) Ball-and-stick Model (c) Space-filling Model

1.7 RESONANCE STRUCTURES

In the Lewis structures for the molecules we have discussed to this point, valence electrons have been shown either between two nuclei or associated with a specific atom. These are **localized** electrons. However, a single Lewis structure does not adequately represent the electronic structures of some molecules. For example, the Lewis structure of ozone (O_3) shows one double bond and one single bond.

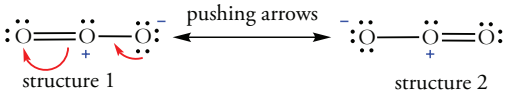


A double bond is shorter than a single bond, so the Lewis structure shown above implies that there is one "long" O—O bond and a "short" O=O bond in ozone. However, the measured oxygen–oxygen bond lengths in the ozone molecule are both 128 pm. Hence, the bonds are identical, and the terminal oxygen atoms are structurally equivalent. Therefore, a Lewis structure with single and double bonds does not accurately describe the ozone molecule. To give the information that a Lewis structure cannot represent, we use the concept of resonance. A molecule is **resonance-stabilized** if it can be represented by two or more Lewis structures that have identical arrangements of atoms, but different arrangements of electrons. Ozone is such a molecule. The "real" structure of ozone is a hybrid of two Lewis structures, neither of which is completely correct.



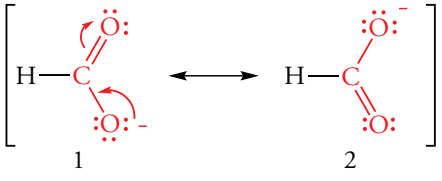
The double-headed arrow between the two Lewis structures indicates that the actual structure lies somewhere between the two structures. The individual Lewis structures are called contributing structures or resonance structures. Each resonance structure for ozone has one O=O bond and one O—O bond. The arrangements of the atoms are the same, but the arrangements of electrons are different.

When we write resonance structures, we use curved arrows to keep track of the electrons. The tail of the arrow begins near the bonded or nonbonded pair of electrons to be "moved" or "pushed," and the arrowhead shows the final destination of the electron pair.



In resonance structure 1, the nonbonded pair of electrons on the right-hand oxygen atom is moved to form a double bond with the central oxygen atom. One of the bonded pairs of electrons between the central oxygen atom and the oxygen atom on the left is also moved to form a nonbonded pair of electrons on the left oxygen atom. The result is resonance structure 2. This procedure of "pushing" electrons from one position to another is only a bookkeeping formalism. Electrons do not really move this way! The actual ozone molecule has delocalized electrons around all three atoms. A single Lewis structure cannot show this phenomenon.

A similar situation exists for the anion that results when a carboxylic acid such as methanoic acid ionizes. The product is a resonance-stabilized methanoate anion. (The anion is called a carboxylate anion.) The two structures, shown below, contribute equally to the resonance hybrid.



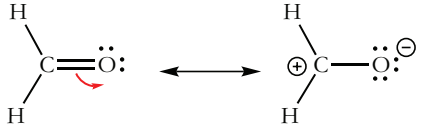
Resonance structures of carboxylate ion

Nonequivalent Resonance Structures

The resonance structures for molecules such as O_3 are equivalent and contribute equally to the structure of the molecule. However, many molecules have nonequivalent resonance structures that do not contribute equally to the structure of the molecule. To decide which resonance form is the more important, we can use the following four guidelines. The rules are applied with priority 1 > 2 > 3 > 4.

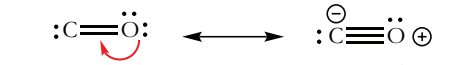
1. Lewis structures with the maximum number of Lewis octets are the most stable.
2. Avoid charge separation if possible. Charges are located on atoms with the most appropriate electronegativity characteristics (e.g., negative charges are placed on electronegative elements).
3. Opposite charges are located on atoms with the minimum separation.
4. Charges can be separated if Lewis octets result.

Let's apply these rules to two electronic structures of methanal (CH_2O). Structure 1, with a carbon—oxygen double bond, has Lewis octets for both carbon and the oxygen. Structure 2 has a Lewis octet for oxygen, but not for carbon. Therefore, structure 1 is preferred over structure 2 (rule 1). Structure 2 also has a formal negative charge on the oxygen atom and a positive charge on the carbon atom. We want to avoid charge separation if possible (rule 2).



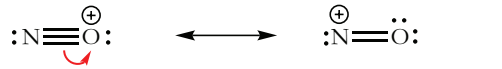
major contributor 1 minor contributor 2

Consider two resonance structures for carbon monoxide (CO). Structure 2, on the right, is more stable than structure 1. It is the major contributor to carbon monoxide because it has a Lewis octet for both the carbon atom and the oxygen atom. Note that the Lewis octet is formed even though there is a formal positive charge on the electronegative oxygen atom! Rule 4 allows this.



minor contributor 1 major contributor 2

Now consider the resonance structures for NO^+.



major contributor 1 minor contributor 2

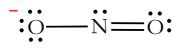
Structure 1, on the left, is more stable than structure 2. Structure 1 is the major contributor to NO^+ because the nitrogen and oxygen atoms each has a Lewis octet. Because the oxygen atom is more electronegative than the nitrogen atom, the positive charge is better tolerated on the nitrogen atom of structure 2 than on the oxygen atom of structure 1. However, structure 2 does not have a Lewis octet on nitrogen; therefore, it is less stable.

Problem 1.10

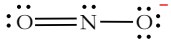
Nitrites (NO_2^-) are added as antioxidants in some processed meats and occasionally at salad bars. Write resonance structures for the nitrite ion.

Sample Solution

Using the procedure for drawing Lewis structures outlined above, we find that there must be one double bond between the nitrogen atom and one of the oxygen atoms.



However, the choice of location of the double bond is arbitrary. The positions of the nitrogen–oxygen single and double bonds can be interchanged as long as the lone pair electrons are located appropriately on each oxygen atom.

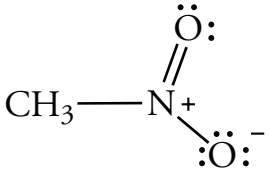


Thus, the nitrite can be represented by two equivalent resonance contributors. Note that the nitrogen atom has no formal charge in either structure. The single-bonded oxygen atom in each case has a formal minus charge.



Problem 1.11

Consider the structure of nitromethane, a compound used to increase the power in some specialized race car engines. A nitrogen–oxygen single bond length is 136 pm; a nitrogen–oxygen double bond length is 114 pm. The nitrogen–oxygen bonds in nitromethane are equal and are 122 pm. Explain the data in terms of the electronic structure of nitromethane.



1.8 VALENCE SHELL ELECTRON PAIR REPULSION THEORY

We can predict the geometry of simple molecules using **valence-shell electron-pair repulsion (VSEPR)** theory. This theory is based on the idea that bonded and nonbonded electron pairs around a central atom repel one another. Hence, they are arranged in a geometry that provides maximum separation in space, and therefore minimum electron repulsion. For bonds to carbon, the following rules apply:

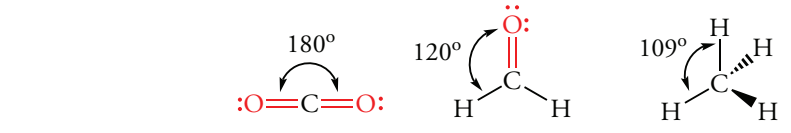
1. Two electron pairs should be arranged at 180° to each other; they are colinear.
2. Three pairs are separated by a 120°; they are in a common plane.
3. Four electron pairs should have a tetrahedral arrangement, with angles of 109.5°.



two electron pairs three electron pairs four electron pairs

To illustrate VSEPR theory, let's consider the geometry of three simple molecules.

1. Carbon dioxide has two equivalent double bonds: each lies as far as possible from the other double bond, forming a 180° angle between the bonds.
2. Methanal (CH_2O) has a double bond and two single bonds to the central carbon atom. These bonds correspond to three regions in space that contain electrons separated by the maximum distance in a trigonal planar arrangement. However, the actual H—C=O bond angle is 121.7°, slightly larger than the predicted 120°. The H—C—H bond angle is slightly smaller than 120°. These deviations from the predicted structure arise because the various bonding electrons are not equivalent.
3. Methane (CH_4) has four bonded electron pairs in single bonds, and they are located in a tetrahedral arrangement. Each H—C—H bond angle is predicted to be 109.5°, which agrees with the experimental value.



molecular geometry: linear trigonal planar tetrahedral

Next we will consider molecules that have both bonded and nonbonded pairs of electrons in the valence shell of the central atom. Water and ammonia have four electron pairs around the central atom. Some of the electron pairs in water and ammonia are bonded to hydrogen atoms, but the central atom also has unshared electron pairs. VSEPR theory describes the distribution of bonded and nonbonded electron pairs. However, molecular structure is defined by the positions of the nuclei. The four pairs of electrons in both water and ammonia are tetrahedrally arranged around the central atom. Water, with only three atoms, is angular, and ammonia, with four atoms, is pyramidal (Figure 1.7).

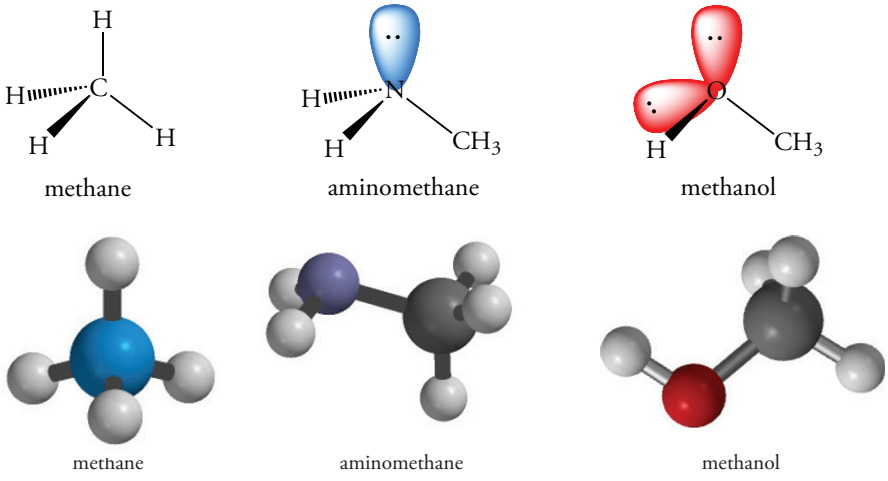
The H—C—H, H—N — H, and H—O—H bond angles are 109.5°, 107°, and 104.5°, respectively. We can explain these differences by considering electron pair repulsions. The decrease in bond angle suggests that the nonbonded electron pair is more spread out than the bonding electron pairs. The nonbonded electrons repel the bonded electron pairs, and hence the bonded atoms are closer together. Therefore, electron pair repulsion decreases as follows.

lone pair—lone pair > lone pair—bonded pair > bonded pair—bonded pair

In methane, the four bonded pairs are equivalent, arranged around the carbon atom at the tetrahedral angle, 109.5°. In ammonia, the lone pair electrons repel the bonded pairs and contract the H—N—H angle to 107°. In water, the two sets of lone pair electrons repel each other and the bonded pairs. Hence, the bonded pairs are forced even closer together than in ammonia.

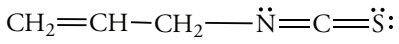
The arrangements of bonds to the oxygen atom of methanol and the nitrogen atom of aminomethane are similar to those in water and ammonia, respectively. The groups bonded to the oxygen atom of methanol form an angular (or "bent") molecule. The groups bonded to the nitrogen atom of methylamine are arranged in a pyramid.

Figure 1.7 VSEPR Model Predicts Geometry Around a Central Atom
All electron pairs in methane, aminomethane, and methanol are directed to the corners of a tetrahedron. However, the geometry around the nitrogen atom in aminomethane is described as trigonal pyramidal; the geometry around the oxygen atom in methanol molecule is angular.



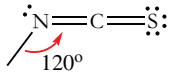
Problem 1.12

The electronic structure of allyl isothiocyanate, a flavor ingredient in horseradish, is shown below. What are the C—N=C and N=C=S bond angles?



Sample Solution

The C—N=C bond angle depends on the electrons associated with the nitrogen atom. This atom has a single bond, a double bond, and a nonbonding pair of electrons. These three electron-containing regions have trigonal planar geometry. Only two of the electron-containing regions are bonding, but the C—N=C bond angle must still be 120°.



1.9 DIPOLE MOMENTS

The measure of the polarity of a bond is the bond moment or **dipole moment**, μ. It is the product of the absolute value of the charge, q, and the distance between the charges, r.

$$\mu = |q|r$$

For diatomic molecules, the bond moment is equal to the dipole moment of the molecule. The dipole moment is expressed in Debye units (D). A dipole moment of 1 D equals the bond moment that results when opposite charges of 1×10^{-10} esu (electrostatic unit) are separated by one Angstrom (1×10^{-10} m); 1 D equals 1×10^{-10} esu Å.

Determining Charge Separation

The dipole moment gives us an idea about the amount of charge separation in a bond. The dipole moment of hydrogen chloride (HCl), for example, is 1.08 D. The bond length of HCl is 1.27 A. Solving for q, the charge is 0.85×10^{-10} esu. The charge of an electron is 4.8×10^{-10} esu. Thus, the partial charge on the chlorine atom in HCl is 0.18 that of an electron.

$$\frac{0.85 \times 10^{-10}\ \text{esu}}{4.8 \times 10^{-10}\ \text{esu/electron}} = 0.18\ \text{electron}$$

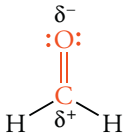
Table 1.4 lists the dipole moments of some bonds . The dipole moment of a specific bond is relatively constant from compound to compound. The C—H dipole moment, for example, is small because the hydrogen and carbon atoms have similar electronegativity values and because the bond length is small. Therefore, the C—H bond is not a polar covalent bond. In contrast, the dipole moment of the C—Cl bond in molecules such as chloromethane is large. Carbon has an electronegativity of 2.5. Chlorine has an electronegativity of 3.0. Because chlorine is more electronegative than carbon, chlorine pulls the bonded electrons closer to itself. The dipole moments of multiple bonds between carbon and oxygen, and between carbon and nitrogen are quite large. Hence, the C=O bond in methanal and the C≡N bond in cyanomethane are both very polar.

Table 1.4

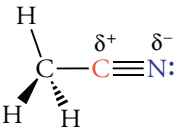
Average Dipole Moments (D)

Structural Unit[1]	*Bond Moments (D)*
H—C	0.4
H—N	1.3
H—O	1.5
H—F	1.7
H—S	0.7
H—Cl	1.1
H—Br	0.8
H—I	0.4
C—C	0.0
C—N	0.2
C—O	0.7
C—F	1.4
C—Cl	1.5
C—Br	1.4
C—I	1.2
C=O	2.3
C≡N	3.5

[1]The more electronegative atom in the bond is on the right.



methanal

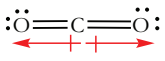


cyanomethane

Bond Polarity and Molecular Geometry

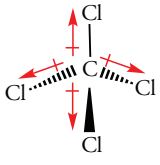
Some molecules have polar bonds, but do not have a *net* dipole moment. The polarity of molecules depends on the polarity of the bonds and the geometry of the molecule. The molecular dipole moment equals the vector sum of the individual bond moments.

To illustrate the relationship between molecular geometries and dipole moments, let's first consider carbon dioxide (CO_2). The C=O bonds are polar, with the dipole directed in opposite directions from the carbon atom toward the more electronegative oxygen atoms. The two bonds are located along a common line in this linear molecule. As a result, the bond moments of the C=O bonds cancel each other, and the molecule has no net dipole moment.

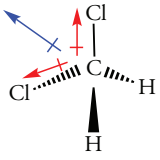


Now consider tetrachloromethane (CCl_4) and dichloromethane (CH_2Cl_2). Both molecules have polar C—Cl bonds with the negative ends of the dipoles pointed toward the chlorine atoms.

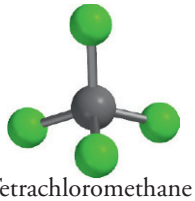
Blue arrow: direction of net dipole moment.



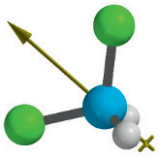
The bond moments cancel and there is no net polarity.



The bond moments do not cancel and there is a net polarity.



Tetrachloromethane



Dichloromethane

However, CCl_4 does not have a dipole moment because the vector sum of the symmetrically arranged C—Cl bonds around carbon is zero. In contrast, dichloromethane has a dipole moment of 1.62 D. The vector sum of the two C—Cl bonds is located at an angle bisecting the Cl—C—Cl bond angle. The C—Cl bonds are largely responsible for the observed dipole moment. The resultant of the two smaller C—H bond moments is in the same direction as the net resultant of the two C—Cl bond moments. The small resultant of the two C—H bond moments therefore reinforces the C—Cl bond moments.

Problem 1.13

The bond moment of C=O in compounds such as formaldehyde is 2.3 D. The bond length is 1.22 A. Determine the partial charge of the oxygen atom.

1.10 MOLECULAR ORBITAL THEORY

In Section 1.4, we represented the electronic structures of molecules as Lewis structures, which enable us to explain the connectivity of atoms in a molecule. This is the most fundamental feature of molecular structure. We then used valence-shell electron-pair repulsion (VSEPR) theory to explain molecular geometry.

VSEPR theory is a *local* model of chemical bonding. That is, it assumes that the electrons in a bond are confined to the space surrounding two adjacent atoms. In contrast, molecular orbital (MO) theory is a *delocalized* model of bonding in which the electron density is distributed across the entire molecule. We will begin our discussion of MO theory with the hydrogen molecule. When we consider any theory of bonding and structure, we discover that the theories are mathematical. However, we are in luck. We can leap right over the mathematical treatment of bonding and structure and use qualitative results predicted by the theory without serious harm to our understanding. We will summarize the theory of structure and bonding with pictures instead of mathematical equations. So, not only is "a picture worth a thousand words," it is also a worthy substitute for a thousand equations.

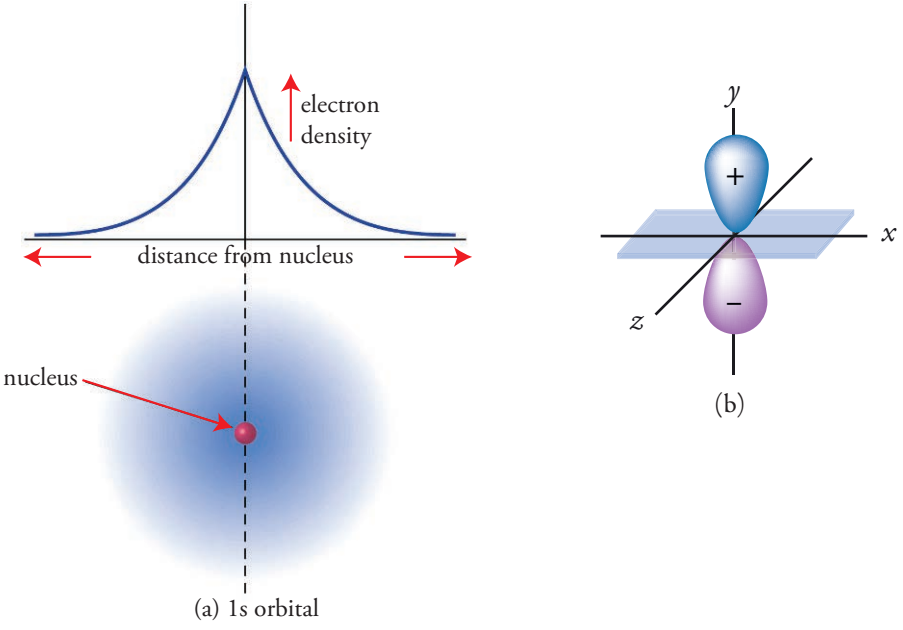


Figure 1.8 Atomic Orbitals
(a) The wave function of an s orbital is spherically symmetrical. The sign of the wave function does not change within the orbital. There is a 90% probability of finding a 1s electron within the shaded area.
(b) The sign of the wave function for a $2p_y$ orbital is positive above the *x*–*z* plane and negative below the *x*–*z* plane. A node exists at a point between the lobes of the orbital, and the entire *x*–*z* plane is a nodal plane. There is a 0% probability of finding a $2p_y$ electron in the *x*–*z* plane.

The 1s orbital is spherical because the value of the square of the wave function at a given distance from the nucleus is the same in all directions. The value of the function changes with distance from the nucleus, but the sign does not change. We place a plus sign within a sphere that represents the 1s orbital. We must not confuse the algebraic sign of equation for the wave function with the positive or negative charges of the electron, the proton, or ions!

A 2p orbital has two lobes. It is not spherical, but is symmetrical around an axis through its two lobes. The sign of the wave function within one lobe is opposite to the sign of the wave function within the other, so we place a plus sign in one lobe and a minus sign in the other lobe (Figure 1.8b). The value of the wave function is zero at a node located between the two lobes of the 2p orbital. The 2p orbital is perpendicular to a plane containing the node.

Molecular Orbitals

Atomic orbitals describe the probability of finding a given electron of an atom in a given region of space. We can combine the atomic orbitals of atoms in molecules to form new **molecular orbitals** (MOs). The molecular orbitals result from adding or subtracting atomic orbitals to give a **linear combination of atomic orbitals** (LCAO). The number of molecular orbitals is conserved. For example, adding two atomic orbitals represented by A_1 and A_2 produces two wave functions M_1 and M_2, described by the following equations.

$$M_1 = c_1A_1 + c_2A_2$$
$$M_2 = c_1A_1 - c_2A_2$$

The coefficients c_1 and c_1 are weighting factors that indicate the degree to which the atomic orbitals contribute to the molecular orbital. The coefficients are equal for diatomic molecules containing identical atoms. We will focus our attention upon the symmetry of pi molecular orbitals.

Like an atomic orbital, a molecular orbital can hold a maximum of two electrons with opposite spins. The shapes of molecular orbitals obtained by merging two atomic orbitals resemble the shapes of the atomic orbitals. When the orbitals merge to give a molecular orbital, they overlap in a region of space common to the bonded nuclei. First, consider the merger of two 1s orbitals. Partial overlap of the spheres yields an egg-shaped molecular orbital (Figure 1.9a). The orbital is symmetrical around an axis through both nuclei. Rotation around this axis does not change the appearance of the orbital. Orbitals that have this characteristic are called sigma (σ) molecular orbitals.

Now let's consider a combination of atomic orbitals that results in a molecular orbital with different symmetry. When two parallel 2p orbitals overlap, the area of overlap occurs above and below the nodal plane and is *not* cylindrically symmetrical (Figure 1.9b). A molecular orbital that results from sideways overlap of atomic orbitals is a pi (π) molecular orbital. A π molecular orbital can hold a maximum of two electrons, and these electrons must have opposite spins.

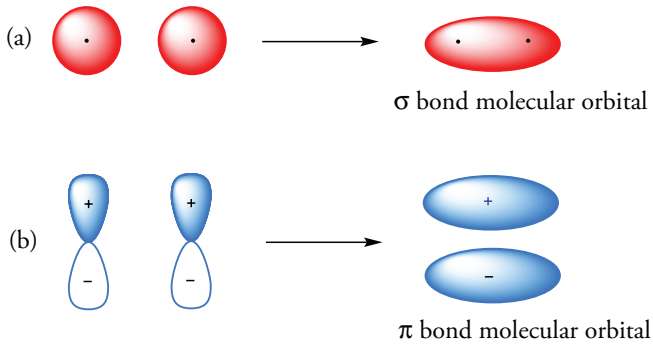


Figure 1.9 Linear Combinations of Atomic Orbitals
(a) When two 1s atomic orbitals of hydrogen atoms overlap, they may do so with reinforcement of the wave functions. The constructive interaction—that is, the addition of wave functions—gives a sigma (σ) molecular orbital. The electron density between two nuclei is located in this cylindrically symmetrical region.
(b) When two 2p orbitals overlap side-by-side, they may do so with reinforcement of the wave functions. The constructive interaction—that is, the addition of wave functions—results in a pi (π) molecular orbital.

1.11 THE HYDROGEN MOLECULE

The molecular orbital containing the bonding electrons in H_2 results from the overlap of two 1s atomic orbitals. The molecular orbital of the hydrogen molecule encompasses both nuclei. They are separated by an optimum distance, the bond length, which results from a balance between attractive and repulsive forces. The nuclei attract the bonding electrons, but repel each other. As two atoms move closer, the resulting increase in the electron density between the two atoms causes an attraction that lowers the potential energy (Figure 1.10). However, as the nuclei move still closer, the repulsion between the two nuclei eventually balances the effect of the electrons and the potential energy increases. The internuclear distance corresponding to the minimum energy is the bond length.

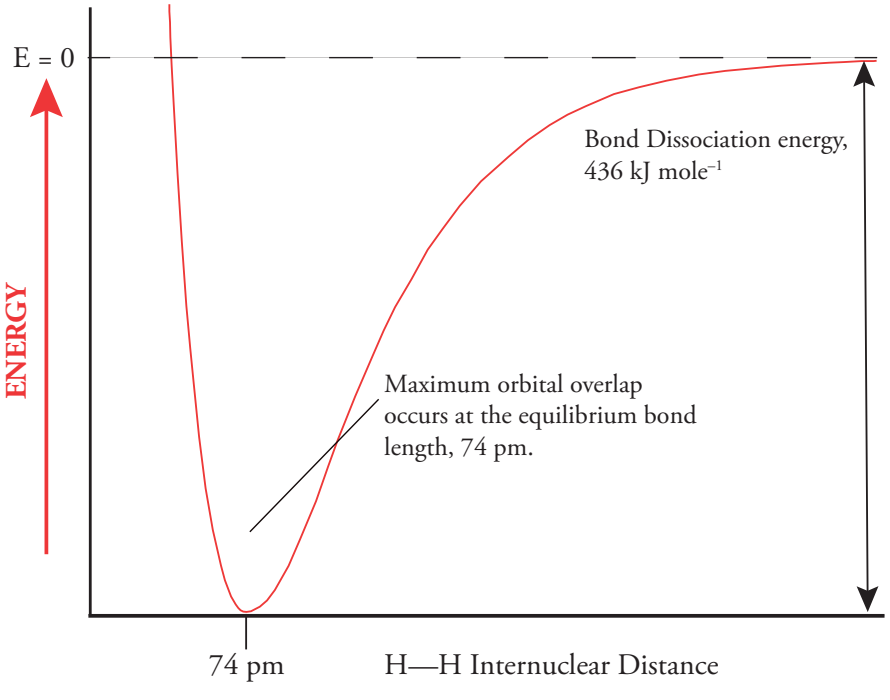


Figure 1.10 Plot of Energy vs. Internuclear Separation for the Hydrogen Molecule
An energy minimum for the interaction of two hydrogen atoms occurs when they are 74 pm apart. This minimum corresponds to bond formation between the two atoms. If the nuclei move closer, the energy rapidly increases because the two positively charged nuclei repel each other more.

If we add two wave functions with opposite signs, this is the same as "subtracting" them. This leads to destructive interference, the wave functions cancel, and there is a node between the two nuclei. The resulting molecular orbital corresponds to a destructive interaction in which the wave functions cancel out where the orbitals overlap. The resulting molecular orbital is called an **antibonding orbital**. The antibonding molecular orbital has a nodal plane between the two atoms. The antibonding molecular orbital is symbolized by σ*, ("sigma-star").

Figure 1.11 shows the energy of the σ and σ* molecular orbitals relative to the energy of the 1s orbitals of the hydrogen atoms. As we noted above, the energy of the bonding molecular orbital 1s is lower than the combined energies of the atomic orbitals. Thus, energy is released as bonding occurs. The antibonding molecular orbital is at higher energy than the atomic orbitals.

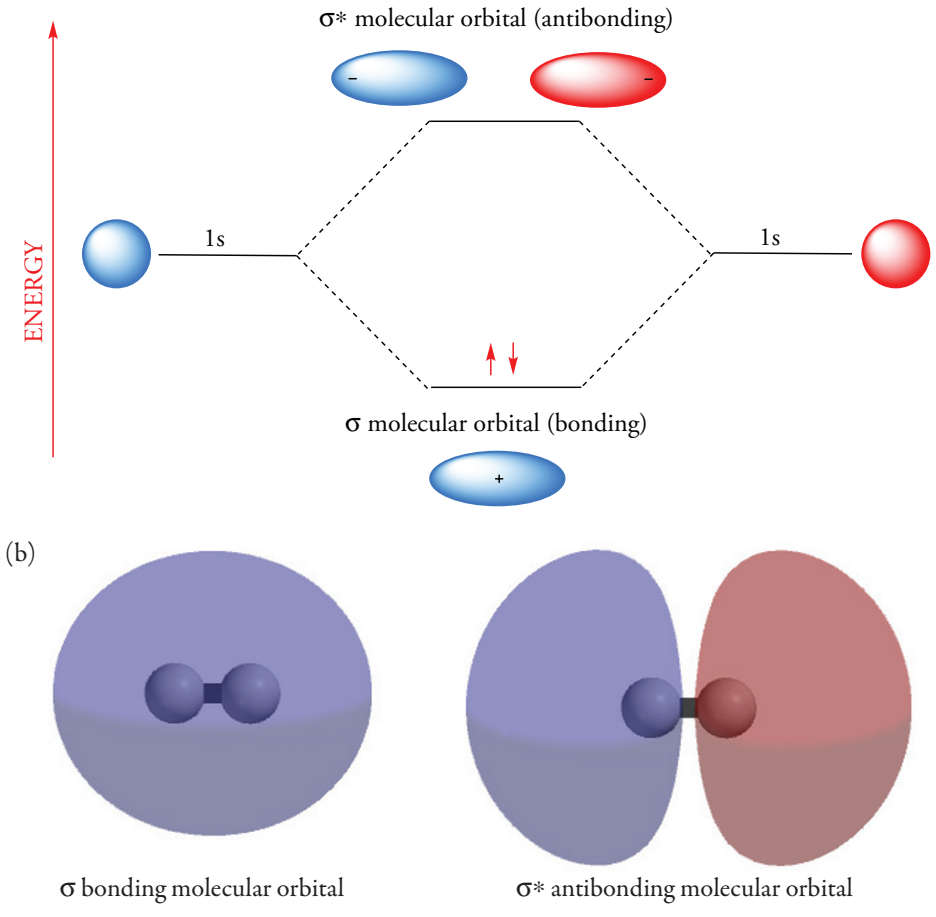
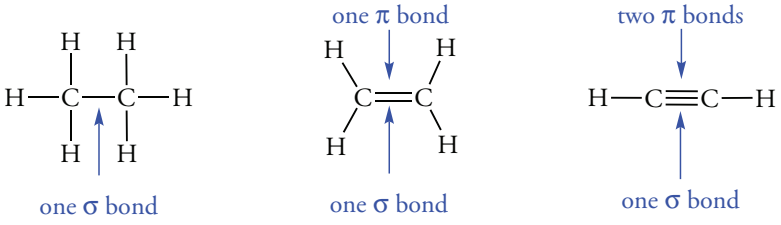


Figure 1.11 Energy of Bonding and Antibonding Molecular Orbitals
(a) Two molecular orbitals are formed by combining two 1s hydrogen orbitals. The bonding molecular orbital, σ, is lower in energy than the antibonding molecular orbital, σ*. There is no electron density between the two nuclei in the antibonding orbital.
(b) Molecular orbital view of hydrogen bonding and antibonding orbitals.

1.12 BONDING IN CARBON COMPOUNDS

The strongest bonds form when two orbitals achieve maximum overlap, which occurs when two orbitals point directly toward each other. The σ bonds between carbon atoms and other atoms, such as the hydrogen atom, result from overlap of orbitals along the internuclear axis. Because the overlap of orbitals in a π bond is less than that of a σ bond, π bonds are weaker than σ bonds.
A single bond in an organic molecule is always a σ bond. A double bond consists of one σ bond and one π bond. A triple bond consists of one σ bond and two π bonds.



Orbital Hybridization

In Lewis structures of ethane (C_2H_6), ethene (C_2H_2), and ethyne (C_2H_2), all carbon atoms have four bonds. In this section, we will consider the atomic and molecular orbitals from which bonds to carbon are made. Carbon has the electron configuration $1s^2 2s^2 2p^2$. We know that the 1s electrons do not participate in bonding because they are held too tightly by the nucleus, and that carbon forms bonds with its 2s and 2p electrons. However, because the 2s orbital is filled and the 2p electrons are distributed between $2p_x$ and $2p_y$ orbitals, the ground state electron configuration does not appear to permit the formation of four bonds. Linus Pauling proposed that the original, ground state orbitals of carbon are mixed, or **hybridized**, to give a new set of atomic orbitals used to make σ and π bonds. The Pauling orbital hybridization process is designed to generate the molecular geometry predicted by VSEPR theory. In the following sections, we will consider the molecular geometries and orbital hybridization of carbon when it forms four σ bonds, three σ bonds and one π bond, and one σ bond and three π bonds. We will also consider the hybridization of oxygen and nitrogen because these atoms are present in many organic compounds. Pauling's orbital hybridization model is universally accepted because of its enormous predictive power, but we shouldn't forget that it is purely a theoretical idea that does not correspond to an actual physical process.

1.13 sp^3 HYBRIDIZATION OF CARBON IN METHANE

We can explain the tetrahedral geometry of methane by imagining that the 2s orbital and the three 2p orbitals of carbon hybridize to form four identical sp^3 hybrid orbitals (Figure 1.12). We can divide the hybridization process into two steps.

1. First, an electron in the 2s orbital is "promoted" to a vacant 2p orbital to produce an excited state of carbon. The 2s orbital in this state has only one electron.
2. Second, the half-filled 2s orbital and the three half-filled 2p orbitals mix to form new sp^3 hybrid orbitals (pronounced "s-p-three," *not* "sp cubed").

These hybrid orbitals are named this way because they result from the combination of one s and three p orbitals. Each sp^3 hybrid orbital has 25% s character and 75% p character. The four sp^3 hybrid orbitals have the same energy. Each orbital has two lobes of unequal volume. The signs of the wave functions in the two lobes are opposite. The larger volume corresponds to a region of higher electron density. We usually consider only the larger lobe when showing bonds made with sp^3 hybrid orbitals. For purposes of clarity, we will usually omit the smaller lobes of each sp^3 hybrid orbital.

The four single bonds and the tetrahedral shape of CH_4 are explained by using sp^3 hybrid orbitals, each of which contains one electron. The sp^3 orbitals extend toward the corners of a tetrahedron, achieving maximum separation of the electrons. The large lobe of each sp^3 hybrid orbital overlaps the 1s orbital of a hydrogen atom. Hence, the carbon atom forms four σ bonds (Figure 1.13).

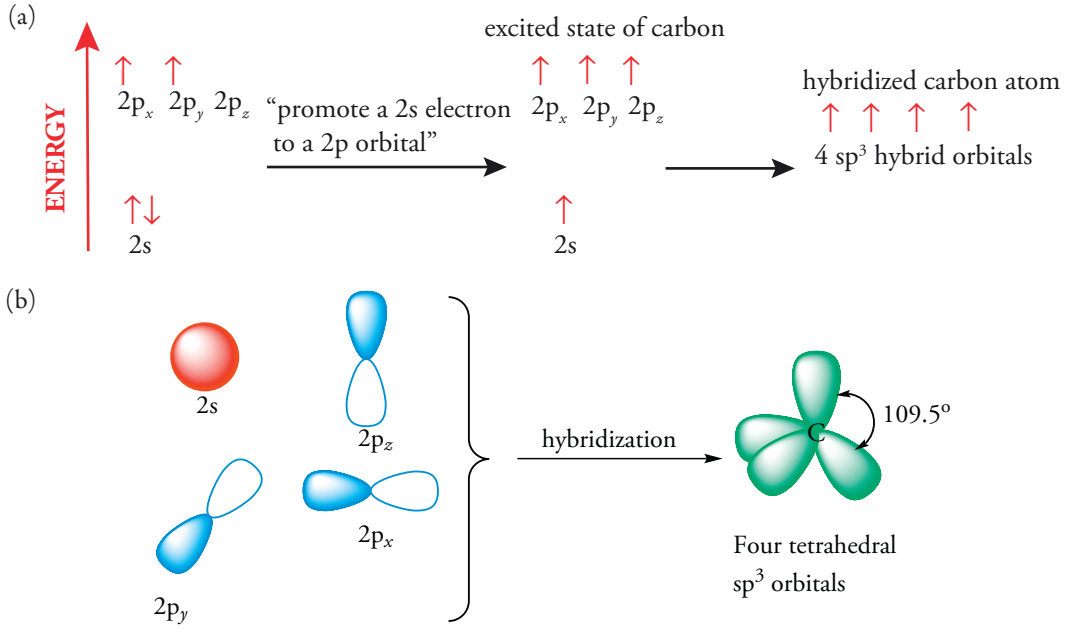
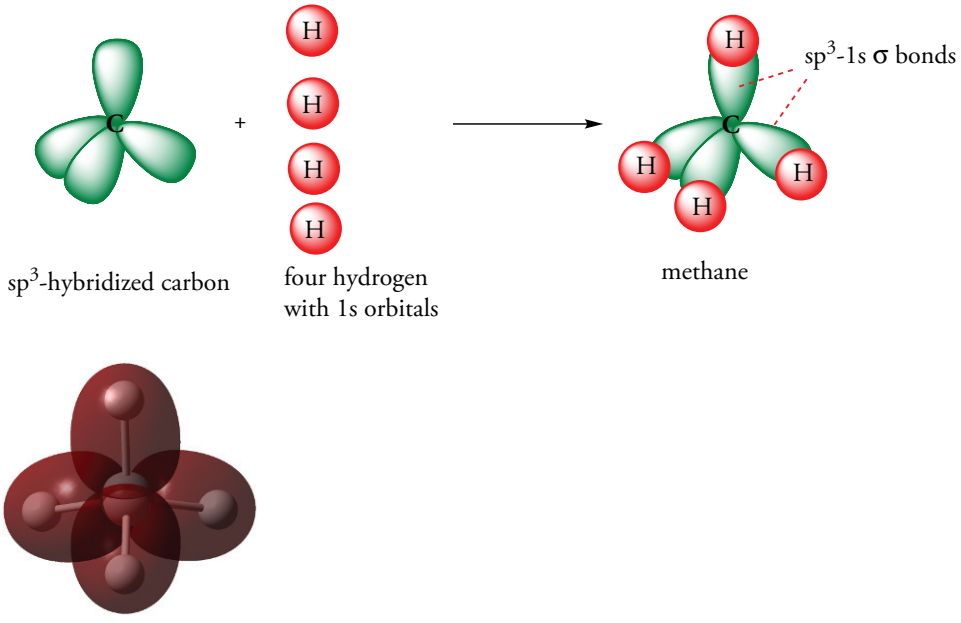


Figure 1.12 sp^3-Hybridized Carbon Atom
(a) The original set of four atomic orbitals on carbon are mixed, or hybridized, to give four new sp^3-hybridized atomic orbitals. (b) We have represented the new hybrid orbitals with a new color to emphasize the notion that the hybrid orbitals replace the original unhybridized orbitals.

Figure 1.13 sp^3-Hybridized Carbon in Methane

The shapes of the sp^3 hybrid atomic orbital in methane. The outer boundary encloses a region of space with a 90% probability of finding an electron. The four identical sp^3 hybrid orbitals point at the corners of a regular tetrahedron.



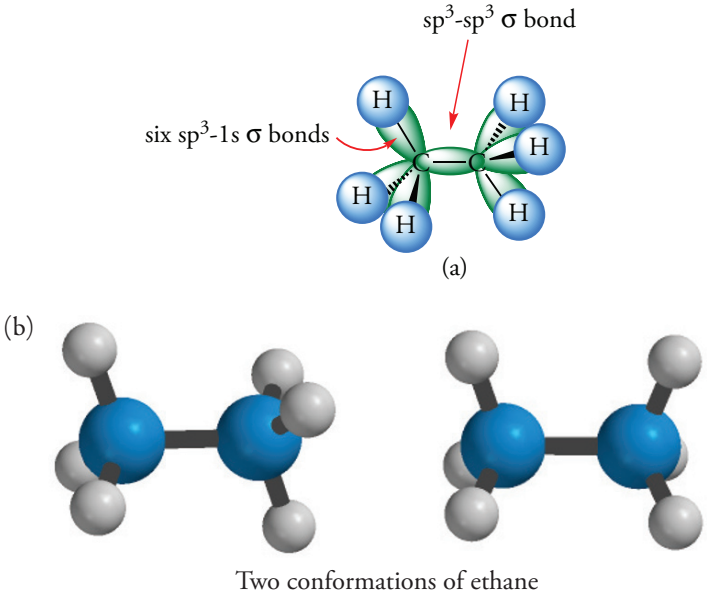
1.14 sp^3 HYBRIDIZATION OF CARBON IN ETHANE

The orbital hybridization model of bonding in methane also accounts for the carbon—carbon bonds in more complex organic compounds. Ethane (CH_3—CH_3) can be thought of as two CH_3 units—methyl groups— obtained by removing one hydrogen atom from each of two methane molecules. The methyl groups are linked by a carbon—carbon bond (Figure 1.14). Each carbon in ethane is sp^3 hybridized. Three of the sp^3 orbitals of each carbon atom overlap with 1s atomic orbitals of hydrogen. These C—H bonds are similar to the $\sigma_{sp^3\text{-}1s}$ bonds in methane. The C—H bond in ethane (111 pm) is slightly longer than the C—H bond in methane (109 pm). The bond energies of the C—H bonds of ethane and methane are 422 and 438 kJ $mole^{-1}$, respectively.

The carbon atoms in ethane are linked by a $\sigma_{sp^3\text{-}sp^3}$ bond. The C—C bond length is 154 pm; the C—C bond energy of ethane is 368 kJ $mole^{-1}$. Each CH_3 unit can be rotated around the C—C internuclear axis. That is, the positions of the hydrogen atoms of each carbon atom with respect to each other can change. Two such orientations, called **conformations**, are shown in Figure 1.14. In these two conformations, as well as any others resulting from different angles of rotation around the C—C bond, the σ bond does not change because the overlap of the sp^3 orbitals of the bonded carbon atoms does not change.

Figure 1.14 Bonding and Structure of Ethane and Conformations of Ethane

(a) The bonding molecular orbital of the C—C bond in ethane is cylindrically symmetrical.
(b) Rotation of the two methyl groups about the C—C bond axis maintains the bond, but changes the relative positions of the C—H bonds.

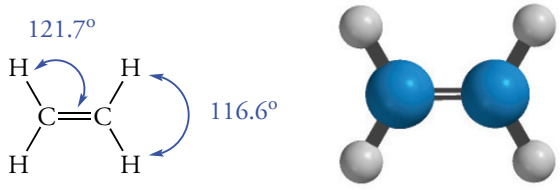


Two conformations of ethane

Which of the conformations represents ethane? *They all do.* Rotation around the carbon—carbon sigma bond occurs constantly in ethane. However, this rotation does not alter the *connectivity* of the carbon–carbon or carbon–hydrogen bonds. We will discuss the conformations of ethane and other hydrocarbons—compounds of carbon and hydrogen—in more detail in Chapter 4.

1.15 sp^2 HYBRIDIZATION OF CARBON IN ETHENE

Now let us consider the bonding electrons in the double bond of ethene, in which each carbon atom is bonded to three atoms. All six nuclei lie in a plane, and all the bond angles are close to 120°. Therefore, ethene is trigonal (three angles) planar.



Since each carbon atom in ethene is bonded to three other atoms, we need three σ bonds. We hybridize carbon by "mixing" a 2s orbital and two 2p orbitals to obtain three sp^2 hybrid orbitals (pronounced "s-p-two"). The third 2p orbital remains unchanged. The three sp^2 hybrid orbitals have the same shapes and energies. The orbitals differ only in their position in space. They lie in a plane and are directed to the corners of an equilateral triangle—therefore separated by 120°—to achieve maximum separation of the electrons (Figure 1.15).

Two of the sp^2 orbitals, containing one electron each, form σ bonds with hydrogen. The third sp^2 orbital, which also contains one electron, forms a σ bond with the other carbon atom in ethene (Figure 1.16). A second carbon–carbon bond in ethylene is a π bond resulting from lateral overlap of the 2p orbitals of each carbon atom. Each 2p orbital is perpendicular to the plane containing the sp^2 orbitals. The 2p orbital of each atom provides one electron to the electron pair for the second bond.

In contrast to the rotation that occurs around the C—C bond of ethane, no rotation occurs around the C=C bond of ethylene. Rotation around the C=C internuclear axis would not disrupt the sp^2–sp^2 σ bond. However, this motion would destroy the overlap of the two 2p orbitals and break the π bond. A large amount of energy, approximately 250 kJ $mole^{-1}$, is required to break the π bond.

Figure 1.15 sp^2 Hybrid Orbitals

(a) Schematic diagram of orbital hybridization. (b) Shapes of sp^2 hybrid orbitals. The shape of an sp^2 hybrid atomic orbital in ethene. The outer boundary encloses a region of space with a 90% probability of finding an electron. The three identical sp^2 hybrid orbitals point at the corners of a triangle.

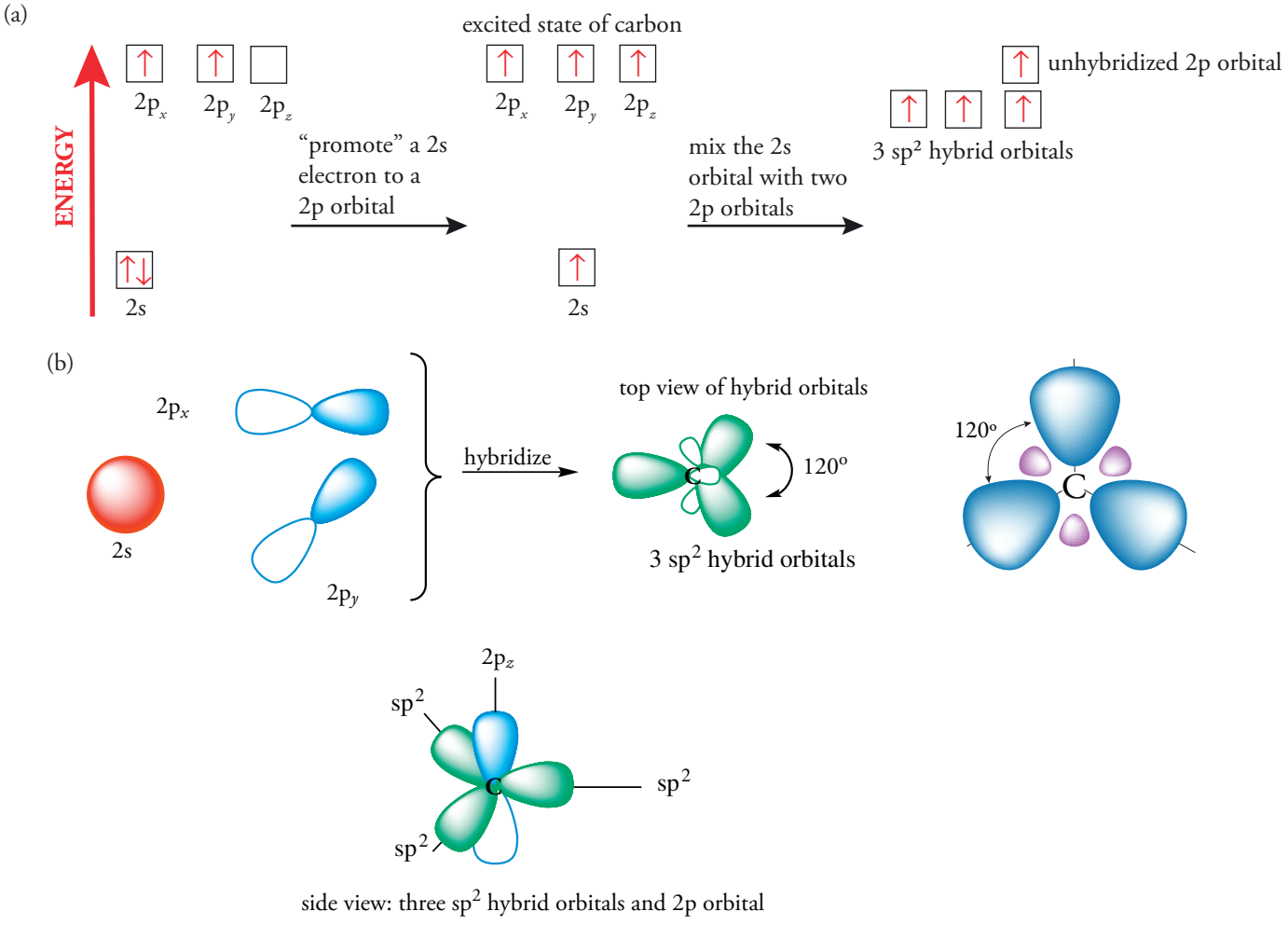
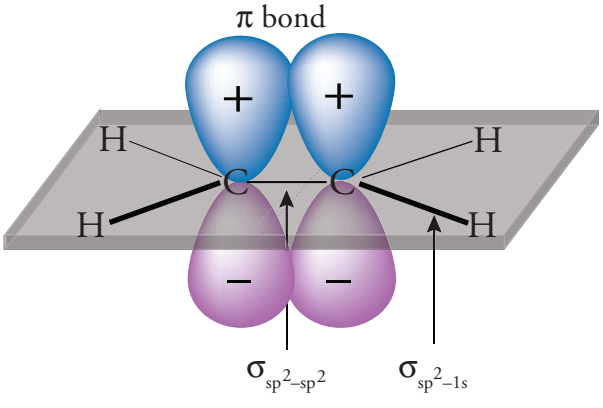
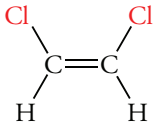


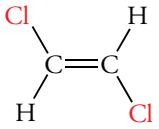
Figure 1.16 Bonding and Structure in Ethene



The three-dimensional relationship between the two CH_2 groups of ethene is rigidly fixed by the π bond. As a consequence, two different compounds, called **geometrical isomers**, can exist in certain substituted ethylene compounds. For example, consider the isomeric structures with one chlorine atom bonded to each sp^2-hybridized carbon atom of ethene.

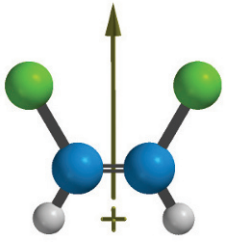


cis-1,2-dichloroethene

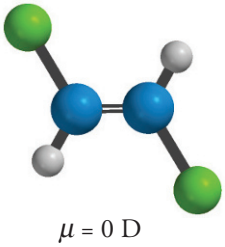


trans-1,2-dichloroethene

The two chlorine atoms are on the same "side" of the double bond in the *cis* isomer and on the opposite "sides" of the double bond in the *trans* isomer. These isomers have different physical properties. For example, the *cis* isomer is a polar compound, but the *trans* isomer is nonpolar because the dipoles of the C—Cl bonds point in opposite directions and cancel.



μ = 1.9 D



μ = 0 D

1.16 sp HYBRIDIZATION OF CARBON IN ETHYNE

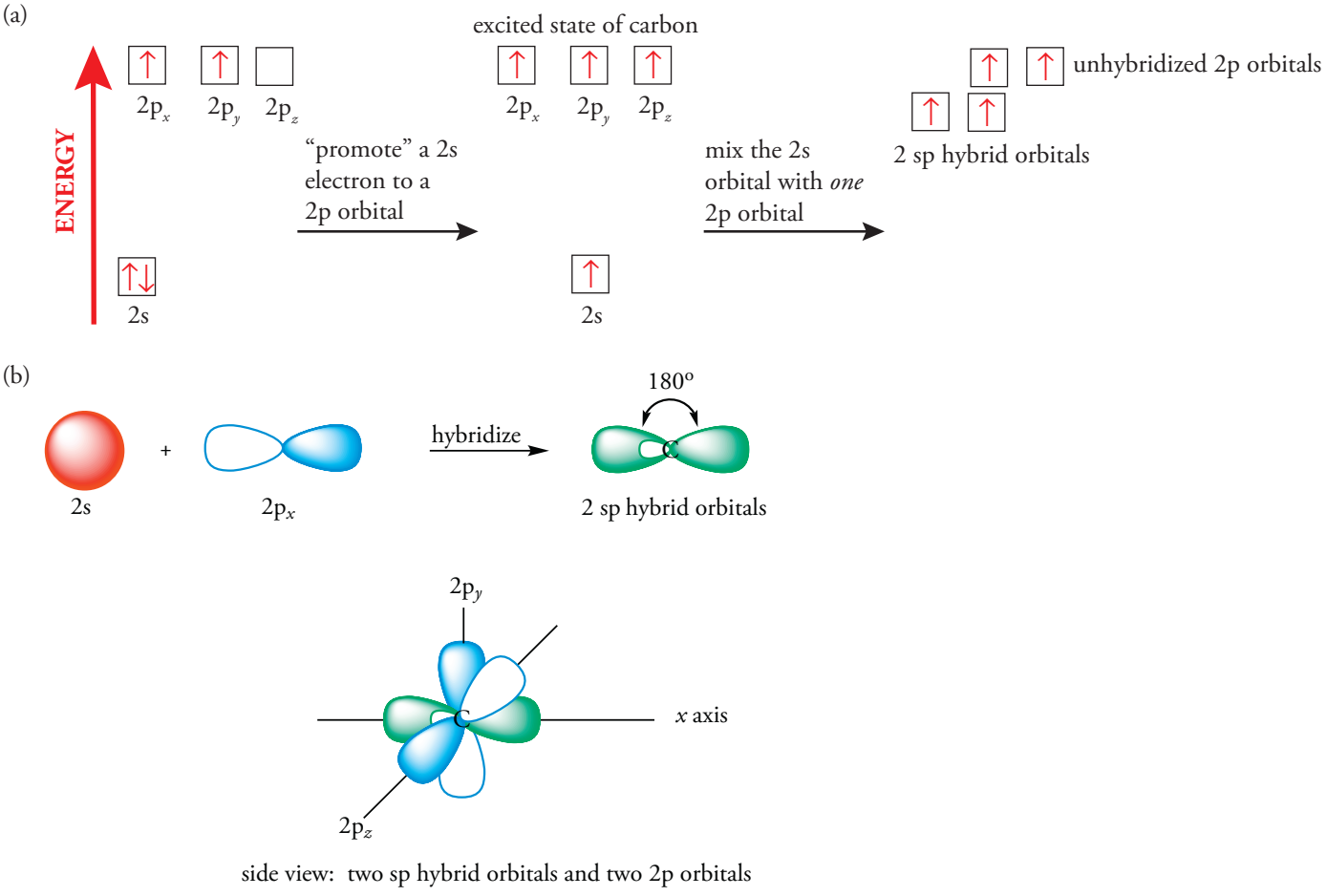
We next consider the bonding in ethyne, a molecule in which each carbon atom is bonded to two atoms by σ bonds. Let's suppose that is composed of two **methine** (CH) units. Since each carbon atom of acetylene is connected to two other atoms, a carbon atom and a hydrogen atom, each methine unit requires two π bonds. We obtain these two bonds as follows.

1. Promote an electron from a filled 2s orbital to a vacant 2p orbital.
2. Mix the 2s orbital with *one* 2p orbital to form two identical sp hybrid orbitals of equal energy. Two half-filled 2p orbitals remain (Figure 1.17).

The sp hybrid orbitals differ only in their position in space. They lie at a 180° angle, which provides for maximum separation of the electrons. The sp hybrid orbitals can form σ bonds. One sp hybrid orbital on each carbon atom forms a σ bond with hydrogen; the other sp hybrid orbital forms a σ bond with the second carbon atom. Hence, all four atoms of acetylene lie on a straight line (Figure 1.18).

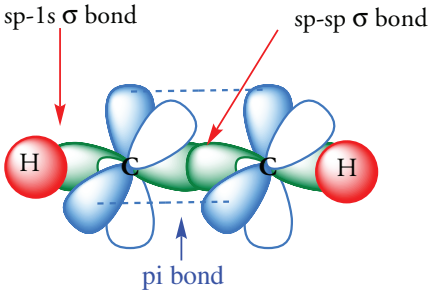
After each carbon atom has formed two σ bonds, each still has two half-filled 2p orbitals. The half-filled 2p orbitals overlap side by side to give two π bonds. One set of 2p orbitals overlaps in "front" and "back" of the molecule to form one π bond. The second set of 2p orbitals overlaps "above" and "below" the molecule to form the second π bond. Thus, the carbon atoms in acetylene are linked by one σ bond and two π bonds to give a triple bond.

Figure 1.17
sp-Hybridized Carbon Atom

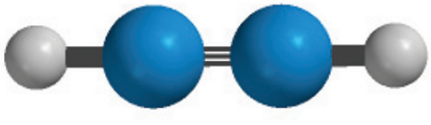


side view: two sp hybrid orbitals and two 2p orbitals

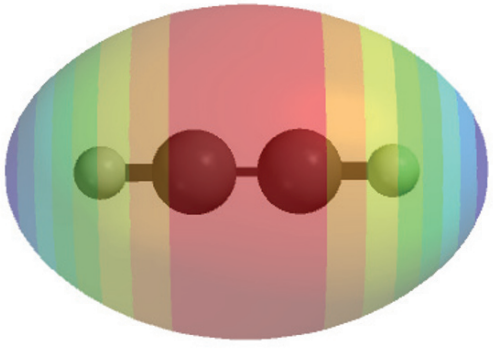
Figure 1.18 Structure and Bonding in Ethyne



Bonding in ethyne: the σ bonds are colinear; the π bonds lie above and below, and in front and behind the carbon-carbon sigma bond.



Ball-and-Stick model of ethyne



Electron density map of ethyne. Although the molecule is nonpolar overall, each C—H bond is polar. The carbon has a small partial positive charge (shaded red), and the hydrogen has an equal and opposite partial negative charge (shaded blue).

1.17 EFFECT OF HYBRIDIZATION ON BOND LENGTH AND BOND STRENGTH

An sp^2 hybrid orbital of carbon has approximately the same shape as an sp^3 hybrid orbital. However, an sp^2 hybrid orbital has 33% s character compared to 25% s character for an sp^3 hybrid orbital. As the percent s character of hybrid orbitals increases, the electrons in the hybrid orbitals are closer to the nucleus. Therefore, the electrons in an sp^2 hybrid orbital are closer to the nucleus than the electrons in an sp^3 hybrid orbital. *Increasing the percent s character of a hybrid orbital effectively increases the electronegativity of the carbon atom.*

Orbital hybridization strongly affects physical properties such as bond lengths and bond energies. The length of a σ bond between carbon and another atom is shorter for a carbon atom with sp^2 hybrid orbitals than for a carbon atom with sp^3 hybrid orbitals. For example, we find that the C—H bond length in ethene is 107 pm, whereas in ethane the C—H bond length is 109 pm. The bonds of sp^2-hybridized atoms also have larger bond energies than bonds of sp^3-hybridized atoms. For example, the C—H bond energy of ethene is 452 kJ $mole^{-1}$ compared to 422 kJ $mole^{-1}$ for the C—H bond energy of ethane (Table 1.5).

The trend toward shorter bond lengths and stronger bonds prevails when we compare sp hybrid orbitals with sp^2 and sp^3 hybrid orbitals. The C—H bond length of ethyne is about 105 pm, and the C—H bond energy is 523 kJ $mole^{-1}$. Carbon–carbon bond lengths also decrease in the order $sp^3 > sp^2 > sp$. The carbon–carbon bond lengths of ethane, ethene, and ethyne are 154, 133, and 120 pm, respectively. These bond lengths decrease partly because the electrons in the hybrid orbitals used to form the σ bonds are progressively closer to the nucleus as the percent s character increases. However, the decrease in the carbon–carbon bond length also results from the increased number of bonds joining the carbon atoms. Two shared pairs of electrons (one σ and one π) draw the carbon nuclei closer together than a single σ bond. Three shared pairs (one σ and two π) pull the carbon atoms still closer (Tables 1.6).

Table 1.5
Average Bond Energies in Ethane, Ethene, and Ethyne

Bond Type	*Bond Energy (kJ $mole^{-1}$)*
H—C (sp^3)	410
H—C (sp^2)	422
H—C (sp)	523
C—C (sp^3)	347
C=C (sp^2)	610
C≡C (sp)	837

Table 1.6
Average Bond Lengths (pm)

H—C (sp^3)	109
H—C (sp^2)	107
H—C (sp)	105
C—C (sp^3)	154
C=C (sp^2)	133
C≡C (sp)	120

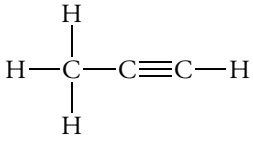
Problem 1.14

What type of overlap is present in the carbon—carbon single bond of propene? What is the C—C=C bond angle?

$CH_3—CH=CH_2$
propene

Problem 1.15

The carbon—carbon single bond length of propyne is 146 pm. Why is this value different from the carbon—carbon single bond length of ethane (154 pm)?


propyne

1.18 HYBRIDIZATION OF NITROGEN

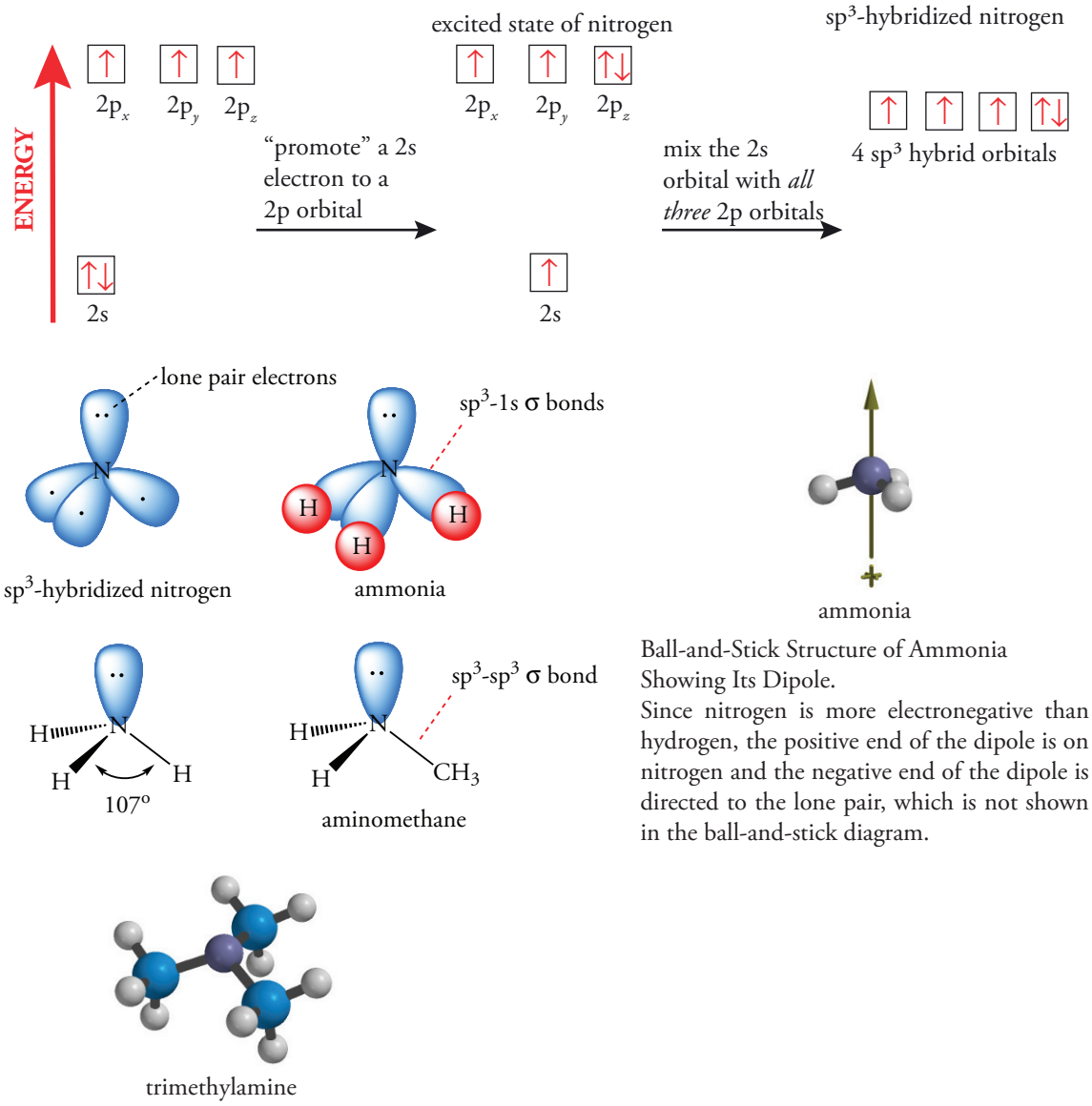
A nitrogen atom forms hybrid orbitals in much the same way as carbon. The only difference in the hybridization scheme is that nitrogen has one more electron than carbon to distribute in its hybridized orbitals (Figure 1.19). The four orbitals around nitrogen point at the corners of a tetrahedron. One sp^3 orbital of nitrogen contains a pair of electrons. The other three orbitals each contain a single electron. Each electron can form a σ bond to another atom such as hydrogen in ammonia or carbon in trimethylamine. In trimethylamine, the three methyl (CH_3) groups are bonded to the central nitrogen atom to form a trigonal pyramidal molecule with C—N—C bond angles of 108°. The value differs slightly from the tetrahedral angle, 109.5°, because lone pair electrons occupy more volume than bonding electrons. The nonbonded electrons repel the bonding electrons, compressing the C—N—C bond angle (Figure 1.20).

In contrast to carbon, nitrogen could form three σ bonds to hydrogen or other atoms to achieve a Lewis octet without hybridizing the atomic orbitals. However, the sp^3 hybrid orbital has 25% s character, and the overlap of the hybrid orbital with the 1s orbital of the hydrogen atom is more efficient than the overlap of a 2p orbital of nitrogen with a 1s orbital of hydrogen. Again, the higher percent s character of the sp^3 hybrid orbital results in a stronger bond and a more stable molecule.

The five valence electrons of nitrogen can also be distributed in three sp^2 hybrid orbitals (Figure 1.20). The three orbitals around nitrogen are coplanar. One sp^2 orbital contains a pair of electrons. The other two orbitals have a single electron. Each electron forms a σ bond to another atom, such as hydrogen or carbon. The single electron in the remaining 2p orbital forms a π bond with the 2p orbital of another atom, such as carbon.

The five valence electrons of nitrogen can also be distributed in two sp hybrid orbitals (Figure 1.21). The two sp orbitals around nitrogen are colinear. One of the sp orbitals contains a pair of electrons. The other sp orbital contains a single electron, which forms a σ bond to an atom such as carbon. The single electrons in each of the two 2p orbitals form π bonds with the electrons in 2p orbitals of another atom such as carbon.

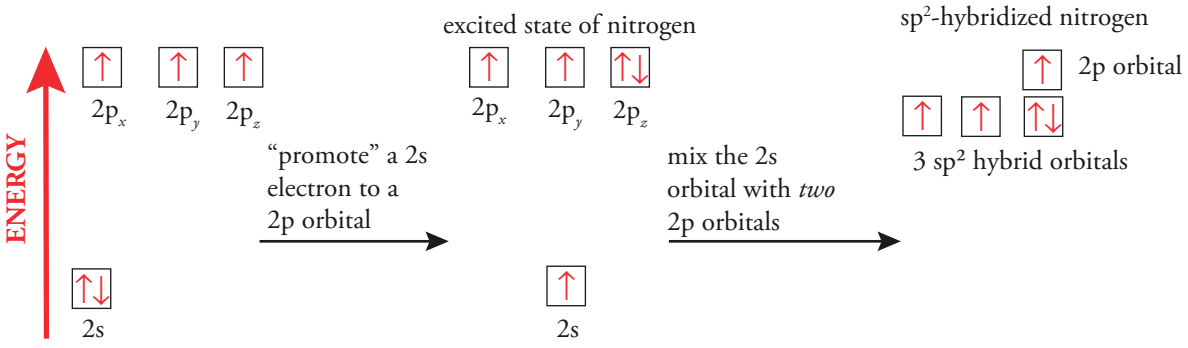
Figure 1.19
sp^3-Hybridized Nitrogen Atom

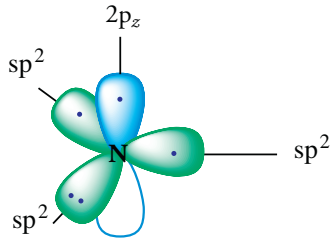


Ball-and-Stick Structure of Ammonia Showing Its Dipole.
Since nitrogen is more electronegative than hydrogen, the positive end of the dipole is on nitrogen and the negative end of the dipole is directed to the lone pair, which is not shown in the ball-and-stick diagram.

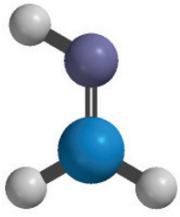
Ball-and-Stick Structure of Triethylamine.
All three hydrogen atoms of ammonia have been replaced with alkyl groups.

Figure 1.20 sp²-Hybridized Nitrogen Atom



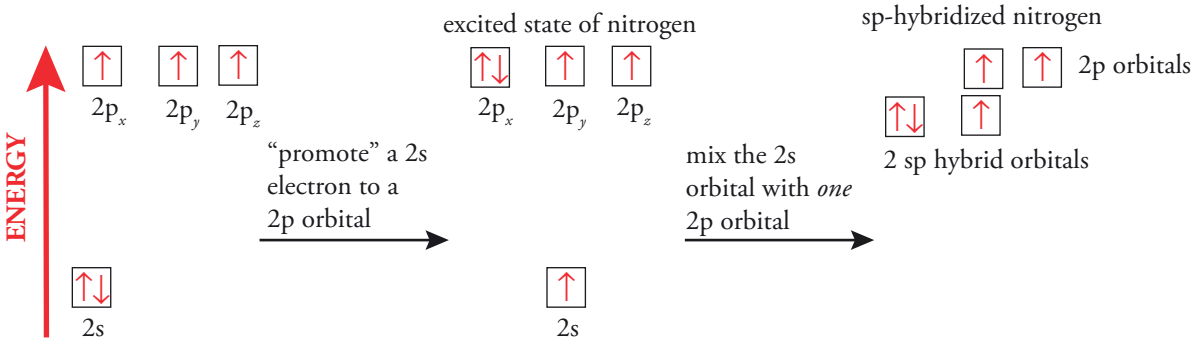


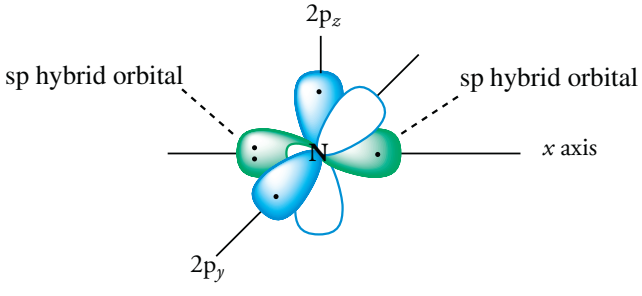
side view: three sp^2 hybrid orbitals and 2p orbital on nitrogen



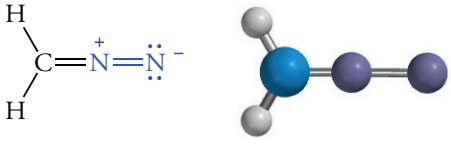
Ball-and-Stick Structure of formaldimine, the nitrogen analog of ethene. The nitrogen and carbon atoms are both sp^2-hybridized.

Figure 1.21 sp-Hybridized Nitrogen Atom





side view: two sp hybrid orbitals and two 2p orbitals



Bond-Line and Ball-and-Stick Structures of Diazomethane. The central nitrogen is sp-hybridized and the terminal nitrogen and carbon atoms are sp^2-hybridized. The terminal nitrogen has two nonbonded electron pairs, and it has a negative charge. Diazomethane is a highly explosive yellow gas.

Problem 1.16

Compare the structures of ethene and a simple compound with a C=N bond. What similarities and differences do you see between these two molecules? Where are the lone pair electrons of nitrogen located?



Problem 1.17

Compare the structures of propyne and cyanomethane, a compound with a C≡N bond. What similarities and differences do you see between these two molecules? In which orbital are the lone pair electrons of nitrogen located?



1.19 HYBRIDIZATION OF OXYGEN

An oxygen atom forms hybrid orbitals in much the same way as carbon. The only difference in the hybridization scheme is that oxygen has two more electrons than carbon to distribute in its hybridized orbitals. Oxygen has six valence electrons to distribute in four sp^3 hybrid orbitals (Figure 1.22). The four orbitals around oxygen form a tetrahedron. Two of the sp^3 hybrid orbitals contain pairs of electrons. The other two hybrid orbitals contain a single electron, which can form a σ bond to an atom such as hydrogen or carbon. For example, the oxygen atom in water bonds to two hydrogen atoms through sp^3-hybridized orbitals to form an angular molecule with an H—O—H bond angle of 104.5°. This angle is somewhat smaller than the 109.5° tetrahedral angle because, as in the case of nitrogen, lone pair electrons occupy more volume than bonding electrons. The nonbonded electrons repel the bonding electrons, compressing the H—O—H bond angle.

Oxygen could form two σ bonds to hydrogen to achieve a Lewis octet without hybridized orbitals. However, the overlap of a 2p orbital of oxygen with a 1s orbital of hydrogen would not form as strong a bond as overlap of an sp^3 hybrid orbital with a 1s orbital. As we saw for ammonia, the percent s character of the sp^3 hybrid results in a stronger bond and a more stable molecule.

Figure 1.22
sp^3-Hybridized Oxygen Atom

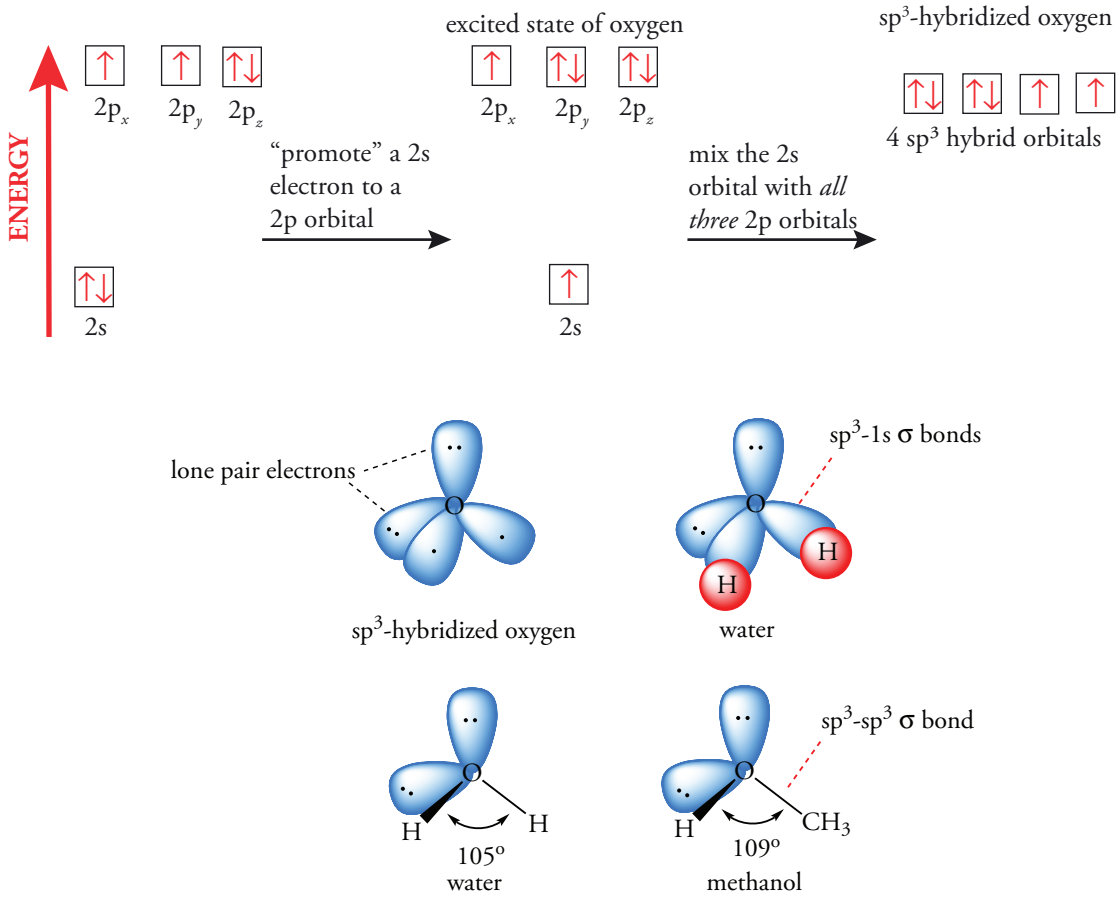


Figure 1.23 Ball-and-Stick Structures of Water and Methanol

The dipole moment of water is 2.39 D; the dipole moment of methanol is 2.12 D.

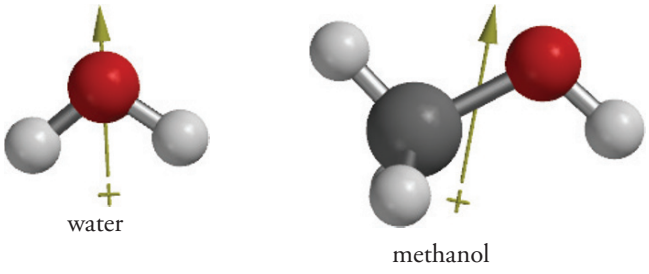
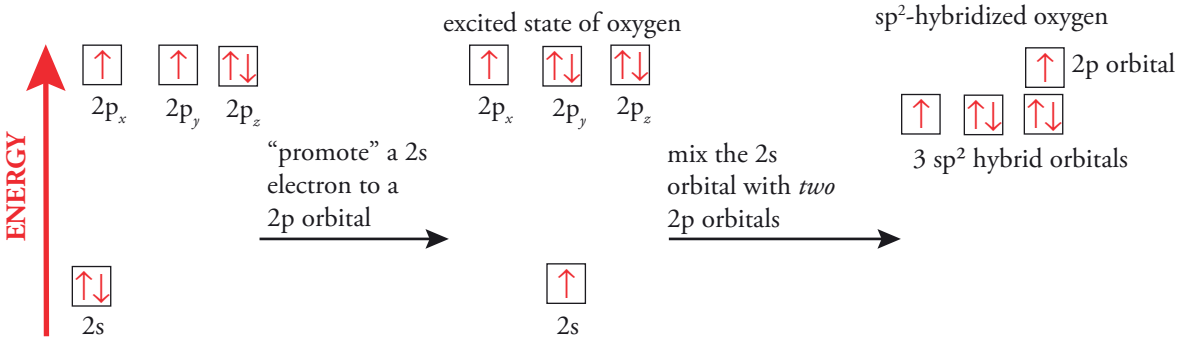
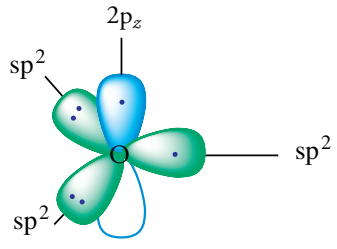


Figure 1.23 shows the dipole moments of water and methanol. The six valence electrons of oxygen can also be distributed in three sp^2 hybrid orbitals (Figure 1.24). The three sp^2 orbitals are coplanar and are separated by 120° in a trigonal planar arrangement. Two of the sp^2 orbitals contain a pair of electrons. The other sp^2 orbital contains a single electron that can form a σ bond to an atom such as carbon. The single electron in the remaining 2p orbital forms a π bond with the 2p orbital of another atom such as carbon.

Figure 1.24 sp^2-Hybridized Oxygen Atom





side view: three sp^2 hybrid orbitals and 2p orbital on oxygen

Methanal (CH_2O) has an sp^2-hybridized oxygen atom. The sp^2 lone pair electrons lie in the same plane as the carbon and hydrogen atoms. Methanal structurally resembles ethene.



We have now considered sp^3-hybridized orbitals for carbon, nitrogen, and oxygen. In each case, VESPR theory predicts tetrahedral electron pair geometry. However, molecular geometry depends upon the positions of the atoms in a molecule. Thus, methane has tetrahedral geometry, ammonia has pyramidal geometry, and water has angular or "bent" geometry (Figure 1.25).

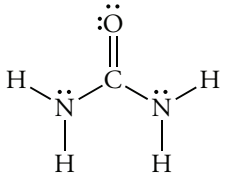
Figure 1.25
Geometries of Methane, Aminomethane, and Ammonia.



methane ammonia water

Problem 1.18

Urea, which contains carbon in its highest positive oxidation state, is a metabolic product excreted in urine. Based on the following Lewis structure, predict the hybridization of both the carbon and oxygen atoms.



Summary of Orbital Hybridization and Its Relation to VSEPR Theory

We have now considered sp, sp^2, and sp^3 hybridized orbitals on carbon and nitrogen, sp^2 and sp^3 hybridized orbitals on oxygen, and explained their relation to electron pair geometry and molecular geometry as predicted by VSEPR theory. These hybrid orbitals can make σ bonds with other atoms. The orbital hybridization method (LCAO) is valuable because it gives us a very good idea of molecular geometry. For example, the bond lengths and bond strengths of O—H bonds are nearly the same in all alcohols regardless of the other groups in the molecule. Table 1.7 summarizes the relation between hybridization, electron pair geometry, and molecular geometry.

A caveat is certainly in order here: while local models of bonds are very informative in some cases, they do not work for molecules in which electrons are delocalized in systems of π electrons. For those systems, we need to use molecular orbital theory.

Table 1. 7
Hybridization, Electron Pair Geometry, and Molecular Geometry

Hybridization	*Electron Pair Geometry*	*Molecular Geometry*	*Nonbonded Electrons*	*σ Bonds*	*π Bonds*	*Example*
sp	Linear	Linear	2 Unpaired (e.g., $2p_y^1$, $2p_z^1$ on adjacent atoms)	2	2	Ethyne
sp^2	Trigonal planar	Trigonal Planar	1 (e.g., $2p_z^1$, $2p_z^1$ on adjacent atoms)	3	1	Ethene
sp^3	Tetrahedral	Tetrahedral	0	4	0	Methane
sp^3	Tetrahedral	Pyramidal	2	3	0	Ammonia
sp^3	Tetrahedral	Angular	4 (Two pairs)	2	0	Water
Reactive Intermediates						
sp^2	Trigonal Planar	Trigonal Planar	None	3	0	Carbocation
sp^2	Trigonal Planar	Trigonal Planar	1	3	0	Carbon Radical
sp^3	Tetrahedral	Pyramidal	2	3	0	Carbanion

EXERCISES

Atomic Properties

1.1 How many valence shell electrons are in each of the following elements?

(a) N (b) F (c) C (d) O
(e) Cl (f) Br (g) S (h) P

1.2 Which of the following atoms has the higher electronegativity? Which has the larger atomic radius?

(a) Cl or Br (b) O or S (c) C or N (d) N or O (e) C or O

Ions and Ionic Compounds

1.3 Write a Lewis structure for each of the following ions.

(a) OH^- (b) CN^- (c) H_3O^+ (d) NO_3^-

1.4 Write a Lewis structure for each of the following ions.

(a) NO_2^- (b) SO_3^- (c) NH_2^- (d) CO_3^-

Lewis Structures of Covalent Compounds

1.5 Write a Lewis structure for each of the following compounds.

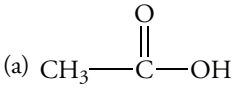
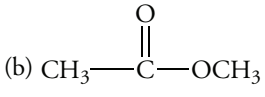
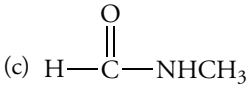
(a) NH_2OH (b) CH_3CH_3 (c) CH_3OH (d) CH_3NH_2 (e) CH_3Cl (f) CH_3SH

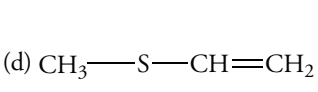
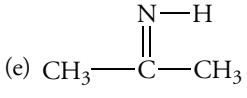
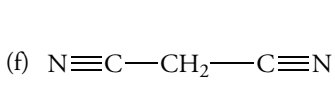
1.6 Write a Lewis structure for each of the following compounds.

(a) HCN (b) HNNH (c) CH_2NH (d) CH_3NO (e) CH_2NOH

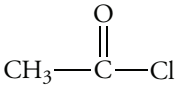
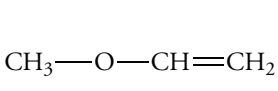
(f) CH_2NNH_2

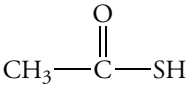
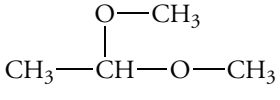
1.7 Add any required unshared pairs of electrons that are missing from the following formulas.

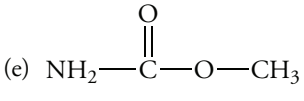
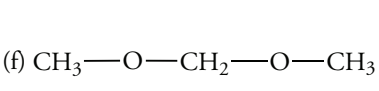
(a)  (b)  (c) 

(d)  (e)  (f) 

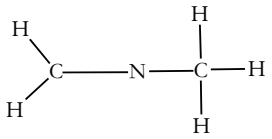
1.8 Add any required unshared pairs of electrons that are missing from the following formulas.

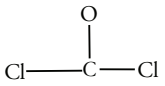
(a)  (b) 

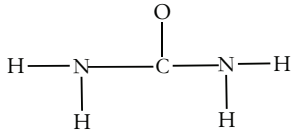
(c)  (d) 

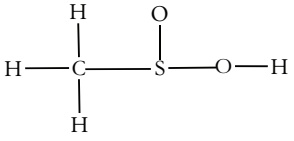
(e)  (f) 

1.9 Using the number of valence electrons in the constituent atoms and the given arrangement of atoms in the compound , write the Lewis structure for each of the following molecules.

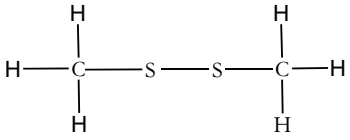
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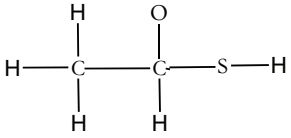
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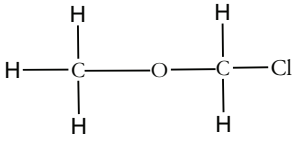
(c) 

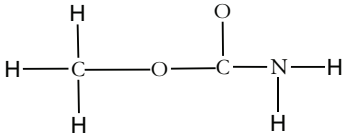
(d) 

1.10 Using the number of valence electrons in the constituent atoms and the given arrangement of atoms in the compound , write the Lewis structure for each of the following molecules.

(a) 

(b) 

(c) 

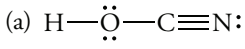
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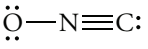
1.11 Two compounds used as dry cleaning agents have the molecular formulas C_2Cl_4 and C_2HCl_3. Write the Lewis structures for each compound.

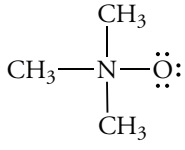
1.12 Acrylonitrile, a compound used to produce fibers for rugs, has the molecular formula CH_2CHCN. Write the Lewis structure for the compound.

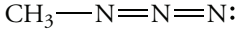
Formal Charge

1.13 Assign the formal charges for the atoms other than carbon and hydrogen in each of the following species.

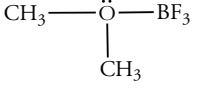
(a) 

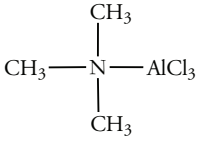
(b) 

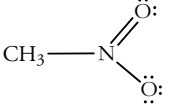
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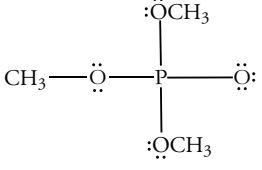
(d) 

1.14 Assign the formal charges for the atoms other than carbon and hydrogen in each of the following species.

(a) 

(b) 

(c) 

(d) 

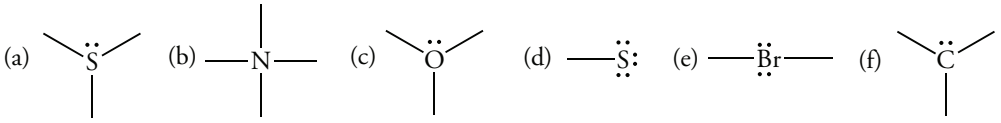
1.15 All of the following species are isoelectronic, that is, they have the same number of electrons bonding the same number of atoms. Determine which atoms have a formal charge. Calculate the net charge for each species.

(a) :C≡O: (b) :N≡O: (c) :C≡N: (d) :C≡C:

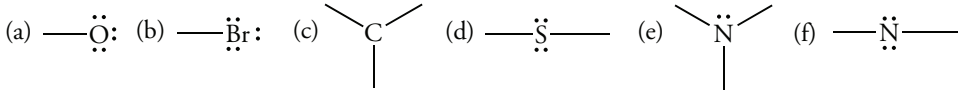
1.16 The following species are isoelectronic, that is, they have the same number of electrons bonding the same number of atoms. Determine which atoms have a formal charge. Calculate the net charge for each species.

(a) :N̈=N=N̈: (b) :Ö=N=Ö:

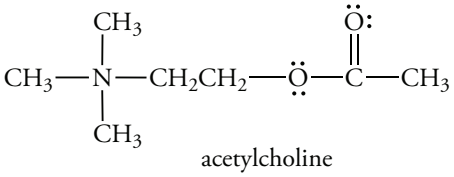
1.17 The following species are isoelectronic. Determine which atoms have a formal charge. Calculate the net charge for each species.



1.18 The following species are isoelectronic. Determine which atoms have a formal charge. Calculate the net charge for each species.

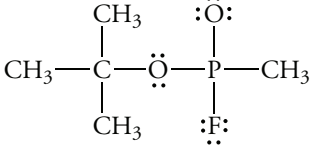


1.19 Acetylcholine, a compound involved in the transfer of nerve impulses, has the following structure. What is the formal charge on the nitrogen atom? What is the net charge of acetylcholine?



acetylcholine

1.20 Sarin, a nerve gas, has the following structure. What is the formal charge of the phosphorus atom?



Sarin

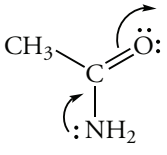
Resonance

1.21 The small amounts of cyanide ion contained in the seeds of some fruits are eliminated from the body as SCN^-. Draw two possible resonance forms for the ion. Which atom has the formal negative charge in each form?

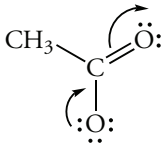
1.22 Are the following pairs contributing resonance forms of a single species? Formal charges are not shown and have to be added. Explain.

(a) :N̈=N=N̈: and :N̈—N≡N: (b) H—C≡N—Ö: and H—C̈=N=Ö:

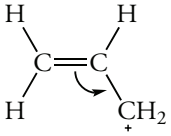
1.23 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrows for the following amide. Calculate any formal charges that result.



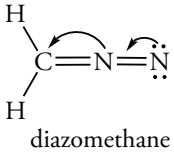
1.24 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrows for acetate Calculate any formal charges that result.



1.25 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrow for the following electron-deficient ion. To what extent do each of the two resonance forms contribute to the structure of the ion?



1.26 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrows for the diazomethane. Do each of the two resonance forms contribute equally to the structure of the ion?



diazomethane

Molecular Shapes

1.27 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following compounds?

(a) C—C—N in CH_3—C≡N (b) C—O—C in CH_3—O—CH_3

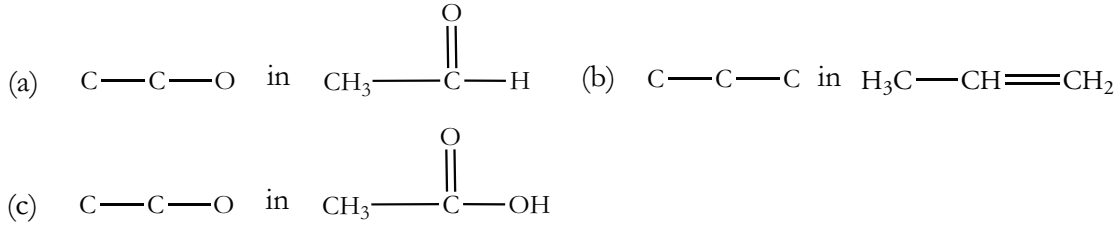
(c) C—N—C in CH_3—NH—CH_3 (d) C—C—C in CH_3—C≡C—H

1.28 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following ions?

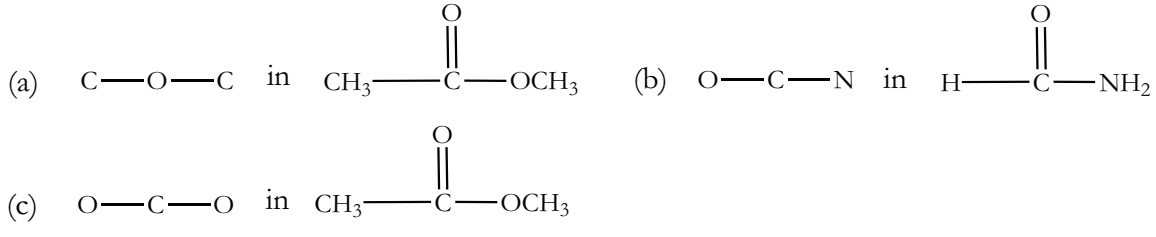
(a) C—O—H in CH_3—OH_2^+ (b) C—N—H in CH_3—NH_3^+

(c) O—C—O in $CH_3CO_2^-$ (d) C—O—C in $(CH_3)_2OH^+$

1.29 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following compounds?



1.30 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following compounds?



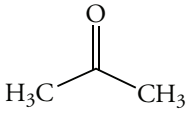
Dipole Moments

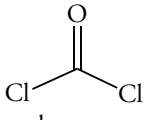
1.31 Fluorine is more electronegative than chlorine, but the dipole moment for a C—F bond (1.4 D) is less than the dipole moment for a C—Cl bond (1.5 D). Explain why this is so.

1.32 Arrange the following bond moments in order of decreasing polarity: H—N, H—O, H—S. Explain the trend that you predict.

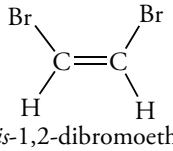
1.33 The dipole moments of both CO and CS are zero. However, SCO has a dipole moment. Explain why. Draw the structure of SCO and then an arrow indicating the direction of the dipole moment.

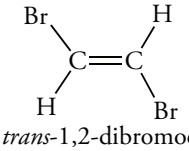
1.34 Which compound has the larger dipole moment, acetone or phosgene? Explain why.


acetone

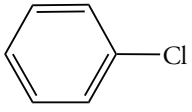

phosgene

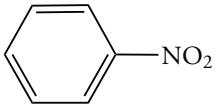
1.35 Which compound has the larger dipole moment, *cis*- or *trans*-1,2-dibromoethene? Explain why.

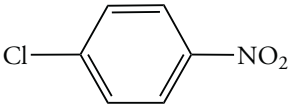

cis-1,2-dibromoethene


trans-1,2-dibromoethene

1.36 The dipole moment of chlorobenzene (C_6H_5Cl) is 1.56 D and that of nitrobenzene ($C_6H_5NO_2$) is 3.97 D. The dipole moment of *para*-chloronitrobenzene is 2.57 D. What does this value indicate about the direction of the moments of the two groups with respect to the benzene ring?

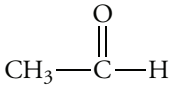

chlorobenzene

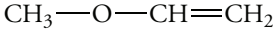

nitrobenzene

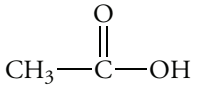

p-chloronitrobenzene

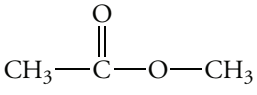
Hybridization

1.37 What is the hybridization of each carbon atom in each of the following compounds?

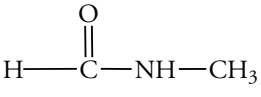
(a) 

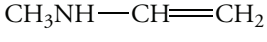
(b) 

(c) 

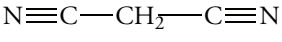
(d) 

1.38 What is the hybridization of each carbon atom in each of the following compounds?

(a) 

(b) 

(c) 

(d) 

1.39 What is the hybridization of the oxygen atom in each compound in Exercise 1.37?

1.40 What is the hybridization of the oxygen atom in each compound in Exercise 1.38?

1.41 Carbocations and carbanions are unstable organic species with a positive and a negative charge, respectively, on the carbon atom. What is the hybridization of the carbon atom in each ion? What are the H—C—H bond angles?



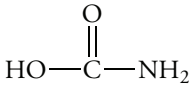
1.42 Assuming that all of the valence electrons are paired and located in hybrid orbitals, what is the H—C—H bond angle in the reactive species CH_2?

1.43 Write the Lewis structure of CO_2. What is the hybridization of the carbon atom? What is the hybridization of the oxygen atoms?

1.44 Write the Lewis structure of NO_2^+, the nitronium ion. What is the hybridization of the nitrogen atom? What is the hybridization of the oxygen atoms?

1.45 Phosgene ($COCl_2$) is a poisonous gas. Write its Lewis structure and determine the hybridization of the carbon atom.

1.46 Carbamic acid is an unstable substance that decomposes to form carbon dioxide and ammonia. Based on the following Lewis structure, what are the hybridizations of the carbon atom and the two oxygen atoms?



Bond Lengths

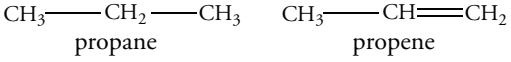
1.47 The oxygen—hydrogen bond lengths in both hydrogen peroxide (HO—OH) and hydroxylamine (NH_2—OH) are the same; 96 pm. Explain why.

1.48 The C=N bond length of methyleneimine (CH_2=NH) is 127 pm. Compare this value to the C=C bond length of ethene (133 pm) and suggest a reason for the difference.

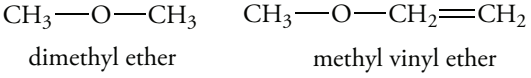
1.49 The nitrogen—oxygen bond lengths of hydroxylamine (NH_2—OH) and the nitronium ion $(NO_2)^+$ are 145 and 115 pm, respectively. Write their Lewis structures and explain why the bond lengths differ.

1.50 The C—F bond length of CF_4 is 138 pm. The estimated bond length of CF_3^+ is 127 pm. Suggest a reason for the difference between these two values.

1.51 The carbon—carbon single bond lengths of propane and propene are 154 and 151 pm, respectively. Why do these values differ?

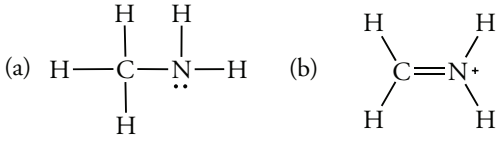


1.52 The carbon—oxygen bond length of dimethyl ether is 142 pm. Predict the lengths of each of the two carbon—oxygen bonds in methyl vinyl ether.

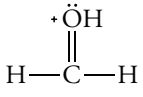


Bond Angles

1.53 What is the C—N—H bond angle in each of the following species?



1.54 What is the C—O—H bond angle of protonated formaldehyde?



1.55 Diimide (HNNH) is a reactive reducing agent. Draw its Lewis structure. Compare its Lewis structure with that of ethene. Based on molecular orbital theory, compare the hybridization of the two compounds. What is the H—N—N bond angle in diimide?

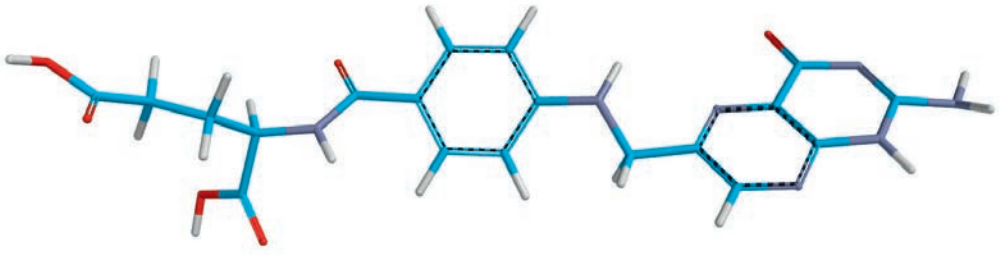
1.56 What is the H—C—H bond angle in allene ($CH_2=C=CH_2$)? What is the C—C—C bond angle? What is the hybridization of each atom?

1.57 What is the Cl—C—Cl bond angle of the CCl_3^- ion, an intermediate formed by treating CCl_3H with base?

1.58 What is the O—N—O bond angle of the nitronium ion $(NO_2)^+$, a reactive intermediate in reactions with benzene compounds?

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2 Part I: Functional Groups and Their Properties



At the present hour, some sixteen million organic compounds have been discovered. Each one has unique physical and chemical properties. Determining the relationships between their structures on one hand and their physical and chemical properties on the other would be virtually impossible without a systematic way to proceed. A major organizing principle of organic chemistry relies on dividing organic molecules into two parts: a backbone or framework of carbon atoms and specific atomic groups, called **functional groups**, attached to the backbone. If we classify organic compounds by their functional groups, they fall into a relatively small number of classes.

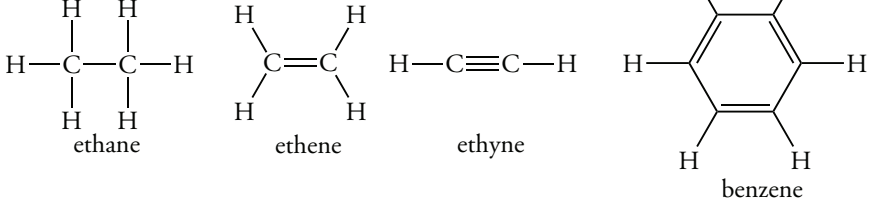
Functional groups strongly influence the physical and chemical properties of the molecule of which they are a part. Functional groups are the sites of chemical reactions in organic compounds. By examining the functional group (or groups) in a molecule, we can predict its physical and chemical properties.

Functional groups can contain many elements, but the most common are oxygen and nitrogen. Sulfur and the halogens are less commonly encountered. Some functional groups are part of the molecular backbone. These include the multiple bonds between backbone carbon atoms of compounds such as ethene (ethylene), ethyne (acetylene), and benzene.

2.1 Introduction to Functional Groups: Hydrocarbons and Haloalkanes

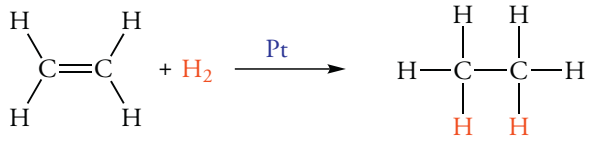
Hydrocarbons

As their name tells us, hydrocarbons contain only carbon and hydrogen. If a hydrocarbon has only carbon–carbon single bonds, it is an **alkane**; if it contains a carbon–carbon double bond, it is an **alkene**; if it contains carbon–carbon triple bonds, it is an **alkyne**; and if it contains a benzene ring, it is an **arene**.

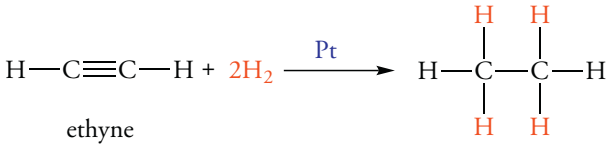


Compounds with carbon—carbon double or triple bonds react with hydrogen gas to give compounds that contain only carbon—carbon single bonds. For example, ethene reacts with hydrogen gas in the presence of a platinum catalyst to give ethane, which has only a single bond between the carbon atoms. Many compounds containing carbon—carbon double bonds undergo similar reactions. Compounds that contain benzene rings, however, are a conspicuous exception, as we will see in Chapter 13.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00002-4
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ethene ethane

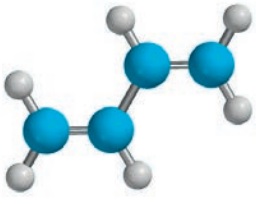


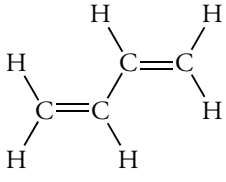
ethyne

Two or more double or triple bonds are present in more complex structures. Many of these compounds undergo reactions similar to those of ethene at each of its multiple bonds. However, benzene, which belongs to a class of compounds called aromatic hydrocarbons, or arenes, reacts differently than ethene or ethyne, for reasons we will explain in Chapter 12.

Problem 2.1

Based on the reaction of hydrogen with ethene, draw the structure of the product of the reaction of excess hydrogen gas with 1,3-butadiene.

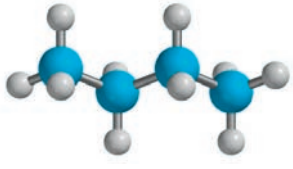


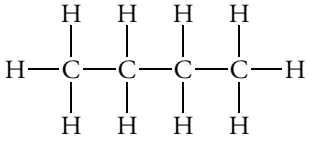


1,3-butadiene

Sample Solution

The molecular structure has two double bonds. Each double bond can react with hydrogen, which places another hydrogen atom on each carbon atom of the double bond, converting it to a single bond. The reaction occurs with a total of two moles of hydrogen gas per mole of l,3-butadiene. The molecular structure of the product, butane, is shown below.





butane

Problem 2.2

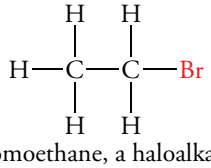
Based on the reaction of hydrogen with ethene, draw the structure of the product of the reaction of excess hydrogen gas with propyne.



propyne

Haloalkanes

In a haloalkane, one or more of the hydrogen atoms of an alkane have been replaced with a halogen, either fluorine, chlorine, bromine, or iodine.



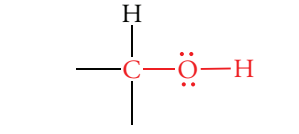
bromoethane, a haloalkane

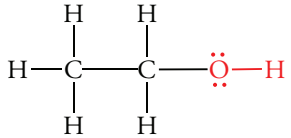
2.2 FUNCTIONAL GROUPS THAT CONTAIN OXYGEN

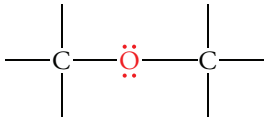
After carbon and hydrogen, the next most common element in organic compounds is oxygen. Oxygen forms two bonds (it is divalent). It can form two C—O single bonds or one C=O double bond in neutral carbon compounds.

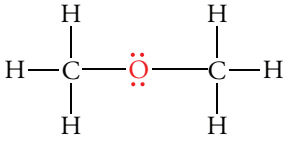
Carbon–Oxygen Single Bonds in Alcohols and Ethers

Carbon–oxygen single bonds are present in alcohols and ethers. Alcohols contain one C—O single bond and an O—H bond. The O—H structural unit, called the **hydroxyl group**, is the functional group of **alcohols**. The functional group of **ethers** is an oxygen atom linked to two carbon atoms by single bonds. The oxygen atoms of both alcohols and ethers have two unshared electron pairs.


hydroxyl group in an alcohol

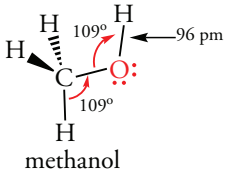

ethanol


ether

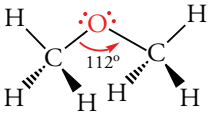

dimethyl ether

The oxygen atoms of alcohols and ethers are sp^3 hybridized. The C—O—H bond angle of alcohols and the C—O—C bond angle of ethers approach the tetrahedral value, 109° (Figure 2.1). The C—O bond is shorter than a C—C bond because oxygen is more electronegative than carbon. Viewed another way, since the atomic radius of oxygen is small than that of carbon and since both atoms are sp^3 hybridized, a C—O bond is shorter than a C—C bond.

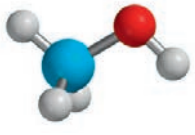
Figure 2.1 Structures of Alcohols and Ethers
In both alcohols and ethers, the C—O σ bond is formed by the overlap of two sp^3 hybrid orbitals, one on the oxygen atom and one on the carbon atom. The C—O bond is slightly shorter, 142 pm, than the C—C bond, 143 pm. The lone pair electrons in both alcohols and ethers are directed toward the corners of a tetrahedron.



methanol



dimethyl ether

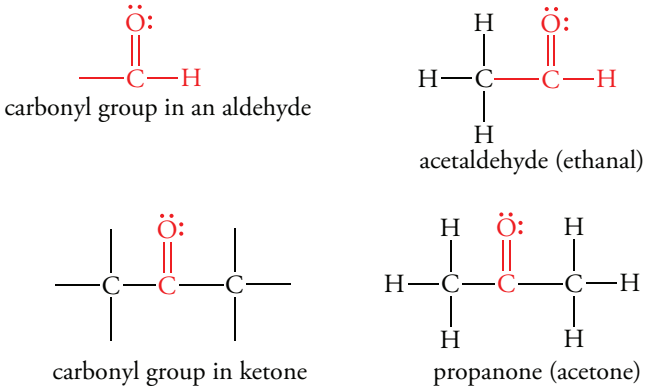




Carbon–Oxygen Double Bonds in Aldehydes and Ketones

A double bond between carbon and oxygen forms a C=O unit, called a **carbonyl group** (pronounced car-bo-neel). The carbon atom of the carbonyl group is called the **carbonyl carbon** atom, and the oxygen atom is called the **carbonyl oxygen** atom. Both **aldehydes** and **ketones** contain carbonyl groups. The carbonyl group bonds to at least one hydrogen atom in aldehydes. In ketones, the carbonyl carbon atom bonds to two other carbon atoms.

The carbonyl carbon atom is sp^2 hybridized, so it has trigonal, planar geometry (Figure 2.2). The σ bonds to carbon result from the overlap of each of its sp^2 hybrid orbitals with an orbital of another atom. For example, the carbonyl carbon atom in acetaldehyde forms a σ_{sp^2-1s} bond to a hydrogen atom. The methyl groups of acetaldehyde and acetone are bonded to the carbonyl carbon by a $\sigma_{sp^2-sp^3}$ bond.



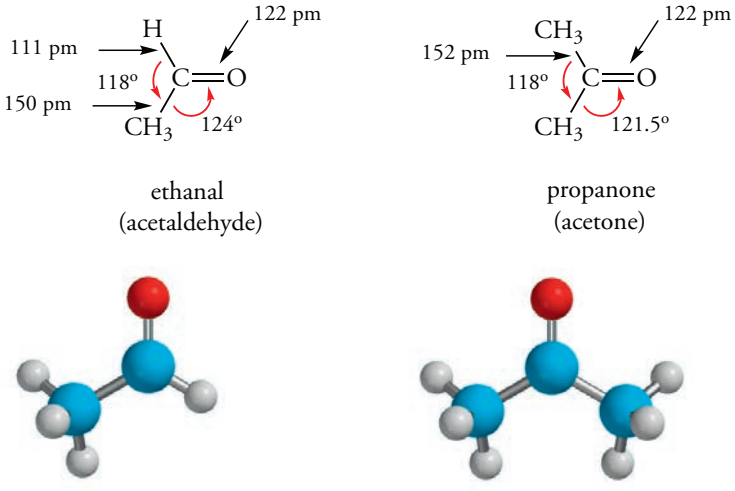
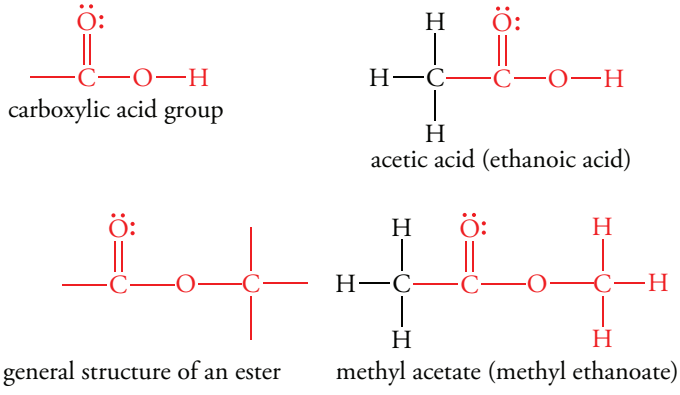


Figure 2.2 Structures of Aldehydes and Ketones
In both aldehydes and ketones, the C=O π bond is formed by the overlap of two sp^2 hybrid orbitals, one on the oxygen atom and one on the carbon atom. The C=O bond is much shorter, 122 pm, than the C—O σ bond in an alcohol, 142 pm. The lone pair electrons on oxygen lie in the plane of the two σ bonds.

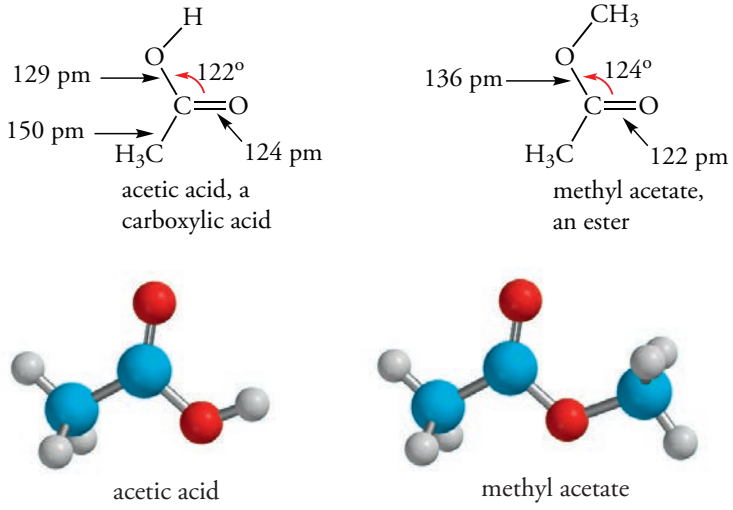
Carbon–Oxygen Bonds in Carboxylic Acids and Esters

A carbonyl group is also present in **carboxylic acids** and **esters**. In a carboxylic acid, the carbonyl carbon atom bonds to a hydroxyl group (—OH). In an ester, the carbonyl carbon atom bonds to an **alkoxy** group such as —OCH_3.

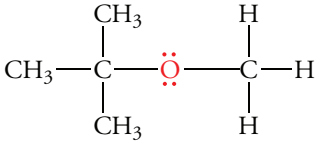


A carboxylic acid or ester has a carbon—oxygen double bond and a carbon—oxygen single bond. The oxygen atom of the C—O single bond is sp^3 hybridized. Thus, the geometry of groups about the oxygen atom resembles that of alcohols and ethers (Figure 2.3).

Figure 2.3 Structures of Carboxylic Acids and Esters
In both carboxylic acids and esters, the C=O π bond is formed by the overlap of two sp^2 hybrid orbitals, one on the oxygen atom and one on the carbon atom. The C—O σ bond forms between an sp^3-hybridized oxygen and the carbonyl carbon.



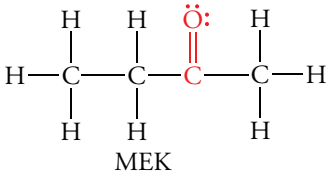
Problem 2.3
MTBE is used as an antiknock additive in gasoline. Identify the oxygen-containing functional group.



MBTE

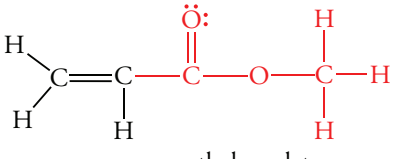
Sample Solution
The structure has only single bonds to the oxygen atom, which is found only in alcohols or ethers. The two single bonds to oxygen are to carbon atoms. Thus, the functional group is an ether. An alcohol would have one bond from the oxygen atom to a hydrogen atom.

Problem 2.4
MEK is an inexpensive commercial solvent that is produced in large quantities by the chemical industry. Identify the functional group in MEK.



MEK

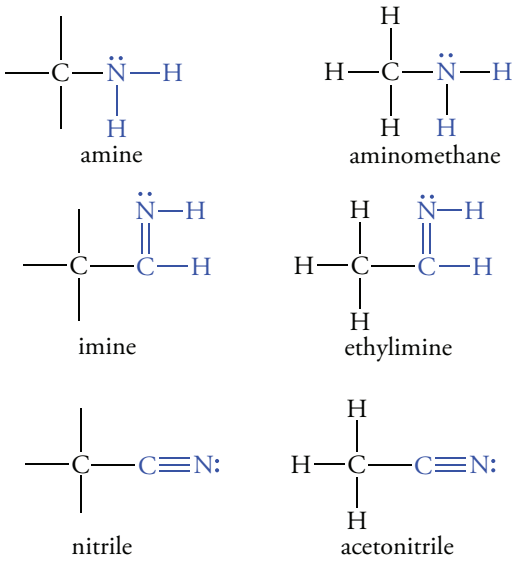
Problem 2.5
Methyl acrylate is used to produce poly(methyl acrylate), a transparent polymer found in windshields and shatter-proof glasses. Identify all functional groups in methyl acrylate.



methyl acrylate

2.3 FUNCTIONAL GROUPS THAT CONTAIN NITROGEN

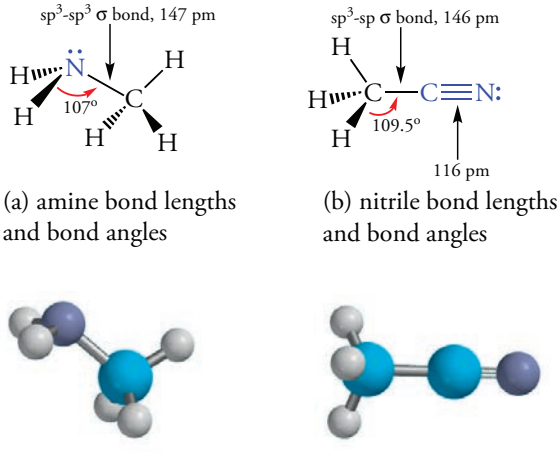
Several functional groups contain nitrogen. A nitrogen atom can form single, double, or triple bonds to a carbon atom. At least one C—N σ bond is present in an **amine**. The other two σ bonds from nitrogen are to either hydrogen or carbon atoms. Compounds with C=N double bonds are called **imines**; those with C≡N triple bonds are called **nitriles**.



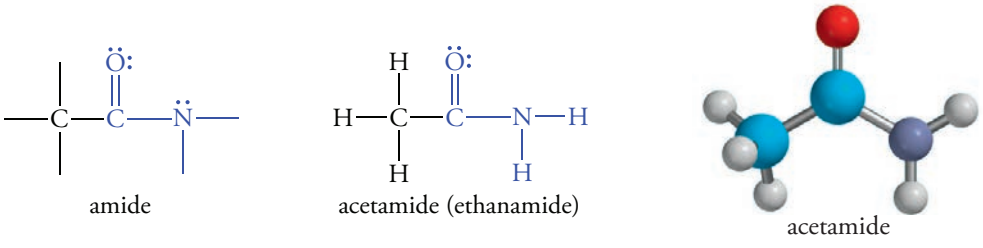
The carbon–nitrogen bond in an amine forms by overlap of an sp^3 hybrid orbital of the nitrogen atom and an sp^3 hybrid orbital of a carbon atom. The C—N bond length, 147 pm, is less than the C—C bond length of 154 pm in ethane (Figure 2.4). The H—N—C bond angle is 107°, a value close to the tetrahedral angle of 109.5°.

In imines, both the carbon atom and the nitrogen atom are sp^2 hybridized. They form a σ bond by overlap of two sp^2 hybrid orbitals and a π bond by overlap of two 2p orbitals. In nitriles, the carbon atom and nitrogen atom are sp hybridized. They form a triple bond that consists of one $\sigma_{sp\text{-}sp}$ bond and two π bonds between two sets of 2p orbitals. The triple bond of nitriles therefore resembles the C≡C triple bond of ethyne. Figure 2.4 shows the molecular geometry of acetonitrile.

Figure 2.4 Structures of Amines and Nitriles

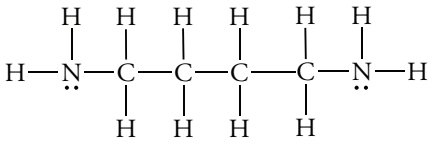


Nitrogen is also present in **amides**. Amides contain nitrogen linked by a single bond to a carbonyl carbon atom. The amide nitrogen atom forms two other bonds to either hydrogen or carbon atoms. Amides have structures similar to carboxylic acids and esters.



Problem 2.6

Putrescine is one of the compounds responsible for the odor of decaying animal tissue. Identify the nitrogen-containing functional groups in putrescine. What is the hybridization of the nitrogen atom?

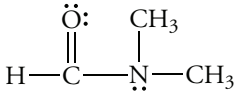


Sample Solution

Both nitrogen atoms have three single bonds. One bond is to a carbon atom and the other two bonds are to hydrogen atoms. Three single bonds to a nitrogen atom are characteristic of an amine. The nitrogen atom of amines is sp^3 hybridized. The nitrogen atom forms σ bonds to the three attached atoms.

Problem 2.7

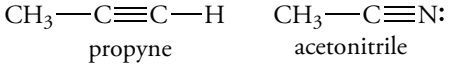
PMF is an excellent solvent for many classes of organic compounds. Identify the functional group in DMF.



DMF

Problem 2.8

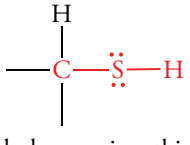
Why is the carbon–nitrogen triple bond of acetonitrile (cyanomethane) shorter than the carbon–carbon triple bond of propyne?



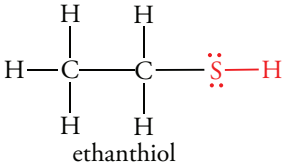
propyne acetonitrile

2.4 FUNCTIONAL GROUPS THAT CONTAIN SULFUR

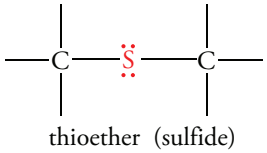
Sulfur forms single bonds to sp^3-hybridized carbon atoms in two classes of compounds: **thiols** (also called **mercaptans**) and **thioethers** (also called **sulfides**). The SH group in thiols is a **sulfhydryl** group. Because sulfur, like oxygen, is a Group VI element, thiols have structures resembling alcohols, and thioethers have structures resembling ethers.



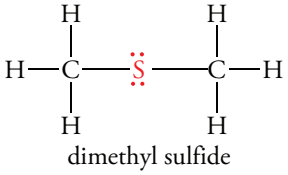
sulfhydryl group in a thiol



ethanthiol



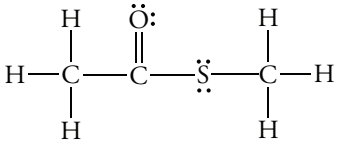
thioether (sulfide)



dimethyl sulfide

Problem 2.9

Acetyl coenzyme A is a substrate in many biochemical reactions. The structure of the simplest compound containing the functional group responsible for the activity of acetyl coenzyme A is given below. What functional group is similar to this sulfur-containing functional group? What is the O—C—S bond angle?



2.5 STRUCTURAL FORMULAS

The backbones of many organic compounds are sp^3-hybridized carbon atoms. In most compounds, this backbone is comparatively unreactive, but the location of a functional group on the backbone influences its reactivity. In this section, we will learn to draw structural formulas that show the arrangement of atoms and bonds in a molecule.

Structural formulas are often drawn in abbreviated or condensed versions to save time and space. Condensed structural formulas show only specific bonds. Other bonds are implied, but left out. For example, because hydrogen forms only a single bond to carbon, C—H bonds are not shown in condensed structural formulas. A condensed formula for butane is shown below.

$$CH_3—CH_2—CH_2—CH_3$$

butane

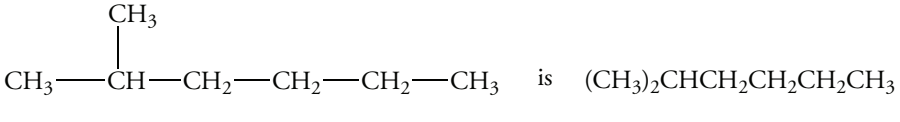
The terminal carbon atoms are understood to have single bonds to three hydrogen atoms. The carbon atoms in the interior of the molecule each have two implied carbon–hydrogen bonds. By convention, the symbol for the hydrogen atom is usually written to the right of the symbol for the carbon atom. The above structure for butane can be condensed further by leaving out the explicit notation for the C—C bonds.

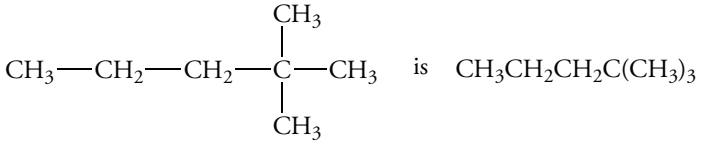
$$CH_3CH_2CH_2CH_3$$

Butane is a small molecule. Larger molecules may consist of repeated units. If a hydrocarbon has repeated structural subunits, they are grouped within parentheses. A subscript following the closing parenthesis tells us how many times the unit is repeated.

$$CH_3(CH_2)_2CH_3$$

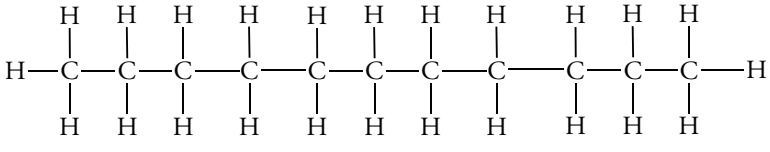
The —CH_2— unit is a **methylene** group. It occurs twice in butane. Two or more identical groups of atoms bonded to a common central atom may also be represented within parentheses with an appropriate subscript in a condensed formula. The groups within parentheses may be placed to the right or left of a carbon atom, depending on the way in which the structure of the molecule is drawn.





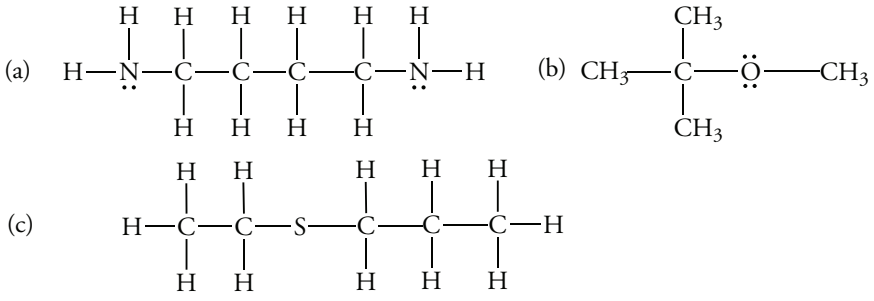
Problem 2.10

A species of cockroach secretes the substance shown below, which attracts other cockroaches. Write three condensed structural formulas for the substance.



Problem 2.11

Write fully condensed formulas for each of the following structures.

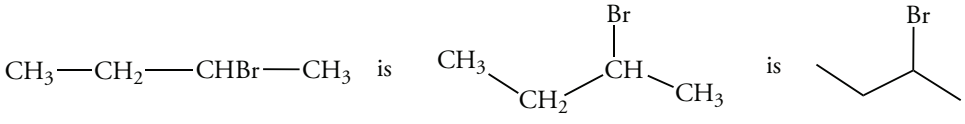


2.6 BOND-LINE STRUCTURES

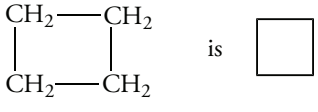
A bond-line structure is a less cluttered drawing than a condensed structural formula. However, to understand the simplified bond-line structure, the reader has to mentally add many more features to comprehend the overall structure. The rules for drawing bond-line structures are shown below.

1. Carbon and hydrogen atoms are not shown unless needed for special emphasis or clarity.
2. All other atoms are shown.
3. Line segments indicate bonds.
4. Multiple bonds are shown with multiple lines.
5. A carbon atom is assumed to be at the end of each line segment or at the intersection of lines.

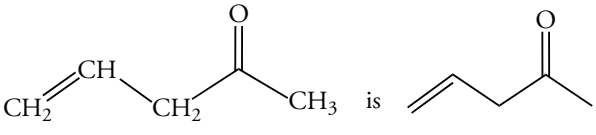
For a bond-line structure, it is best to start by drawing a zigzag arrangement of the carbon atoms and then mentally remove them.



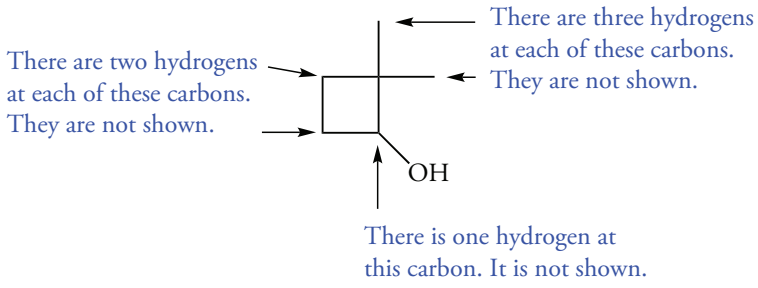
Bond-line structures are also used to show cyclic structures or "rings." Rings of carbon atoms are shown as regular polygons. For example, an equilateral triangle represents a three-membered ring, a square represents a four-membered ring, and so on.



When a molecule contains double or triple bonds, carbon atoms are not shown, but oxygen and nitrogen atoms are.



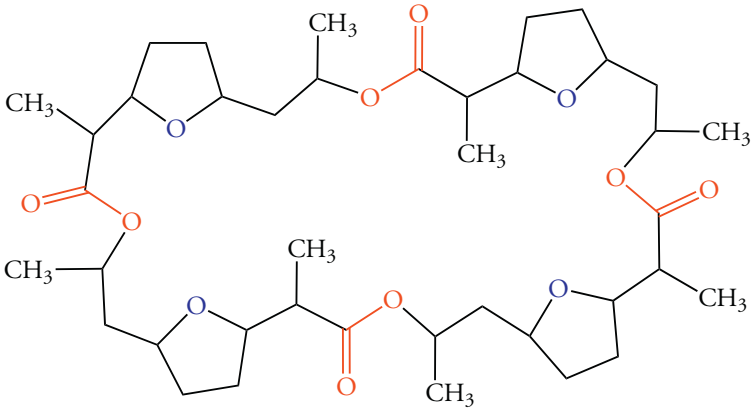
When writing bond-line structures, remember that carbon, nitrogen, and oxygen form 4, 3, and 2 bonds, respectively.



Recognizing Structural Features in Complex Molecules

The structural features that allow us to predict the physical and chemical properties of naturally occurring molecules are often only a small part of a larger structure. When we "read" such structures, we should ignore the many lines that show carbon—carbon bonds and focus on the functional groups. Are there multiple bonds? If atoms such as oxygen and nitrogen are present as part of functional groups, how are they bonded and what other atoms are nearby? For example, if a carbonyl group (C=O) is present, it may be part of an aldehyde, ketone, acid, ester, or amide. These functional groups can be distinguished by looking at the atoms bonded to the carbonyl carbon atom.

Consider the structure of nonactin, an antibiotic that transports ions across cell membranes. The many oxygen atoms in the large ring bind potassium ions. Nonactin allows free passage of potassium ions across bacterial cell membranes, killing the cells.

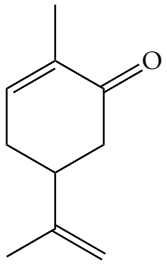


nonactin

What are the oxygen-containing functional groups in this complex structure? Concentrate on one oxygen atom at a time. Four oxygen atoms form part of carbonyl groups. Now look at the atoms bonded to the carbonyl carbon atoms of the C=O groups. In each case, the carbonyl carbon bonds to a carbon atom and to an oxygen atom. Both carboxylic acids and esters have such features. The single-bonded oxygen atom of carboxylic acids is in an OH group, whereas the oxygen atom of esters is bonded to another carbon atom. Convince yourself that nonactin has four ester groups. (They are shown in red.) Now concentrate on the second type of oxygen-containing functional group in the molecule. Oxygen atoms are present in four five-membered rings. These functional groups are ethers. (The ether oxygen atoms are shown in blue.)

Problem 2.12

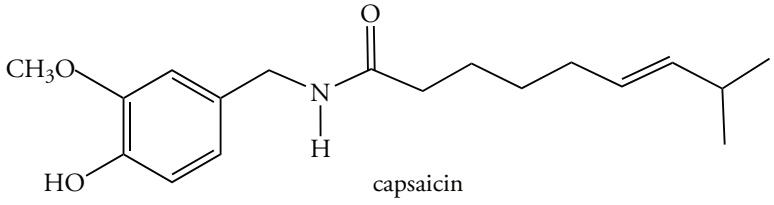
What are the functional groups of carvone, which is found in oil of caraway?



carvone

Problem 2.13

Identify the functional groups in capsaicin, the molecule responsible for the spiciness of chili peppers.



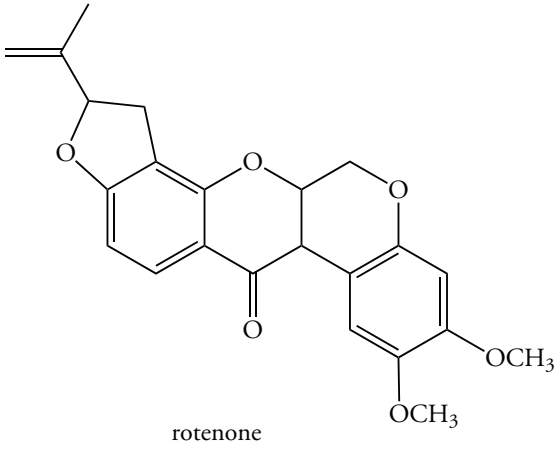
capsaicin

Sample Solution

The six-membered ring on the left of the structure is a benzene ring. A carbon–carbon double bond is located on the right of the structure. The nitrogen atom is bonded by a single bond to a carbonyl carbon atom, a characteristic of an amide. One of the two oxygen atoms bonded to the benzene ring by a single bond is also bonded to a CH_3 group. Two single bonds from an oxygen atom to carbon atoms are characteristics of an ether. The other oxygen atom bonded to the benzene ring is also bonded to a hydrogen atom. The —OH group is a hydroxyl group.

Problem 2.15

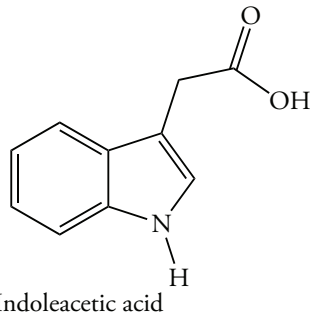
Rotenone is an insecticide used in home gardening. What oxygen-containing functional groups are in this molecule?



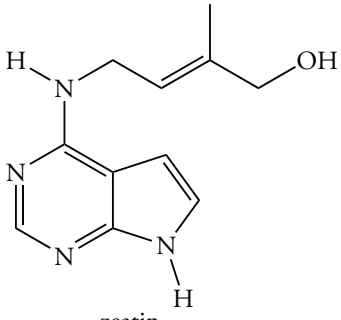
rotenone

Problem 2.15

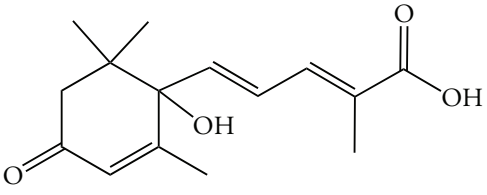
What is the molecular formula of each of the following plant growth hormones?



Indoleacetic acid
(promotes shoot growth)



zeatin
(promotes root growth)



abscisic acid
(inhibits germination)

2.7 ISOMERS

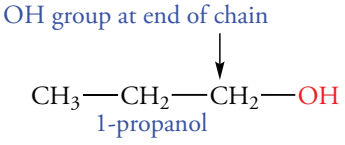
Compounds that have the same molecular formula whose atoms are linked in different ways are called **isomers**. We call an atomic linkage a structure. As we examine the structure of organic compounds in detail, we will find that subtle structural differences profoundly affect the physical and chemical properties of isomers.

We can divide isomers into two broad classes. Substances that differ in their connectivity are **constitutional isomers**. Isomers that have the same connectivity but differ in the arrangement of the atoms in space are **stereoisomers.** We will consider stereoisomers in greater detail in Chapter 8 and thereafter.

Constitutional isomers can differ in their carbon backbones. Consider the structural differences in the two isomers of C_4H_{10}, butane and isobutane. Butane has an uninterrupted chain of carbon atoms (Figure 2.5), but isobutane has only three carbon atoms connected in sequence. The fourth carbon atom is bonded to the chain as a "branch".

Constitutional isomers can also have different functional groups. For example, both ethyl alcohol and dimethyl ether have the same molecular formula: C_2H_6O. Although the molecular formulas of the two compounds are identical, their functional groups differ (Figure 2.5). The atomic connectivity is C—C—O in ethyl alcohol and the oxygen atom is part of an alcohol. In contrast, the C—O—C connectivity in the isomer forms an ether.

Constitutional isomers can have the same functional groups, but they are located at different points on the carbon skeleton. For example, the isomers 1-propanol and 2-propanol have hydroxyl group on different carbon atoms.



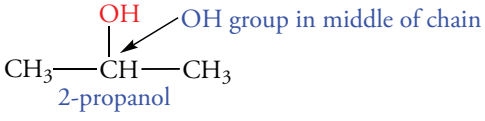
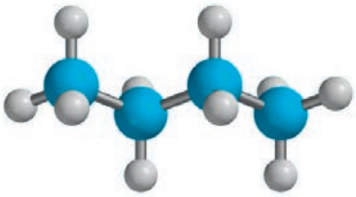
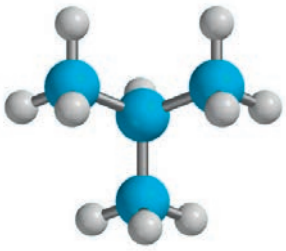


Figure 2.5 Structures of Constitutional Isomers

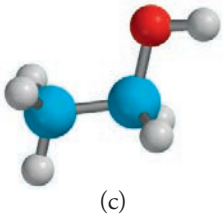
Constitutional isomers have the same molecular formulas, but they have different connectivities. n-Butane and isobutane are examples of constitutional isomers, as are ethanol and dimethyl ether.



(a)
n-butane
$CH_3CH_2CH_2CH_3$
(no branch)



(b)
isobutane
$CH_3CH(CH_3)CH_3$
(branch in middle of chain)

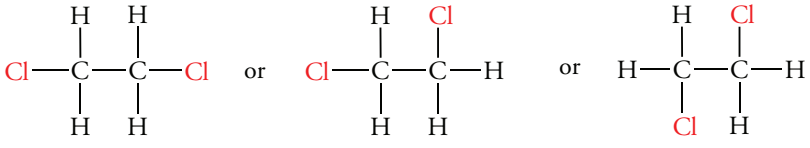


(c)
ethanol
CH_3CH_2OH



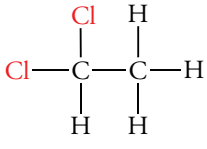
(d)
dimethyl ether
CH_3OCH_3

Sometimes two structural formulas appear to be isomers, but represent the same compound. For example, 1,2-dichloroethane can be written in several ways. But, the bonding sequence is Cl—C —C—Cl in each formula, so all three structural formulas represent the same molecule.



1,2-dichloroethane (CH_2ClCH_2Cl)

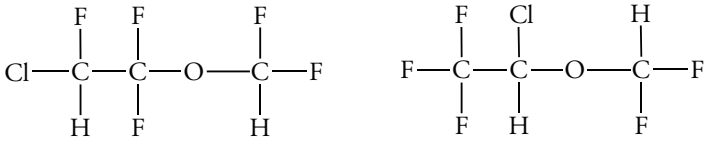
The isomer of 1,2-dichloroethane is 1,1-dichloroethane. In 1,1-dichloroethane, the two chlorine atoms are bonded to the same carbon atom, but in 1,2-dichloroethane, the two chlorine atoms are bonded to different carbon atoms. The different condensed structural formulas, $CHCl_2CH_3$ and CH_2ClCH_2Cl, also tell us that in the first case two chlorine atoms are bound to the same carbon and that in the second case the two chlorine atoms are bound to adjacent carbons.



1,1-dichloroethane ($CHCl_2CH_3$)

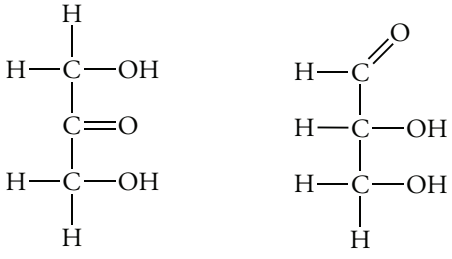
Problem 2.16

The structural formulas of two compounds used as general anesthetics are shown below. Are they isomers? How do they differ?



Problem 2.17

Compare the following structures of two intermediates in the metabolism of glucose. Are they isomers? How do they differ?

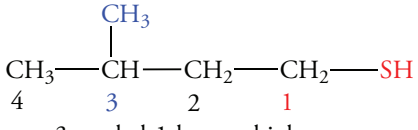


Nomenclature

As the number of atoms represented in a molecular formula increases, the number of isomers increases exponentially. Each isomer must be uniquely identified by a name. Nomenclature in organic chemistry is the systematic method of naming compounds. The method was devised at a meeting in Geneva, Switzerland, in 1892. Compounds are now named by rules developed by the International Union of Pure and Applied Chemistry (IUPAC). The rules generate a single definitive name for each compound. A universal, systematic method for naming organic compounds is essential to avoid confusion. In the past, different names have often been given to the same compound. For example, CH_3CH_2OH has been called alcohol, spirit, grain alcohol, ethyl alcohol, and ethanol. For a small molecule like ethane this variety of names presents no problem, but for larger molecules a systematic name is essential.

A chemical name consists of three parts: **prefix**, **parent**, and **suffix**. The parent indicates how many carbon atoms are in the main carbon backbone. The suffix identifies most of the functional groups present in the molecule, for example *-ol* for alcohols, *-al* for aldehydes, and *-one* for ketones. The prefix specifies the location of the functional group designated in the suffix and any other groups on the parent chain.

Once the rules are applied, there is only one name for each structure and one structure for each name. For example, the compound partly responsible for the odor of skunk is 3-methyl-1 -butanethiol.



3-methyl-1-butanethiol

Butane is the parent name of the four-carbon unit written horizontally. The prefix "3-methyl" identifies and locates the CH_3 written above the chain of carbon atoms. The prefix "l -" and the suffix "thiol" specify the position and identity of the sulfhydryl (SH) group. This method of assigning numbers to the carbon chain and other features of the IUPAC system will be discussed in greater detail in subsequent chapters.

In spite of the IUPAC system, many common names are so well established that both common and IUPAC names are accepted. The IUPAC name for CH_3CH_2OH is ethanol, but the common name ethyl alcohol is often used.

As we introduce the nomenclature of each class of organic compounds, we will see that determining a systematic name is straightforward when the rules are followed. In this text, we will often give common names within parentheses after the IUPAC name.

Part II: Identification of Functional Groups by Infrared Spectroscopy

2.8 SPECTROSCOPY

Spectroscopy is a study of the interaction of electromagnetic radiation with molecules. Electromagnetic radiation encompasses X-rays; ultraviolet, visible, and infrared radiation; microwaves; and radio waves. Electromagnetic radiation can be described as a wave that travels at the speed of light (3×10^8 m/s). Waves are characterized by a wavelength (λ, Greek lambda) and a frequency (ν, Greek nu). The wavelength is the length of one wave cycle, from crest to crest or trough to trough (Figure 2.1). The wavelength is expressed in the metric unit convenient for each type of electromagnetic radiation. The frequency is the number of waves that move past a given point in a unit of time. Frequency is usually expressed in hertz (Hz). Wavelength and frequency are inversely proportional and are related by $\lambda = c/\nu$, where c is the speed of light. As the wavelength of the electromagnetic radiation increases, the corresponding frequency decreases.

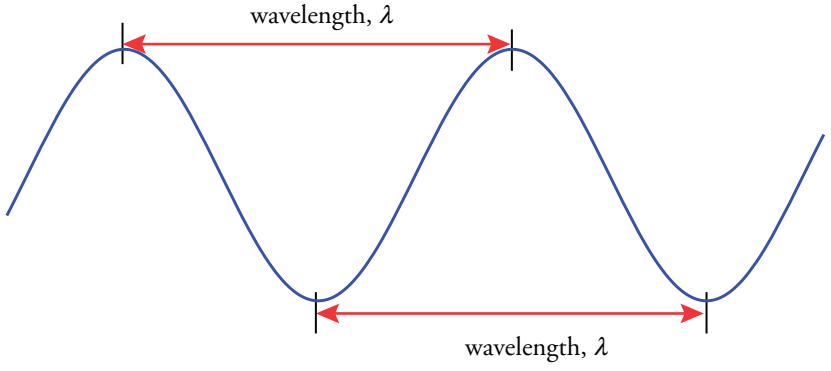


Figure 2.6 Electromagnetic Radiation
The wavelength, λ, of electromagnetic radiation is the distance between any two peaks or troughs of the wave.

The energy, E associated with electromagnetic radiation is quantized. The relationship is given by

$$E = h\nu$$

where h is Planck's constant. The energy of electromagnetic radiation is therefore directly proportional to its frequency. Since wavelength is inversely proportional to frequency, $\lambda = c/\nu$, we can rewrite this as

$$E = \frac{hc}{\lambda}$$

The energy of electromagnetic radiation is also directly proportional to the quantity $1/\lambda$. This quantity is the **wavenumber**.

$$E = hc\left(\frac{1}{\lambda}\right)$$

The electromagnetic spectrum spans a huge range of frequencies and energies. Its frequency ranges from 10^{18} Hz for X-rays, which corresponds to the internuclear separation in molecules (100 pm), to 10^9 Hz for radio waves. The visible portion of the electromagnetic spectrum spans the range from 400 to 700 nm (Figure 2.7).

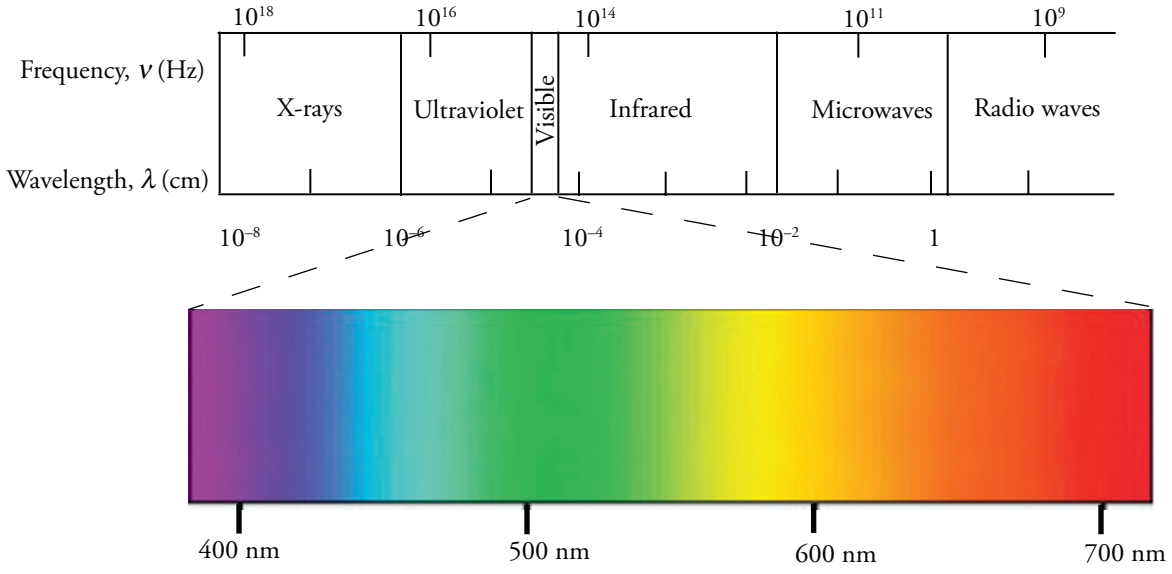
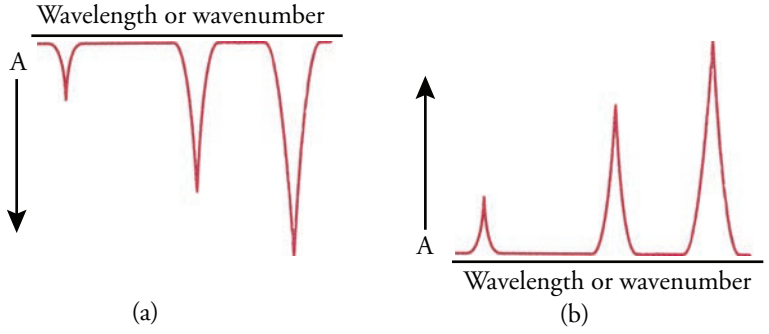


Figure 2.7 Electromagnetic Spectrum
The wavelength or the reciprocal of the wavelength, the wavenumber, is used to identify absorptions of organic molecules. The visible spectrum is only a tiny sliver of the entire electromagnetic spectrum.

Molecules can absorb only certain discrete amounts of energy. That is, the energy levels of molecules are quantized. To change the energy content of a molecule from E_1 to E_2, the energy difference ($E_2 - E_1$) comes from characteristic electromagnetic radiation with a specific frequency (and wavelength). The energy absorbed by the molecule can change its electronic or vibrational energy. For example, ultraviolet radiation causes changes in the electron distribution in π orbitals; infrared radiation causes bonds to stretch and bond angles to bend.

In the various types of spectroscopy, radiation passes from a source through a sample that may or may not absorb certain wavelengths of the radiation. As the wavelength is systematically changed, a detector determines which wavelengths of light the sample absorbs. At a wavelength corresponding to the energy ($\Delta E = E_2 - E_1$) necessary for a molecular change, the molecule absorbs the radiation emitted by the source. The amount of light absorbed by the molecule (absorbance) is plotted as a function of wavelength. At most wavelengths, the amount of radiation detected by the detector equals that emitted by the source because the molecule does not absorb radiation. At such wavelengths, a plot of absorbance on the vertical axis versus wavelength yields a horizontal line (Figure 2.8). When the molecule absorbs radiation of a specific wavelength, the amount of radiation arriving at the detector is less than that emitted by the source. This difference is recorded as an absorbance.

Figure 2.8 Features of a Spectrum
The portion of the spectrum where no absorption occurs is the base line. This horizontal line may be located at the top or bottom of a graph. Absorption then is recorded as a "peak" extending down from the base line. In an infrared spectrum (a), the base line is at top of the spectrum. In an NMR spectrum (b), the base line is at the bottom of the spectrum.



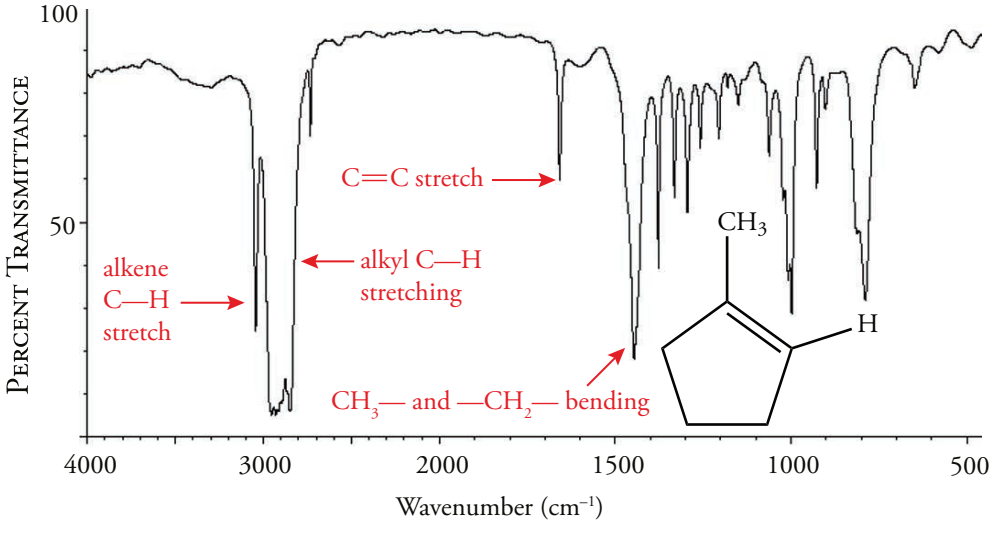
2.9 INFRARED SPECTROSCOPY

The atoms in a molecule do not remain at fixed positions with respect to each other. Molecules constantly vibrate at various frequencies that depend on molecular structure. Similarly, the angle between two atoms bonded to a common central atom regularly expands and contracts by a small amount at a frequency that also depends on molecular structure. These vibrational and bending frequencies correspond to the frequency of light in the infrared region of the electromagnetic spectrum.

Each bond in a molecule absorbs light at a unique frequency. Therefore, each molecule has a unique infrared (IR) spectrum. Figure 2.9 shows the infrared spectrum of 1-methylcyclopentene. The wavenumber ($1/\lambda$), given on the bottom of the graph, has units of reciprocal centimeters, cm^{-1}. The wavenumber is plotted against percent transmittance of light by the sample. Thus, a strong absorption results in a small transmittance. Because the wavenumber of absorbed light is directly proportional to its energy, absorptions at high wavenumber (toward the left of the graph) represent molecular vibrations that require high energy. The forest of absorptions between about 1500 and 500 cm^{-1} is called the "fingerprint" region of the IR spectrum. We will discuss the origins of some characteristic absorption bands in the fingerprint region in Section 2.13.

Even though each molecule has a unique IR "signature," each functional group has characteristic absorption bands so that we can readily identify the functional groups in the molecule.

Figure 2.9 Infrared Spectrum of 1-Methylcylcopentene



The Relation of Vibrational Frequencies and the Masses of Bonded Atoms

Although the total of all molecular vibrations results in a complex infrared spectrum, some simple methods allow us to interpret and compare absorptions. As a first approximation, the motion of two bonded atoms relative to each other can be considered independently of the rest of the molecule. The vibrational frequency of the individual bond depends on the force constant (f) of the bond and the masses of the two atoms (m_1 and m_2) by the following equation.

$$1/\lambda = \frac{1}{2\pi c}\sqrt{\frac{f(m_1 + m_2)}{m_1 m_2}}$$

The force constants for bonds are roughly proportional to their bond dissociation energies. Hence, the force constants increase in the order single bond < double bond < triple bond. Furthermore, because polar bonds, such as the carbonyl group, have higher bond dissociation energies than carbon–carbon double bonds, the force constant for a C=O group is larger than for a C=C group. The effect of atomic mass is relatively small, except for bonds to hydrogen. We can determine the contribution of mass by substituting the atomic weights in the $(m_1 + m_2)/m_1 m_2$, part of the expression.

$$\text{C—C,}\quad \frac{12.0 + 12.0}{12.0 \times 12.0} = 0.17 \qquad \text{C—O,}\quad \frac{12.0 + 16.0}{12.0 \times 16.0} = 0.17$$

$$\text{C—H,}\quad \frac{12.0 + 1.0}{12.0 \times 1.0} = 1.08$$

Therefore, C—H, N—H, and O—H stretching frequencies are far from C—C, C—N, and C—O stretching frequencies. Stretching C—H, N—H, and O—H bonds requires more energy, and they are found on the left side of the IR spectrum (Table 2.1).

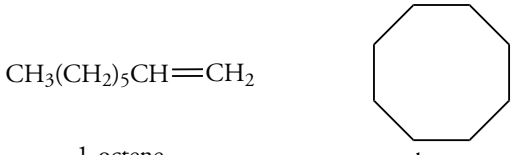
Table 2.1
Approximate Values of Infrared Absorptions

Bond	*Absorption Region (cm^{-1})*
C—C, C—N, C—O	800–1300
C=C, C=N, C=O	1500–1900
C≡C, C≡N	2000–2300
C—H, N—H, O—H	2850–3650

2.10 IDENTIFYING HYDROCARBONS

In Section 2.1, we found that hydrocarbons are classified as saturated or unsaturated depending on the presence of multiple bonds. We can detect multiple bonds by infrared spectroscopy. Both 1-octene and cyclooctane have the same molecular formula, C_8H_{16}. However, their spectra clearly show that 1-octene contains a double bond and cyclooctane does not.

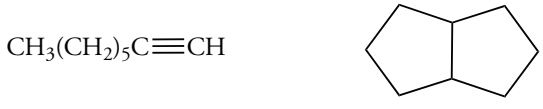
The absence of an absorption in the IR spectrum is often as important as the presence of an absorption. Thus, if we convert one functional group to another, comparing the IR spectra of the reactant and product will tell us if the desired reaction occurred.



1-octene cyclooctane

The structural features present in 1-octene and absent in cyclooctane are a carbon–carbon double bond and sp^2-hybridized C—H bonds. Since these features give rise to characteristic group absorptions, 1-octene has them and cyclooctane does not. Therefore, we can easily tell the two compounds apart.

Similar considerations allow us to tell the difference between 1-octyne and an isomeric bicyclic hydrocarbon, bicyclo[3.3.0]octane.



1-octyne bicyclo[3.3.0]octane

The structural features present in 1-octyne and absent in the bicyclic hydrocarbon are a carbon–carbon triple bond and an sp-hybridized C—H bond. Once again, these features give rise to characteristic group absorptions, and 1-octyne has them and the isomeric bicyclic hydrocarbon does not.

The infrared energy absorbed by a C—H bond depends on the hybridization of the carbon atom (Table 2.2). Carbon–hydrogen bonds become stronger in the order $sp^3 < sp^2 < sp$ because the increased s character of the carbon atom holds the bonding electrons closer to the carbon atom. The energy required to stretch the bond therefore increases in the same order.

Table 2.2
Characteristic Infrared Group Frequencies

Class	*Group*	*Wavenumber (cm^{-1})*
Alkane	C—H	2850–3000
Alkene	C—H	3080–3140
	C=C	1630–1670
Alkyne	C—H	3300–3320
	C≡C	2100–2140
Alcohol	O—H	3400–3600
	C—O	1050–1200
Ether	C—O	1070–1150
Aldehyde	C=O	1725
Ketone	C=O	1700–1780

The sp^3-hybridized C—H bonds in saturated hydrocarbons such as octane (Figure 2.10a) absorb infrared radiation in the 2850–3000 cm^{-1} region. The sp^2-hybridized C—H bonds in alkenes such as 1-octene absorb energy at 3080 cm^{-1}. This peak appears separately from the absorptions associated with the sp^3-hybridized C—H bonds in this molecule (Figure 2.10b). The isomeric cyclooctane would not have the 3080 cm^{-1} absorption. An sp-hybridized C—H bond in a molecule such as 1-octyne (Figure 2.10c) absorbs infrared radiation at 3320 cm^{-1}. An isomeric bicyclic hydrocarbon with no multiple carbon–carbon bonds, and hence no sp^2- or sp-hybridized carbon atoms, would have absorptions only in the 2850–3000 cm^{-1} region.

Hydrocarbons can also be classified by the infrared absorptions of their carbon–carbon bonds. Carbon—carbon bond strength increases in the order single < double < triple. Thus, the wavenumber position (cm^{-1}) of the absorption corresponding to stretching these bonds increases in the same order. Saturated hydrocarbons, both alkanes and cycloalkanes, contain many carbon–carbon single bonds that absorb in the 800–1000 cm^{-1} region, but the intensity is very low. Carbon–carbon single bonds present in unsaturated compounds also absorb in the same region. Many other molecular bond stretching vibrations and bond angle bending modes occur in the same region and are much more intense. Therefore, this region often has limited diagnostic value. Moreover, we already know that most organic compounds have carbon–carbon single bonds.

Figure 2.10a Infrared Spectrum of *n*-Octane

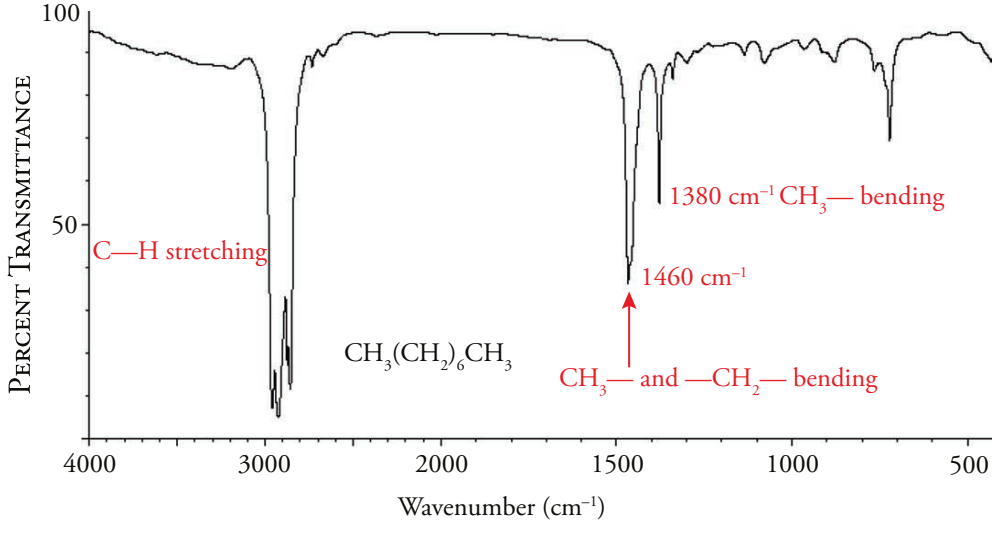


Figure 2.10b Infrared Spectrum of 1-Octene

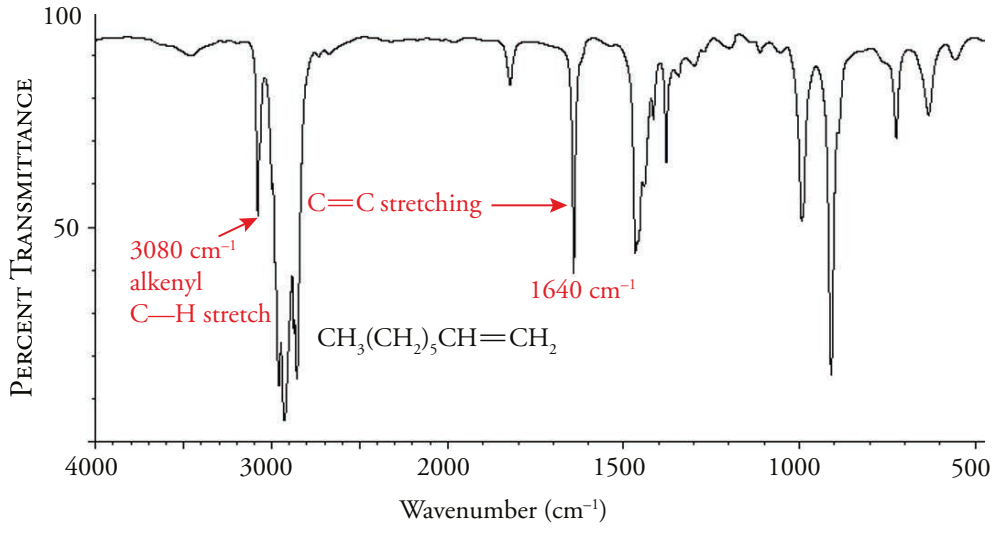
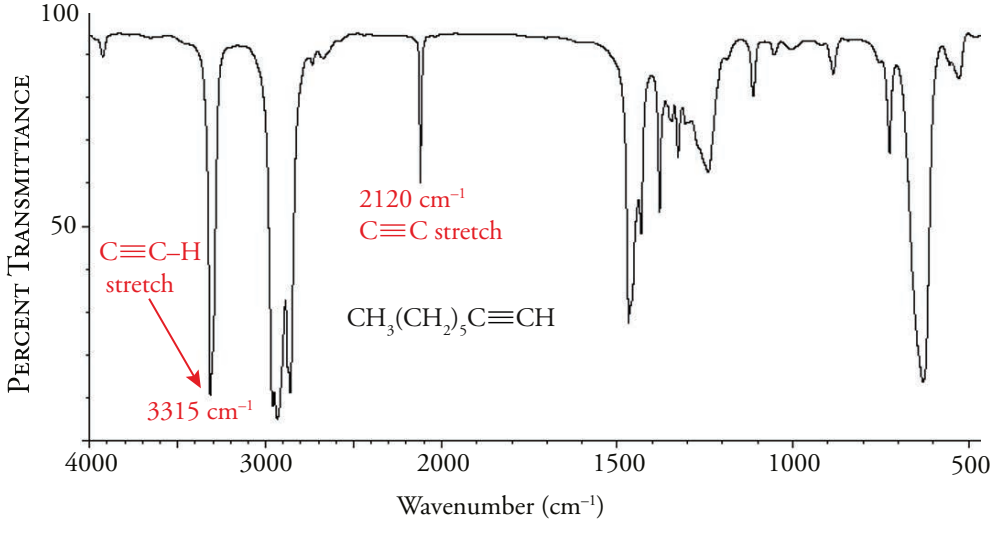


Figure 2.10c Infrared Spectrum of 1-Octyne



Problem 2.18

Explain how you could distinguish between the following two compounds by infrared spectroscopy.



Sample Solution

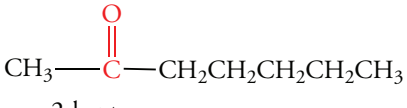
Each compound has structural features that are not present in its isomer. For example, the alkyne has a carbon–carbon triple bond as well as an sp-hybridized C—H bond. This compound has absorptions in the 2100–2140 and the 3300–3320 cm^{-1} region, and the alkene does not have absorptions in either region.

2.11 IDENTIFYING OXYGEN-CONTAINING COMPOUNDS

Many functional groups contain oxygen with characteristic infrared absorptions (Table 2.2). The characteristic group frequencies of aldehydes and ketones range from 1700 to 1780 cm^{-1}. The carbon–oxygen double bond of carbonyl compounds requires more energy to stretch than the carbon–oxygen single bond of ethers and alcohols. Therefore, aldehydes and ketones absorb infrared radiation at higher wavenumber positions than alcohols and ethers (1050–1200 cm^{-1}).

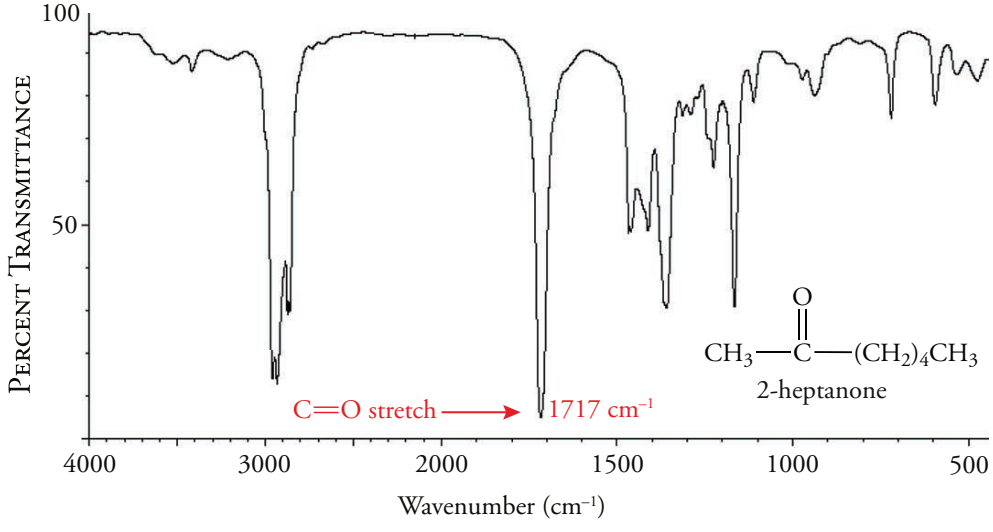
The Carbonyl Group

The absorption for a carbonyl group is extremely intense, and it is easily detected because it lies in a region of the infrared spectrum that has no conflicting absorptions. Note that carbon—carbon double bond stretching vibrations are at a slightly lower wavenumber position than those of carbonyl compounds. Figure 2.11 shows a typical spectrum of a ketone for 2-heptanone. The carbonyl stretching vibration occurs at 1712 cm^{-1}.

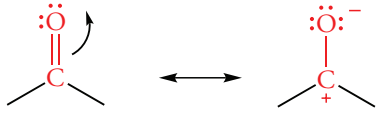


2-heptanone

Figure 2.11 Infrared Spectrum of 2-Heptanone



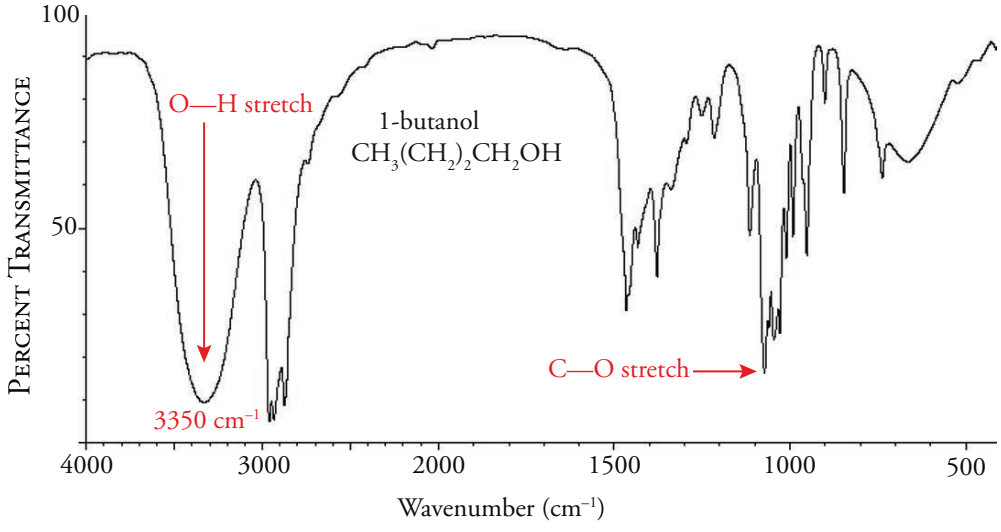
The position of the carbonyl group absorption depends on the inductive and resonance effects of atoms bonded to the carbonyl carbon atom. A carbonyl group has two contributing resonance structures.



contributing resonance structures of a carbonyl group

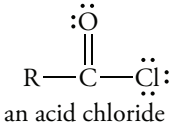
The carbon—oxygen single bond stretching vibration of alcohols and ethers appears in a region complicated by many other absorptions. However, the absorption of a carbon—oxygen single bond is more intense than the absorption of carbon—carbon single bonds. The presence of a hydroxyl group is better established by the oxygen—hydrogen stretching vibration that occurs as an intense broad peak in the 3360 cm^{-1} region. The spectrum of 1-butanol illustrates this absorption (Figure 2.12). Ethers can be identified by a process of elimination. If a compound contains an oxygen atom and the infrared spectrum does not have the absorptions that are characteristic of a carbonyl group or a hydroxyl group, we can conclude that the compound is an ether.

Figure 2.12 Infrared Spectrum of 1-Butanol



Problem 2.19

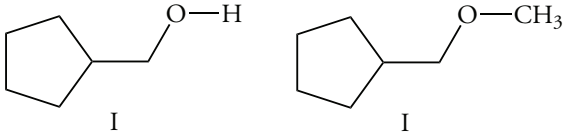
The carbonyl group of an acid chloride absorbs at 1800 cm^{-1}. Explain why this value is at a higher wavenumber than for an aldehyde or ketone.



Sample Solution

Chlorine does not effectively donate electrons by resonance via its 3p orbitals. Thus, the dipolar resonance form of a carbonyl group is less important, and the carbonyl group has more double bond character than an aldehyde or ketone. The chlorine atom also inductively withdraws electrons, destabilizing the dipolar resonance form. As a result, the carbonyl infrared absorption for an acid chloride requires more energy than for an aldehyde or ketone, and occurs at a higher wavenumber position.

Problem 2.20 Explain how you could distinguish between the following two compounds by infrared spectroscopy.

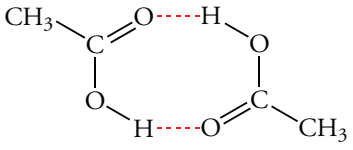


I I

Carboxylic Acids

A carboxylic acid has both a carbonyl group and a hydroxyl group. For either a pure liquid or in solution, the C=O stretching absorption of carboxylic acids occurs near 1710 cm^{-1}. Under these conditions, a carboxylic acid exists as a hydrogen-bonded dimer. Thus, the position of the C=O stretching absorption is close to that of aldehydes and ketones. However, the absorption of carboxylic acids is much broader than those of aldehydes and ketones, and this characteristic is one of the hallmarks of the infrared spectra of carboxylic acids.

The O—H stretching absorption of carboxylic acids is also a highly characteristic feature. It occurs in the same region of the spectrum as that of alcohols. However, as in the case of the C=O absorption, the O—H absorption is very broad (2400–3600 cm^{-1}). As a consequence, this absorption strongly overlaps the region of C—H stretching absorption, which is often largely obscured. The presence of broad absorptions in both the 3000 and the 1700 cm^{-1} regions clearly identifies carboxylic acids (Figure 2.13).



acetic acid, hydrogen-bonded dimer

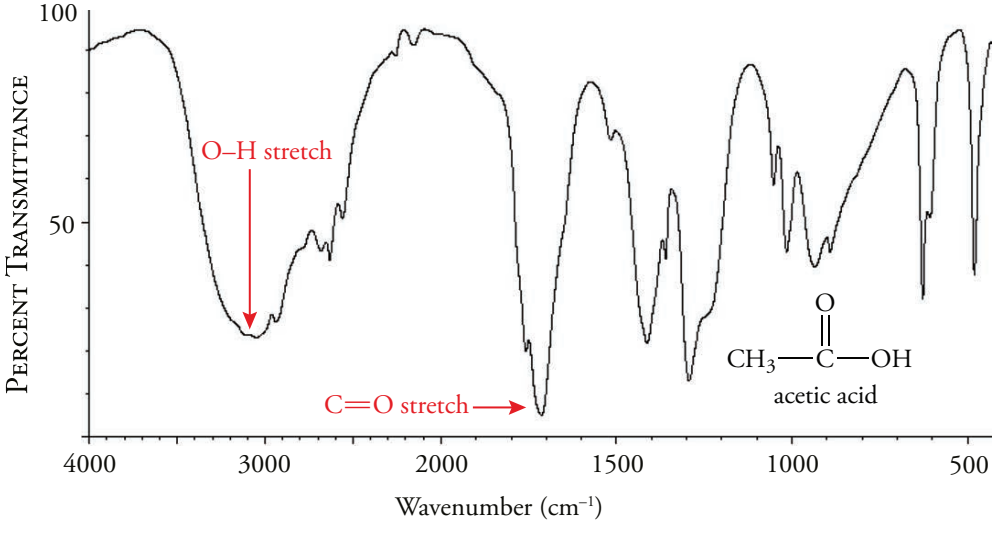
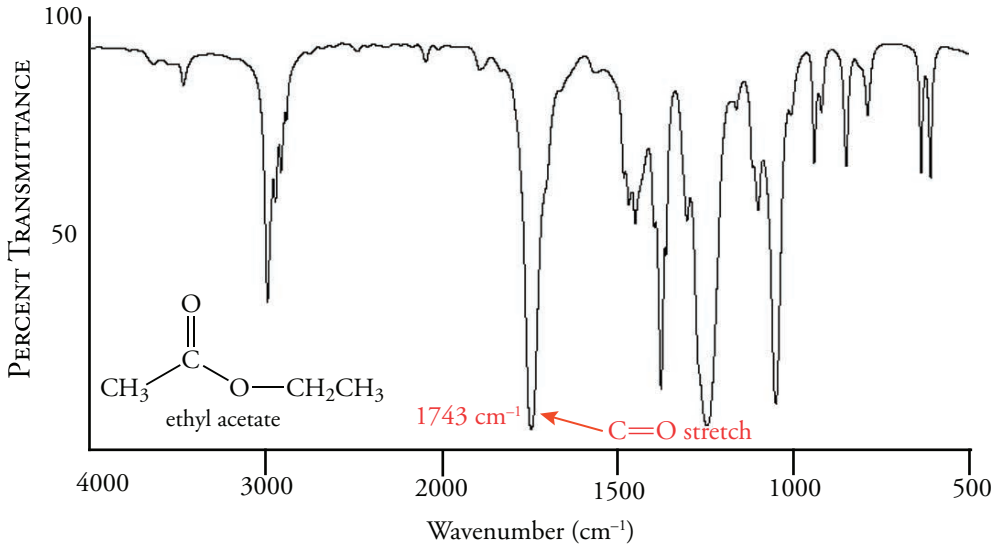


Figure 2.13
Infrared Spectrum of Acetic Acid

Esters

Simple esters have an absorption at about 1740 cm^{-1}, a higher wavenumber than aldehyde and ketone absorptions. Esters also have a C—O stretching absorption in the 1000–1300 cm^{-1} region. Because other absorptions also occur in this region, such data are useful only as a confirmation when an ester is suspected from other data such as the carbonyl stretching absorption. We recall that alcohols, ethers, and carboxylic acids have C—O absorptions in the same region. Figure 2.14 shows the infrared spectrum of ethyl acetate.

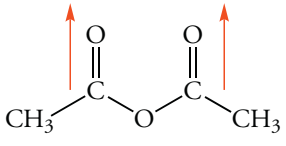
Figure 2.14
Infrared Spectrum of Ethyl Acetate



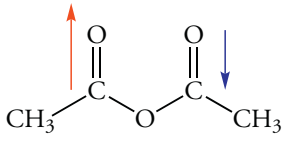
Carboxylic Acid Anhydrides

The anhydrides of carboxylic acids have two conspicuous spectral features. First, there are two carbonyl absorptions, one at about 1820 cm^{-1} and the other at about 1760 cm^{-1}. They are a consequence of symmetric and asymmetric vibration modes.

Anhydrides typically have a strong C—O stretching frequency in the range of 1040–1050 cm^{-1}. Acetic anhydride has a strong C—O stretching frequency too, but it is shifted to 1125 cm^{-1}.

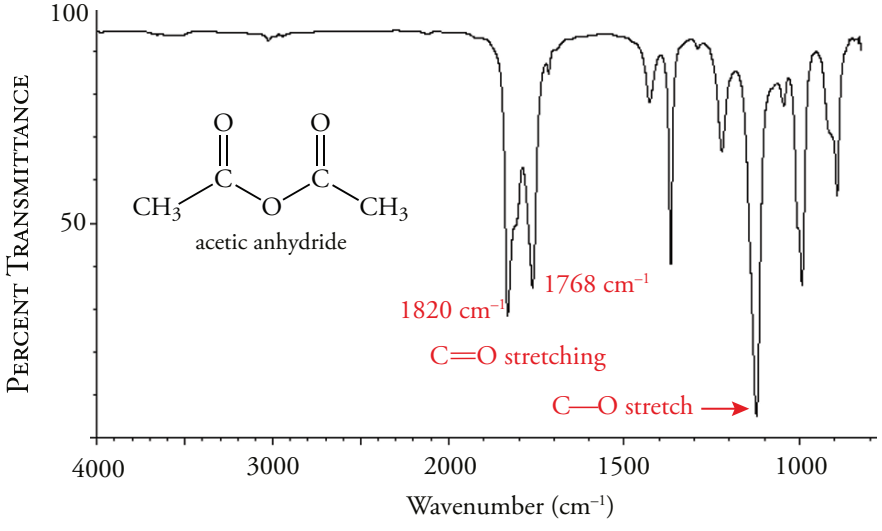


symmetric stretch
1820 cm^{-1}



asymmetric stretch
1768 cm^{-1}

Figure 2.15
Infrared Spectrum of Acetic Anhydride



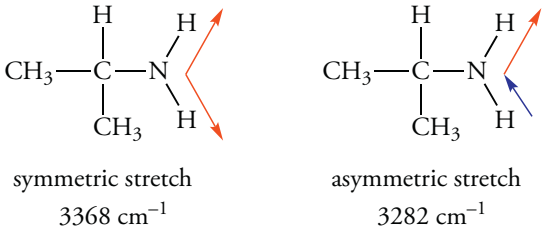
2.12 IDENTIFYING NITROGEN-CONTAINING COMPOUNDS

We noted earlier that N—H stretching frequencies are far from C—C, C—N, and C—O stretching frequencies. Stretching these bonds requires more energy, and they are found on the left side of the IR spectrum. We will see that this is true for amines and amides.

Amines

The N—H bond stretching vibrations of amines appear in the same region as O—H bond stretching. However, these peaks look quite different from those of an alcohol O—H bond. If the nitrogen in an amine is bonded to one carbon, it is a **primary amine** with the general formula R—NH_2. If the nitrogen in an amine is bonded to two carbon atoms, it is a **secondary amine** with the general formula R_2NH. If the nitrogen in an amine is bonded to three carbon atoms, it is a **tertiary amine** with the general formula R_3N.

For primary amines, there are two N—H peaks that occur over a range from 3250 to 3550 cm^{-1}. As in the spectra of acid anhydrides, the peak at highest energy results from symmetric stretching; the lower energy peak results from asymmetric stretching. Isopropylamine provides an example (Figure 2.16). C—N bond stretching occurs in the 1000–1250 cm^{-1} region. C—N peaks are weak.



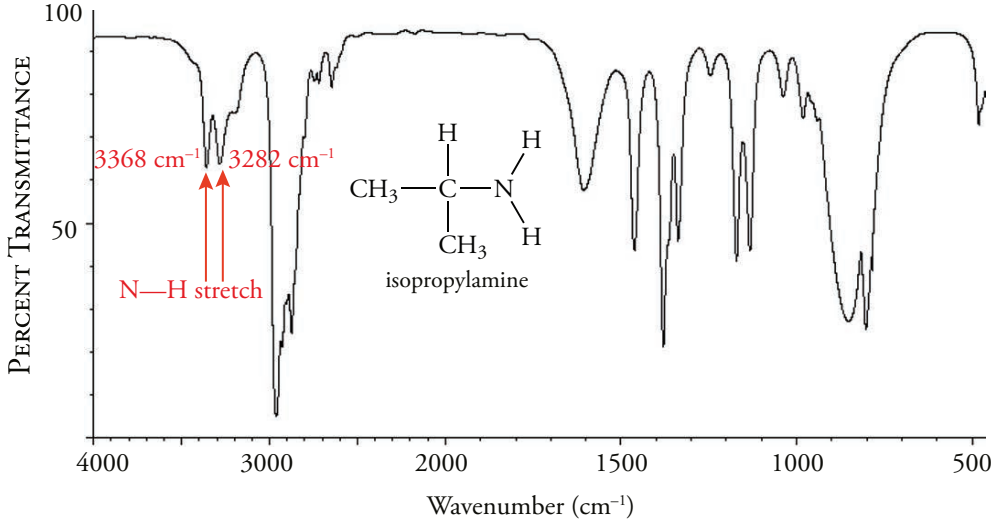


Figure 2.16
Infrared Spectrum of Isopropylamine

Secondary amines have a single N—H peak that occurs over a range from 3250 to 3550 cm^{-1}. *N*-methylaniline provides an example (Figure 2.17). Thus, comparing the N—H peaks of primary and secondary amines easily allows us to distinguish them.

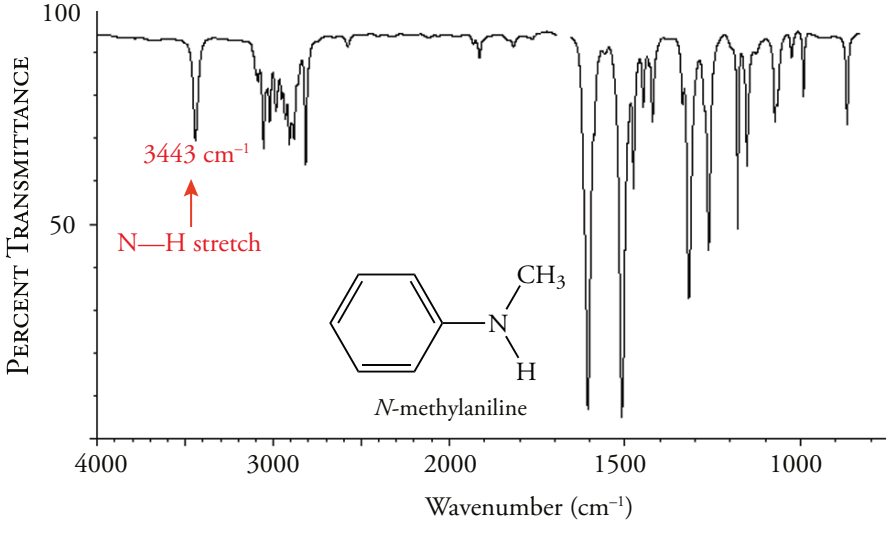
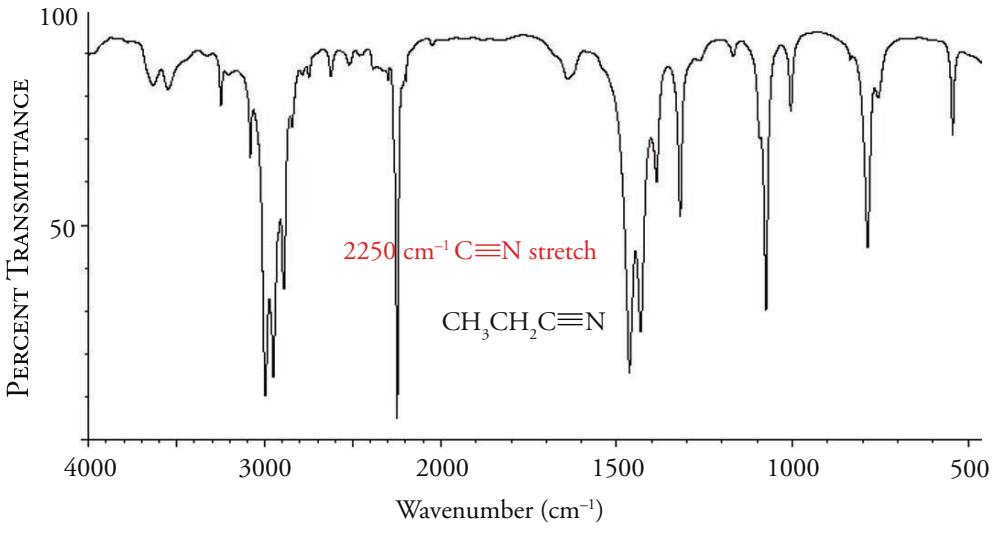


Figure 2.17
Infrared Spectrum of *N*-methylaniline

Nitriles

Nitriles contain a C≡N bond whose absorption band occurs around 2250 cm^{-1}, a region of the spectrum where no other absorptions appear. Therefore, nitriles can be easily identified by infrared spectroscopy (Figure 2.18).

Figure 2.18
Infrared Spectrum of Propionitrile

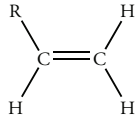
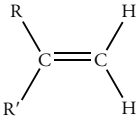
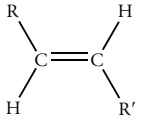
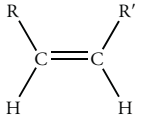
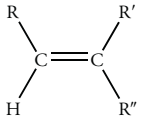


2.13 BENDING DEFORMATIONS

All of the infrared absorptions we have described thus far are stretching vibrations that result from atomic motions along the axis of the bond. However, a second vibration can occur in a direction perpendicular to the bond. Such motion, called **bending**, is common for C—H bonds. Bending motions, or **modes**, occur in directions defined with respect to a selected plane. In the case of alkenes and aromatic compounds, bending motions for several C—H bonds often occur in concert with one another, and they provide important information about isomeric structures.

Many bending modes also exist for alkyl groups. The various bending motions that are possible for organic compounds give rise to the extremely complex portion of the spectrum that we earlier called the "fingerprint" region.

Table 2.3
Out-of-Plane C—H Bending Modes of Alkenes

Bond	*Absorption (cm^{-1})*
	995–985 910–905
	895–885
	980–965
	690 (ambiguous)
	840–790

Alkenes

Alkenes have out-of-plane bending modes in the 1000–800 cm^{-1} region. The absorptions are sufficiently intense to be useful in assigning structures (Table 2.3). Terminal alkenes produce the two most reliable absorption patterns. The two C—H bonds of terminal alkenes— $R_2C{=}CH_2$ —bend in concert, and the absorption occurs in the 895–885 cm^{-1} region. For compounds of the type $RCH{=}CH_2$, the two methylene C—H bonds absorb in the 910–905 cm^{-1} region, and the other C—H bond absorbs in the 995–985 cm^{-1} region. These two types of terminal alkenes can therefore be distinguished.

Both *trans*- and *cis*-substituted alkenes as well as trisubstituted alkenes each have one C—H out-of-plane bending mode. However, the absorption for the *cis* isomer is often ambiguous.

Bending Modes in Aromatic Compounds

The absorptions due to the out-of-plane bending of aromatic compounds depend on the substitution pattern. The C—H bonds on adjacent carbon atoms bend out of the plane of the aromatic ring in unison. Table 2.4 lists absorptions as a function of the number of adjacent hydrogen atoms.

For monosubstituted aromatic compounds such as toluene (methylbenzene), there is an absorption at 730 cm^{-1} for the out-of-plane bending of five adjacent hydrogen atoms. There is another absorption in the 745–690 cm^{-1} region that characterizes monosubstituted, 1,3-disubstituted, and 1,2,3-trisubstituted aromatic compounds (Figure 2.19).

For *m*-xylene (1,3-dimethylbenzene), an out-of-plane bending absorption occurs at 690 cm^{-1}. Absorptions also occur at 770 cm^{-1} for the three adjacent hydrogen atoms at C-4, C-5, and C-6, and at 880 cm^{-1} for the single C—H bond at C-2 (Figure 2.20).

For *p*-xylene (1,4-dimethylbenzene), there is a strong peak at 795 cm^{-1} corresponding to out-of-plane vibrations. The strong absorbance at 484 cm^{-1} corresponds to bending of the entire ring in and out of the plane (Figure 2.21). Figure 2.22 shows the spectrum of *o*-xylene. It is also disubstituted, but the substitution pattern is different from the other zylenes, and so is the IR spectrum.

Table 2.4
Out-of-Plane Bending Modes of Aromatic Ring Hydrogen Atoms

Number of Adjacent Hydrogen Atoms	*Wavenumber (cm^{-1})*
5	770–730
4	770–735
3	810–750
2	860–800
1	900–860

Problem 2.21

Draw the structures of the two dehydration products of 1-methylcyclohexanol and describe how infrared spectroscopy can be used to establish their structures.

Figure 2.19
IR Spectrum of Toluene

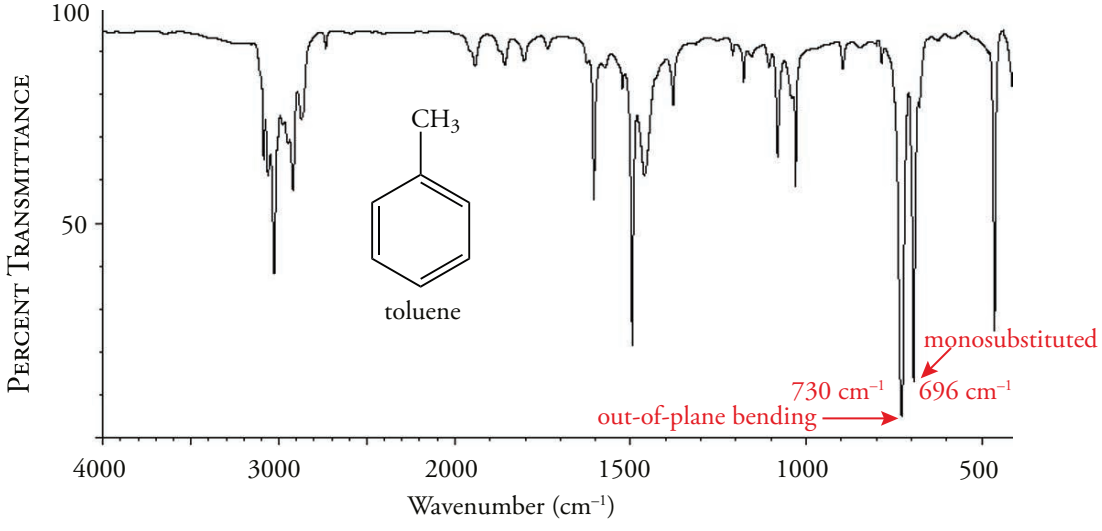
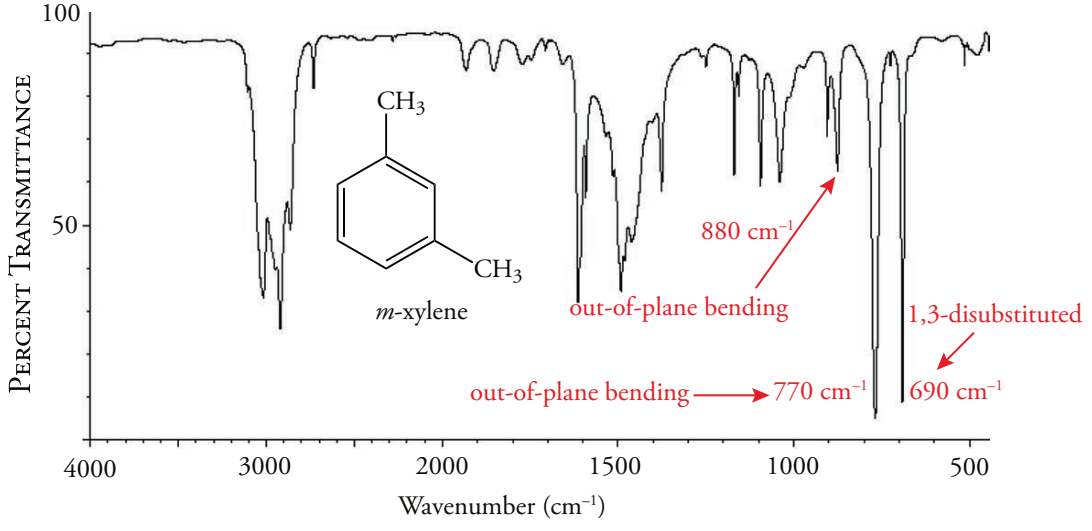


Figure 2.20
IR Spectrum of *m*-Xylene



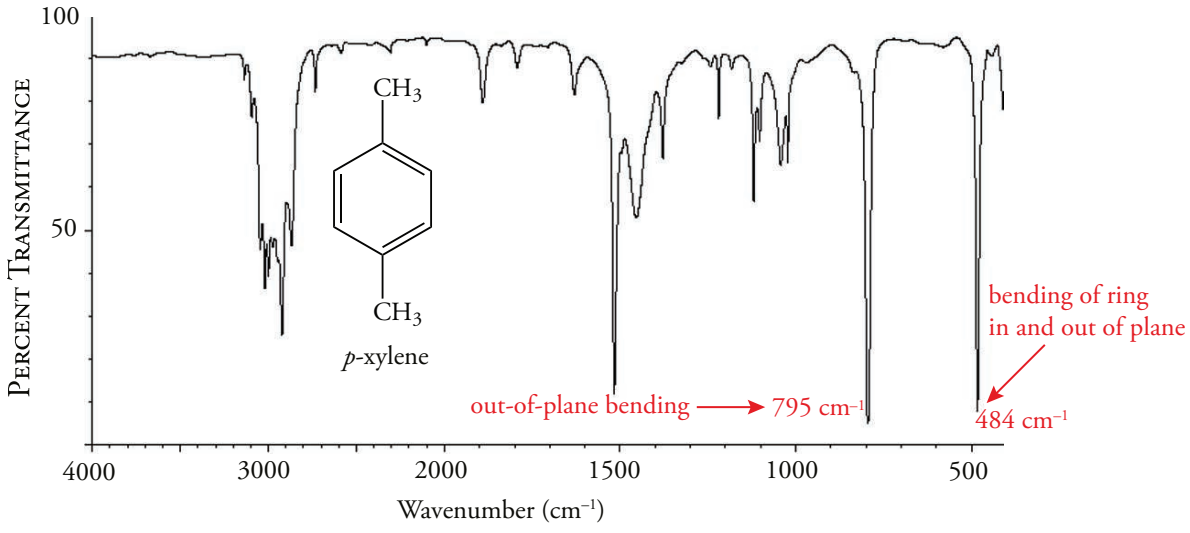


Figure 2.21 IR Spectrum of *p*-Xylene

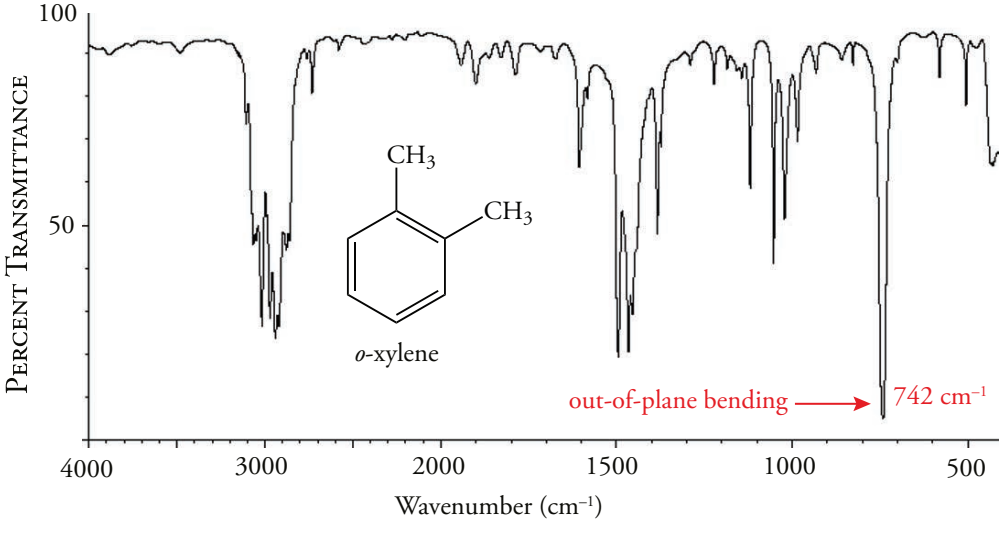
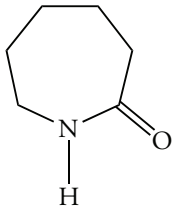


Figure 2.22 IR Spectrum of *o*-Xylene

END-OF-CHAPTER EXERCISES

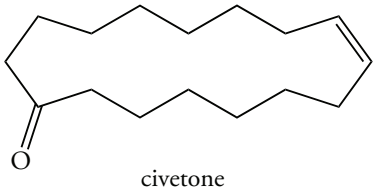
Functional Groups

2.1 Identify the functional groups contained in each of the following structures.
(a) caprolactam, a compound used to produce a type of nylon



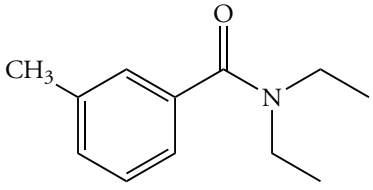
caprolactam

(b) civetone, a compound in the scent gland of the civet cat



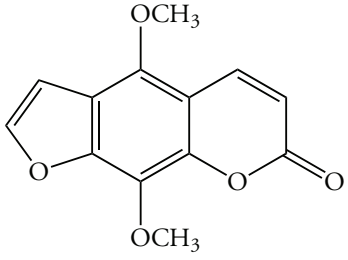
civetone

(c) DEET, the active ingredient in some insect repellents



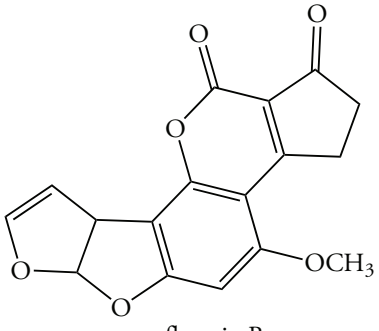
DEET

2.2 Identify the oxygen-containing functional groups in each of the following compounds.
(a) isopimpinellin, a carcinogen found in diseased celery



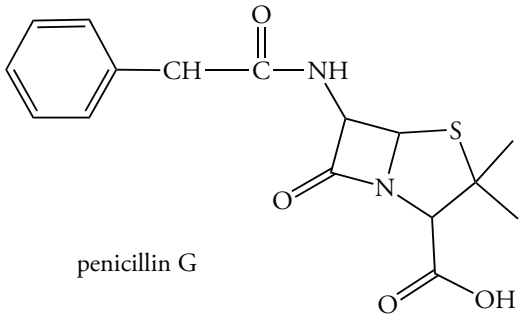
isopimpinellin

(b) aflatoxin B_1, a carcinogen found in moldy foods



aflatoxin B_1

(c) penicillin G, an antibiotic first isolated from a mold.



penicillin G

Molecular Formulas

2.3 Write the molecular formula for each of the following.

(a) $CH_3—CH_2—CH_2—CH_2—CH_3$ (b) $CH_3—CH_2—CH_2—CH_3$ (c) $CH_2=CH—CH_2—CH_3$

(d) $CH_3—CH_2—C\equiv C—H$ (e) $CH_3—CH_2—CH_2—CH=CH_2$ (f) $CH_3—CH_2—C\equiv C—CH_3$

2.4 Write the molecular formula for each of the following.

(a) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ (b) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ (c) $CH_3CH_2C\equiv CH$

(d) $CH_3CH_2C\equiv CCH_3$ (e) $CH_3CH_2CH_2CH=CHCH_3$ (f) $CH_2=CHCH_2CH_3$

2.5 Write the molecular formula for each of the following.

(a) $CH_3—CH_2—CHCl_2$ (b) $CH_3—CCl_2—CH_3$ (c) $Br—CH_2—CH_2—Br$

(d) $CH_3—CHBr—CHBr_2$ (e) $CH_3—CF_2—CH_2F$ (f) $F—CH_2—CHF—CH_2—F$

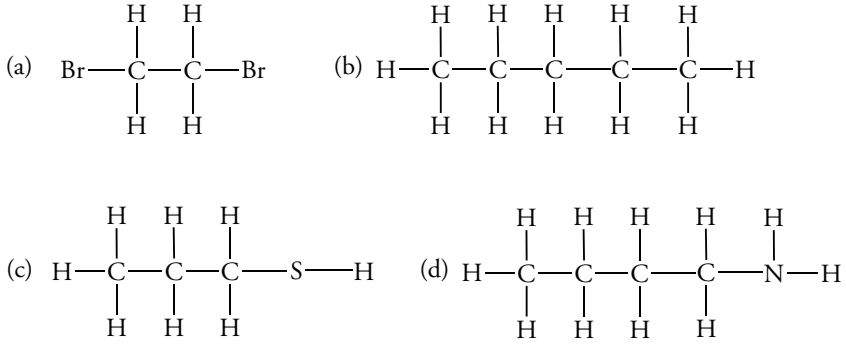
2.6 Write the molecular formula for each of the following.

(a) $CH_3—CH_2—CH_2—OH$ (b) $CH_3—CH_2—O—CH_2—CH_3$ (c) $CH_3—CH_2—SH$

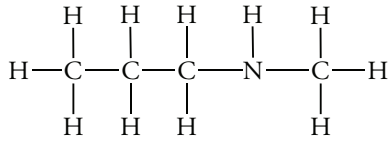
(d) $CH_3—CH_2—S—CH_3$ (e) $CH_3—CH_2—CH_2—NH_2$ (f) $CH_3—CH_2—NH—CH_3$

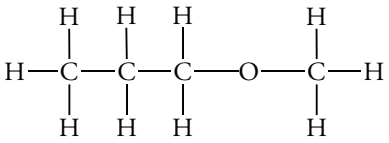
Structural Formulas

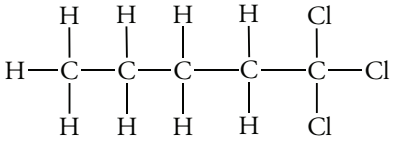
2.7 For each of the following, write a condensed structural formula in which only the bonds to hydrogen are not shown.

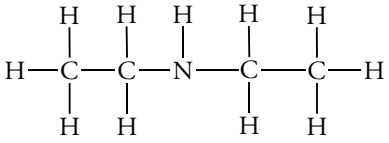


2.8 For each of the following, write a condensed structural formula in which only the bonds to hydrogen are not shown.

(a) 

(b) 

(c) 

(d) 

2.9 Write a condensed structural formula in which no bonds are shown for each of the structures in problem 2.7.

2.10 Write a condensed structural formula in which no bonds are shown for each of the structures in problem 2.8.

2.11 Write a complete structural formula, showing all bonds, for each of the following condensed formulas.
(a) $CH_3CH_2CH_2CH_3$ (b) $CH_3CH_2CH_2Cl$ (c) $CH_3CHClCH_2CH_3$

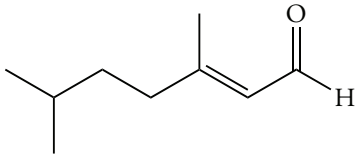
(d) $CH_3CH_2CHBrCH_3$ (e) $CH_3CH_2CHBr_2$ (f) $CH_3CBr_2CH_2CH_2CH_3$

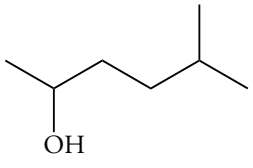
2.12 Write a complete structural formula, showing all bonds, for each of the following condensed formulas.
(a) $CH_3CH_2CH_3$ (b) $CH_3CH_2CHCl_2$ (c) $CH_3CH_2CH_2CH_2SH$

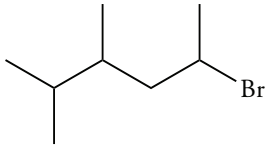
(d) $CH_3CH_2C{\equiv}CCH_3$ (e) $CH_3CH_2OCH_2CH_3$ (f) $CH_3CH_2CH_2C{\equiv}CH$

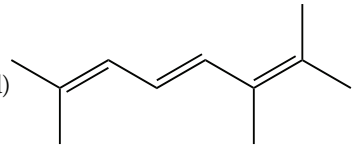
Bond-Line Structures

2.13 What is the molecular formula for each of the following bond-line representations?

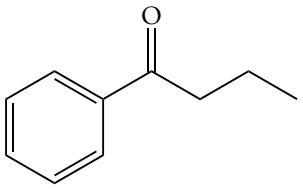
(a) 

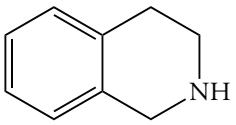
(b) 

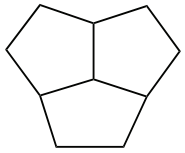
(c) 

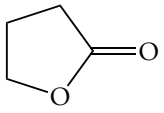
(d) 

2.14 What is the molecular formula for each of the following bond-line representations?

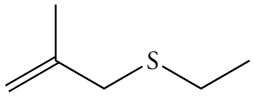
(a) 

(b) 

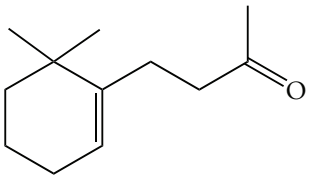
(c) 

(d) 

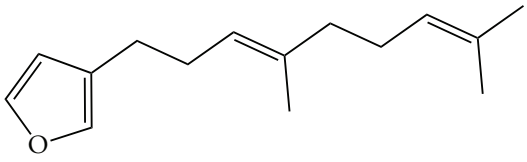
2.15 What is the molecular formula for each of the following bond-line structures?
(a) a scent marker of the red fox



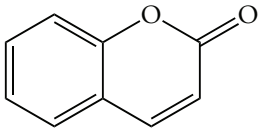
(b) a compound responsible for the odor of the iris



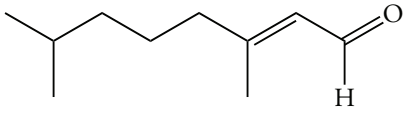
(c) a defense pheromone of some ants



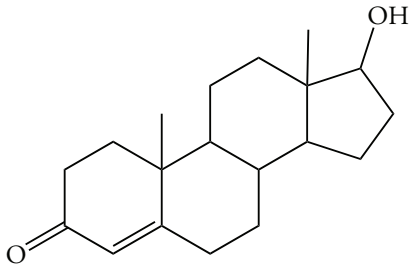
2.16 What is the molecular formula for each of the following bond-line structures?
(a) a compound found in clover and grasses



(b) an oil found in citrus fruits

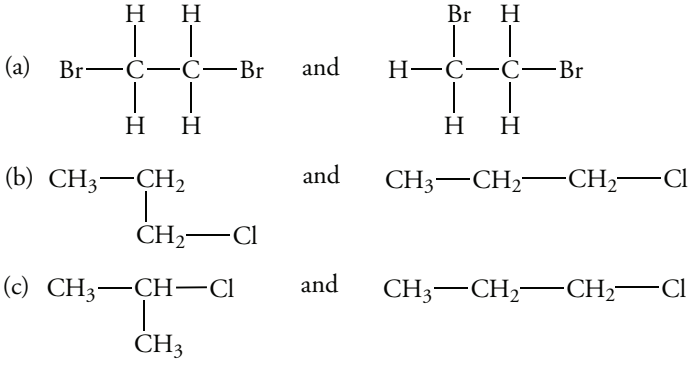


(c) a male sex hormone

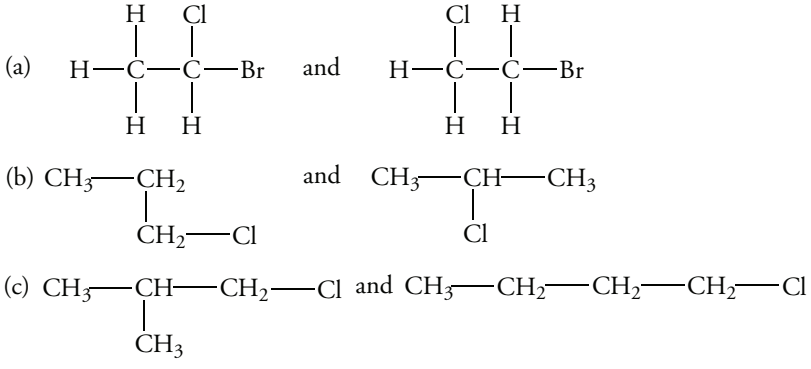


Isomerism

2.17 Indicate whether the following pairs of structures are isomers or different representations of the same compound.



2.18 Indicate whether the following pairs of structures are isomers or different representations of the same compound.



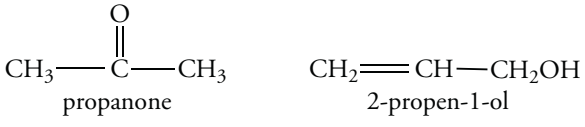
2.19 There are two isomers for each of the following molecular formulas. Draw their structural formulas.
(a) $C_2H_2Br_2$ (b) C_2H_6O (c) C_2H_4BrCl

(d) C_2H_7Cl (e) C_2H_7N (f) $C_2H_3Br_3$

2.20 There are three isomers for each of the following molecular formulas. Draw their structural formulas.
(a) $C_2H_3Br_2Cl$ (b) C_3H_8O (c) C_3H_8S

Infrared Spectroscopy

2.21 How can infrared spectroscopy be used to distinguish between propanone and 2-propen-l-ol?



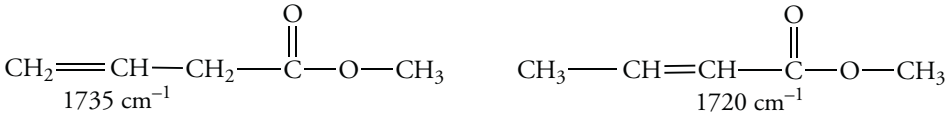
2.22 How can infrared spectroscopy be used to distinguish between 1-pentyne and 2-pentyne?

2.23 The carbonyl stretching vibration of ketones is at a longer wavelength than the carbonyl stretching vibration of aldehydes. Suggest a reason for this observation.

2.24 The carbonyl stretching vibrations of esters and amides occur at 1735 and 1670 cm^{-1}, respectively. Suggest a reason for this difference.

2.25 An infrared spectrum of a compound with molecular formula $C_4H_8O_2$ has an intense broad band between 3500 and 3000 cm^{-1} and an intense peak at 1710 cm^{-1}. Which of the following compounds best fits this data?
I: $CH_3CH_2CO_2CH_3$ II: $CH_3CO_2CH_2CH_3$ III: $CH_3CH_2CH_2CO_2H$

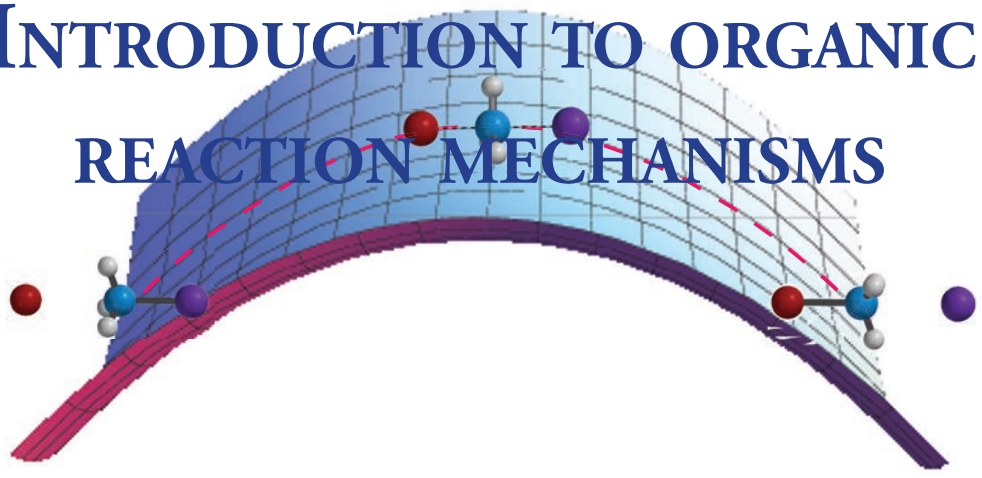
2.26 Explain why the carbonyl stretching vibrations of the following two esters differ.



2.27 Explain how the two isomeric nitration products of isopropylbenzene can be distinguished using infrared spectroscopy.

2.28 Explain how the structures of the three isomeric trimethylbenzenes can be established using infrared spectroscopy.

3 Introduction to Organic Reaction Mechanisms



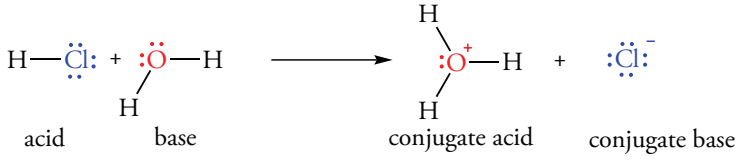
In Chapter 2, we classified organic compounds by their functional groups. In this chapter, we will see that reactions can also be divided into classes based upon their reaction mechanisms. A reaction mechanism is the step-by-step process by which reactants are converted to products. When we study a reaction mechanism, we want to discover whether or not it goes to completion. This question is answered by determining the equilibrium constant for the reaction. We also want to know how fast the reaction occurs. This question is answered by determining the kinetic behavior of the reaction. We will discuss many reaction mechanisms in this text. We will expand upon the ideas introduced in this chapter throughout the text.

3.1 Acid–Base Reactions

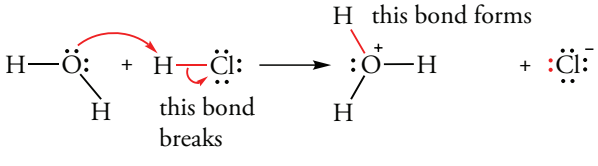
Many organic reactions occur in the presence of acids and bases such a hydrochloric acid, sodium hydroxide, and ammonia. The properties of many organic compounds, including carboxylic acids and amines, are dominated by their acid–base properties. Acids and bases can be subdivided into several classes.

Brønsted–Lowry Acids and Bases

A Brønsted–Lowry acid is a proton donor; a Brønsted–Lowry base is a proton acceptor. When an acid transfers a proton to a base, another base and acid are produced. The acid loses a proton and becomes a *conjugate base.* When a base accepts a proton, it becomes a *conjugate acid*. For example, consider the example shown below for the reaction that occurs when the acid HCl transfers a proton to water. The base, water, becomes the conjugate acid, hydronium ion; chloride ion is the conjugate base. There are no HCl molecules in an aqueous solution.



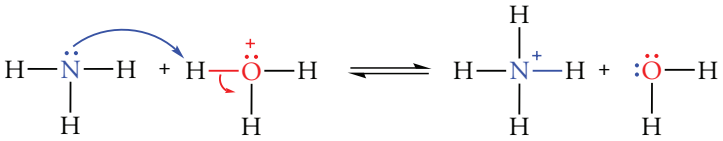
We can write the acid–base reaction shown above with curved arrows to indicate the movement of pairs of electrons during the proton transfer process. Electrons move from the start of the arrow toward the arrow head. The sequence of arrows in the reaction as it is written below shows that a nonbonded pair of electrons of the oxygen atom of water forms a bond to the hydrogen atom of HCl and the bonded pair of electrons in the H—Cl bond moves to the chlorine atom.



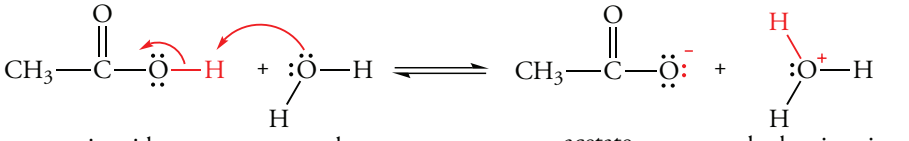
When we show arrows and distinguish lone pairs, we do not wish to imply that there are somehow arrows running around in the solution, or that we can tell nonbonding electrons apart; of course, we cannot. This arrow convention is a book-keeping procedure that we will use many times to keep track of the changes that occur in organic reactions.

The most common Brønsted base is the hydroxide ion. It can accept a proton from an acid to give water. Ammonia is also a base; it can accept a proton from an acid to give the ammonium ion. A curved arrow in the following equation shows the movement of the pair of electrons in the reaction of ammonia with hydronium ion.

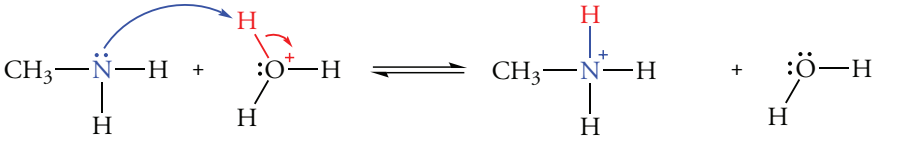
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00003-6
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Carboxylic acids, which we introduced in Chapter 2, are Brønsted acids that can donate a proton to a water molecule or to other bases. For example, when acetic acid dissolves in water, the conjugate base of acetic acid, acetate, and the conjugate acid, hydronium ion form.

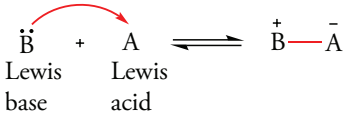


Amines are organic bases whose acid–base chemistry is like that of ammonia. For example, methylamine behaves as a Brønsted base because the nonbonded electron pair of the nitrogen atom can accept a proton from an acid such as hydronium ion. When methylamine accepts a proton, the conjugate acid, methyl-ammonium ion, is produced.



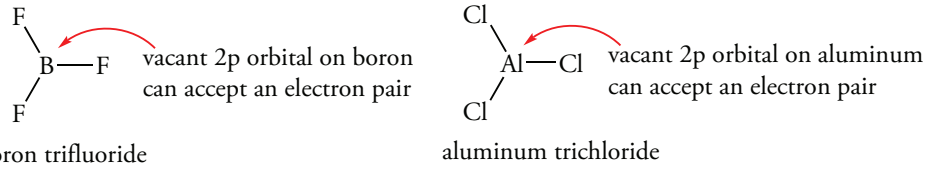
Lewis Acids

Although the Brønsted concept of acids and bases focuses on the transfer of a proton, electron pairs are more fundamental to the process. Covalent bonds are formed or broken when a proton is transferred from one atom to another. To account for this possibility, Gilbert N. Lewis proposed a definition of acids that focuses on electron pairs. A **Lewis acid** is an electron pair acceptor; a **Lewis base** is an electron pair donor. This is a general definition of an acid and a base. For example, hydrochloric acid, a Brønsted acid, is also a Lewis acid because it contains a proton that accepts an electron pair. Ammonia is a Lewis base because it can act as an electron pair donor. However, many other species can serve as electron pair acceptors or donors. Consider the following general reaction between a Lewis acid and a Lewis base.



Both the Lewis acid and the Lewis base in this reaction are neutral. However, when the Lewis base donates an electron pair to the Lewis acid, the Lewis acid portion of the product acquires a formal charge of –1 and the Lewis base portion acquires a formal charge of +1. The charges of the Lewis acid and base need not be zero. For example a Lewis acid could have a +1 charge, and a Lewis base could have a –1 charge. Other combinations of charge are possible.

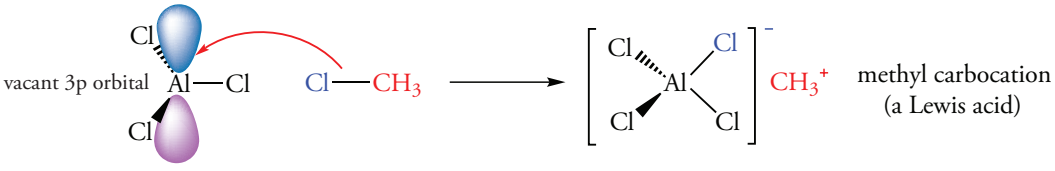
When a Lewis base donates an electron pair to a Lewis acid, the electron pair of the base forms a covalent bond between the acid and base. The Lewis acid provides a vacant orbital that is filled by the electron pair from the Lewis base. Two Lewis acids often used as acid catalysts in organic chemistry are boron trifluoride (BF_3) and aluminum trichloride ($AlCl_3$). Each has only six electrons in its valence shell, and each can accept an electron pair from a Lewis base. In BF_3, a vacant 2p orbital accepts the electron pair; in $AlCl_3$, a vacant 3p orbital accepts the electron pair.



boron trifluoride

aluminum trichloride

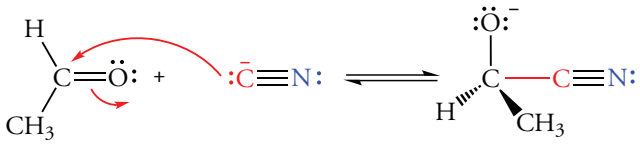
A somewhat less obvious example of a Lewis acid–base reaction is the reaction of chloromethane with aluminum chloride to give a tetrachloroaluminate ion and a methyl carbocation, a potent Lewis acid. We will discuss this reaction in Chapter 13.



aluminum trichloride
(a Lewis acid)

tetrachloroaluminate ion
(a Lewis base)

Another example of a Lewis acid–base reaction is the reaction of cyanide ion with a carbonyl group of ethanal (acetaldehyde). Cyanide ion is a Lewis base, and the carbonyl carbon atom of ethanal is a Lewis acid. We will discuss this reaction in Chapter 17.

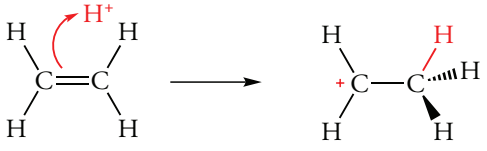


ethanal,
Lewis acid

cyanide,
Lewis base

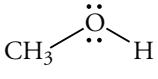
Problem 3.1

A hydrogen ion can react with ethene to give a charged intermediate called an ethyl carbocation. Classify the reactants using Lewis acid–base nomenclature.



Problem 3.2

Methanol can act either as a Brønsted acid or a Brønsted base. Explain why this is the case. What is the conjugate base of methanol? What is the conjugate acid of methanol?



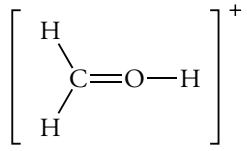
methanol

Problem 3.3

Write the structure of the cation formed by protonation of dimethyl ether (CH_3OCH_3) by sulfuric acid. What is the H–O–C bond angle? Which atom bears the formal positive charge?

Problem 3.4

Methanal reacts with acid such as HCl to form a protonated adduct. Draw the structure of the cation. What is the C–O–H bond angle? (Note: lone pairs are not shown.)



methanal, protonated adduct

3.2 CHEMICAL EQUILIBRIUM AND EQUILIBRIUM CONSTANTS

In principle, all chemical reactions are reversible, and given sufficient time an equilibrium will be established for any chemical reaction. At equilibrium, the reactions in the forward and reverse directions occur at equal rates, and there is no *net* change in the concentrations of reactants and products. The extent to which reactants are converted to products is expressed by an equilibrium constant.

The equilibrium constant for a reaction reflects the relative energies of the reactants and products. The difference in energy between products and reactants provides a force that drives a reaction to a specific equilibrium position. Chemical energetics, that is, thermodynamics, tells us how this driving force, called the *free energy*, is partitioned between the potential energy change, the *enthalpy*, and a change in the molecular order, or *entropy*, of the system.

For a general chemical reaction at equilibrium, where A and B are reactants, C and D are products, and *a*, *b*, *c*, and *d* are their coefficients in the balanced reaction, the value of the equilibrium constant expression is a constant at a specific temperature.

$$a\mathrm{A} + b\mathrm{B} \underset{\text{reverse reaction}}{\overset{\text{forward reaction}}{\rightleftharpoons}} c\mathrm{C} + d\mathrm{D}$$

$$K_{\text{equilibrium}} = \frac{[\mathrm{C}]^c\,[\mathrm{D}]^d}{[\mathrm{A}]^a\,[\mathrm{B}]^b}$$

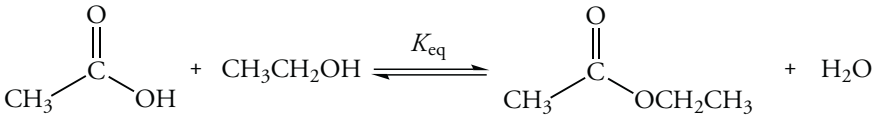
The equilibrium constant, K_{eq}, is a measure of the tendency of a chemical reaction to go from reactants to products in the direction written. If the equilibrium constant is much greater than 1.0, little reactant is present at equilibrium, and the reaction has a large tendency to occur. On the other hand, if the equilibrium constant is much less than 1.0, little product is present at equilibrium, and the reaction has a small tendency to occur in the direction written. Consider the equilibrium constant for the addition reaction of ethene with hydrogen bromide at 25°C.

$$\underset{\text{ethene}}{\mathrm{CH_2{=}CH_2}} + \mathrm{HBr} \overset{K_{eq}}{\rightleftharpoons} \mathrm{CH_3CH_2Br}$$

$$K_{\text{equilibrium}} = \frac{[\mathrm{CH_3CH_2Br}]}{[\mathrm{CH_2{=}CH_2}][\mathrm{HBr}]} = 10^8$$

Because the equilibrium constant is very large, almost no reactant remains at equilibrium. That is, the reaction quantitatively gives a single product. Reactions with equilibrium constants greater than 10^4 are quantitative because the amount of reactant remaining at equilibrium is about 0.01 % or less.

In contrast, the condensation reaction of ethanoic acid and ethanol to produce ethyl ethanoate at 25°C gives a mixture of reactants and products at equilibrium, and the amount of product is much less than 100%.



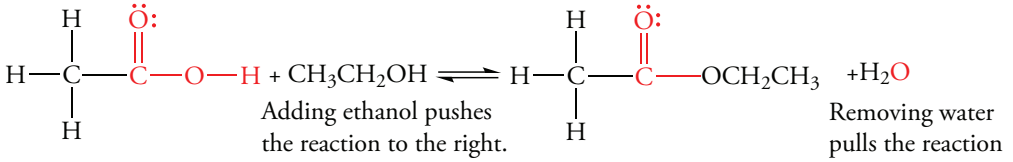
ethanoic acid ethanol ethyl ethanoate

$$K_{equilibrium} = \frac{[CH_3CO_2CH_2CH_3]\,[H_2O]}{[CH_3CO_2H]\,[CH_3CH_2OH]} = 4.0$$

Le Chatelier's Principle

Le Chatelier's principle states that a change in the conditions of a chemical system at equilibrium alters the concentrations of reactants and products, and a new equilibrium results. For example, if more reactant is added to a reaction at equilibrium, the concentrations of both reactants and products change to reestablish the equilibrium, and the equilibrium constant remains unchanged. After adding reactant, the total concentration of reactant initially increases, but then it decreases to establish a new equilibrium concentration. As a result, the concentration of the product increases. In short, the change imposed on the system by adding reactant is offset when some of the added reactant is converted to product. If a product is removed from a chemical system at equilibrium, the forward reaction occurs to give more product. We saw above the equilibrium constant for the formation of ethyl ethanoate from ethanoic acid and ethanol is 4.0. What if we would like to obtain a quantitative yield of product? We can achieve this in two ways:

1. Add ethanol to the reaction mixture to push the reaction to the right.
2. Remove water from the reaction to pull the reaction to the right.

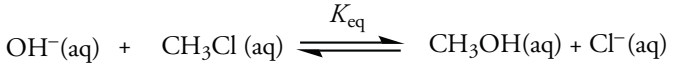


Adding ethanol pushes the reaction to the right.

Removing water pulls the reaction to the right.

Problem 3.5

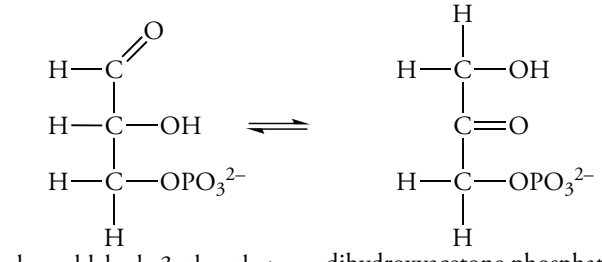
Chloromethane reacts in a substitution reaction with sodium hydroxide in aqueous solution to produce methanol and sodium chloride. Write the equilibrium constant expression for this substitution reaction. The equilibrium constant is 5×10^{16}. Is the reaction quantitative?



chloromethane

Problem 3.6

One reaction in glycolysis, a pathway for the metabolism of glucose, is the interconversion of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. At equilibrium, approximately 96% of the mixture is dihydroxyacetone phosphate. Calculate the equilibrium constant.



glyceraldehyde 3-phosphate dihydroxyacetone phosphate

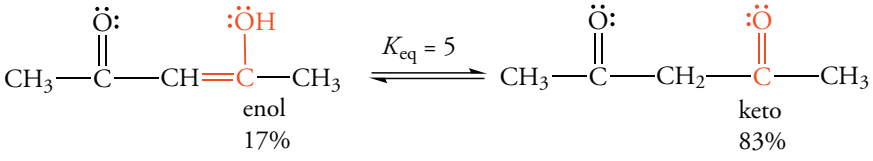
Sample Solution

The amount of glyceraldehyde-3-phosphate is 4%. Molar concentrations must be used in the equilibrium constant expression. However, the order of the concentration terms in the equilibrium constant expression is the same. Thus, the ratio of the concentrations is the same as the ratio of the percent composition of the two components.

$$K_{eq} = \frac{[\text{dihydroxyacetone phosphate}]}{[\text{glyceraldehyde-3-phosphate}]} = \frac{96}{24} = 4.0$$

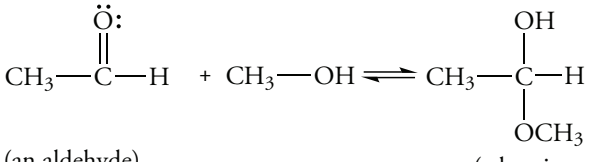
Problem 3.7

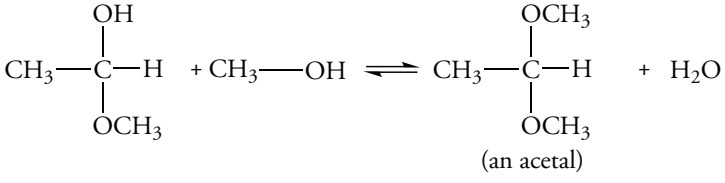
The equilibrium constant for the following rearrangement reaction, an enolization reaction, is 5. Calculate the percent composition of the equilibrium mixture.



Problem 3.8

Aldehydes react with alcohols to give hemiacetals and acetals by two equilibrium reactions. What experimental conditions would increase the yield of the acetal derived from the aldehyde?





3.3 pH AND p*K* VALUES

The strengths of acids are measured by their tendencies to transfer protons to water, which we regard as the reference solvent. A solution of a weak acid (HA) contains both undissociated acid and hydronium ions, and the concentration of ions is low. Strong acids ionize completely.

$$HA + H_2O \underset{}{\overset{K_{eq}}{\rightleftharpoons}} A^- + H_3O^+$$

K_a and pK_a

The strength of an acid with the general formula HA is given by the equilibrium constant for ionization, which is obtained from the equation for ionization.

$$K_{equilibrium} = \frac{[H_3O^+][A^-]}{[HA][H_2O]}$$

The concentration of water, about 55 M, is so large compared to that of the other components of the equilibrium mixture that its value changes very little when the acid HA is added. Therefore, the concentration of water is included in the acid ionization constant, K_a.

Table 3.1
K_a and pK_a Values of Common Acids

Acid	K_a	pK_a
HBr	10^{9}	–9
HCl	10^{7}	–7
H_2SO_4	10^{5}	–5
HNO_3	10^{1}	–1
HF	6×10^{-4}	3.2
CH_3CO_2H	2×10^{-5}	4.7
$(CF_3)_3COH$	2×10^{-5}	4.7
CH_3CH_2SH	3×10^{-11}	10.6
CF_3CH_2OH	4×10^{-13}	12.4
CH_3OH	3×10^{-16}	15.5
$(CH_3)_3COH$	1×10^{-18}	18
CCl_3H	10^{-25}	25
HC≡CH	10^{-25}	25
NH_3	10^{-36}	36
$CH_2{=}CH_2$	10^{-44}	44
CH_4	10^{-49}	49

$$K_a = K_{eq}[H_2O] = \frac{[H_3O^+][A^-]}{[HA]}$$

Acids with $K_a > 10$ are strong acids. Most organic acids have $K_a < 10^{-4}$ and are weak acids. Acid dissociation constants are often expressed as pK_a values, where p$K_a = -\log K_a$. Note that *pK_a values increase as K_a decreases.* Table 3.1 lists the acid ionization constants of some common acids.

Ethanoic acid (acetic acid) is an example of a weak organic acid. An aqueous solution of ethanoic acid contains ethanoate ion (acetate ion) and hydronium ions.

$$CH_3CO_2H + H_2O \underset{}{\overset{K_a}{\rightleftharpoons}} CH_3CO_2^- + H_3O^+$$

weaker acid — stronger acid

Ethanoic acid is a weaker acid than H_3O^+, and ethanoate ($CH_3CO_2^-$) is a stronger base than H_2O. The equilibrium between an acid and a base on the one hand and their respective conjugate base and acid on the other can be viewed as a contest, where the goal is to gain a proton. A strong acid, with its great tendency to lose protons, has a weak conjugate base that has a low affinity for protons. Thus, as the tendency of an acid to lose a proton increases, the tendency of its conjugate base to accept a proton decreases. At equilibrium, the favored side of an acid–base reaction has the weaker acid and weaker base.

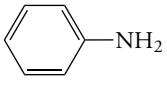
K_b and pK_b

We can turn the above arguments around and compare the strengths of weak bases, A^-, such as acetate, by the extent to which they can retrieve a proton from water. A base, A^-, removes a proton from water to form hydroxide ion and the conjugate acid, HA. The base dissociation constant, K_b, for the reaction is analogous to the acid dissociation constant, K_a.

$$A^- + H_2O \rightleftharpoons HA + OH^-$$

$$K_b = K_{eq}[H_2O] = \frac{[HA][OH^-]}{[A^-]}$$

Table 3.2
K_b and pK_b Values of Common Bases

Acid	K_b	pK_b
	4×10^{-10}	9.4
$CH_3CO_2^-$	5×10^{-10}	9.3
$C{\equiv}N^-$	1.6×10^{-5}	4.8
NH_3	1.7×10^{-5}	4.8
CH_3NH_2	4.3×10^{-4}	3.4
CH_3O^-	3×10^{-16}	–1.5

Again by analogy with the strengths of weak acids, the strengths of weak bases, K_b, are conveniently expressed as pK_b values, where p$K_b = -\log K_b$. The pK_b values increase with decreasing basicity. Table 3.2 lists the K_b and pK_b values of some common organic bases. A strong base has a large K_b (small pK_b). Therefore, in an aqueous basic solution, hydroxide ion, a strong base, reacts with a weak acid such as ethanoic acid to give a solution that contains the weaker base, ethanoate anion as the major product.

$$CH_3CO_2H + OH^- \underset{}{\overset{K_b}{\rightleftharpoons}} CH_3CO_2^- + H_2O$$

strong base — weak base

$$A^- + H_2O \rightleftharpoons HA + OH^-$$

$$K_b = K_{eq}[H_2O] = \frac{[HA][OH^-]}{[A^-]}$$

Weak bases do not have a large attraction for the protons of an acid. A small fraction of the molecules of a weak base are protonated at equilibrium. For example, methylamine is a weak base. When it dissolves in water, a low concentration of methylammonium ions forms.

$$CH_3NH_2 + H_2O \underset{}{\overset{K_b}{\rightleftharpoons}} CH_3NH_3^+ + OH^-$$

weak base — strong base

The strengths of bases such as amines are often listed using the pK_a values of their conjugate acids. Since a strong base (large K_b and small pK_b) holds a proton more tightly, its corresponding conjugate acid is a weak acid (small K_a and large pK_a). This relationship between the pK_b and pK_a for a conjugate acid–base pair is given by the following relationships.

$$K_a \times K_b = 1 \times 10^{-14} \text{ and } pK_a + pK_b = 14$$

Table 3.3 list the pK_a values of the ammonium ions of some simple amines.

Table 3.3
K_b and K_a, and pK_a and pK_b Values of Amines and Ammonium Ions

Compound	K_b	K_a	pK_a	pK_b
NH_3	1.8×10^{-5}	5.5×10^{-10}	4.74	9.26
CH_3NH_2	4.6×10^{-4}	2.2×10^{-11}	3.34	10.7
$CH_3CH_2NH_2$	4.8×10^{-4}	2.1×10^{-11}	3.20	10.8
CH_3NHCH_3	4.7×10^{-4}	2.1×10^{-11}	3.20	10.8

Applying pK_a Values in Organic Acid–Base Reactions

Many organic reactions occur by one or more steps in which a proton is added to a basic site or is removed from an acidic site. It turns out that we can predict the position of an acid–base reaction from the pK_a values of the two acids that participate in the proton transfer steps. The equilibrium constant for the general equilibrium between two acids, HA and HB, is given by the ratio of the acid dissociation constants, K_{HA}/K_{HB}.

$$HA + B^- \rightleftharpoons A^- + HB$$

$$K_{eq} = \frac{K_{HA}}{K_{HB}}$$

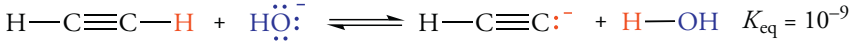
If we take the negative logarithm of K_{eq}, we obtain the following equation:

$$pK_{eq} = pK_{HA} - pK_{HB}$$

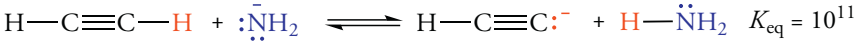
The reaction of acetylene, a weak acid, pK_a 25, with a base B^- to give the acetylide anion illustrates this relationship.



To convert acetylene to its conjugate base, we need a stronger base than the conjugate base of acetylene. In other words, the acid HB must be a weaker *acid* than acetylene. Because the pK_a of acetylene is 25, the conjugate acid of B^- must have $pK_a > 25$. Can we use OH^- as the base? The pK_a of water, the conjugate acid of OH^-, is 15.7. Thus, hydroxide is not strong enough to remove a proton from acetylene with an equilibrium constant greater than 1.0. In fact, the equilibrium constant is only about 10^{-9}.



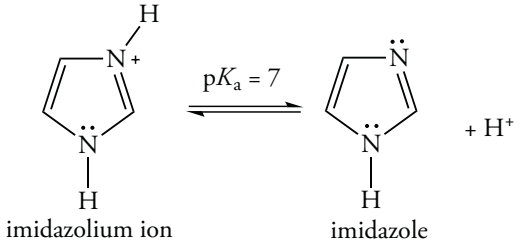
Now let's consider using the amide ion (NH_2^-), the conjugate base of ammonia ($pK_a = 36$). Amide ion is more basic than the conjugate base of acetylene. The calculated equilibrium constant is 10^{11}. Thus, amide ion reacts with acetylene to give a quantitative yield of the desired anion.



We will use this process to determine the position of equilibrium reactions throughout our study of organic chemistry. We will always know in advance that the position of the equilibrium is on the side of the weaker acid.

Problem 3.9

The amino acid histidine contains an imidazole ring. The pK_a of the imidazolium ion, the conjugate acid of imidazole, is 7.0. What is the K_a of the imidazolium ion? What fraction of the conjugate acid exists as imidazole at pH = 7?



imidazolium ion imidazole

Problem 3.10

The pK_b values for diethylamine $(CH_3)_2NH$ and triethylamine $(CH_3)_3N$ are 3.51 and 2.99, respectively. Which compound is the stronger base? What are the pK_a values for the related ammonium ions? Which ammonium ion is the stronger acid?

Problem 3.11

Given the pK_a values of acetylene and amide anion we discussed earlier, predict the position of the equilibrium for the following reaction; is the equilibrium constant greater or less than 1.0?

$$CH_3{-}C{\equiv}C{:}^- + CH_3CH_2NH_2 \rightleftharpoons CH_3{-}C{\equiv}C{-}H + CH_3CH_2NH{:}^-$$

Problem 3.12

Given the pK_a values for the ions shown below, calculate the equilibrium constant for the following reaction.

$$\underset{pK_a\ 9.8}{(CH_3)_3NH^+} + NH_3 \rightleftharpoons (CH_3)_3NH_2 + \underset{pK_a\ 9.4}{NH_4^+}$$

Sample Solution

The reaction as written produces a stronger acid (lower pK_a) than the reactant. Acid–base reactions proceed in the direction to give the weaker acid and weaker conjugate base. Thus, we know that the above reaction is not favorable and must have $K_{eq} < 1$. Designating $(CH_3)_3NH^+$ as HA and NH_4^+ as HB, we can substitute in the following equation and calculate the equilibrium constant.

$$pK_{eq} = pK_{HA} - pK_{HB} = 9.8 - 9.4 = 0.4$$

For $-\log K_a = 0.4$, we obtain, $K_a = 0.4$.

It is often easier to understand calculations of this type by using equilibrium constants rather than pK_a values. First convert the pK_a values into their corresponding equilibrium constants, which are 2.5×10^{-10} and 6.85×10^{-10} for the trimethylammonium ion and ammonium ion, respectively. Then, substitute the equilibrium constants into the following expression.

$$K_{eq} = \frac{K_{HA}}{K_{HB}} = \frac{2.5 \times 10^{-10}}{6.8 \times 10^{-10}} = 0.4$$

3.4 EFFECT OF STRUCTURE ON ACIDITY

Because acid–base reactions play such a prominent role in organic chemistry, we will now focus upon the effect of structure on acidity and basicity. We will consider four properties of the acid and its conjugate base.

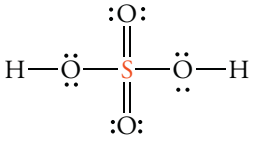
1. Periodic trends.
2. Resonance effects.
3. Inductive effects.
4. Hybridization effects.

Effect of Periodic Trends on Acidity and Basicity

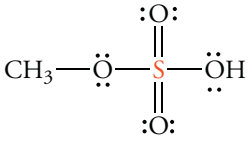
The strength of an acid, HA, depends in part upon the strength of the H—A bond. The bond strength decreases as we move down a column of the periodic table. This trend results from progressively less effective overlap of higher energy atomic orbitals with the hydrogen 1s orbital. Because bond strength is inversely related to the acidity, the acidity of the halogen acids increases in the order HF < HCl < HBr < HI. For the same reasons, H_2O is a weaker acid than H_2S.

Acidity increases from left to right in a given row of the periodic table. The order of increasing acidity is CH_4 < NH_3 < H_2O < HF. This trend reflects the stabilization of the negative charge, which varies directly with the electronegativity of the atom of the conjugate base. That is, the order of increasing strength of conjugate bases is F^- < OH^- < NH_2^- < CH_3^-.

Many organic compounds are structurally related to inorganic acids and bases. As a consequence, we can predict the acid–base properties by comparing an organic acid with its inorganic counterpart. We know that sulfuric acid is a strong acid. Thus, we expect methanesulfonic acid to be a strong acid because it has an O—H bond that is structurally similar to the O—H bond in sulfuric acid.

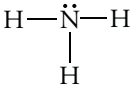


sulfuric acid,
a strong acid

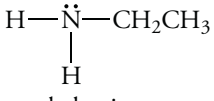


methanesulfonic acid,
a strong acid

We can make similar comparisons with bases. For example, we know that ammonia is a weak base. Therefore, we expect ethylamine ($CH_3CH_2NH_2$), structurally related to ammonia, also to be a weak base. Both compounds have an unshared pair of electrons, and our assumption is correct.



ammonia
pK_b 4.74
(weak base)



ethylamine
pK_b 3.25
(weak base)

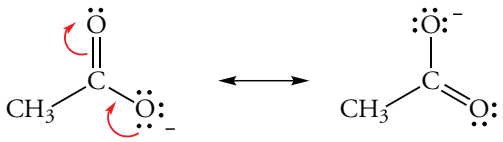
Effect of Resonance on Acidity and Basicity

A reaction in which relatively unstable reactants are converted to more stable products has a large equilibrium constant. We can apply this general idea to acidity. When an electrically neutral acid ionizes, a conjugate base having a negative charge is produced. Stabilizing the negative charge in the conjugate base increases K_a. One way the conjugate base is stabilized is by delocalization of the negative charge over two or more atoms. This effect is called *resonance stabilization.* When the conjugate base of an acid is resonance stabilized, acid strength increases substantially. For example, both methanol and ethanoic acid ionize to form conjugate bases with a negative charge on oxygen. However, ethanoic acid is **ten billion** (10^{10}) times more acidic than methanol.

$$CH_3OH + H_2O \rightleftharpoons CH_3O^- + H_3O^+ \quad K_a = 10^{-16}$$

$$CH_3CO_2H + H_2O \rightleftharpoons CH_3CO_2^- + H_3O^+ \quad K_a = 1.8 \times 10^{-5}$$

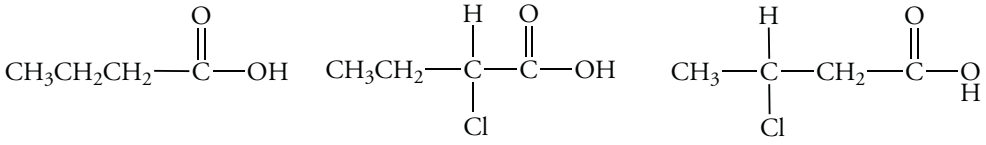
Ethanoic acid is more acidic because the conjugate base, ethanoate ion, is resonance stabilized. The negative charge of the ion is distributed equally over two oxygen atoms. In contrast, the conjugate base of methanol, methoxide ion (CH_3O^-), has its negative charge concentrated on a single oxygen atom.



Inductive Effects

The acidity of organic compounds also depends in part upon the presence of atoms or functional groups that can polarize neighboring bonds in the acid and the conjugate base. These groups, which can be electron withdrawing or electron donating, act through bonds by an *inductive effect*.

Any atom or group of atoms in an organic molecule that withdraws electron density from the bond between hydrogen and another atom—such as carbon, oxygen, or nitrogen—increases its acidity by an inductive effect. However, the inductive effect decreases with increasing distance between the electron-withdrawing group and the acidic site. For example, the acidity of butanoic acid increases when a chlorine atom replaces a hydrogen atom in 2-chlorobutanoic acid, but the effect is less in 3-chlorobutanoic acid since the chlorine atom is farther away from the acidic hydrogen of the carboxylic acid.



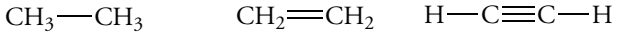
butanoic acid
pK_a = 4.82

2-chlorobutanoic acid
pK_a = 2.86

3-chlorobutanoic acid
pK_a = 4.02

Effect of Hybridization on Acidity

In many organic compounds, the ionizable, acidic hydrogen atom is attached to an electronegative atom such as oxygen. However, some organic compounds have slightly acidic hydrogen atoms bonded to a carbon atom. These "carbon acids" are usually quite weak acids. Therefore, a very strong base is required to remove a proton from them.



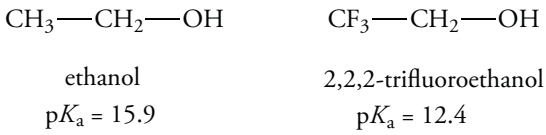
ethane
$K_a = 10^{-49}$

ethene
$K_a = 10^{-44}$

ethyne
$K_a = 10^{-25}$

The acid ionization constants, K_a values, of hydrocarbons are extremely small, but there are substantial differences between various classes of hydrocarbons. The acidity of hydrocarbons is related to the hybridization of the carbon atom of the C—H bond. The acidity, K_a, of a carbon acid increases in the order $sp^3 < sp^2 < sp$. The order of acidities parallels the contribution of the lower energy of the 2s orbital to the hybrid orbitals in the σ bond. The average distance of hybrid orbitals from the nucleus depends on the percent contribution of the s and p orbitals. For an sp^3 hybrid orbital, the contribution of the 2s orbital is 25% because one 2s and three 2p orbitals contribute to the four hybrid orbitals. The contribution of the 2s orbital is 33% for an sp^2 orbital and 50% for an sp hybrid orbital. Because an sp hybrid orbital has more s character than an sp^2 or sp^3 orbital, its electrons are located closer to the nucleus. Because the strength of an acid depends upon the stability of the conjugate base, a carbanion in which the negative charge is on an sp-hybridized carbon atom is more stable than a carbanion of an sp^2-hybridized or sp^3-hybridized carbon atom.

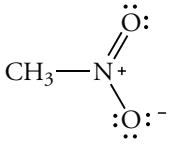
Problem 3.13 The pK_a values of ethanol and 2,2,2-trifluoroethanol are 15.9 and 12.4, respectively. What is responsible for this difference?



ethanol
pK_a = 15.9

2,2,2-trifluoroethanol
pK_a = 12.4

Problem 3.14
The pK_a values of nitromethane and methane are 10.2 and approximately 49, respectively. What is responsible for this difference?



nitromethane

Problem 3.15
Based on periodic trends and structurally similar compounds, predict which is the stronger acid, CH_3OH or CH_3SH.

3.5 STANDARD FREE ENERGY CHANGES IN CHEMICAL REACTIONS

In principle, all chemical reactions are reversible, and given sufficient time an equilibrium is established. At equilibrium, the forward reaction and reverse reaction occur at equal rates. The extent to which reactants are converted to products is expressed by an equilibrium constant. This is true for every chemical reaction, not just the acid–base reactions we described above.

The value of the equilibrium constant for a reaction depends on the relative energies of the reactants and products. The change in energy that occurs when a reaction goes from reactants to equilibrium between reactants and products is the "force" that "drives" a reaction to equilibrium This driving force, called the *free energy,* is partitioned between the potential energy change, the *enthalpy*, and a change in the molecular order, or *entropy*, of the system.

The Standard Free Energy Change and the Equilibrium Constant

The standard Gibbs free energy change ($\Delta G°$) is the energy change in a chemical reaction. The superscript symbol (°) indicates that the reaction occurs at 25 °C and 1 atm pressure. The Gibbs free energy of formation ($\Delta G°_f$) of a compound is the free energy change for the formation of the compound from the elements in their standard state at 25 °C (298 K). The change in the Gibbs free energy for a reaction ($\Delta G°_{rxn}$) is the difference between the free energy of the products and the free energy of the reactants.

$$\Delta G°_{rxn} = \Delta G°_f \text{ (products)} - \Delta G°_f \text{ (reactants)}$$

When the reactants have higher free energy than the products ($\Delta G°_{rxn} < 0$), the reaction is *exergonic*. That is, the reaction releases energy. *Ergon* is the Greek word for work, so the free energy change is a measure of the ability of a chemical reaction to do work. A reaction in which the reactants have lower free energy than the products ($\Delta G°_{rxn} > 0$) is *endergonic*.

The following equation describes the relation between the standard free energy change, $\Delta G°_{rxn}$, and the equilibrium constant.

$$\Delta G°_{rxn} = -2.303RT\log K_{eq}$$

R = 8.314 kJ kelvin^{-1} mole^{-1} (1.987 cal kelvin^{-1} mole^{-1})
T = absolute temperature (kelvin)

When the free energy of the products is less than the free energy of the reactants, $\Delta G°_{rxn} < 0$ and

$K_{eq} > 1$. Some organic reactions have very large equilibrium constants, large negative values of $\Delta G°_{rxn}$, and are quantitative. However, many reactions have much smaller equilibrium constants and correspondingly smaller $\Delta G°_{rxn}$ values. For example, the esterification reaction of ethanoic acid and ethanol has an equilibrium constant of 4 and $\Delta G°_{rxn} = -1.7$ kJ mole^{-1} at 298 K.

Table 3.4 provides some values of K_{eq} and the corresponding $\Delta G°_{rxn}$ values as well as the percentage of product at equilibrium for a general reaction in which reactant X is converted to product Y. As $\Delta G°_{rxn}$ becomes more negative, there is a stronger driving force for the reaction. For $\Delta G°_{rxn}$ values more negative than –17 kJ mole^{-1} (–4.1 kcal mole^{-1}), the reaction is quantitative for all practical purposes because less than 0.01% of the reactant remains at equilibrium.

Table 3.4
Relation Between $\Delta G°$ (kJ mole^{-1}) and K_{eq} at 25 °C

$$X \rightleftharpoons Y$$

$\Delta G°$	K_{eq}	% Y	$\Delta G°$	K_{eq}	% Y
0.00	1.0	50	–4.3	5.67	85
–0.50	1.22	55	–5.45	9.00	90
–1.0	1.50	60	–7.30	19.0	95
–1.5	1.86	65	–9.65	49.0	98
–2.1	2.33	70	–11	99	99
–2.7	3.00	75	–17	999.9	99.9
–3.4	4.00	80	–22	9999.9	99.99

Problem 3.16

Calculate $\Delta G°_{rxn}$ for the following substitution reaction using the $\Delta G°_f$ values given below for the reactants and products.

$$CH_3—Cl(aq) + OH^-(aq) \longrightarrow CH_3—OH(aq) + Cl^-(aq)$$

$\Delta G°_f$ (kJ mole^{-1})	– 51.4	157.2	–175.1	–131.2

Sample Solution

Use the sum of the $\Delta G°_f$ values for the reactants and products and the following relationship.

$$\Delta G°_{rxn} = \Delta G°_f \text{ (products)} - \Delta G°_f \text{ (reactants)}$$

$$\Delta G°_{rxn} = \{ [(-175.1 - 131.2)] - [(-157.2 - 51 .4)] \} \text{ kJ mole}^{-1} = -97.7 \text{ kJ mole}^{-1}$$

The sum of the $\Delta G°_f$ values for the products is more negative than the sum of the $\Delta G°_f$ values for the reactants. Thus, the reaction has $\Delta G°_{rxn} < 0$.

Problem 3.17

The $\Delta G°_{rxn}$ for the addition reaction of HBr to ethene at 25 °C is –50 kJ mole^{-1}. Calculate K_{eq} at this temperature.

$$\underset{\text{ethene}}{CH_2=CH_2} + HBr \longrightarrow \underset{\text{bromoethane}}{CH_3—CH_2—Br}$$

Problem 3.18

Using the following ΔG°_{rxn} values for the addition of HBr to propene to give two possible bromoalkanes, determine which product is the more stable.

$$\underset{\text{propene}}{CH_3—CH=CH_2} + HBr \longrightarrow \underset{\text{1-bromopropane}}{CH_3—CH_2—CH_2—Br} \qquad \Delta G^\circ_{rxn} = -31.9 \text{ kJ mole}^{-1}$$

$$\underset{\text{propene}}{CH_3—CH=CH_2} + HBr \longrightarrow \underset{\text{2-bromopropane}}{CH_3—CHBr—CH_3} \qquad \Delta G^\circ_{rxn} = -36.6 \text{ kJ mole}^{-1}$$

3.6 ENTHALPY CHANGES IN CHEMICAL REACTIONS

The first law of thermodynamics states that energy is conserved in all physical and chemical processes, including, of course, chemical reactions. We can represent this fact by the following general reaction.

$$m\,A + n\,B \rightleftharpoons p\,X + q\,Y + \text{energy}$$

Because energy is conserved, the amount of energy flowing out of the reaction vessel in which the reaction takes place into the surroundings in the forward reaction exactly equals the amount of energy flowing from the surroundings into the reaction vessel in the reverse reaction.

The heat energy released or absorbed in a reaction measured at constant pressure is the **enthalpy change**, ΔH_{rxn}. If heat flows out of the reaction into the surroundings, the reaction is *exothermic*. For an exothermic reaction, $\Delta H^\circ_{rxn} < 0$. If heat flows into of the reaction from the surroundings, the reaction is *endothermic*. For an endothermic reaction, $\Delta H^\circ_{rxn} > 0$.

Standard conditions refer to measurements made at 298 K and 1 atm. Enthalpy changes for reactions carried out at standard conditions are therefore standard enthalpy changes, ΔH°. The following conventions are used.

1. The standard enthalpy of formation (ΔH°_f) of a compound is the enthalpy change when the compound is formed in its standard state from the elements in their standard states. The superscript (°) indicates that the reaction occurs under standard conditions.
2. The standard state of any element or compound is its most stable form at 298 K and 1 atm pressure.

The standard enthalpy change for the general reaction we showed above is given by the following equation

$$\Delta H^\circ_{rxn} = [p\Delta H^\circ_f(X) + q\Delta H^\circ_f(Y)] - [m\Delta H^\circ_f(A) + n\Delta H^\circ_f(B)]$$

We can interpret the enthalpy change for a reaction in terms of the structure of the reactants and products. All substances contain stored chemical energy in their bonds. When a chemical bond forms, energy is released; the process is exothermic. Conversely, breaking a chemical bond requires energy; the process in endothermic. Therefore, the energy change for a chemical reaction reflects the differences in the energies of the bonds that are broken and formed. When reactants are converted to products, the stored chemical energies are not the same because the number and types of bonds are altered. If the products of a reaction contain less stored energy than the reactants, the net difference is released as heat energy, ΔH°_{rxn}. The magnitude of the standard enthalpy change for a reaction does not tell us anything about the mechanism by which the reaction occurs. It depends only on the difference in enthalpy between the products and reactants.

3. The standard enthalpy of formation of any element in its standard state is defined as 0 kJ mole^{-1}.

The standard enthalpy change for the general reaction we showed above is given by the following equation

$$\Delta H^\circ_{rxn} = [p\Delta H^\circ_f(X) + q\Delta H^\circ_f(Y)] - [m\Delta H^\circ_f(A) + n\Delta H^\circ_f(B)]$$

We can interpret the enthalpy change for a reaction in terms of the structure of the reactants and products. All substances contain stored chemical energy in their bonds. When a chemical bond forms, energy is released; the process is exothermic. Conversely, breaking a chemical bond requires

energy; the process in endothermic. Therefore, the energy change for a chemical reaction reflects the differences in the energies of the bonds that are broken and formed. When reactants are converted to products, the stored chemical energies are not the same because the number and types of bonds are altered. If the products of a reaction contain less stored energy than the reactants, the net difference is released as heat energy, ΔH°_{rxn}. The magnitude of the standard enthalpy change for a reaction does not tell us anything about the mechanism by which the reaction occurs. It depends only on the difference in enthalpy between the products and reactants.

3.7 BOND DISSOCIATION ENERGIES

The energy required to break a chemical bond of a molecule in the gas phase into two fragments, each having one half of the electrons present in the original bond, is called the bond dissociation energy. The general reaction for breaking a single bond is shown below.

$$X{:}Y \longrightarrow X\cdot + Y\cdot \qquad \Delta H^\circ_{rxn} > 0$$

The energy released when a given bond forms exactly equals the energy required to break it. The energy changes for breaking and forming the covalent bond in H—H are shown below.

$$H\cdot + H\cdot \longrightarrow H{:}H \qquad \Delta H^\circ_{rxn} = -434 \text{ kJ mol}^{-1}$$

$$H{:}H \longrightarrow H\cdot + H\cdot \qquad \Delta H^\circ_{rxn} = +434 \text{ kJ mol}^{-1}$$

The standard enthalpy change for bond dissociation is usually given by the symbol DH°. A list of some bond dissociation energies is given in Table 3.5. The bond cleaved is indicated by a dash. For CH_3—H, the DH° value for cleaving the carbon–hydrogen bond refers to the following process.

$$CH_3\text{—}H \longrightarrow CH_3\cdot + H\cdot \qquad DH^\circ = +438 \text{ kJ mole}^{-1}$$

Table 3.5
Bond Dissociation Energies of Representative Compounds

Bond	*DH° (kJ mol^{-1})*	*Bond*	*DH° (kJ mol^{-1})*
H—H	435	CH_3—H	438
F—F	159	CH_3—F	451
Cl—Cl	242	CH_3—Cl	349
Br—Br	192	CH_3—Br	293
I—I	150	CH_3—I	234
		CH_3—OH	380
H—F	586		
H—Cl	431	CH_3CH_2—H	422
H—I	366	CH_2=CH—H	452
H—OH	297	HC≡C—H	523
		CH_3—CH_3	368
		CH_2=CH_2	610
		HC≡CH	830

Effect of Electronegativity on Bond Energies

The bond dissociation energy increases as the difference in the electronegativities of the bonded atoms increases. For example, the bond dissociation energies of carbon–halogen bonds increase in the order C–I < C–Br < C–Cl < C–F. The polarities of the carbon–halogen bond are in the same order. When a carbon–halogen bond breaks so that one electron remains with each fragment, a process called *homolytic bond cleavage*, the electropositive element (carbon) must "recover" its electron from the electronegative element. As the electronegativity of the atom "losing" the electron increases, the bond dissociation energy increases.

Effect of Hybridization on Bond Energies

The energy of a C—H bond increases in the order $sp^3 < sp^2 < sp$, as we can see from the bond energies of ethane, ethene, and ethyne given in Table 3.3. We have already discussed the reasons for this trend. The average distance of the electrons in the hybrid orbitals from the nucleus depends on the percent contributions of the s and p orbitals. The contribution of the 2s orbital is 25% in an sp^3 orbital and rises to 50% in an sp hybrid orbital. Because the sp^3 hybrid orbital has the smallest s character, the electrons in the orbital are farther from the nucleus and the bond formed with this orbital is the weakest. Also, the electronegativity of carbon increases in the order $sp^3 < sp^2 < sp$, so as we noted in the above paragraph, increasing the electronegativity difference between bonded atoms increases bond strength.

Effect of Multiple Bonds on Bond Energies

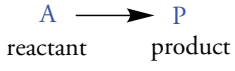
The bond energy between common atoms increases in the order single < double < triple. This trend partly reflects the effect of the closer approach of the σ bonding electrons to the nucleus as the percent s character in the hybrid orbitals increases. However, the substantial increase in the carbon–carbon bond strength is largely a consequence of the increased number of bonds joining the carbon atoms.

3.8 INTRODUCTION TO REACTION MECHANISMS

A reaction mechanism is a step-by-step pathway that accounts for the structural change and its associated energy change at every stage of the reaction. Such precise detail has been achieved for very few reactions. However, we can often make reasonable guesses about the mechanisms of chemical reactions that are similar to other well-studied reactions.

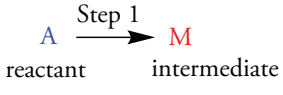
Concerted and Multistep Reactions

In some reactions, bond breaking and bond formation occur simultaneously in a single step. Such processes are **concerted** reactions. The description of such a reaction mechanism resembles that of an ordinary chemical equation; however, we will see later that a considerable amount of complexity often underlies the apparently simple nature of a concerted reaction.

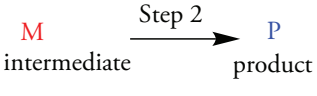


Many reactions occur in a series of steps. For example, the conversion of reactant A into product X may occur in two steps. An intermediate, which is not shown in the balanced chemical equation, forms and then reacts.

Step 1. An intermediate forms.



Step 2. The intermediate is converted to product.



In a multistep reaction, the individual steps usually have different rates. The overall rate of conversion of reactant into product can occur no faster than the slowest individual step, called the *rate-determining step*.

Types of Bond Cleavage

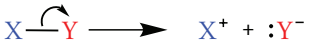
Bonds can break in a variety of ways. When a bond is broken so that one electron remains with each of the two fragments, the process is called **homolytic** cleavage. The fragments that contain unpaired electrons are **radicals** (sometimes called "free" radicals).



general reaction for homolytic bond cleavage

Homolytic cleavage of a bond to carbon produces a carbon radical that is highly reactive because it has only seven electrons in its valence shell.

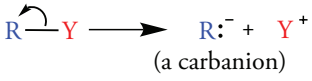
Heterolytic cleavage of a bond produces a cation and an anion.



general reaction for heterolytic bond cleavage

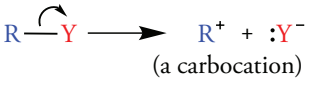
Heterolytic cleavage of a bond to carbon can produce two different carbon species. In the general reaction shown below, Y represents an atom or a small number of atoms and the symbol "R" represents the remainder of the carbon-containing structure.

1. If the bond breaks so that its electrons remain with the carbon atom, a carbanion results. A carbanion has an octet of electrons. It can act as a Lewis base or as a "nucleus loving" species called a **nucleophile.**



(a carbanion)

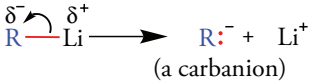
2. If the bond breaks so that its electrons are lost by the carbon atom, a positively charged **carbocation** results. The carbocation has a sextet of electrons and is an electron-deficient species. It can act as a Lewis acid or as an "electron-loving" species called an **electrophile.**



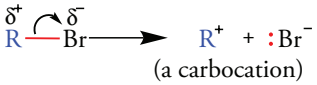
(a carbocation)

Whether heterolytic cleavage of a C—Y bond produces a carbanion or a carbocation depends on the electronegativity of Y. There are two possibilities.

1. If Y is a less electronegative element, such as a metal, the bond tends to break heterolytically to form a carbanion.
2. If Y is a nonelectronegative element other than carbon, a halogen atom, for example, the bond has the opposite polarity and tends to break heterolytically to form a carbocation.



(a carbanion)



(a carbocation)

3.9 STRUCTURES AND STABILITIES OF CARBON RADICALS, CARBOCATIONS, AND CARBANIONS

The intermediates produced by cleavage of bonds to carbon give reactive intermediates with only three bonds to carbon: carbocations, carbon radicals, and carbanions. These trivalent species are all highly reactive, and they rapidly react to give more stable, tetravalent carbons.

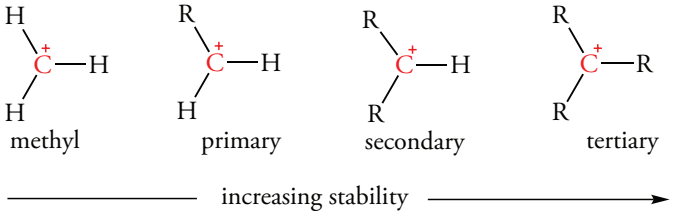
Carbocations

The positively charged carbon atom of a carbocation has only six electrons in its outer shell. However, the formal charge of +1 on the carbocation is shared to some extent by the atoms bonded to it. This distribution of charge over several atoms can result from an inductive effect, in which electron density flows, as if through a wire, through the sigma bonding network. In some cases, the positive charge of the cationic center is delocalized over two or more atoms by a resonance effect. These are exactly the same effects we considered in our discussion of acidity and basicity (Section 3.4). We will focus upon inductive effects in this section. We will discuss the resonance stabilization of carbocations later.

The inductive stabilization of a carbocation occurs when the positively charged carbon atom withdraws electron density from the groups attached to it. Thus, an sp^3-hybridized carbon, such as

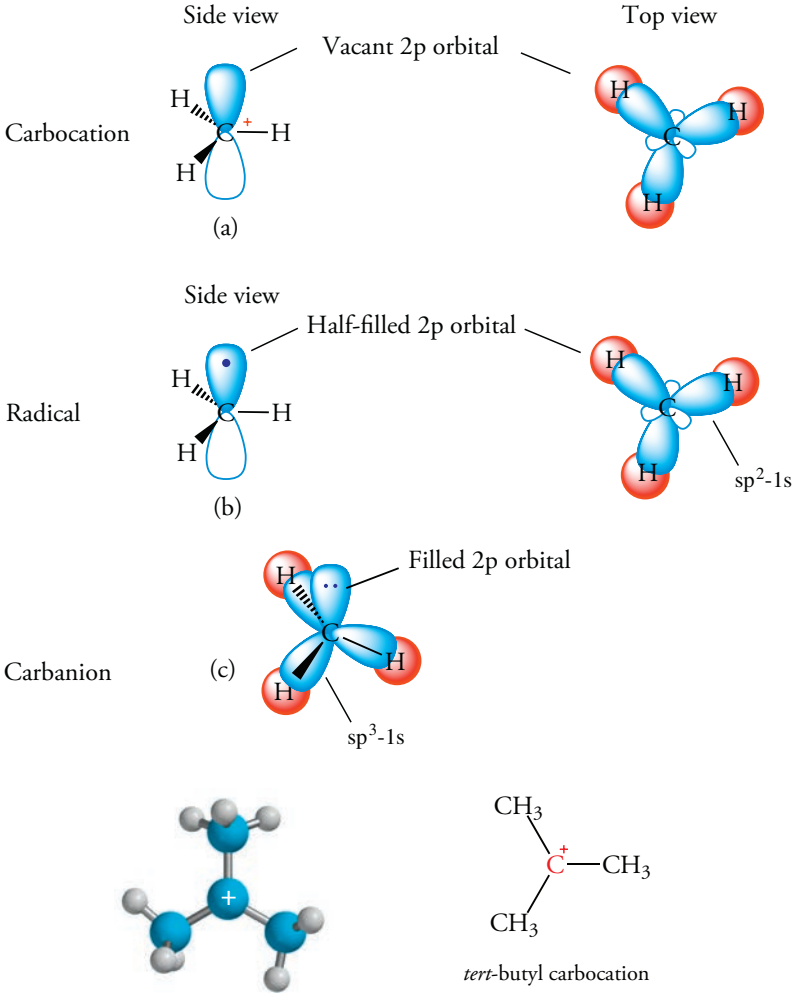
a methyl ($-CH_3$) group or other alkyl groups, can donate electron density through the σ bond to the positively charged carbon atom. *Alkyl groups stabilize a carbocation by donating electron density to it.*

Reactive intermediates are classified according to the number of carbon atoms directly bonded to the trivalent carbon. A carbon atom that is bonded to one other carbon is a **primary carbon**, if it is bonded to two carbon atoms it is a **secondary carbon,** and if it is bonded to three other carbon atoms it is a **tertiary carbon**. The abbreviations for these types of carbons are 1°, 2°, and 3°, respectively. The stability of a carbocation increases as the number of carbon atoms attached to the positive center increases, that is, in the order CH_3^+ < 1° C^+ < 2° C^+ < 3° C^+, as shown below.



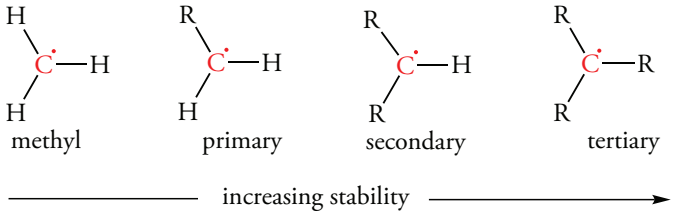
The positively charged carbon atom in a carbocation is trigonal planar and sp^2 hybridized. It has a vacant 2p orbital that is orthogonal to the plane that contains the three directly bonded atoms, as shown in Figure 3.1. The vacant 2p orbital is a potential electron acceptor, and carbocations are potent Lewis acids (which, we recall, are electron-pair acceptors).

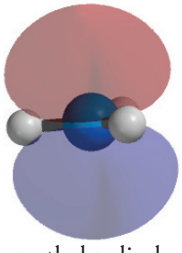
Figure 3.1 Structures of Reactive Carbon Intermediates



Carbon Radicals

Like carbocations, radicals are electron-deficient species. A carbon radical has seven electrons in the valence shell in contrast to six electrons for carbocations. Like carbocations, carbon radicals are stabilized by the inductive effect of groups bonded to the radical center. Because radicals are not as electron deficient as carbocations, the differences in the stability of radicals are smaller than for carbocations. The order of carbon radical stability parallels the order of carbocation stability. Like a carbocation, a carbon radical has a trivalent, sp^2-hybridized carbon atom. The methyl radical has a planar structure with H—C—H bond angles of 120°. The trivalent carbon atom also has an unhybridized 2p orbital that is perpendicular to the plane of the C–H bonds. It contains the unpaired electron (Figure 3.1b).



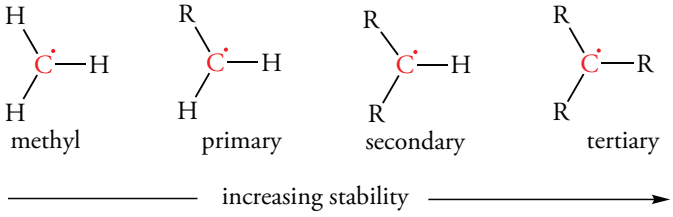

methyl radical

Methyl Radical

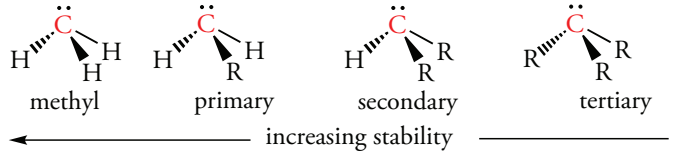
In a methyl radical (or any other), the central carbon is sp^2 hybridized, and the single, unpaired electron is in a 2p orbital orthogonal to the plane that contains the hydrogen atoms.

Carbanions

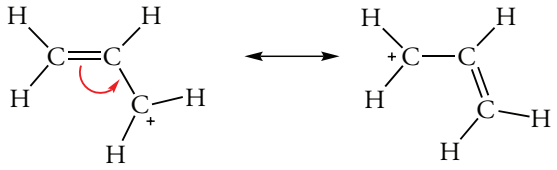
A carbanion has a negatively charged, trivalent carbon atom that has eight electrons in its valence shell. Thus, a carbanion is not electron deficient. Carbanions are strong Lewis bases (electron pair donors) with the same electronic structures as amines. In contrast to carbocations and carbon radicals, a carbanion is destabilized by electron-donating groups bonded to the anionic center because the center already has an octet of electrons. Thus, the order of stability of carbanions is opposite that of carbocations and radicals. Since we have seen that alkyl groups are electron releasing with respect to hydrogen, we can generalize and say that electron-releasing groups stabilize carbocations and destabilize carbanions.



The negatively charged carbon atom of a carbanion is sp^3 hybridized. Like the other sp^3-hybridized species we have considered, the four hybrid orbitals are directed toward the corners of a tetrahedron. One of the sp^3 hybrid orbitals contains an unshared pair of electrons (Figure 3.1c). As a result, the three groups that are bonded to the carbanionic center form a pyramidal species.



Carbocations, radicals, and carbanions can be stabilized by resonance. For example, if a carbon atom with a π bond is bonded to the trivalent carbon atom of the intermediate, the empty orbital of that carbon atom can interact with the 2p orbitals of the π bond. The result is a resonance-stabilized intermediate. The resonance forms of a resonance-stabilized allylic carbocation intermediate are shown below.

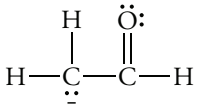


Problem 3.19

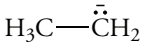
Trichloromethane ($CHCl_3$) is a stronger acid (pK_a = 25) than methane (pK_a = 49). Explain this difference based on the stability of the respective conjugate bases.

Problem 3.20

The conjugate base derived from ethanal (acetaldehyde) is more stable than the conjugate base of ethane. Explain why.



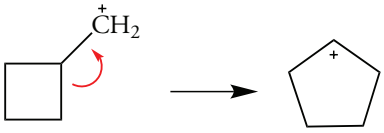
conjugate base of ethanal



conjugate base of ethane

Problem 3.21

Explain whether you expect the following carbocation rearrangement to be favorable based on the stabilities of the reactant and product. Is the reaction spontaneous?



3.10 FACTORS THAT INFLUENCE REACTION RATES

A chemical reaction rate is a change in the concentration of the reactant or product per unit time. Concentration is usually expressed as molarity. Time is measured in seconds or minutes. In this text, we will only consider changes in reaction rates that result from changes in the structures of a series of related compounds. That is, we will only be interested in *relative rates.* And, relative rates of reaction are compared by examining *rate constants*. The rate at which a given compound reacts is called its *reactivity*.

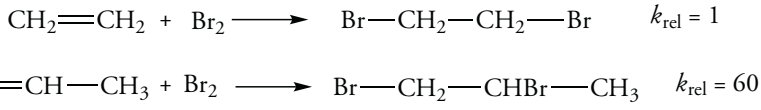
Four major factors affect the rate of a reaction, and hence the rate constant for the reaction.

1. The structure of the reactants.
2. The concentration of reactants.
3. Temperature.
4. The presence of catalysts.

We will briefly consider each of these factors to prepare for more detailed discussions in later chapters.

The Effect of Structure on Reactivity

The structure of a reactant is the most important feature controlling the rate of a chemical reaction. For example, the addition reaction of ethylene (C_2H_4) with Br_2 occurs at a rate that is 60 times slower than the rate for addition reaction of propene with Br_2.



Although the same number and types of bonds are broken and formed in these two reactions, the rates of the reaction differ considerably. These data tell us that the methyl group (CH_3—) of propene increases the reactivity of the π bond. This is a topic we'll consider in greater detail later.

The Effect of Reactant Concentration on Reaction Rates

The rate of a reaction depends in part on the concentration of the reactant because as the concentration of reactants is increased, the reactant molecules are more likely to collide. For a general reaction

$$aA + bB \longrightarrow \text{product}$$

where a and b are the coefficients of the balanced equation. The rate, or velocity, v, at which this reaction occurs is defined algebraically by the rate law for the reaction, as shown below.

$$v = k[A]^m[B]^n$$

where [A] and [B] are the molar concentrations of the reactants, and the exponents m and n represent the *order* of the reaction in reactants A and B, respectively. The proportionality constant k is the *rate constant.* Sometimes the values for the exponents in the rate expression are equal to the coefficients in the balanced equation ($a = m$ and $b = n$). However, we should not expect that equality. The coefficients in the balanced equation are a consequence of the stoichiometry of the reaction. The exponents in the rate equation depend on the experimental conditions and upon the mechanism of the reaction. We shall return to this point later.

The exponents in a rate equation are determined experimentally, and they describe the effect of concentration on the rate of reaction. For example, in the substitution reaction of CH_3Cl and OH^-, the reaction rate increases when the concentration of either reagent increases. If we double the concentration of OH^-, the reaction rate increases by a factor of two; doubling the concentration of CH_3Cl also doubles the reaction rate. This means that the exponents in the rate equation both equal 1. When this is so, we say that the reaction is **first order** with respect to OH^- and first order with respect to CH_3Cl and is **second order overall**. This relationship is expressed by the following equation.

$$CH_3Cl + OH^- \longrightarrow CH_3OH + Cl^-$$

$$\text{rate, } v = k\,[CH_3Cl][OH^-]$$

Not all substitution reactions are second order. Some reactions are first order in the reactant containing the leaving group—in the reaction shown above this is a chloride anion—but are not affected by the concentration of the nucleophile—hydroxide in the example discussed above. We will consider such reactions in Chapter 10.

The Effect of Temperature on Reaction Rates

The rates of chemical reactions increase with an increase in temperature because the reactant molecules collide more frequently and with greater energy. However, not every collision between reactant molecules results in the formation of products. In most collisions, the molecules simply bounce off each other. Collisions between molecules that result in a chemical reaction are called *effective collisions*. An effective collision in a chemical reaction occurs when the molecules have the proper orientation, and have at least a certain amount of energy, called the *activation energy* (E_a). Molecules that collide with less than the activation energy bounce apart without reacting. The fractions of molecules having the necessary activation energy at different temperatures are shown in Figure 3.2.

Increasing temperature increases the rate constant of a reaction because the average kinetic energy of the molecules is directly proportional to the absolute temperature (KE = 3/2 $k_b T$, where k_b is the Boltzmann constant). As the kinetic energy increases, so does the number of collisions. Also, and more importantly, increasing the temperature increases the fraction of molecules that have energy equal to or greater than the activation energy at higher temperatures (Figure 3.2). As a rule of thumb, the rates of organic reactions increase between twofold and fourfold for each increase of 10 °C. If the rate is doubled for a 10° C increase, a 30° C change in temperature would increase the reaction rate by approximately $2^3 = 8$ times. Table 3.6 shows the effect of temperature on the rate constant for the reaction of chloromethane with hydroxide ion, whose rate law we described above.

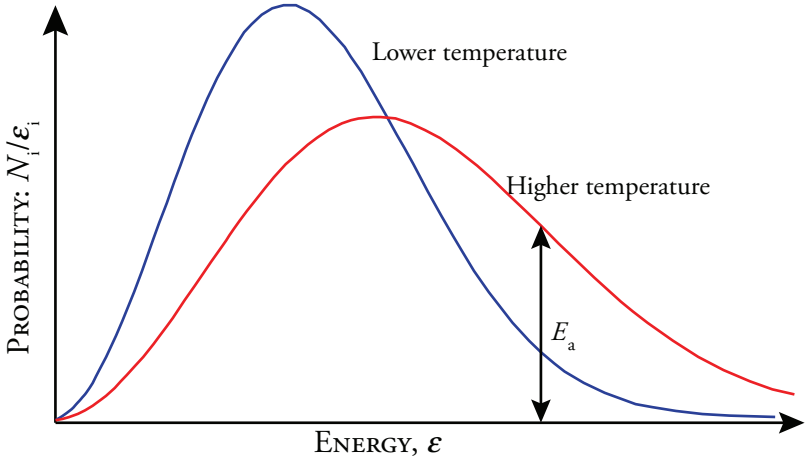


Figure 3.2 Distribution of Molecular Energies and Temperature
The Boltzmann distribution is a plot of the fraction of molecules having a given energy vs. energy. The fraction of molecules having activation energy, E_a, increases as the temperature increases, so the rate of the reaction increases as the temperature increases.

Table 3.6
Effect of Temperature on Rates of a Substitution Reaction[1]

Temperature °C	*Rate Constant (L mol^{-1} sec^{-1})*
35	2.6×10^{-5}
45	8.5×10^{-5}
55	2.6×10^{-4}
65	7.8×10^{-4}

1. The rate increases by approximately a factor of 3 for each 10 °C increase in temperature.

The Effect of Catalysts on Reaction Rates

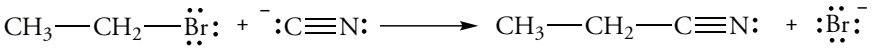
A catalyst is a substance that increases a reaction rate. Catalysts are usually required only in small amounts. The catalyst is not consumed, even though it does interact with the reactant during the reaction. Although a catalyst increases the rate of a reaction, it does not change the equilibrium constant for the reaction because it does not change the standard free energies of either the reactants or products.

The addition reaction of ethene and hydrogen occurs only at very high temperatures in the gas phase. However, in the presence of platinum suspended on the surface of carbon, a *heterogeneous reaction*—that is, a reaction that takes place in two different phases—occurs rapidly at room temperature. The catalyst is still active at the completion of the reaction, and it can be used to catalyze further reactions if more reactants are added.

$$CH_2{=}CH_2 + H_2 \xrightarrow{Pt\ /\ C} H{-}CH_2{-}CH_2{-}H$$

Problem 3.22
The rate constant for the nucleophilic substitution reaction of CH_3Br with OH^- is 6.6×10^{-4} L mole^{-1} s^{-1} at 310 K. Compare this value to the rate constant for the reaction of CH_3Cl with OH^- (Table 3.6). Which reaction is faster? What does this information indicate about the leaving group characteristics of Cl^- and Br^- ?

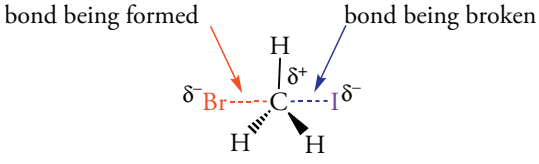
Problem 3.23
Bromoethane reacts with cyanide ion according to the following equation. When the concentration of the cyanide ion is doubled, the rate of the reaction is doubled. When the concentration of bromoethane is tripled, the rate of the reaction is tripled. What is the kinetic order with respect to each reactant? What is the overall kinetic order of the reaction? Write the rate equation for the reaction.

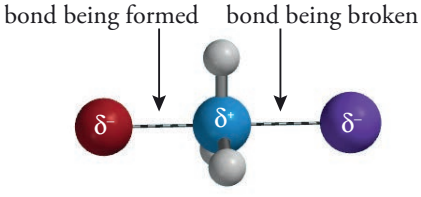


3.11 REACTION RATE THEORY

The activation energy for a given reaction depends on the types of bonds broken and formed in the reaction. During a reaction, the arrangement of the atoms changes as bonds are distorted and eventually broken, and new bonds form. When reactant atoms move close together, some repulsion results from the proximity of the electrons surrounding each atom. As bonding patterns change during a reaction, each specific arrangement of atoms has an associated energy. *The atomic arrangement whose structure has the maximum energy on the minimum energy pathway from reactants to products is the* ***transition state****.* We can think of the transition state as the highest point of a mountain pass, not the highest point of the mountain peak.

The transition state in the substitution reaction in which bromide ion replaces iodide in iodomethane has both the bromide and iodide ions partially bonded to the carbon atom.





Dotted lines are used to represent bonds that are partially broken or partially formed. The carbon–chlorine bond breaks on one side of the transition state structure while the carbon–oxygen bond forms on the other side. Transition state structures represent species that cannot be isolated because they are too short-lived and present in only infinitesimal concentrations. The structure of the transition state for a reaction is inferred from kinetic data. Transition states are not intermediates. An intermediate is a species with a finite lifetime, and some intermediates can be isolated. An intermediate forms in one reaction, has a discrete structure, and then reacts in a second reaction.

Reaction Coordinate Diagrams

Reaction coordinate diagrams show the energy of a chemical system relative to the structure of reacting species as they are converted from reactant to product (Figures 3.3 and 3.4). A reaction coordinate diagram has a vertical axis that shows the energy of the reacting system. The horizontal axis qualitatively represents some change in the structure of the reacting species, such as the formation of a bond or the cleavage of a bond. The reaction coordinate diagram places the reactants on the left of the axis and proceeds to the products located at the right of the axis. Figure 3.3 shows the standard free energy change for a reaction that is "uphill," or *endergonic*, $\Delta G°_{rxn} > 0$. Figure 3.4 shows the standard free energy change for a reaction that is "downhill," or *exergonic*, $\Delta G°_{rxn} < 0$. The standard free energy change is *independent* of the path by which the reaction occurs. It depends only on the *difference* in energy between the initial and final states.

The transition state is represented at the highest point on the graph. This point is the state of maximum energy on the minimum energy pathway leading from reactants to products: We can think of the transition state as the top of a mountain pass or "saddle point." The difference between the energy of the reactants and the transition state is the activation energy ($E_a > 0$). When the reacting molecules reach the transition state, they may release energy and proceed to form products.

The activation energy and the temperature of the reaction control the speed of a reaction. A reaction that has a large activation energy is slow because only a small fraction of the molecules collide with sufficient energy to reach the transition state. The rate of the reaction increases when the temperature increases because the kinetic energy of molecules increases with increasing temperature. As a result, more molecular collisions occur with energy equal to or greater than the activation energy.

Figure 3.3 Reaction Coordinate Diagram for an Endergonic Reaction

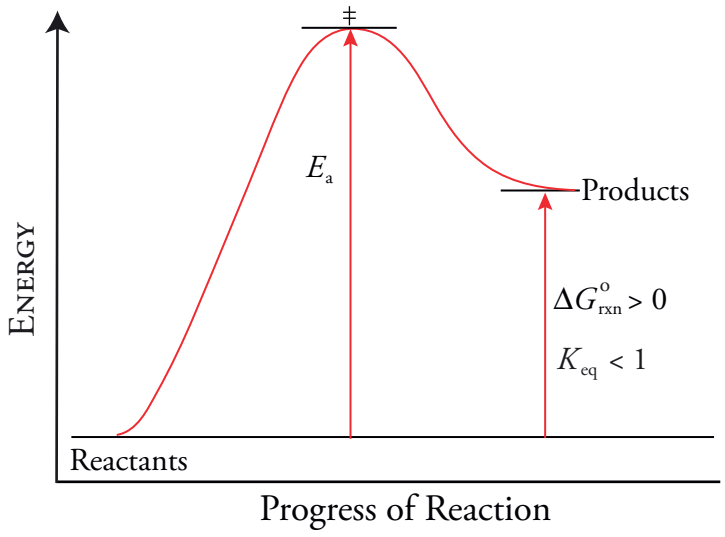
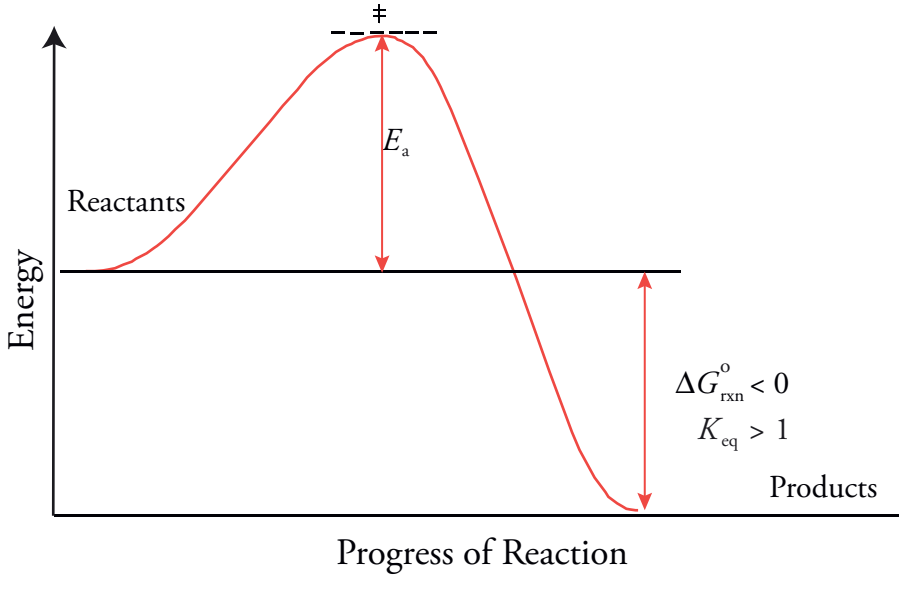


Figure 3.4 Reaction Coordinate Diagram for an Exergonic Reaction



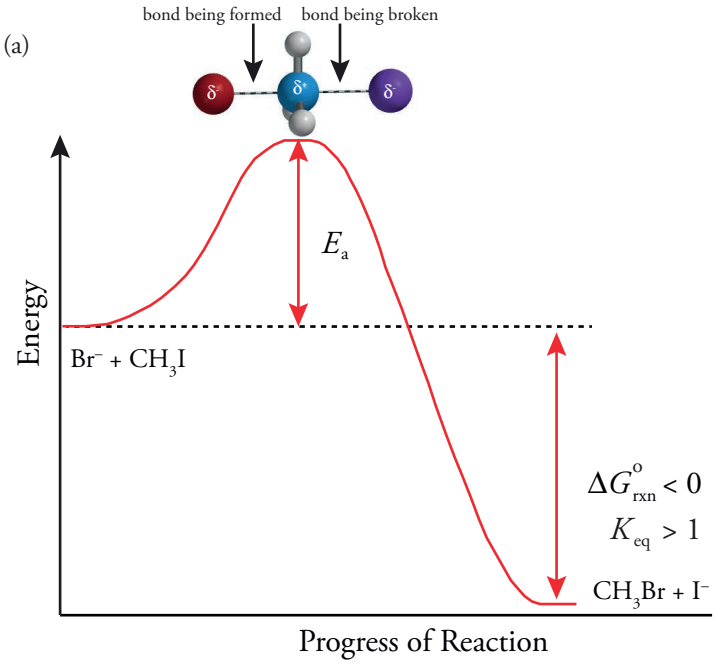
Reaction Coordinate Diagrams and Reaction Mechanisms

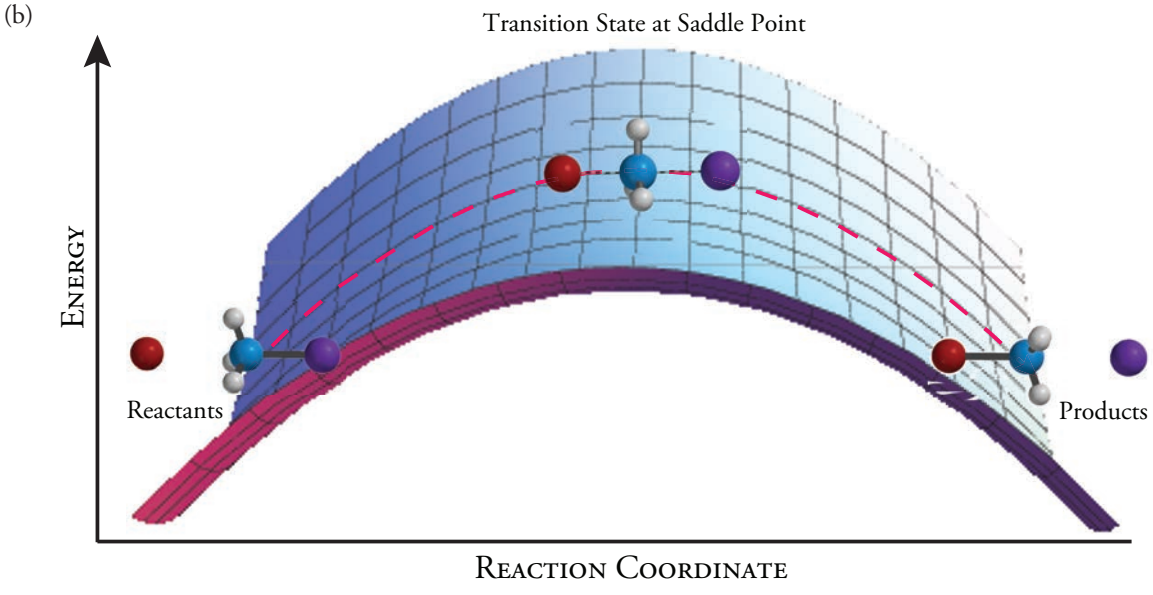
A reaction coordinate diagram shows the energy associated with the sequence of events for single- or multiple-step reactions. The energies of the transition states and of any intermediates formed are of particular importance. The effect of variations in structure on these energies will form the basis for most of the reactions studied in this text.

First, let's consider the reaction coordinate diagram for the substitution reaction of chloromethane with hydroxide ion. We recall that the kinetics of the reaction show that it is first order in each reactant and second order overall. These data are consistent with a single-step, concerted mechanism. As we will show in Chapter 10, the reactants must be oriented so that the nucleophile, the carbon atom, and the leaving group are collinear. In the transition state, both hydroxide and chloride are partially bonded to the carbon atom. The energy of the transition state is higher than the energy of the reactants and products because energy is required to partially break the carbon–chlorine bond, and the total energy of carbon–oxygen bond formation has not yet been fully released (Figure 3.5). Other nucleophilic substitution reactions that occur in a single step have similar reaction coordinate diagrams.

Figure 3.5 Reaction Coordinate Diagram for a Substitution Reaction

(a) The reaction of iodomethane with bromide ion occurs in a single step. The activation energy reflects the stability of the transition state relative to the stability of the reactants.
(b) The transition state occurs at the highest energy position on the pathway of minimum energy; it is at a saddle point.





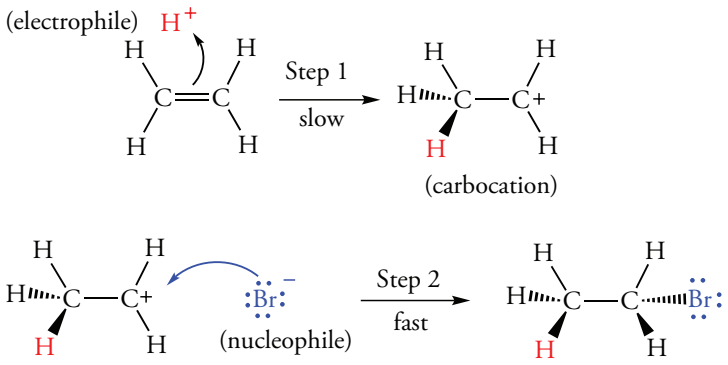
Some reactions occur in two or more steps. For a general reaction that occurs in two steps, we write two equilibria.

$$\text{Reactants} \rightleftharpoons \text{Intermediates} \rightleftharpoons \text{Products}$$

In this process, an intermediate that forms via a transition state for the first reaction subsequently reacts via a different transition state in a second reaction. A new intermediate is required for each additional step in the reaction sequence. Thus, a two-step reaction sequence has two transition states and one reaction intermediate.

Reaction coordinate diagrams are shown in Figure 3.6 for two general cases of two-step reactions. In the first case, the activation barrier for the formation of the intermediate has higher energy than the activation barrier for the reaction of the intermediate (Figure 3.5a). This means that the rate constant for the first step is smaller than the rate constant for the second step. In the second case, the activation barrier for the formation of the intermediate is of lower energy than the activation barrier for the reaction of the intermediate (Figure 3.5b). This means that the rate constant for the first step is larger than the rate constant for the second step.

For example, HBr adds to ethene in a two-step process.



In the first step, a proton acts as an electrophile. It forms a bond to carbon using the π electrons of the double bond. This step produces an intermediate carbocation forms, which then react in a second step with the nucleophilic bromide ion. Each of the steps is shown in the reaction coordinate diagram in Figure 3.6.

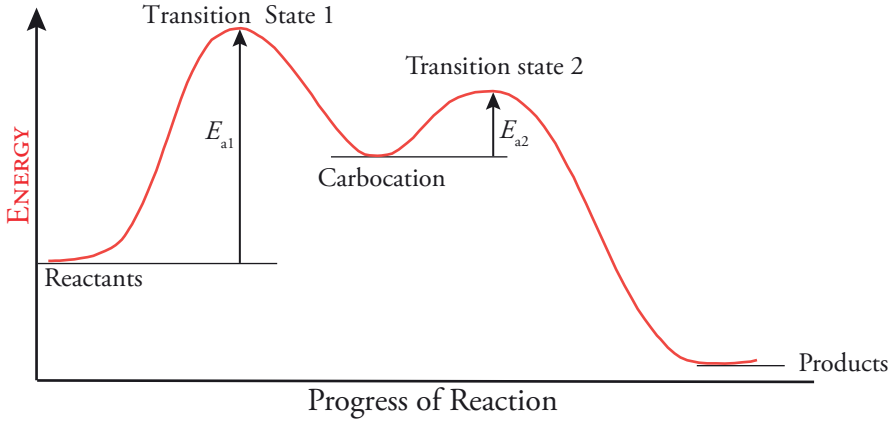


Figure 3.6 Energy Diagram for the Addition of HBr to an Alkene
The first, rate-determining step in the addition of HBr to ethene is the attack of the electrons of the double bond on a proton to give a carbocation. The second step occurs at a faster rate because the activation energy of the second step is lower than that of the first step.

In the first transition state, a hydrogen ion begins to bond to carbon as π electrons are removed from the double bond. The energy then decreases until an carbocation intermediate forms. In the second step, the carbocation starts to bond to the nucleophilic bromide ion. Note that the energy of the carbocation is lower than the energy of the two transition states; it is a reaction intermediate, *not* a transition state. The slow or *rate-determining step* for the reaction is the formation of the carbocation intermediate. Finally, as the carbon–bromine bond becomes fully formed, the reaction coordinate diagram shows that the energy of the products is lower than the energy of the reactants.

Catalysis

A catalyst provides a path for the reaction that is different from the path of the uncatalyzed reaction. The reaction path starts with the same reactants and concludes with the same products. The effect of a catalyst on the path of a reaction may add additional steps to the mechanism. Consider the hypothetical reaction of A and B to give a product we will simply call "X" in a reaction that has a high activation energy.

$$A + B \longrightarrow X$$

The high activation energy can be reached by only a few high-energy molecular collisions, and as a result the reaction is slow. However, in the presence of a catalyst, represented by C, the following reactions may occur.

$$A + C \longrightarrow A{-}C$$
$$A{-}C + B \longrightarrow X + C$$

The catalyst may combine with A in a reaction with a low activation energy. Similarly, the reaction of A–C with B may also have a low activation energy. Therefore, a larger fraction of molecules will be able to react faster via this catalyzed pathway than they could without the catalyst at the same temperature.

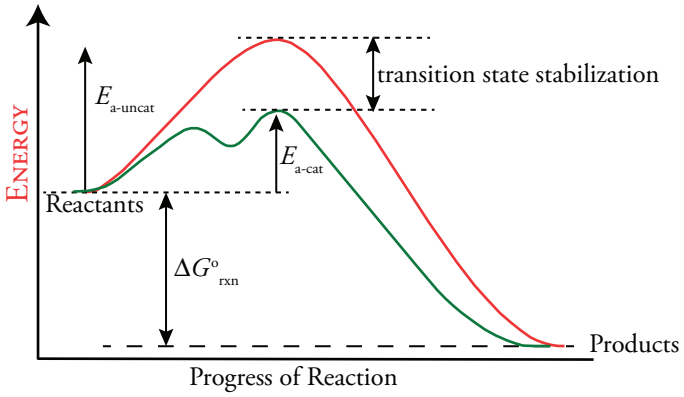


Figure 3.7 Energy Diagram for a Catalyzed and an Uncatalyzed Reaction
The activation energy for a catalyzed reaction is smaller than the activation energy for reaction in the absence of a catalyst. The catalyzed reaction may require a different number of steps than the uncatalyzed reaction.

The path for the addition reaction of ethene and hydrogen catalyzed by platinum on carbon has a different, lower activation energy than the uncatalyzed reaction. The metal catalyst used in the addition of hydrogen to ethylene functions by attaching both reactants to its surface. The hydrogen molecule dissociates into hydrogen atoms on the surface, and each hydrogen atom successively bonds to the ethylene molecule. The catalyzed reaction rate is faster because the activation energy of each of the many steps is lower than that for the step in the uncatalyzed reaction (Figure 3.7).

Transition State Structure: The Hammond Postulate

How can we picture the structure of the transition state when it is merely a transient species that is part of a continuum of structures along a reaction pathway? The answer is that we infer its structure based on what we know about the structure of the species that leads to it and the species formed from it. The species that produces it is the reactant. The species that forms may be the final product or a reactive intermediate, such as a carbocation formed in a multistep reaction.

Consider the generalized reaction coordinate diagrams shown in Figure 3.8 for strongly exothermic and endothermic reactions. In the strongly exothermic case, the energies of the transition state and the reactants are close to each other. Therefore, the transition state occurs at a point not far along the reaction coordinate. For such a situation, the structure of the transition state resembles the structure of the reactant more than the structure of the product. This correlation is summarized by the **Hammond postulate,** which states that the structures of transition states closely resemble those species with the most nearly similar energies. Thus, we usually find that the structure of the transition state for an exothermic process resembles the structure of the reactant. It follows that the structure of the transition state for an endothermic process resembles the structure of the product.

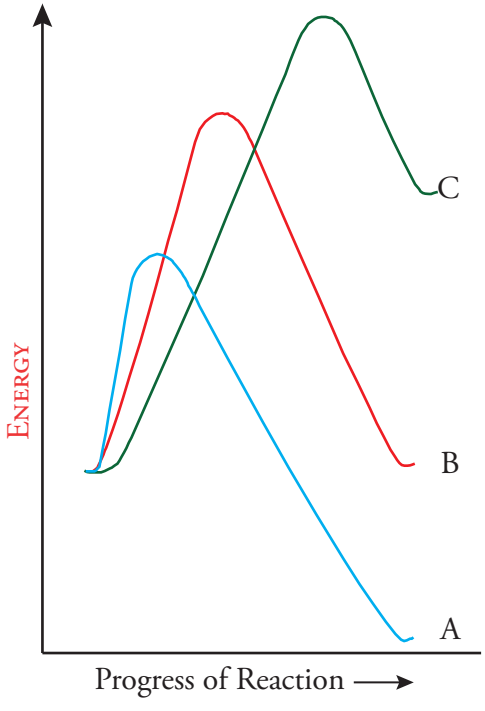


Figure 3.8 The Hammond Postulate
The location of the transition state along the reaction coordinate axis depends on the activation energy. Curve A for an exothermic process has an "early" transition state that is closer to the reactant side. Curve B is for a reaction with no difference in enthalpy between reactants and products. The transition state is in the middle. Curve C is for an endothermic process, which has a "late" transition state that is closer to the product side.

Problem 3.24

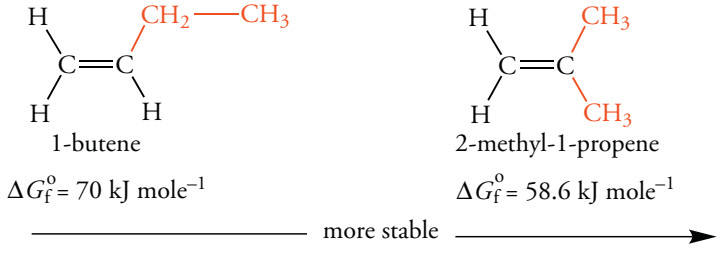
The rate constants for the nucleophilic substitution reaction with hydroxide ion with CH_3Cl and CH_3Br at 310 K are 3.2×10^{-5} and 6.6×10^{-4} L mole^{-1} s^{-1}, respectively. Which reaction has the larger activation energy, E_a?

Problem 3.25

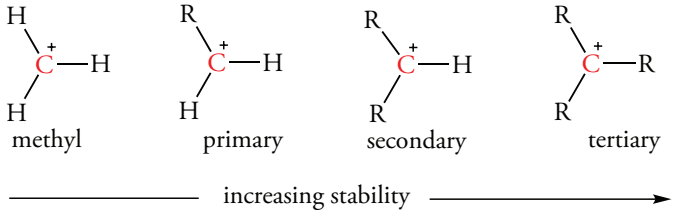
The hydrolysis reaction of ethyl ethanoate in basic solution occurs in three steps. How many transition states are there? How many intermediates form in this reaction?

3.12 STABILITY AND REACTIVITY

One of the most important concepts in all of chemistry is the relation between the stability of a compound and the rate at which it undergoes chemical reactions. Although we might think that the terms stability and reactivity are related, they are not. The term "stability" is related to standard free energy change for making a compound from its elements, that is $\Delta G^\circ_{\text{formation}}$. If we compare two closely related structural isomers, the one with the more negative $\Delta G^\circ_{\text{formation}}$ is more stable. For example, 2-methyl-1-propene is more stable than 1-butene.

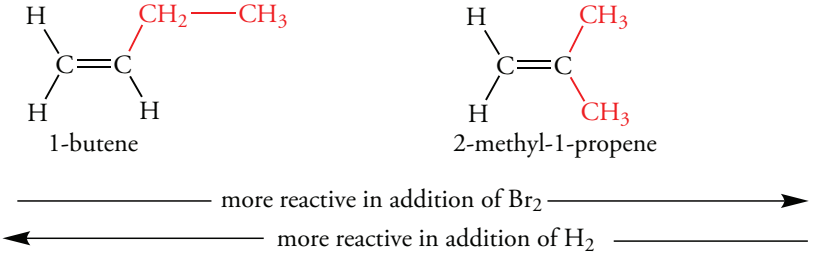


A change in a compound that lowers it energy, or stabilizes it, lowers its free energy. The term stability is used to describe reactants, products, and even intermediates. For example, carbocations are intermediates in some chemical reactions. Tertiary carbocations are stabilized by the three carbon groups bonded to the positively charged carbon atom. A primary carbocation is not as stable because only one carbon group is bonded to its positively charged carbon atom.



In contrast to the term stability, which refers to a *thermodynamic* property, the term *reactivity* refers to the *rate* at which a compound reacts. That is, a compound's reactivity refers to the activation energy required for that substance to form a particular transition state. Thus, we must refer to a specific reaction to discuss reactivity. Reactivity is not directly related to stability; rather it is the difference in the stability of the reactant and the stability of the transition state.

A substance may be more reactive than another substance with one reagent, and the order of reactivity may be reversed for some other reagent. For example, 1-butene is more reactive than 2-methyl-1-propene in the addition of H_2. However, the order of reactivity to the addition of bromine is reversed.



The difference in reactivity is related to the different mechanisms for the two reactions.

END-OF-CHAPTER EXERCISES

Acids and Bases

3.1 Write the structure of the conjugate acid of each of the following species.

(a) H–O–O–H (b) NH_2–NH_2 (c) CH_3–S–CH_3

(d) CH_3–O–CH_3 (e) CH_3–NH_2 (f) CH_3–OH

3.2 Write the structure of the conjugate base of each of the following species.

(a) CH_3–SH (b) CH_3–NH_2 (c) CH_3–O–SO_3H

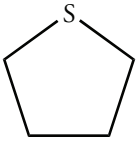
(d) CH_2=CH_2 (e) HC≡CH (f) CH_3–CN

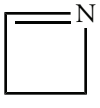
3.3 Write the structure of the conjugate acid of each of the following species.

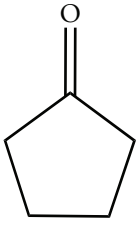
(a) CH_2=O (b) CH_3–NH–CH_3 (c) CH_2=NH (d) CH_3–C(=O)–OH

3.4 Write the structure of the conjugate acid of each of the following species.

(a) 

(b) 

(c) 

(d) 

3.5 Identify the Lewis acid and Lewis base in each of the following reactions.

(a) CH_3–CH_2–Cl + $AlCl_3$ ⟶ CH_3–CH_2+ + $AlCl_4^-$

(b) CH_3–CH_2–SH + CH_3O^- ⟶ CH_3–CH_2–S^- + CH_3OH

(c) CH_3–CH_2–OH + NH_2^- ⟶ CH_3–CH_2–O^- + NH_3

(d) $(CH_3)_2N^-$ + CH_3OH ⟶ $(CH_3)_2$NH + CH_3O^-

3.6 Identify the Lewis acid and Lewis base in each of the following reactions.

(a) $(CH_3)_2$O + HI ⟶ $(CH_3)_2$OH+ + I^-

(b) CH_3–CH_2+ + H_2O ⟶ CH_3–CH_2–OH_2+

(c) CH_3–CH=CH_2 + HBr ⟶ $(CH_3)_2$CH+ + Br^-

(d) CH_3–C≡CH + CH_3NH^- ⟶ CH_3–C≡C^- + CH_3NH_2

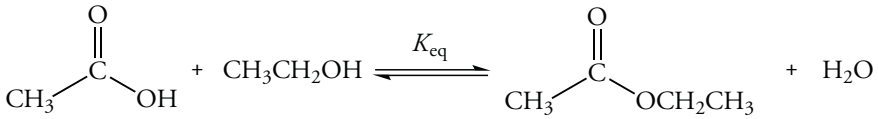
Equilibrium Constant Expressions

3.7 Write the equilibrium constant expression for the reaction of ethanal and methanol to give an acetal.

$CH_3CHO + 2\,CH_3OH \rightleftharpoons CH_3CH(OCH_3)_2 + H_2O$

3.8 Write the equilibrium constant expression for the reaction of acetylene (C_2H_2) to give cyclooctatetraene (C_8H_8).

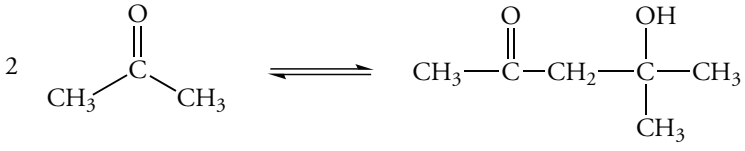
3.9 How do the equilibrium constant expressions differ for the hydrolysis reaction of ethyl ethanoate (written right to left) and the esterification reaction of ethanol and ethanoic acid (written left to right)? What is the equilibrium constant for the hydrolysis reaction?



ethanoic acid ethanol ethyl ethanoate

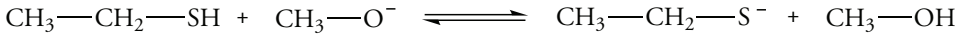
$$K_{equilibrium} = \frac{[CH_3CO_2CH_2CH_3]\ [H_2O]}{[CH_3CO_2H]\ [CH_3CH_2OH]} = 4.0$$

3.10 At equilibrium, the yield of the condensation product of acetone is about 5%. Calculate the equilibrium constant for the reaction.

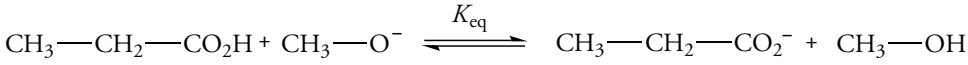


pH and p*K* Values

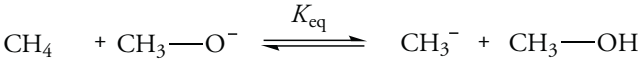
3.11 Without reference to tables of pK_a values, predict the position of the following equilibrium.



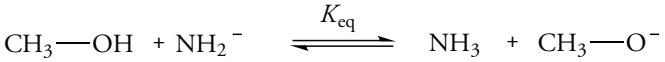
3.12 Without reference to tables of pK_a values, predict the position of the following equilibrium.



3.13 The approximate pK_a values of CH_4 and CH_3OH are 49 and 16, respectively. Which is the stronger acid? Will the equilibrium position of the following reaction lie to the left or to the right?



3.14 The approximate pK_a values of NH_3 and CH_3OH are 36 and 16, respectively. Which is the stronger acid? Will the equilibrium position of the following reaction lie to the left or to the right?



Structure and Acid Strength

3.15 Write the structures of the two conjugate acids of hydroxylamine (NH_2–OH). Which is the more acidic?

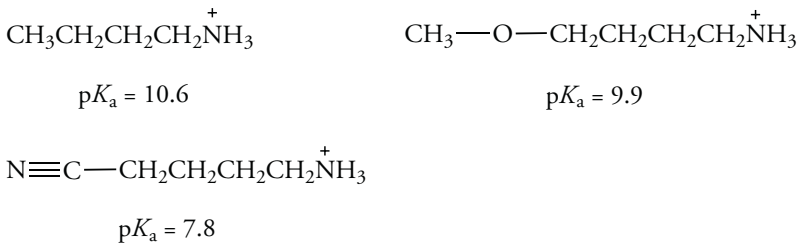
3.16 Write the structures of the two conjugate bases of hydroxylamine (NH_2–OH). Which is the more basic?

3.17 Which is the stronger acid, chloroethanoic acid ($ClCH_2CO_2H$) or bromoethanoic acid ($BrCH_2CO_2H$)? Why?

3.18 Which acid has the larger pK_a, chloroethanoic acid (($ClCH_2CO_2H$) or dichloroethanoic acid ((Cl_2CHCO_2H)? Why?

3.19 Based on the pK_a values of substituted butanoic acids (Section 3.4), predict the pK_a of 4-chlorobutanoic acid.

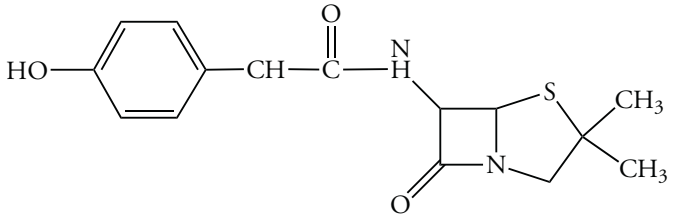
3.20 Explain the trends in the pK_a values of the following ammonium ions.



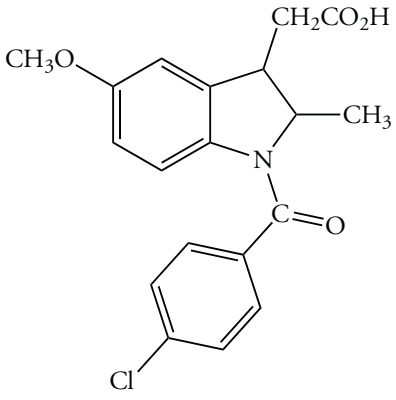
3.21 Explain why the hydrogen of the CH_3 of propene is more acidic than hydrogen of the CH_3 of propane.

3.22 Ethanonitrile (CH_3CN) is a stronger acid than ethane. Explain why.

3.23 The pK_a of acetic acid (CH_3CO_2H) is 4.8. Explain why the carboxylic acid group of Amoxicillin (pK_a = 2.4), a synthetic penicillin, is more acidic than acetic acid, whereas the carboxylic acid group of Indomethaxin (pK_a = 4.5), an anti-inflammatory analgesic used to treat rheumatoid arthritis, is of comparable acidity.

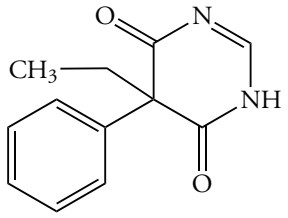


Amoxicillin



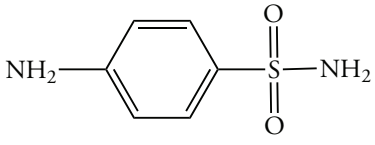
Indomethaxin

3.24 The pK_a of the OH group of phenobarbital is 7.5, whereas the pK_a of CH_3OH is 16. Explain why phenobarbital is significantly more acidic.



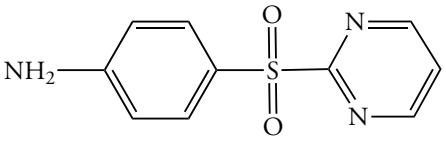
phenobarbital

3.25 The N–H bond of ammonia is not very acidic (pK_a = 33). However, the pK_a for the N–H bond of sulfanilamide, a sulfa drug, is 10.4. Suggest a reason for the higher acidity of sulfanilamide.



sulfanilamide

3.26 The pK_a of sulfadiazine, a sulfa drug, is 6.5. Why is this compound more acidic than sulfanilamide?



sulfadiazine

Equilibrium Constants and Standard Free Energy Changes

3.27 A reaction has $K_{eq} = 1 \times 10^{-5}$. Are the products more or less stable than the reactants? Is the reaction exergonic or endergonic?

3.28 Which reaction would be exergonic, one with K_{eq} = 100 or one with K_{eq} = 0.01?

3.29 Could a reaction have K_{eq} = 1? What relationship would exist between the free energies of the reactants and products as shown in the reaction coordinate diagram?

3.30 Which reaction has an equilibrium constant greater than 1, one with $\Delta G°_{rxn}$ = + 15 kJ mole^{-1} or one with $\Delta G°_{rxn}$ = –15 kJ mole^{-1}?

3.31 The $\Delta G°_{rxn}$ for the following reaction is +2 kJ mole^{-1}. What is K_{eq} at 25 °C?

$$CH_3SH + HBr \rightleftharpoons CH_3Br + H_2S$$

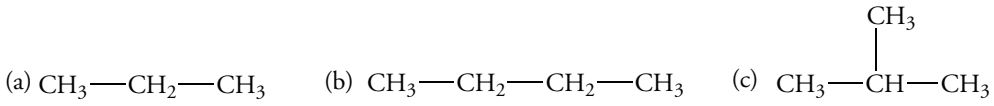
3.32 The equilibrium constant for the isomerization of butane to 2-methylpropane is 4.9. What is $\Delta G°_{rxn}$?

Bond Cleavage and Reaction Intermediates

3.33 Write the structure of the radical formed by abstraction of a hydrogen atom by a chlorine atom for each of the following compounds.

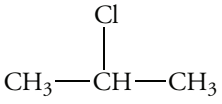
(a) CH_3CH_3 (b) CH_3CI (c) CH_2Cl_2

3.34 Write the structures of all possible radicals formed by abstraction of a hydrogen atom by a chlorine atom for each of the following compounds.



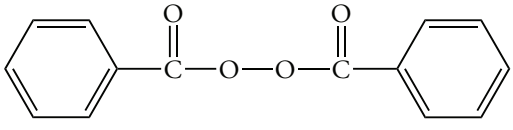
3.35 The oxygen–chlorine bond of methyl hypochlorite (CH_3–O–Cl) can cleave heterolytically. Based on the electronegativity values of chlorine and oxygen, predict the charges on the cleavage products.

3.36 2-Chloropropane reacts with the Lewis acid $AlCl_3$ to give $AlCl_4^-$ and a carbon intermediate. What is the intermediate?



3.37 Hydrogen peroxide (H–O–O–H) reacts with a proton to give a conjugate acid, which undergoes heterolytic oxygen–oxygen bond cleavage to yield water. What is the second product?

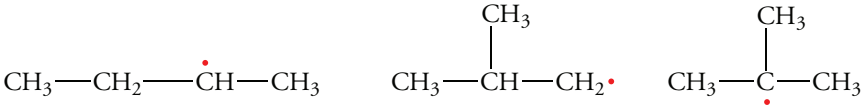
3.38 Benzoyl peroxide is used in creams to control acne. It is an irritant that causes proliferation of epithelial cells. It undergoes a homolytic cleavage of the oxygen–oxygen bond. Write the structure of the product, indicating all of the electrons present on all of the oxygen atoms.



benzoyl peroxide

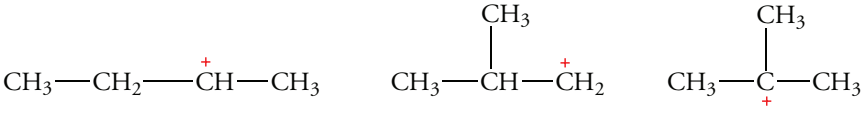
Stability of Reactive Intermediates

3.39 Arrange the following intermediates in order of increasing stability.



I II III

3.40 Arrange the following intermediates in order of increasing stability.



I II III

3.41 Explain why more energy is required for heterolytic bond cleavage of the carbon–bromine bond of 1-bromopropane than is needed to cleave the carbon–bromine bond of 2-bromopropane.

$CH_3CH_2CH_2Br$
1-bromopropane

$CH_3CHBrCH_3$
2-bromopropane

3.42 Explain why less energy is required to cleave the carbon–chlorine bond of 3-chloropropene than needed to cleave the carbon–chlorine bond of 1-chloropropane.

$CH_2{=}CHCH_2Cl$ 3-cloropropene

$CH_3CH_2CH_2Cl$ 1-chloropropane

3.43 Chloroform ($CHCl_3$) reacts with a strong base in an unusual elimination reaction to give dichlorocarbene (CCl_2). Write the Lewis structure for this species. What features of the chlorine atoms might stabilize this carbene compared to CH_2 ?

3.44 Draw the Lewis structure of OH^+. How does it differ from OH^-? Is OH^+ a nucleophile or an electrophile?

Activation Energy and Rates of Reaction

3.45 Given the following information about two reactions, which one will occur at the faster rate at a common temperature?

Reaction	ΔH°_{rxn}	E_a
A → X	–120 kJ mole^{-1}	+100 kJ mole^{-1}
B → Y	–100 kJ mole^{-1}	+120 kJ mole^{-1}

3.46 Given the information in Exercise 3.44, which one is more exothermic?

3.47 Given the activation energies for the following free radical reactions, which one occurs at the faster rate?

$CH_4 + F\cdot \longrightarrow CH_3\cdot + HF \qquad E_a = 5$ kJ mole^{-1}

$CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl \qquad E_a = 16$ kJ mole^{-1}

3.48 Consider the activation energies for the following nucleophilic substitution reactions. Which reaction occurs at the faster rate?

$CH_3{-}I + Cl^- \longrightarrow CH_3{-}Cl + I^- \qquad E_a = 104$ kJ mole^{-1}

$CH_3{-}I + Br^- \longrightarrow CH_3{-}Br + I^- \qquad E_a = 96$ kJ mole^{-1}

Kinetic Order of Reaction

3.49 Sodium cyanide reacts with chloroethane by the following equation. When the concentration of cyanide ion is tripled, the reaction rate triples. When the concentration of chloroethane doubles, the reaction rate doubles. What is the overall kinetic order of the reaction? Write the rate equation for the reaction.

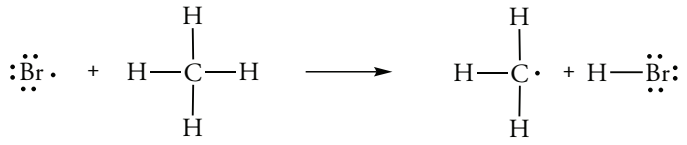
$$N{\equiv}C{:}^- + CH_3{-}CH_2{-}Cl \longrightarrow CH_3{-}CH_2{-}C{\equiv}N{:} + Cl^-$$

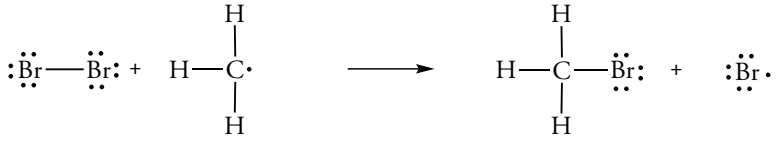
3.50 Reaction of *tert*-butyl alcohol with concentrated HBr gives *tert*-butyl bromide. When the concentration of the alcohol is doubled, the reaction rate doubles. When the concentration of acid is tripled, the reaction rate triples. If more bromide ion in the form of sodium bromide is added, the rate is unaffected. What is the kinetic order with respect to each reactant? What is the overall kinetic order of the reaction?

$$HBr + \begin{array}{c} CH_3 \\ | \\ CH_3{-}C{-}OH \\ | \\ CH_3 \end{array} \longrightarrow \begin{array}{c} CH_3 \\ | \\ CH_3{-}C{-}Br \\ | \\ CH_3 \end{array} + H_2O$$

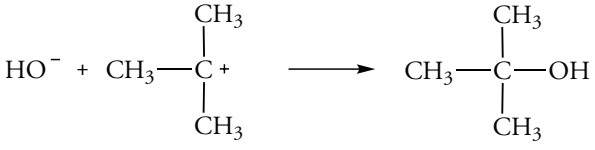
Reaction Mechanisms

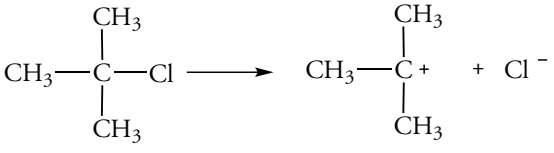
3.51 Identify the processes of bond cleavage and bond formation for each of the following reactions.

(a) 

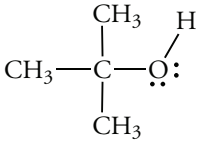
(b) 

3.52 Identify the processes of bond cleavage and bond formation for each of the following reactions.

(a) 

(b) 

3.53 In the presence of a strong acid, *tert*-butyl alcohol acts as a base. The resulting conjugate acid produces water and an intermediate. Write the structure of the intermediate. What type of bond cleavage occurs?



tert-butyl alcohol

3.53 Dimethyl ether (CH_3–O–CH_3) can be prepared by adding a strong base such as NaH to methanol (CH_3OH) and then adding iodomethane (CH_3I) to the reaction mixture. Write plausible steps for this reaction.

Reaction Coordinate Diagrams

3.54 What are the differences between a reaction intermediate and a transition state?

3.55 A reaction occurs in three steps. How many transition states are there? How many intermediates form?

3.56 Draw a reaction coordinate diagram for a two-step exothermic reaction in which the second step is a rate determining.

Hammond Postulate

3.57 The $\Delta H°_{rxn}$ for abstracting each of the possible hydrogen atoms of propane by a bromine atom are indicated below. Based on the data and the fact that the starting materials are the same, what might be surmised about the relative energies of activation for the two reactions? Do the transition states more closely resemble the reactants or the products?

$CH_3–CH_2–CH_3 + Br\cdot \quad CH_3–CH_2–CH_2\cdot + HBr \quad \Delta H° = +42 \text{ kJ mole}^{-1}$

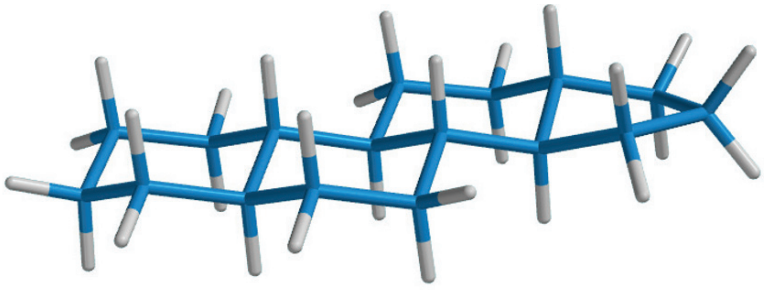
$CH_3–CH_2–CH_3 + Br\cdot \quad CH_3–\dot{C}H–CH_3 + HBr \quad \Delta H° = +29 \text{ kJ mole}^{-1}$

3.58 The $\Delta H°_{rxn}$ for abstracting each of the possible hydrogen atoms of propane by a bromine atom are indicated below. Based on the data and the fact that the starting materials are the same, what might be surmised about the relative energies of activation for the two reactions? Do the transition states more closely resemble the reactants or the products?

$CH_3–CH_2–CH_3 + Cl\cdot \quad CH_3–CH_2–CH_2\cdot + HCl \quad \Delta H° = -20 \text{ kJ mole}^{-1}$

$CH_3–CH_2–CH_3 + Cl\cdot \quad CH_3–\dot{C}H–CH_3 + HCl \quad \Delta H° = -33 \text{ kJ mole}^{-1}$

4 Alkanes and Cycloalkanes: Structures and Reactions



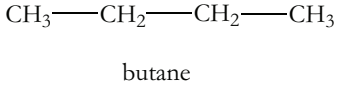
Hydrocarbons, as their names indicate, contain only hydrogen and carbon. They occur as mixtures in natural gas, petroleum, and coal, which are collectively known as fossil fuels since they contain the remnants (fossils) of ancient organisms, including plants, animals, and microorganisms that have been buried for millions of years at high temperature and pressure under anaerobic conditions.

Hydrocarbons fall into two broad classes based on the types of bonds between the carbon atoms. A hydrocarbon that has only carbon–carbon single bonds is **saturated**. Hydrocarbons that contain carbon–carbon multiple bonds are **unsaturated**. Alkanes and cycloalkanes are two types of saturated hydrocarbons. **Alkanes** have carbon atoms bonded in chains; **cycloalkanes** have carbon atoms bonded to form a ring.

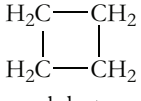
4.1 CLASSES OF HYDROCARBONS

Compounds that have a chain of carbon atoms, some of which are attached to functional groups, are called **acyclic** compounds, meaning "not cyclic." Compounds that contain rings of carbon atoms, and that may also contain functional groups, are **carbocyclic** compounds, commonly called cycloalkanes. One example is cyclobutane, which is shown above. Some cyclic compounds contain at least one atom in the ring other than carbon; those atoms are called **heteroatoms**. Cyclic compounds containing one or more **heteroatoms** are called **heterocyclic** compounds. The structures of an acyclic compound 2-heptanone, a carbocyclic compound, carvone, and the heterocyclic compound nicotinic acid are shown below.

Aromatic rings, which we briefly introduced in Chapter 2, are also "hydrocarbons," but they are an entirely different class of compounds, which we will discuss in Chapters 12 and 13.

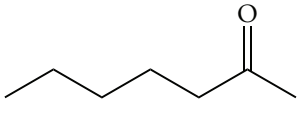


butane



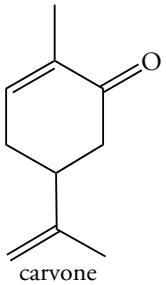
cyclobutane

an acyclic compound



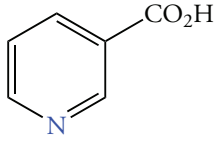
2-heptanone
in oil of cloves

a cyclic compound



carvone
in spearmint oil

a heterocyclic compound



nicotinic acid
a B vitamin

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00004-8
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4.2 ALKANES

Saturated hydrocarbons that have a continuous chain of carbon atoms do not have any "branches." They are called **normal alkanes**. Their structures are often drawn with the carbon chain in a horizontal line.

$CH_3—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3$

octane
(a normal alkane)

The names and condensed structural formulas of 20 normal alkanes are given in Table 4.1. The first four compounds have common names. The names of the higher-molecular-weight compounds are derived from Greek numbers that indicate the number of carbon atoms in the chain. Each name has the suffix *-ane*, which identifies the compound as an alkane.

Table 4.1
Names of Normal Alkanes

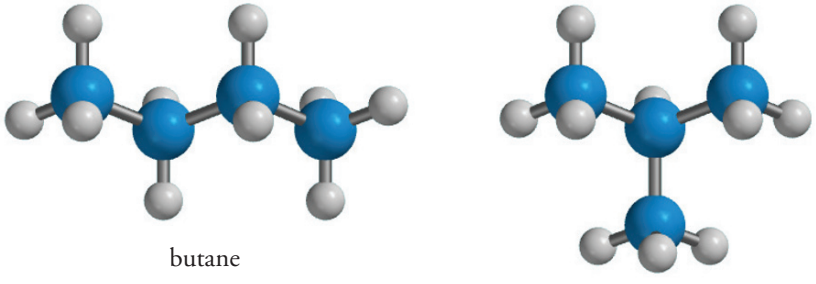
Number of Carbon Atoms	*Name*	*Molecular Formula*
1	Methane	CH_4
2	Ethane	C_2H_6
3	Propane	C_3H_8
4	Butane	C_4H_{10}
5	Pentane	C_5H_{12}
6	Hexane	C_6H_{14}
7	Heptane	C_7H_{16}
8	Octane	C_8H_{18}
9	Nonane	C_9H_{20}
10	Decane	$C_{10}H_{22}$
11	Undecane	$C_{11}H_{24}$
12	Dodecane	$C_{12}H_{26}$
13	Tridecane	$C_{13}H_{28}$
14	Tetradecane	$C_{14}H_{30}$
15	Pentadecane	$C_{15}H_{32}$
16	Hexadecane	$C_{16}H_{34}$
17	Heptadecane	$C_{17}H_{36}$
18	Octadecane	$C_{18}H_{38}$
19	Nonadecane	$C_{19}H_{40}$
20	Eicosane	$C_{20}H_{42}$

Saturated hydrocarbons in which one or more groups are bonded to a secondary carbon are called **branched alkanes**. The carbon atom bonded to three or four other carbon atoms is the **branching point**. The carbon atom attached to the chain of carbon atoms at the branching point is part of an **alkyl group**. For example, isobutane is the simplest example of a branched alkane. It has three carbon atoms in the main chain and one branch, a $—CH_3$ group.

$CH_3—CH_2—CH_2—CH_3$ butane

$CH_3—CH(CH_3)—CH_3$ *iso*butane

Ball-and-stick structures of butane and isobutane.



butane *iso*butane

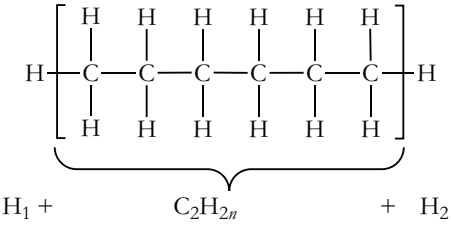
Isopentane and neopentane are isomers of pentane. Isopentane is a branched alkane with four carbon atoms in the main chain and one branching methyl group. Neopentane has three carbon atoms in the main chain and two methyl groups bonded to the central carbon. If an alkane does not have branches, it is said to be a **normal alkane**.

$CH_3—CH_2—CH_2—CH_2—CH_3$ pentane

$CH_3—CH(CH_3)—CH_2—CH_3$ isopentane

$C(CH_3)_4$ neopentane

Both normal and branched alkanes have the general molecular formula C_nH_{2n+2}. For example, the molecular formula of hexane is C_6H_{14}.

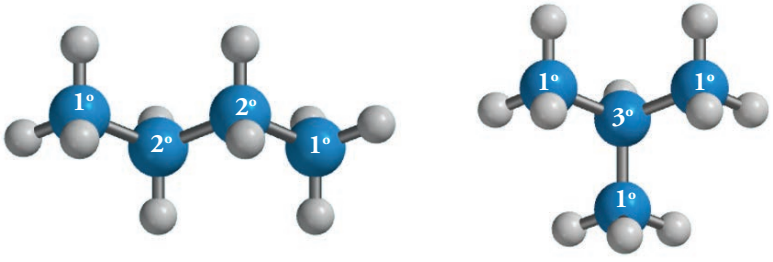


Each carbon atom in this normal alkane, where $n = 6$, has at least two hydrogen atoms bonded to it, which accounts for the $2n$ in the general formula. Each of the two terminal carbon atoms has another hydrogen atom bonded to it, which accounts for the +2 in the subscript on hydrogen in the general formula.

Classification of Carbon Atoms

Hydrocarbon structures are classified according to the number of carbon atoms directly bonded to a specific carbon atom. We will use this classification in later chapters to describe the reactivity of functional groups attached to the various carbon atoms in a structure.

A carbon atom bonded to only one other carbon atom is a **primary carbon atom**, which is designated by the symbol 1°. The carbon atom at each end of a carbon chain is primary. For example, butane has two primary carbon atoms. A carbon atom that is bonded to two other carbon atoms is a **secondary carbon atom**, designated by the symbol 2°. For example, the middle carbon atoms of butane are secondary (Figure 4.1a).



(a) *n*-butane (b) *iso*butane

Figure 4.1 Classification of Carbon Atoms
(a) The terminal carbon atoms of butane are primary (1°); they are bonded directly to one other carbon atom. The internal carbon atoms are secondary; they are bonded to two carbon atoms. (b) The terminal carbon atoms of *iso*-butane are primary; they are bonded to one other carbon atom. The internal carbon atom is tertiary (3°); it is bonded to three carbon atoms.

A carbon atom bonded to three other carbon atoms is **tertiary** and is designated by 3°. For example, when we examine the structure of isobutane, we see that one of the four carbon atoms is tertiary; the other three are primary (Figure 4.1b). A **quaternary carbon** atom (4°) is bonded to four other carbon atoms.

Problem 4.1

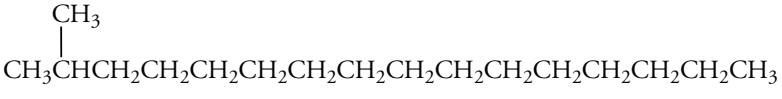
One of the components of the wax of a cabbage leaf is a normal alkane containing 29 carbon atoms. What is the molecular formula of the compound?

Sample Solution

For $n = 29$, there must be $(2 \times 29) + 2$ hydrogen atoms. The molecular formula is $C_{29}H_{60}$.

Problem 4.2

The following compound is a sex attractant released by the female tiger moth. Classify the carbon atoms in this compound as primary, secondary, or tertiary.

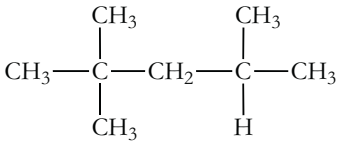


Sample Solution

Each of the two terminal carbon atoms and the branching —CH_3 group are primary carbon atoms, because each is bonded to only one other carbon atom. The second carbon atom from the left is bonded to two atoms in the chain as well as to the branching —CH_3 group, so it is tertiary. All 14 remaining carbon atoms are bonded to two carbon atoms, so they are secondary.

Problem 4.3

The octane number is a scale used to rate gasoline. The octane number of the following compound, called *iso*-octane, is 100. Classify the carbon atoms of this compound.



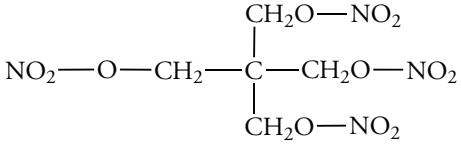
iso-octane

Sample Solution

The carbon atoms in all five —CH_3 groups are primary. The carbon atom bonded to three —CH_3 groups near the left side of the structure is also bonded to a —CH_2 unit. This carbon atom is quaternary. The —CH_2 and CH carbon atoms are secondary and tertiary, respectively.

Problem 4.4

Pentaerythritol tetranitrate is a drug used to reduce the frequency and severity of angina attacks. Classify the carbon atoms in this compound.



Pentaerythritol tetranitrate

4.3 NOMENCLATURE OF ALKANES

Many alkanes exist as isomers. There are two isomers of C_4H_{10}, called butane and isobutane, and three isomers of C_5H_{12}, called pentane, isopentane, and neopentane. It is easy to learn their names. However, as the number of carbon atoms in an alkane increases, the number of isomers increases geometrically (Table 4.2). Many of these possible isomers have never been found in petroleum or produced in a chemistry laboratory, but each could be made in the laboratory. A system for naming the many isomeric alkanes is clearly necessary.

Table 4.2
Number of Alkane Isomers

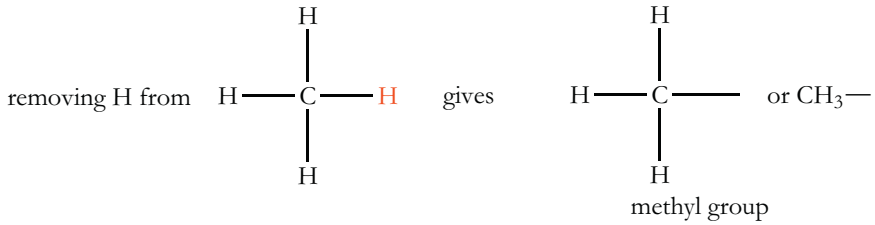
Molecular Formula	*Number of Isomers*
CH_4	1
C_2H_6	1
C_3H_8	1
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35
$C_{10}H_{22}$	75
$C_{20}H_{42}$	336,319
$C_{30}H_{62}$	4,111,846,763
$C_{40}H_{82}$	62,491,178,805,831

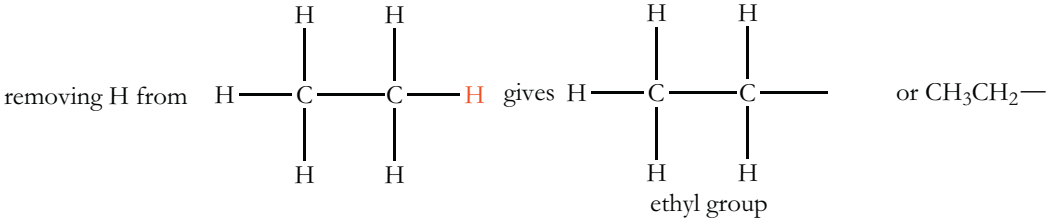
IUPAC Rules for Naming Alkanes

Alkanes and other organic compounds are named by the rules set forth by the International Union of Pure and Applied Chemistry (IUPAC). When these rules are followed, every chemical compound has a unique name. The IUPAC name consists of three parts: prefix, parent, and suffix.



The **parent** is the longest continuous carbon chain in a molecule that contains the functional group. The **suffix** identifies the functional group for most classes of organic compounds. A parent alkane has the ending *-ane*. Some functional groups, such as the halogens, are identified in the prefix. For example, the prefixes chloro and bromo identify chlorine and bromine. The prefix also indicates the identity and location of any branching alkyl groups. An alkane that has "lost" one hydrogen atom is called an **alkyl** group. Alkyl groups are named by replacing the *-ane* ending of an alkane with *-yl*. The parent name of CH_4 is methane. Thus, CH_3— is a methyl group. The parent name of C_2H_6 is ethane, so CH_3CH_2— is an ethyl group.



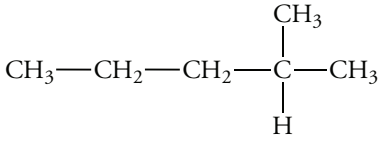


The general shorthand representation of an alkyl group is R—, which stands for the "rest" or "remainder" of the molecule.

The name of an alkane specifies the length of the carbon chain and the location and identity of alkyl groups attached to it.

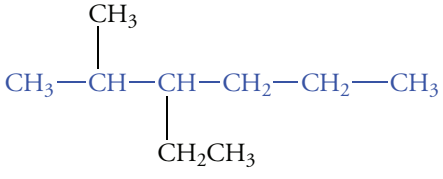
The IUPAC rules for naming alkanes are as follows:

1. The longest continuous chain of carbon atoms is the parent.

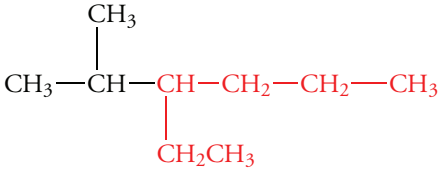


The parent chain contains five carbons.

If two possible parent chains have the same number of carbon atoms, the parent is the one with the larger number of branch points.

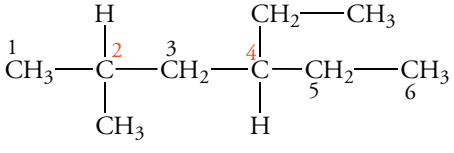


The parent chain has six carbons with two branches: a methyl group and an ethyl group.



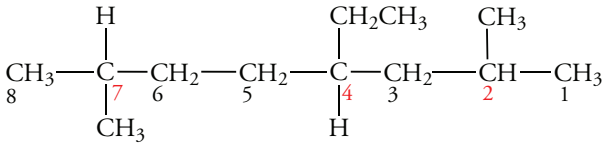
The six carbon parent chain with one branch is not correct.

2. Number the carbon atoms in the longest continuous chain starting from the end of the chain nearer the first branch.



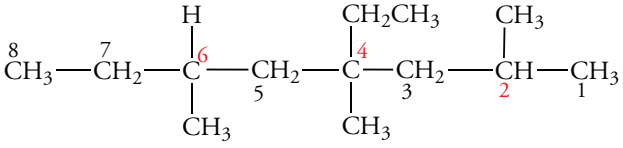
The parent chain contains six carbons, so it is a hexane with two branches: a methyl group at C-2 and an ethyl group at C-4.

If the first branch occurs at an equal distance from each end of the chain, number from the end that is nearer the second branch.



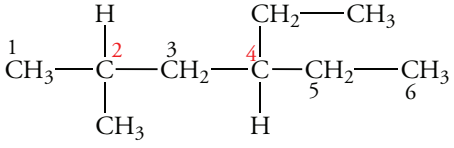
The parent has eight carbons, so it is an octane. It has methyl groups at C-2 and C-7 and an ethyl group at C-4.

3. Each branch or substituent has a number that indicates its location on the parent chain. When two substituents are located on the same carbon atom, each must be assigned the same number.



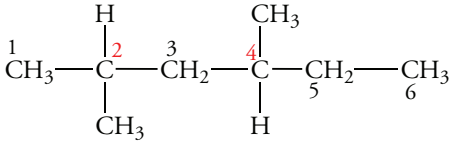
This octane has methyl groups at C-2, C-4, and C-6, and an ethyl group at C-4.

4. The number for the position of each alkyl group is placed immediately before the name of the group and is joined to the name by a hyphen. Alkyl groups and halogen atoms are listed in alphabetical order.



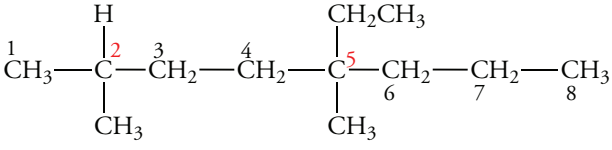
The name of this compound is 4-ethyl-2-methylhexane, *not* 2-methyl-4-ethylhexane.

Two or more groups of the same type are indicated by the prefixes di-, tri-, tetra-, and so forth. The numbers that indicate the locations of the branches are separated by commas.



The name of this compound is 2,4-dimethylhexane

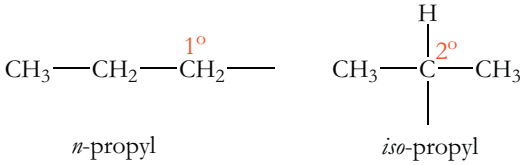
5. The prefixes di-, tri-, tetra-, and so forth, do not alter the alphabetical ordering of the alkyl groups.



The name of this compound is 5-ethyl-2,5-dimethyloctane, *not* 3,5,-dimethyl-5-ethyloctane.

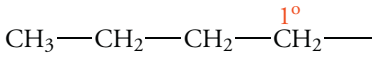
Names of Alkyl Groups

There is only one alkyl group derived from methane and ethane. However, for a longer chain of carbon atoms, several isomeric alkyl groups are usually possible depending on which carbon atom "loses" a hydrogen atom. Many of these alkyl groups are known by their common names. For example, propane has two primary carbon atoms and a secondary carbon atom. If a primary carbon atom loses a hydrogen atom, a primary alkyl group, propyl, is produced. Propyl and other primary alkyl groups derived from normal alkanes are **normal alkyl groups**. The term "normal" means that the alkane has no branches. If the secondary carbon atom of propane loses a hydrogen atom, a secondary alkyl group known as the isopropyl group is formed. The abbreviations of propyl and isopropyl are *n*-Pr and *i*-Pr.

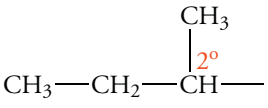


n-propyl *iso*-propyl

Several alkyl groups can be derived from the two isomers of butane, C_4H_{10}. These alkyl groups have the formula C_4H_9. Two alkyl groups are derived from butane and two from isobutane. If a primary carbon atom of butane loses a hydrogen atom, an *n*-butyl group results; if a secondary carbon atom of butane loses a hydrogen atom, a secondary alkyl group, *sec*-butyl, forms.

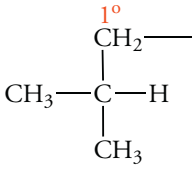


n-butyl

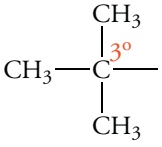


sec-butyl

Removing a hydrogen atom from a primary carbon atom of isobutane gives a primary alkyl group called the *iso*-butyl group. Removing a hydrogen atom from the tertiary carbon atom of isobutane gives a tertiary alkyl group called the *tert*-butyl (*t*-butyl) group. Thus, there are four isomeric C_4H_9— alkyl groups.

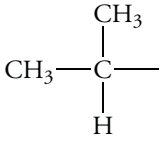


*iso*butyl

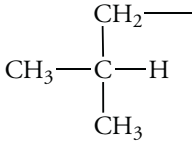


tert-butyl

Alkyl groups are named by an IUPAC procedure similar to that used to name alkanes with the longest continuous chain beginning at the branch point. For example, the IUPAC name for an isopropyl group is 1-methylethyl, and the IUPAC name for an *iso*-butyl group is 2-methylpropyl. The point of attachment of the alkyl group is numbered carbon 1.



2-methylethyl
(*iso*propyl)

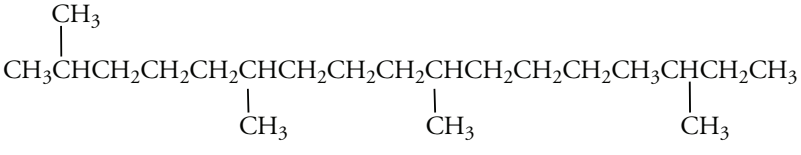


2-methylpropyl
(*sec*-butyl)

Complex alkyl groups are enclosed within parentheses when used to name hydrocarbons. Thus, 4-isopropylheptane is also 4-(1-methylethyl)heptane. The methyl within parentheses shows that it modifies ethyl, not heptane. The nonsystematic names for the alkyl groups containing three and four carbon atoms are commonly used, and IUPAC rules allow for their continued use.

Problem 4.5

Name the following compound, which is produced by the alga *Spirogyra*.

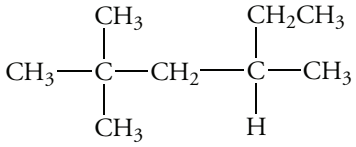


Sample Solution

The longest continuous chain has 16 carbon atoms and is named as a substituted hexadecane. The chain is numbered from left to right to locate the four methyl groups at positions 2, 6, 10, and 14. The compound is 2,6,10,14-tetramethylhexadecane.

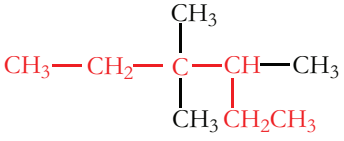
Problem 4.6

Name the following compound.



Sample Solution

First identify the longest continuous chain. That gives the parent, hexane.



Three methyl groups are attached to the parent—numbering from the left, two are at C-3, and one at C-4. Thus, the compound is 3,3,4-trimethylhexane. Numbering from right to left would give 4,4,3-trimethylhexane. This name is incorrect because the sum of 3 + 3 + 4 is less than the sum of 4 + 4 + 3.

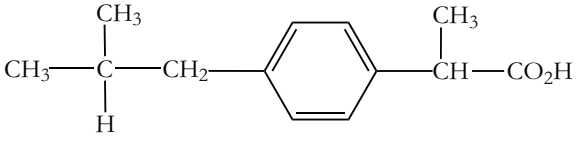
Problem 4.7

Write the structures of each of the following compounds.

(a) 3,3-dimethylhexane (b) 4-methyl-3-ethyloctane (c) 4-(1-methylethyl)octane

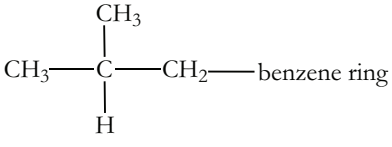
Problem 4.8

Identify the alkyl group on the left of the benzene ring in ibuprofen, an analgesic present in Nuprin®, Advil®, and Motrin® .



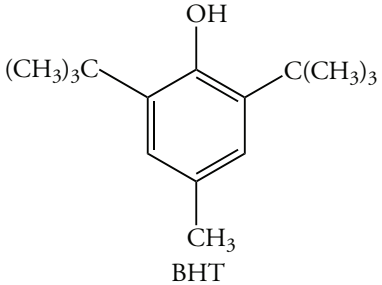
Sample Solution

There are four carbon atoms in the alkyl group, which is derived from isobutane—not butane. The benzene ring is bonded to the terminal carbon atom—not the internal carbon atom. This group is the isobutyl group.



Problem 4.9

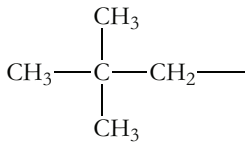
The food preservative BHT has the following structure. Identify the alkyl groups bonded to the benzene ring.



BHT

Problem 4.10

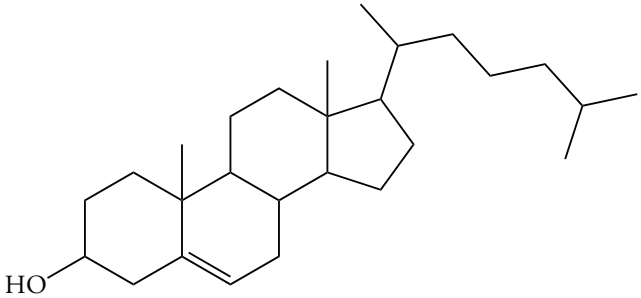
The common name for the five-carbon alkyl group with a quaternary carbon atom is neopentyl. What is its IUPAC name?



neopentyl

Problem 4.11

Name the eight-carbon alkyl group that is bonded to the five-membered ring of cholesterol.



cholesterol

4.4 CONFORMATIONS OF ALKANES

In Chapter 1, we saw that ethane can exist in various spatial arrangements, called **conformations**, which result from rotation of the CH_3 groups around the carbon–carbon σ bond. When the CH_3 groups rotate around the C—C bond, the positions of the hydrogen atoms change with respect to one another, but the connectivities of all the bonds remain the same. Thus, various conformations have different shapes but are not structural isomers.

The study of the chemical and physical properties of different conformations of organic compounds is called **conformational analysis**. To understand the relationship between structure and physical properties, we need to know how structural differences change the conformations of molecules, and which conformations predominate at equilibrium. To understand the relationship between structure and chemical reactivity, we must know the energy difference between the most stable conformation and the conformation required to bring atoms into proximity for reaction. If a substantial conformational change is required to "prepare" a molecule for reaction, then the energy associated with that change affects the rate of the reaction.

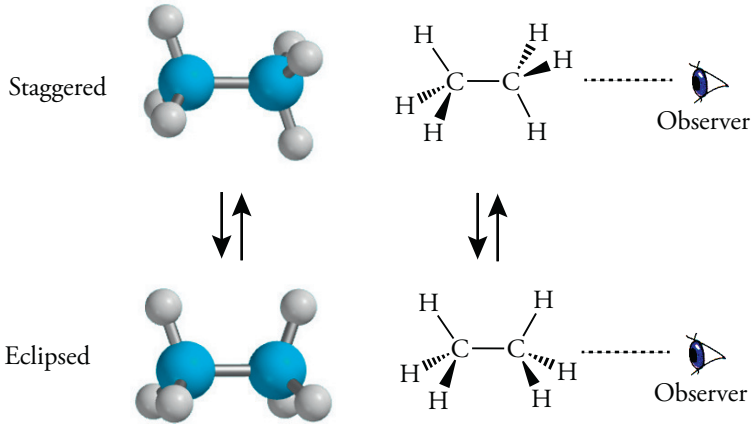
In succeeding sections, we will study the conformations of small organic molecules, such as ethane, propane, butane, and cyclohexane. At first glance, this might seem to be an unpromising topic. However, once we understand the conformations of small molecules, we will be able to apply conformational concepts to much larger molecules, such as carbohydrates or complex drugs. The conformation of a molecule accounts for its highly specific biological function.

Conformations of Ethane

Rotation around the C-1 to C-2 bond interconverts conformational isomers. Figure 4.2 shows two such arrangements. The hydrogen atoms are in a different spatial relation to one another in the two structures. These two conformational isomers are **conformers**. Since the conformational isomers are interconverted by bond rotation, they are sometimes called **rotamers**.

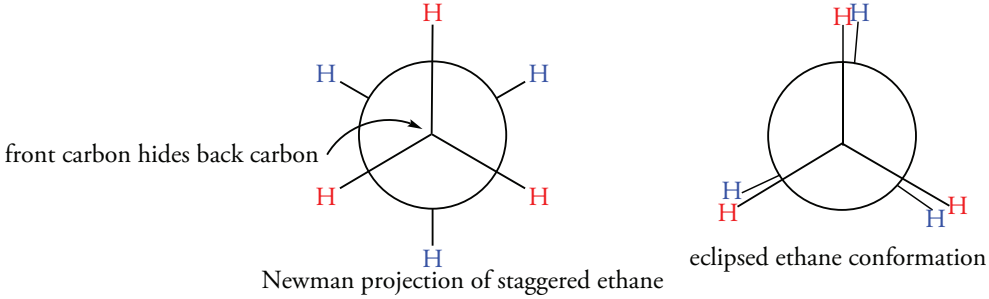
Ethane can exist in an infinite number of conformations. The conformation in which the hydrogen atoms and the bonding electrons are the farthest away from one another has the lowest energy. This conformation is **staggered**. The conformation in which the hydrogen atoms are closest to one another has the highest energy. This conformation is **eclipsed**. In the eclipsed conformation, each C—H bond on one carbon atom lines up with a C—H bond on another carbon atom, as the moon sometimes eclipses the sun. "Sawhorse" representations of the conformations of ethane are shown in Figure 4.2. These representations are three-dimensional and show the carbon–carbon bond as well as all of the C—H bonds.

Figure 4.2
Conformations of Ethane
Rotating the methyl group on the right by 60° converts a staggered conformation into an eclipsed conformation. Viewing the carbon–carbon bond end-on in the eclipsed conformation, we would see the carbon atom and three hydrogens of the carbon on the right. The left carbon and its three hydrogens would be hidden.



Newman Projection Formulas

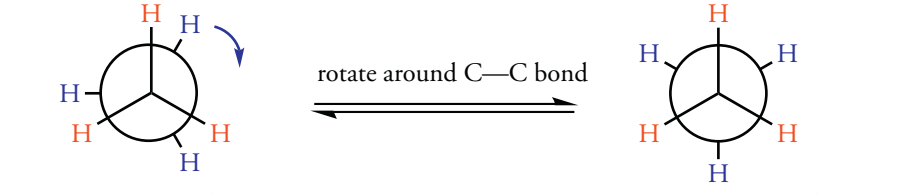
Newman projection formulas of structures concentrate on the two carbon atoms around which rotation may occur. The two atoms are viewed end on. The "front" atom is represented by a point with three bonds. The "back" atom is represented by a circle with three bonds that reach only to the perimeter of the circle. Although there is a bond between the two carbon atoms, it is hidden because it is located along the viewing axis.



A Newman projection of the eclipsed conformation of ethane shows only the three C—H bonds of the front carbon atom. The bonds and hydrogen atoms at the back are hidden by the front eclipsing bonds and hydrogen atoms. However, the bonded hydrogen atoms of the back carbon atom can be shown by viewing the conformation slightly off the bond axis so that all bonds can be seen.

Barrier to Rotation in Ethane

Conformations interconvert by rotation around σ bonds. When the eclipsed conformation of ethane is rotated by 60° around the C—C axis, the staggered conformation is produced. Continued rotation by another 60° gives a new eclipsed conformation equivalent to the first. Continued rotation results in a series of staggered and eclipsed conformations. Figure 4.3 shows a plot of potential energy versus the angle of rotation for a complete 360° rotation around the C—C bond. The energy difference between the staggered and eclipsed conformations is 12.5 kJ $mole^{-1}$.



The eclipsed conformation has a higher energy because of **torsional strain** because the bonded electrons in the C—H bonds repel one another as they approach and pass one another other in the eclipsed conformation. Hence, there is a small barrier to rotation. Dividing the energy difference between the staggered and eclipsed conformations by 3, we obtain the energy of a hydrogen–hydrogen eclipsing interaction, 4.2 kJ mole^{-1}. The difference in energy between eclipsed and staggered conformations is so small that rapid interconversion among these conformations occurs at room temperature. Therefore, rotation around the C—C bond is virtually free or unrestricted at room temperature.

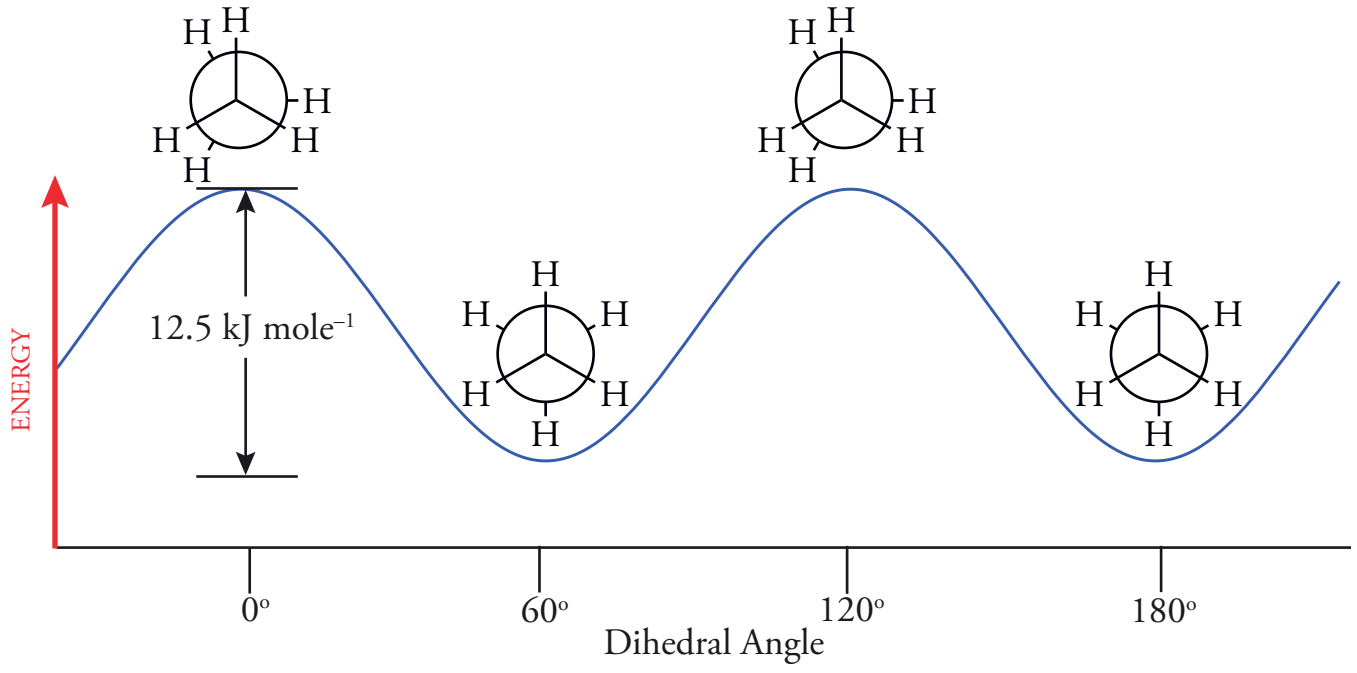


Figure 4.3
Rotational Barrier for Conformations of Ethane
Rotation around the carbon–carbon bond of ethane in 60° increments gives a series of alternating eclipsed and staggered conformations. The eclipsed conformation is 12.6 kJ mole^{-1} higher in energy than the staggered conformation. Each hydrogen–hydrogen interaction contributes 4.2 kJ mole^{-1} to the total energy barrier.

Table 4.3
Van der Waals Radii

Group	*Radius (pm)*
CH_3	200
CH_2	200
Br	195
Cl	180
F	135
H	120

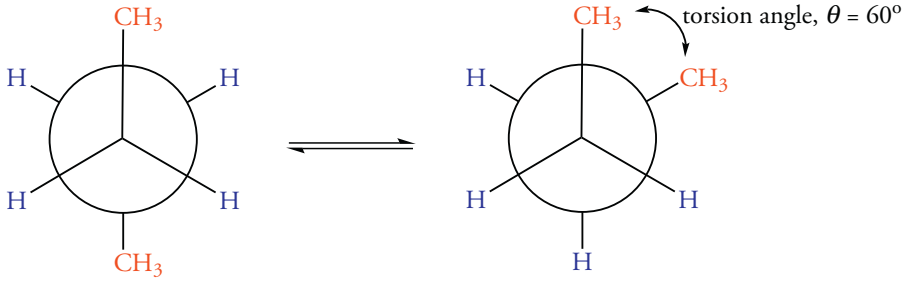
Conformations of Propane

Figure 4.4 shows the energy of propane as rotation occurs around a carbon–carbon bond. As in ethane, the eclipsed conformation has the higher energy. The energy difference is 13.8 kJ mole^{-1}. The eclipsed conformation of propane has two hydrogen–hydrogen eclipsing interactions and one hydrogen–methyl group eclipsing interaction. Because each of the two hydrogen–hydrogen eclipsing interactions is 4.2 kJ mole^{-1}, we conclude that the hydrogen–methyl interaction is 5.4 kJ mole^{-1}.

When two or more atoms are forced together, they repel each other, and experience **van der Waals repulsion** as the electrons associated with each atom start to occupy a common space. The effective size of atoms is given by the van **der Waals radii** (Table 4.3), which are related to how close atoms or groups can come without severe repulsion. Van der Waals repulsion is also called **steric hindrance**, and the energy of that interaction is **steric strain**. In the eclipsed conformation of propane, the hydrogen atoms at C-1 and C-3 are not close enough to produce a large van der Waals repulsion.

Conformations of Butane

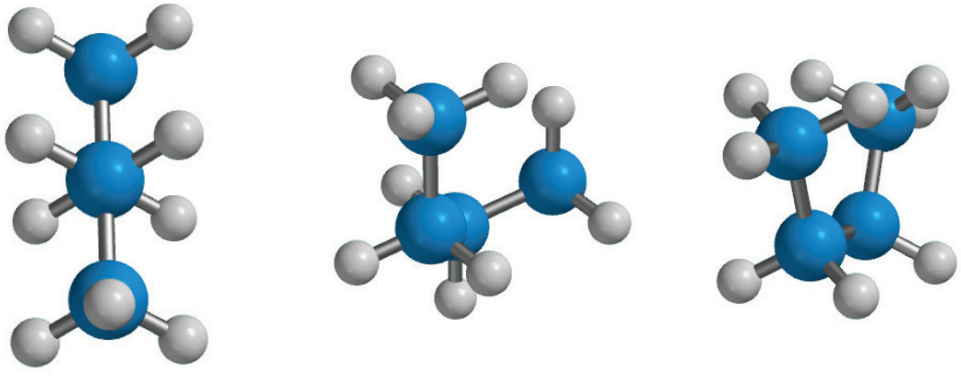
Like ethane and propane, butane can exist in both eclipsed and staggered conformations that result from rotation around either the C-1 to C-2 bond or between the C-2 and C-3 bond. The angle between a front bond and a back bond in a Newman projection is called the **torsional angle** or **dihedral angle**, θ. In the **gauche** conformation of butane, the methyl groups lie at a 60° dihedral angle. The dihedral angle between the methyl groups is 180° in the ***anti*** conformation.



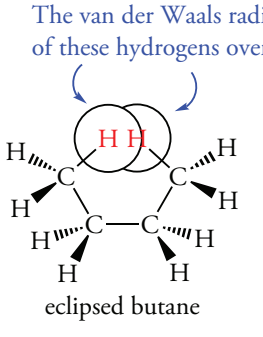
anti butane gauche butane

The two staggered conformations of butane differ in energy by 3.8 kJ mole^{-1}. The anti conformation is more stable, and at 298 K, the ratio of anti to gauche conformation is about 2:1. The anti and gauche conformations interconvert about 10^8 times per second at room temperature.

Since there is no torsional strain in the two staggered conformations of butane, and the dihedral angle between each set of bonded pairs is 60°, why do the energies of the two conformations differ? In the gauche conformation, the two methyl groups lie at a 60° angle and the resulting van der Waals repulsion causes steric strain. We can understand why van der Waals repulsion occurs in the gauche conformation by using the simple atom-counting process we described previously for the eclipsed conformation of propane. Consider a planar arrangement of six atoms in which all bond angles are the tetrahedral angle, 109°.



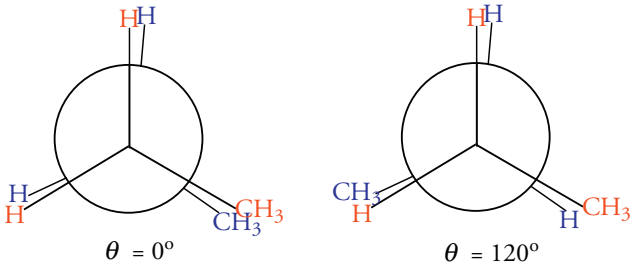
anti butane gauche butane eclipsed butane



eclipsed butane

In this arrangement, atoms 1 and 6 would have to occupy the same region of space! Although the atoms in the gauche conformation of butane are not in a common plane, they are close enough to experience significant van der Waals repulsion.

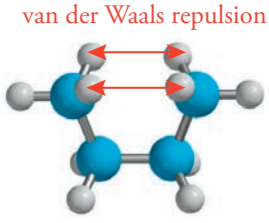
The two staggered conformations of butane are more stable than the two possible eclipsed conformations, which are present to only a limited extent.



eclipsed butane conformations

Let's consider the eclipsed conformation having a dihedral angle of 120°. This conformation has one hydrogen–hydrogen eclipsing interaction and two hydrogen–methyl eclipsing interactions. Thus, the energy is greater than that of the anti conformation by $4.2 + 2 \times 5.4 = 15$ kJ mole^{-1}.

The eclipsed conformation with $\theta = 0$ has two sets of hydrogen–hydrogen eclipsing interactions and one methyl–methyl interaction. The total energy of this conformation is estimated as 21 kJ mole^{-1} greater than the anti conformation. Because the two hydrogen–hydrogen eclipsing interactions account for 8.4 kJ mole^{-1}, we calculate a value of 12.6 kJ mole^{-1} for the methyl–methyl eclipsing interaction. This value is substantially larger than the 4.2 and 5.4 kJ mole^{-1} for the hydrogen–hydrogen and the hydrogen–methyl eclipsing interactions. When the dihedral angle is 0°, all four carbon atoms lie in a plane. The hydrogen atoms on the two terminal methyl groups have severe van der Waals repulsion.



eclipsed butane

Figure 4.5 shows a plot of potential energy of the various conformations of butane as a function of dihedral angle. The maxima of the graph correspond to the eclipsed conformations and the minima to the staggered conformations.

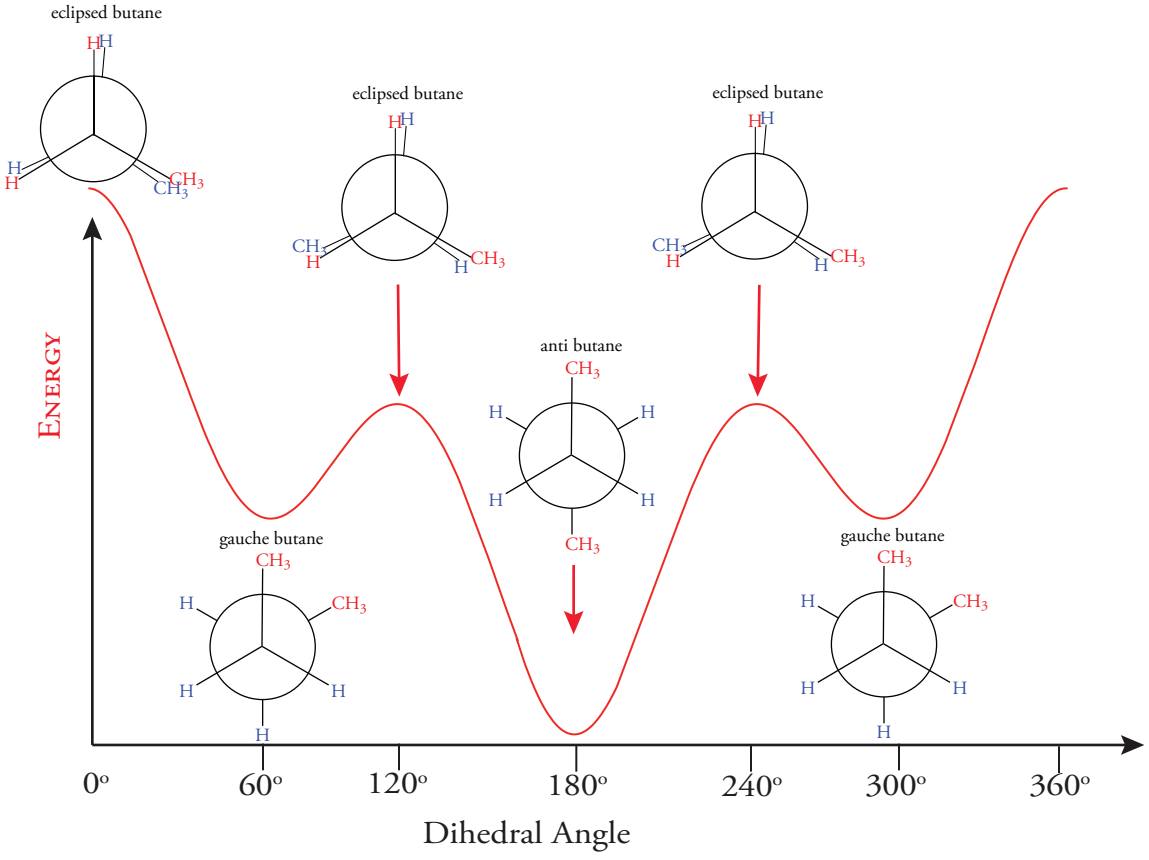


Figure 4.5
Rotational Barrier for Conformations of Butane
Rotation around the C2—C3 bond of butane starting from a methyl–methyl eclipsed conformation gives two nonequivalent eclipsed and two nonequivalent staggered conformations. The gauche conformation is 3.8 kJ mole^{-1} higher in energy than the anti conformation.

Problem 4.12
Predict the energy difference between the eclipsed and staggered conformations of 2-methylpropane around the C-1 to C-2 bond.

Conformations of Acyclic Compounds

We can expand our discussion of the relative energies of the conformations of ethane, propane, and butane to the energies of the conformations of the higher alkanes. We now know the following properties of ethane, propane, and butane.

1. The lowest energy conformations have a staggered arrangement for all bonds.
2. Staggered conformations with $\theta = 180°$ are more stable that those with $\theta = 60°$.
3. The energy of eclipsing increases in the order hydrogen–hydrogen < hydrogen–alkyl < alkyl–alkyl conformation.

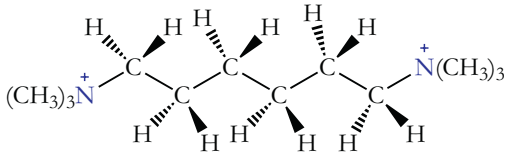
Table 4.4 summarizes the energies of each of the possible interactions in the conformations of alkanes

Table 4.4

Energies of Steric Interactions in Alkanes

Interaction	*Major cause*	*Energy (kJ mole^{-1})*
Eclipsed H/H	Torsional	4.2
Eclipsed H/CH_3	Torsional	5.4
Eclipsed CH_3/CH_3	Torsional + steric	12.6
Gauche CH_3/CH_3	Steric	3.8
Gauche H/H (reference)	Torsional + steric	0

The conformations of substituted alkanes are affected by their functional groups. Charged groups attract each other if they have opposite charges, and repel each other if they have like charges. For example, hexamethonium, which blocks nerve transmission at neuromuscular junctions by binding the acetylcholine receptor, has ammonium ions at C-1 and C-6. The two positively charged nitrogen atoms stay as far apart as possible, considerably stabilizing the all *anti* conformation.

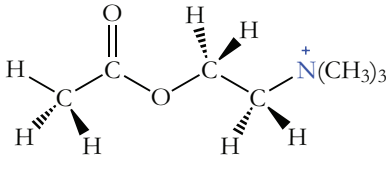


hexamethonium, all *anti* conformation

Conformations and Biological Activity

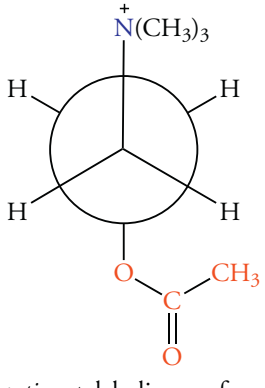
The conformational flexibility of small cellular molecules determines how they bind to proteins called receptors. The interaction of a receptor protein with a small molecule, called a ligand, plays a significant role in regulating physiological functions. An understanding of small molecule-receptor binding is required to design drugs that mimic the response of physiologically active cellular molecules, or that inhibit the activity of the receptor protein.

The neurotransmitter acetyl choline provides an example of this phenomenon.

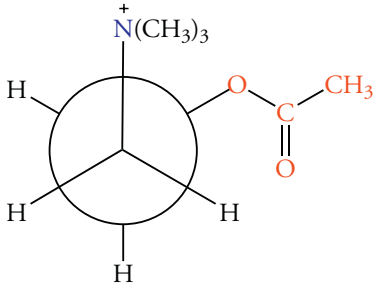


acetyl choline

Different conformations of acetylcholine bind different receptors. The gauche conformation binds the muscarinic receptor of postganglionic parasympathetic nerves; the *anti* conformation binds nicotinic receptors at ganglia and the acetylcholine receptor at neuromuscular junctions.



anti acetylcholine conformation

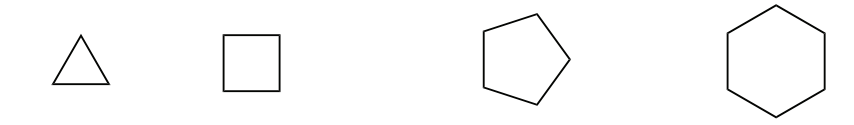


gauche acetylcholine conformation

The physiological properties of different conformations of biologically active molecules have been studied by examining the properties of geometric isomers of structurally related compounds. These compounds, which are cyclic analogs of the naturally occurring compounds, have functional groups placed to mimic the conformations of the open chain compounds.

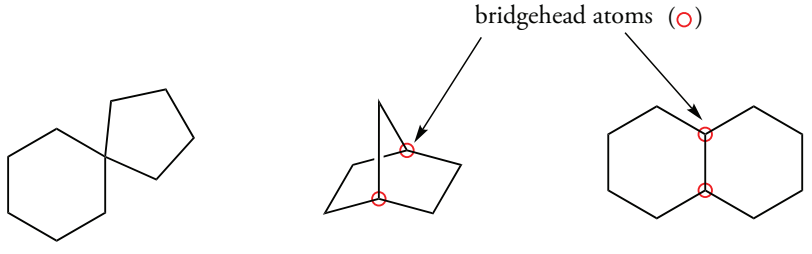
4.5 CYCLOALKANES

Cycloalkanes with one ring have the general formula C_nH_{2n} compared with the general formula $C_nH_{(2n+2)}$ for acyclic alkanes. Cycloalkanes have two fewer hydrogen atoms than alkanes because another carbon–carbon bond is needed to form the ring. Cycloalkanes are drawn as simple polygons in which the sides represent the carbon–carbon bonds. It is understood that each corner of the polygon is a carbon atom bonded to two hydrogen atoms.



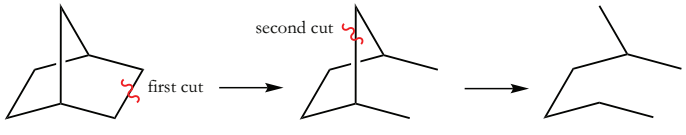
cyclopropane cyclobutane cyclopentane cyclohexane

Multiple rings in a molecule can share one or more common atoms. **Spirocyclic** compounds share one carbon atom between two rings. These compounds are relatively rare in nature. Fused ring compounds share two common atoms and the bond between them. These compounds are prevalent in steroids, which contain four fused rings. **Bridged ring** compounds share two nonadjacent carbon atoms, which are called the bridgehead carbon atoms. These compounds are less prevalent in nature than **fused ring** compounds, but more common than spirocyclic compounds. A few examples are shown below.



spirocyclic compound bicyclic compound fused-ring compound

Each ring system shown above has two rings: they are **bicyclic** compounds. This is obvious for the spirocylic compound and the fused ring compound. The bridged ring compound appears at first sight to have three rings, but it has only two. We can determine how many rings are present in a ring system by determining the minimum number of "cuts" that are required to give an acyclic compound. Two such cuts are necessary for the bridged ring system shown above. The first cut gives a single ring, and the second cut gives an acylic compound.



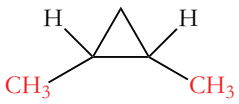
Geometric Isomerism

Constitutional isomers are compounds with different carbon skeletons, different functional groups, and different functional group locations. These isomers have different sequential arrangements of atoms. Now let us consider a different type of isomerism. Compounds that have the same sequential arrangement of atoms, but different spatial arrangements, are stereoisomers. This type of isomerism is stereoisomerism. Stereoisomers can exit in several ways in various classes of compounds. For example, cycloalkanes can exist as stereoisomers called **geometric isomers**.

We will begin with cyclopropane, whose three carbon atoms define a plane. Any group attached to the ring may be held "above" or "below" the plane of the ring. If we attach two methyl groups on adjacent carbon atoms on the same side of the plane of the ring, the substance is called a ***cis*** isomer; it is *cis*-1,2-dimethylcyclopropane. If the two methyl groups are attached on the opposite sides of the

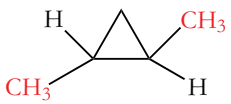
plane of the ring, the compound is the ***trans*** isomer. Thus, 1,2-dimethylcyclopropane can exist as both *cis* and *trans* isomers. This specific type of stereoisomerism is also known as **geometric isomerism**.

cis isomer

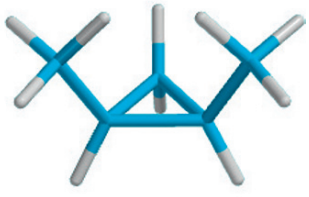


Both methyl groups are on the same side of the plane of the ring atoms.

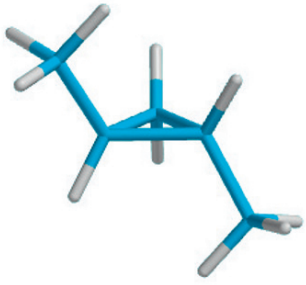
trans isomer



One methyl group is above the plane; the other is below the plane of the ring atoms.

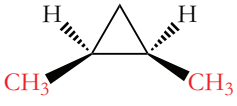


cis-1,2-dimethylcyclopropane

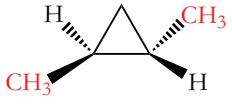


trans-1,2-dimethylcyclopropane

In the structures shown below, the ring atoms are in the plane of the page. Heavy wedge-shaped lines indicate groups above the ring plane, and dashed wedges indicate groups below the plane of the ring.



cis-1,2-dimethylcyclopropane

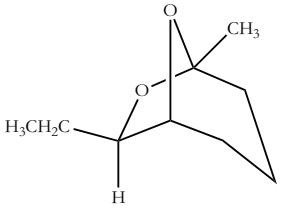


trans-1,2-dimethylcyclopropane

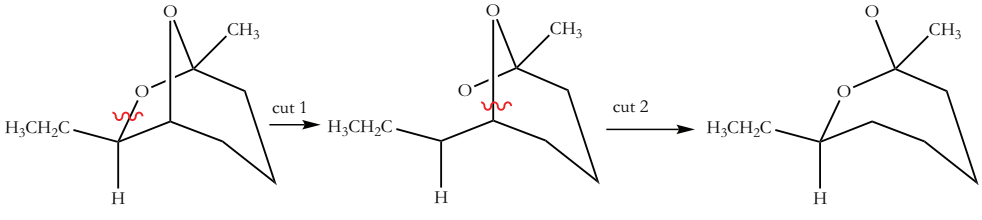
Geometric isomers have different physical properties. It is impossible to convert one geometric isomer into the other without breaking a bond.

Problem 4.13

Classify brevicomin, the sex attractant of a species of pine beetle, according to the number of rings it contains.

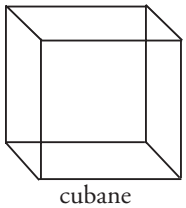


Sample Solution Select one site to "cut" and then continue at other sites until no ring remains. Two cuts at C—O bonds are required to give an acylic compound, so brevicomin is a bicyclic compound.



Problem 4.14

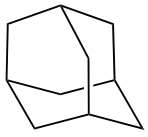
Cubane, classified as a pentacyclic compound, appears to have six rings. Apply the bond-cutting procedure to show that it really does have five rings.



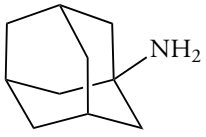
cubane

Problem 4.15

Adamantane has a carbon skeleton also found as part of the structure of diamond. Amantadine, which has an amino group bonded to the adamantane structure, is useful in the prevention of infection by influenza A viruses. What are the molecular formulas of adamantane and amantadine? How many rings are in each structure?



adamantane



adamantadine

Problem 4.16

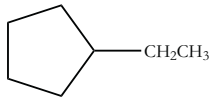
Disparlure, the sex attractant pheromone of the female gypsy moth, has the following general structure. Are geometric isomers possible for this molecule?



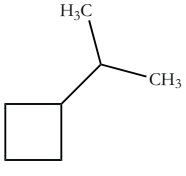
disparlure

Nomenclature of Cycloalkanes

Cycloalkanes are named according to the IUPAC system by using the prefix *cyclo-*. When only one position contains a functional group or alkyl group, only one compound is possible, as in ethylcyclopentane and isopropylcyclobutane, whose structures are shown below.

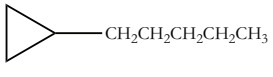


ethylcyclopentane

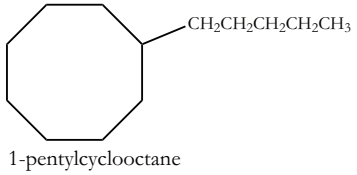


isopropylcyclobutane

If the alkyl chain has more carbon atoms than the cycloalkane ring, the compound is named as a cycloalkane. For example, a compound that has a pentyl group bonded to a cyclopropane ring is named as a **cycloalkylalkane** because there are more carbon atoms in the alkyl group than in the ring. In contrast, a compound that has a pentyl group bonded to a cyclooctane ring is named as a alkylcycloalkane because there are more carbon atoms in the ring than in the alkyl group.



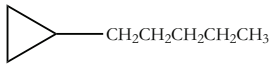
1-cyclopropylpentane



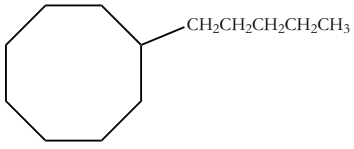
1-pentylcyclooctane

When two substituents such as alkyl groups or halogens atoms are attached to the ring, the ring atoms are numbered from the carbon atom bearing the atom having "alphabetical priority." For example, ethyl has priority over methyl. That substituent is at position 1, and the ring is numbered in a clockwise or counterclockwise direction to give the lower number to the position with the next substituent attached to the ring, as in *trans*-1-bromo-3-ethylcyclohexane and *cis*-1-ethyl-2-methylcyclopentane.

If the alkyl chain has more carbon atoms than the cycloalkane ring, the compound is named as a cycloalkane. For example, a compound that has a pentyl group bonded to a cyclopropane ring is named as a **cycloalkylalkane** because there are more carbon atoms in the alkyl group than in the ring. In contrast, a compound that has a pentyl group bonded to a cyclooctane ring is named as a alkylcycloalkane because there are more carbon atoms in the ring than in the alkyl group.

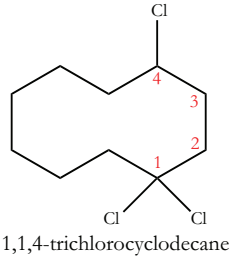


1-cyclopropylpentane

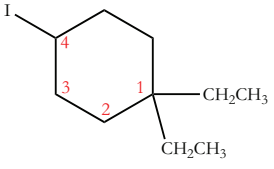


1-pentylcyclooctane

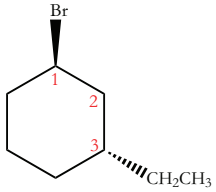
When two substituents such as alkyl groups or halogens atoms are attached to the ring, the ring atoms are numbered from the carbon atom bearing the atom having "alphabetical priority." For example, ethyl has priority over methyl. That substituent is at position 1, and the ring is numbered in a clockwise or counterclockwise direction to give the lower number to the position with the next substituent attached to the ring, as in *trans*-1-bromo-3-ethylcyclohexane and *cis*-1-ethyl-2-methylcyclopentane.



1,1,4-trichlorocyclodecane



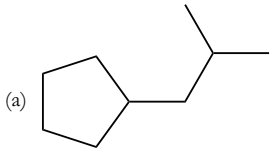
1,1-diethyl-4-iodo-cyclohexane

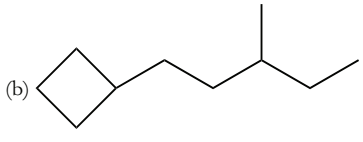


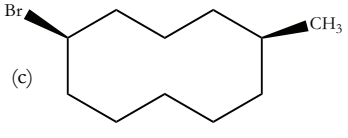
trans-1-bromo-3-ethylcyclohexane

Problem 4.17

What are the names of the following compounds?







Relative Stabilities of Cycloalkanes

Next, let us consider the structures of cycloalkanes and ask if there are any differences in their stabilities. To do this, we can compare the standard enthalpy changes that occur when the compounds are formed from their elements, a quantity called the standard heat of formation, $\Delta H°_f$. Table 4.5 lists the heats of formation of cycloalkanes.

Table 4.5
Heats of Formation of Cycloalkanes

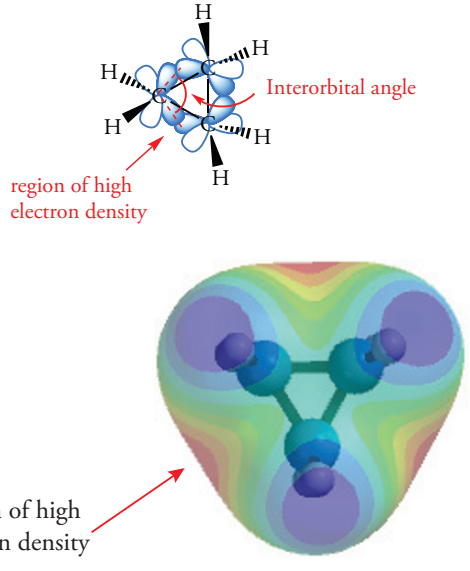
Cycloalkane	$\Delta H°_{formation}$ *kJ mole^{-1}*	$\Delta H°_{f}$ *(per CH_2 group) kJ mole^{-1}*	*Strain Energy kJ mole^{-1}*
Cyclopropane	+53	+17.8	115
Cyclobutane	+28.4	+7.1	111
Cyclopentane	–77.10	–15.4	26
Cyclohexane	–123.19	–20.5	0
Cycloheptane	–118.1	–16.9	26
Cyclooctane	–124.4	–15.9	40
Cyclononane	–132.6	–14.7	53
Cyclodecane	–154.3	–15.4	52
Alkane (reference)		–20.6	0

Column three of Table 4.5 also lists the heat of formation per CH_2 unit in cycloalkanes, which is obtained by dividing the heat of formation by the number of carbon atoms— the same as the number of —CH_2— groups in the compound. If the stabilities of the cycloalkanes were all more or less the same, then the values in column three of Table 4.5 should also be about the same. But, they aren't. If we examine the heats of formation of alkanes that differ from one another by one CH_2 unit, we find that they differ by 20.6 kJ mole^{-1}. The heat of formation per CH_2 group for cyclohexane is 20.5 kJ mole^{-1}, not much different from the value observed for the alkanes. The heats of formation per CH_2 group for most cycloalkanes are similar, ranging from 15 to 20 kJ mole^{-1}. There are two conspicuous exceptions: cyclopropane and cyclobutane. The standard heats of formation of the latter two compounds are *positive*, which indicates that they are unstable. Why is that?

To answer this question, let's examine the bonding in cyclopropane to see why its heat of formation is positive rather than negative. Cyclopropane has a positive standard heat of formation which indicates that its carbon–carbon bonds are not as strong as those in alkanes or in cycloalkanes having five or more carbon atoms. The strongest bonds form when two orbitals achieve maximum overlap because this minimizes nuclear repulsion. Maximum overlap occurs when orbitals are directed toward each other along the internuclear axis, shielding the nuclear charges from each other. The linear overlap of sp^3 hybrid orbitals results in tetrahedral C—C—C bond angles in alkanes and in most cycloalkanes. Strong sp^3–sp^3 carbon–carbon σ bonds are not possible in cyclopropane, a planar molecule whose C—C—C bond angle is 60°, which is far from the tetrahedral bond angle of 109°. Therefore, the electron density in the carbon–carbon bonds is distributed in an arc that lies outside the area described by the internuclear axis (Figure 4.6). These "bent" bonds are weaker than other carbon–carbon σ bonds.

Figure 4.6
Structure and Bonding in Cyclopropane

Cycloalkanes that do not have internuclear angles of 109.5° cannot have efficient overlap of hybrid orbitals. The internuclear bond angle of cyclopropane is 60°, far less than 109.5°. However, the interorbital angle is larger. As a result, the electron density lies "outside" the bond axis and is called a *bent bond*, or sometimes, more whimsically, a banana bond.



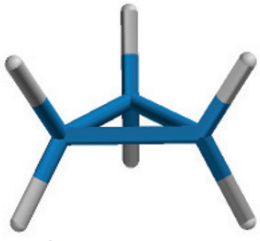
Because orbital overlap in cyclopropane is poor, cyclopropane is less stable per CH_2 unit than cycloalkanes, in which effective overlap of sp^3 hybrid orbitals can occur. This instability is termed **ring strain**. Ring strain is calculated by multiplying the number of carbon atoms (n) by 20.6 kJ mole^{-1}, the "strain-free" heat of formation value for a CH_2 unit, and subtracting this quantity from the experimental heat of formation. The strain energy of cyclopropane is approximately 114 kJ mole^{-1}. The strain energies of cycloalkanes are given in column four of Table 4.5. These values represent the "extra" energy contained in the molecule as a result of ring strain.

$$\Delta H^\circ_f - n(20.6 \text{ kJ mole}^{-1}) = \text{ring strain energy}$$

Now let's compare the strain energies of cyclobutane and cyclopropane. Cyclobutane has an internuclear angle of 90°, closer to the tetrahedral angle than the 60° internuclear bond angle in cyclopropane. Thus, the carbon–carbon bonds in cyclobutane are not as bent as in cyclopropane and should be less strained. But when we look at the ring strain of the two compounds, we find that the total strain energy of cyclobutane is only slightly smaller than the strain energy of cyclopropane. However, there are four strained carbon–carbon bonds in cyclobutane rather than three. To take this difference into account, we divide the total ring strain by the number of carbon–carbon bonds. When we do this, we find that the ring strain per bond is 38 kJ mole^{-1} for cyclopropane and 28 kJ mole^{-1} for cyclobutane. Therefore, the strain energy per bond is greater in cyclopropane than in cyclobutane. For cycloalkanes with more than six carbon atoms, the strain energy per bond ranges from 1 to 5 kJ mole^{-1} and averages about 2 kJ mole^{-1}.

4.6 CONFORMATIONS OF CYCLOALKANES

Many naturally occurring compounds in plants and animals contain cyclic structures. For example, steroids are polycyclic structures consisting of five- and six-membered rings made up of only carbon atoms. Carbohydrates are heterocyclic compounds containing one oxygen atom in a ring along with four or five carbon atoms. Rings of this type are components of the nucleotides that make up DNA and RNA. These are important compounds, and we will see them again and again.



Cyclopropane

Cyclopropane

Cyclopropane has only three carbon atoms, so it is a planar molecule. It is strained because the "bent" carbon–carbon bonds overlap poorly. The total ring strain in cyclopropane is 114 kJ mole^{-1}. This strain energy is not exclusively angle strain, which results from weaker bonds formed by less efficient overlap of the hybrid orbitals of the ring carbon atoms. Other kinds of strain also contribute to the total ring strain. Cyclopropane has six pairs of hydrogen–hydrogen eclipsed interactions. We recall that a hydrogen–hydrogen eclipsing interaction in ethane is 4.2 kJ mole^{-1}. Although the bond angles are not the same in cyclopropane as in ethane, we can estimate that the total torsional strain energy is $6 \times 4.2 = 25.2$ kJ mole^{-1}. Because the total strain energy is 114 kJ mole^{-1}, about three quarters of the total strain energy results from bond angle strain.

Cyclobutane

Cyclobutane is not planar. If it were, there would be eight pairs of eclipsed hydrogen atoms, which would account for $8 \times 4.2 = 33.6$ kJ mole^{-1} of the total strain energy of cyclobutane. However, in contrast to cyclopropane, cyclobutane is not planar but "puckered" (Figure 4.7). Puckering, which arises when hydrogen atoms are twisted away from each other, reduces hydrogen–hydrogen eclipsing interactions. This twisting does not produce a fully staggered arrangement of hydrogen atoms because the decrease in torsional strain energy is balanced by some increase in the bond angle strain.

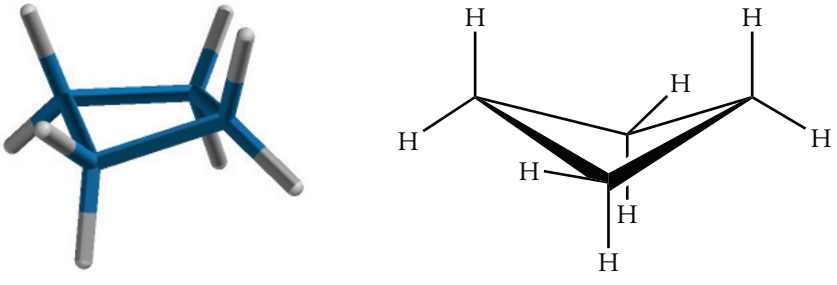


Figure 4.7
Conformation of Cyclobutane
The conformation of cyclobutane is a slightly bent or twisted ring, which moves the hydrogen atoms away from one another so that they are not completely eclipsed.

Cyclopentane

A cyclopentane ring can exist in a planar conformation with little angle strain because the internal angle of a pentagon is 108°, quite close to the tetrahedral angle of 109°. However, if cyclopentane were planar, all 10 hydrogen atoms would be eclipsed, and the torsional energy would be $10 \times 4.2 = 42$ kJ mole^{-1}. This undesirable state of affairs can be minimized by twisting the cyclopentane ring into a lower energy, nonplanar, conformationally mobile conformation called the **envelope** conformation (Figure 4.8).

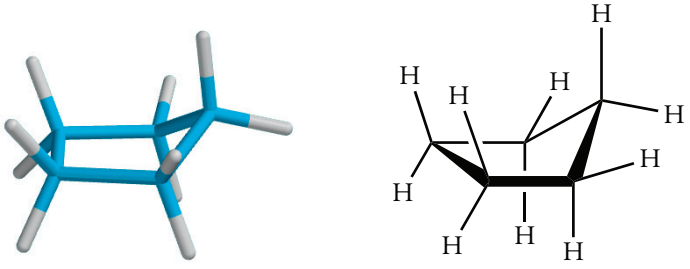


Figure 4.8
Conformations of Cyclopentane
Cyclopentane is a twisted ring in the form of an "envelope" so that one of the carbon atoms is out of the plane of the ring. This decreases the number of eclipsing interactions of hydrogen atoms on adjacent carbons.

Cyclohexane

Cyclohexane exists mainly in a conformation in which all C—H bonds on neighboring carbon atoms are staggered, with dihedral angles equal to 60°. Figure 4.9 shows a bond-line representation of the **chair conformation** of cyclohexane. Four of the carbon atoms form the "seat" of the chair, one carbon atom is the "back" of the chair, and one carbon atom is the "foot rest."

Hydrogen atoms in the chair conformation fall into two sets. Six point up or down with respect to the average plane of the ring of carbon atoms. They are **axial**. If a particular axial hydrogen atom points "up," the axial hydrogen atoms on the two adjacent carbon atoms point "down." This up-down relationship alternates all the way around the ring. The remaining six hydrogen atoms lie approximately in the average plane of the ring. They extend away from the ring and are called **equatorial** atoms. Each carbon atom has one equatorial and one axial C—H bond.

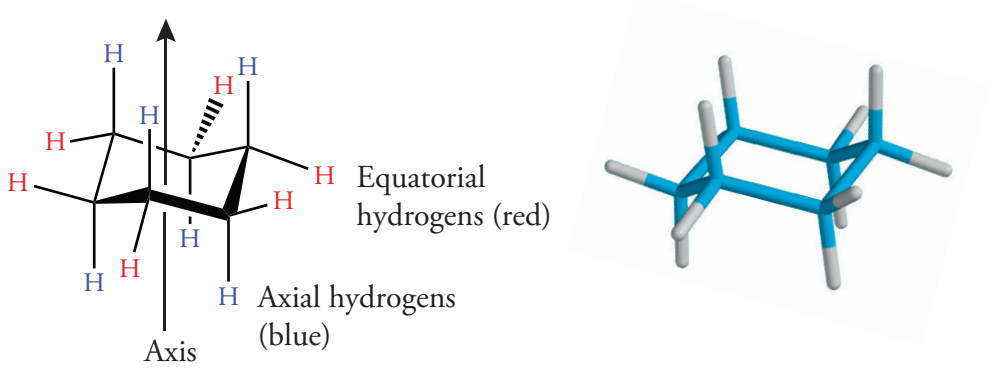
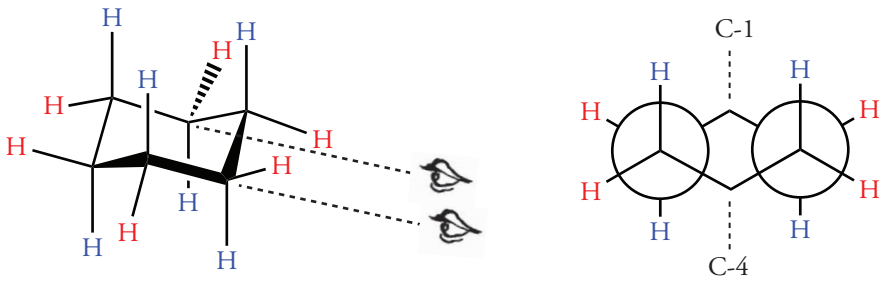


Figure 4.9
Conformations of Cyclohexane
The equatorial C—H bonds lie in a band around the "equator" of the ring. Each carbon atom has one axial hydrogen that is perpendicular to the plane of the ring. The axial hydrogens alternate up and down moving from any axial hydrogen on one carbon to the adjacent carbon.

Cyclohexane is best studied by building a molecular model, either with a physical model or with a molecular modeling program. When we make a model of the chair conformation of cyclohexane, we can easily see the torsional relationships and the orientation of the equatorial and axial hydrogen atoms. We can also analyze the arrangement of equatorial and axial hydrogen atoms in a Newman projection formula by sighting along both the C-2 to C-3 and the C-5 to C-6 bonds (Figure 4.10). (The same perspective would result by sighting along any pair of parallel carbon–carbon bonds.) Note that the C-1 and C-4 atoms are in a gauche relationship similar to the gauche relationship between the C-1 and C-4 atoms of butane. The same relationship occurs between any two atoms separated by a CH_2CH_2 unit throughout the ring.

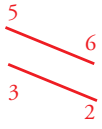
Figure 4.10
Newman Projection Formula of Cyclohexane
The C-2 to C-3 and C-5 to C-6 bonds of cyclohexane are both viewed and the two ethane-like Newman projections are written side-by-side. The C-1 and C-4 atoms are placed to join the two units, as if they were the pedals of a bicycle.



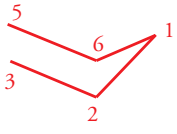
Drawing Cyclohexane Rings

We can draw the carbon skeleton of a cyclohexane ring with three sets of parallel lines having different slopes. To do this, we proceed as follows.

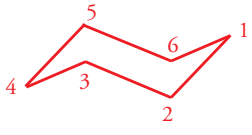
1. Draw one set of parallel lines that slant slightly downward. These are the "seat" of the chair. This orientation matches the chair conformations shown in Figures 4.9 and 4.10. The carbon atoms correspond to bonds from C-2 to C-3 and from C-5 to C-6.



2. Second, place C-1 above and to the right of C-2. Connect C-1 to C-6.



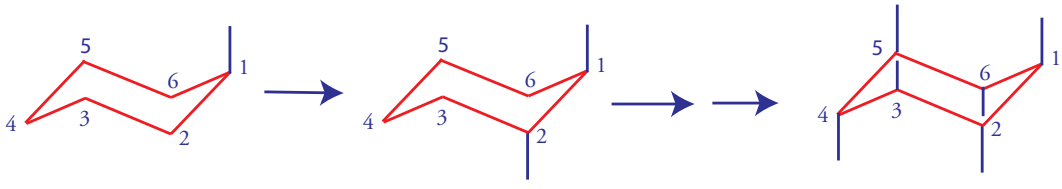
3. Third, place C-4 to the left and below C-3. Then, connect C-3 and C-5 to C-4.



When we look at this procedure, we see that we have three sets of parallel lines:

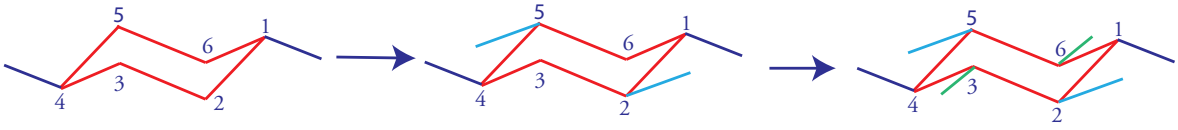
1. The lines joining C-3- to C-2 and C-5 to C-6 are parallel.
2. The lines joining C-1- to C-1 and C-5 to C-4 are parallel.
3. The lines joining C-3- to C-4 and C-1 to C-6 are parallel.

Having drawn the carbon skeleton, we next add the axial and equatorial bonds. It is easy to draw the axial bonds. Beginning at C-1 go around the ring with alternating up and down lines. Up bonds are at C-1, C-3, and C-5; down bonds are at C-2-, C-4, and C-6.



It is less easy to draw the equatorial bonds. Like the bonds in the ring itself, we can draw them as three sets of parallel lines.

1. The lines for the equatorial bonds at C-1 and C-4 are parallel.
2. The lines for the equatorial bonds at C-2 and C-5 are parallel.
3. The lines for the equatorial bonds at C-2 and C-5 are parallel.



4.7 CONFORMATIONAL MOBILITY OF CYCLOHEXANE

Chair–Chair Interconversion of Cyclohexane Rings

The most stable conformation of cyclohexane is a chair, but different chair conformations rapidly interconvert at room temperature. This process—known as a **ring inversion**, a **chair–chair interconversion**, or simply a **"ring flip"**—is shown in Figure 4.11. When the cyclohexane ring flips, every equatorial bond becomes axial and every axial bond becomes equatorial. This process can be clearly seen by practicing with molecular models. To flip a cyclohexane ring, hold the four atoms of the "seat" in place while rotating one "end" carbon downward and rotating the other "end" carbon upward. At each of these two "end" atoms, an equatorial position becomes an axial position and vice versa. The hydrogen atoms on every other carbon atom also undergo the same transformation. Viewed as a rotation around σ bonds, ring flipping turns out to be analogous to rotation around the σ bonds in acyclic compounds.

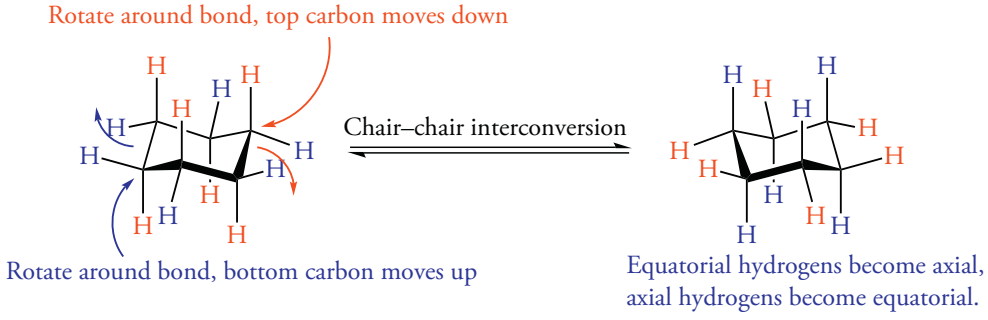


Figure 4.11
Chair–Chair Interconversion of Cyclohexane
The interconversion of two chair conformations of cyclohexane changes all equatorial hydrogens to axial hydrogens, and all axial hydrogens to equatorial hydrogens.

Boat Conformation of Cyclohexane

In the process of "flipping," the chair conformation of cyclohexane can pass through another conformation known as the **boat conformation** (Figure 4.12). The boat conformation of cyclohexane is approximately 29 kJ mole^{-1} less stable than the chair conformation. This strain is due to several factors, all of which are structurally related to the methyl–methyl eclipsed conformation of butane. We can view the steric interactions in boat cyclohexane by drawing a Newman projection. When we look along the C-2 to C-3 and the C-5 to C-6 bonds, we see that there are four pairs of eclipsed hydrogen atoms. Also, the C-1 and C-4 atoms are eclipsed, and hydrogen atoms on each carbon atom are close enough to cause even more strain.

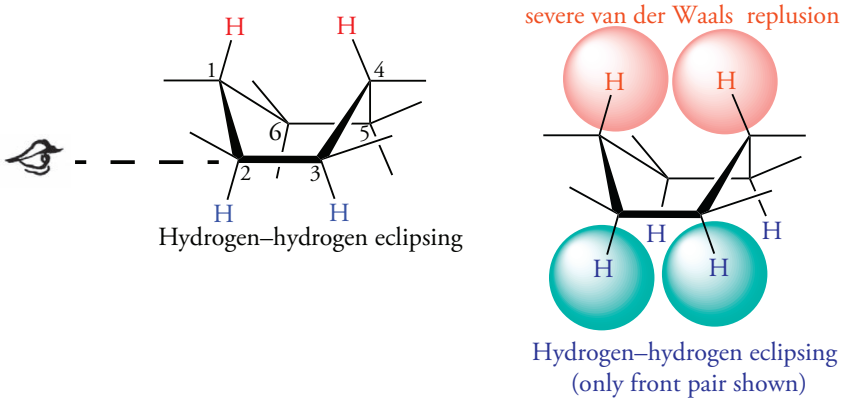
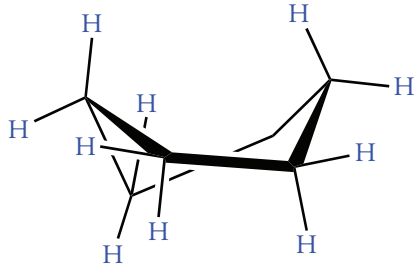


Figure 4.12
Boat Conformation of Cyclohexane
The hydrogens on C-2 to C-3 and C-5 to C-6 bonds of the boat conformation are eclipsed. Also the hydrogens at C-1 and C-4 are so close that their van der Waals radii overlap. As a result, the boat conformation is very unstable.

Twist Boat Conformation of Cyclohexane

Because the boat conformation of cyclohexane is 29 kJ mole^{-1} less stable than the chair conformation, only a tiny fraction of cyclohexane molecules exist in a boat conformation. The steric energy of the boat conformation can be lowered by rotation around the C-2 to C-3 and C-5 to C-6 bonds, which decreases the hydrogen–hydrogen eclipsing interactions. The result is a **twist boat** conformation. It is about 22 kJ mole^{-1} less stable than the chair conformation. This energy difference means that only about 0.01% of the cyclohexane molecules are in the twist boat conformation at room temperature.

The potential energies of the chair, boat, and twist boat conformations of cyclohexane can be related to one another as shown in an energy diagram (Figure 4.13). The point of maximum energy corresponds to a conformation in which a fifth carbon atom is brought into the plane of the four carbon atoms that form the "seat" of the chair. This conformation is called a **half chair**, with a potential energy of about 42 kJ mole^{-1} higher than the chair conformation. This conformation state is strained because there are increased torsional interactions as well and bond angle strain. As the half chair converts to the twist boat, its potential energy decreases. Twist boat conformations rather easily interconvert. A twist boat converts to a chair conformation by passing through a half–chair conformation. These processes take place continuously as chair conformations interconvert.



twist boat conformation

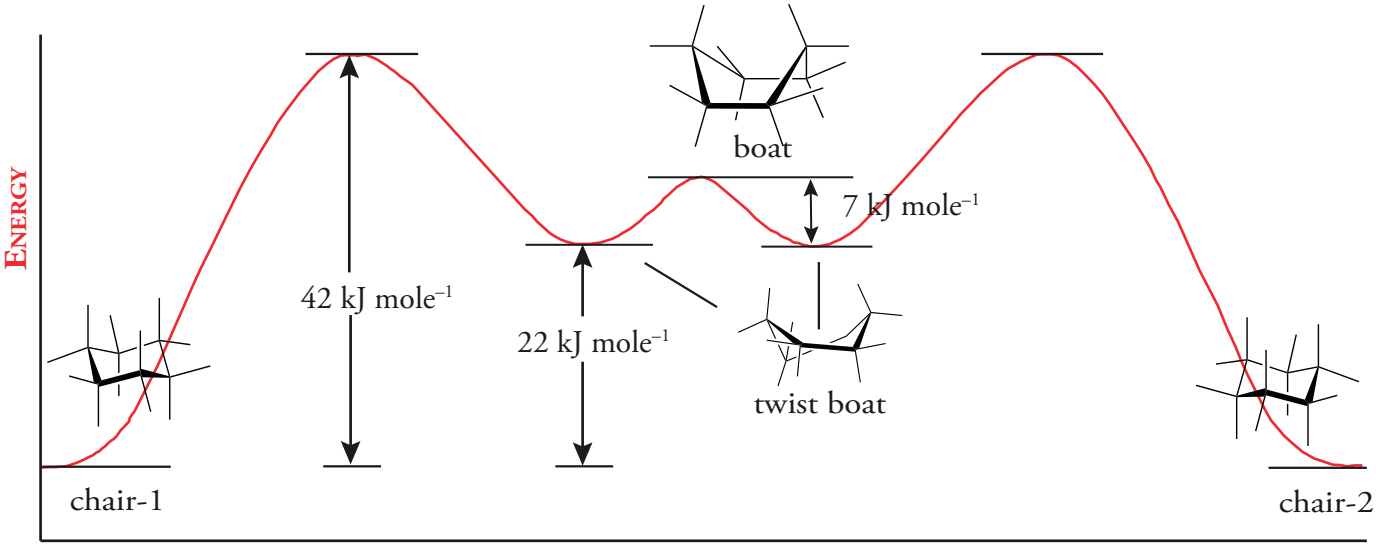
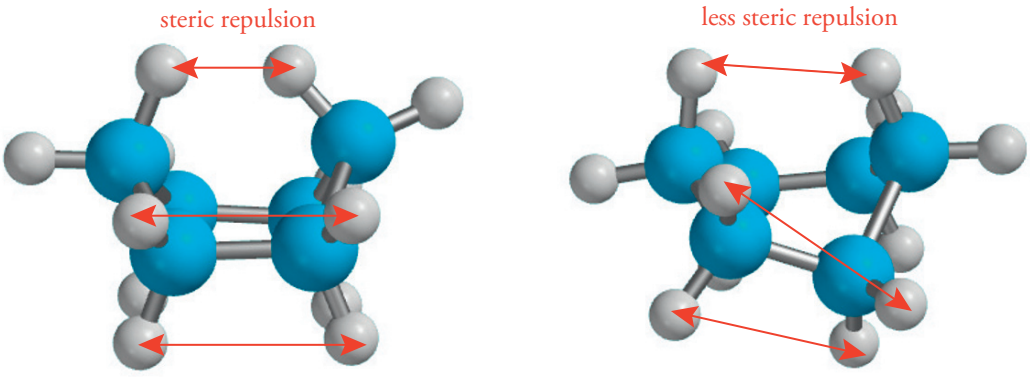


Figure 4.13
Conformational Energies of Cyclohexane
The chair–chair interconversion of cyclohexane passes through twist boat conformations that are in equilibrium with a boat conformation.



boat conformation of cyclohexane

twist boat conformation of cyclohexane

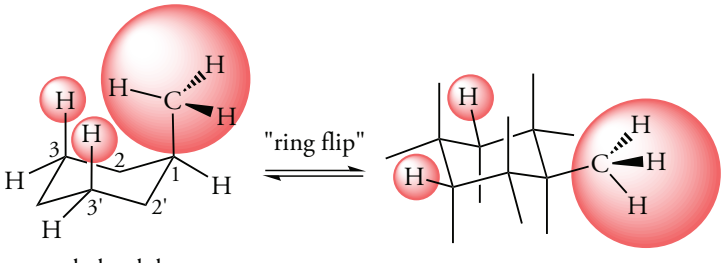
4.8 MONOSUBSTITUTED CYCLOHEXANES

We have seen that when a cyclohexane ring flips, all equatorial bonds become axial and all axial bonds become equatorial. Now let's consider the consequences of flipping a substituted cyclohexane ring. The chair–chair interconversion of monosubstituted cyclohexanes occurs very rapidly. However, the two conformations of monosubstituted cyclohexanes, unlike those of cyclohexane, are not equally stable.

Let's consider methylcyclohexane in a chair conformation with an equatorial methyl group. When the ring flips, the equatorial methyl group moves into an axial position (Figure 4.14). These two structures are different conformations, not structural isomers. A methyl group in an axial position is 8.1 kJ mole^{-1} less stable than a methyl group in an equatorial position. At equilibrium, about 95% of the mixture has an equatorial methyl group.

Figure 4.14 Conformations of Methyl Cyclohexane

Methylcyclohexane rapidly interconverts between two conformations of unequal energy. At room temperature, 95% of the conformations have an equatorial methyl group and 5% have an axial methyl group. The axial conformation has unfavorable interactions with axial hydrogens at C-3 and C-3′.



methylcyclohexane (axial methyl group)

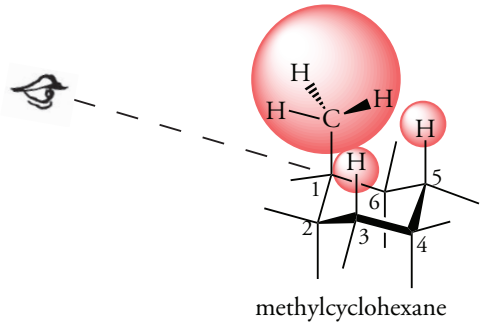
methylcyclohexane (equatorial methyl group)

Figure 4.15 1,3-Diaxial Interactions in Methylcyclohexane

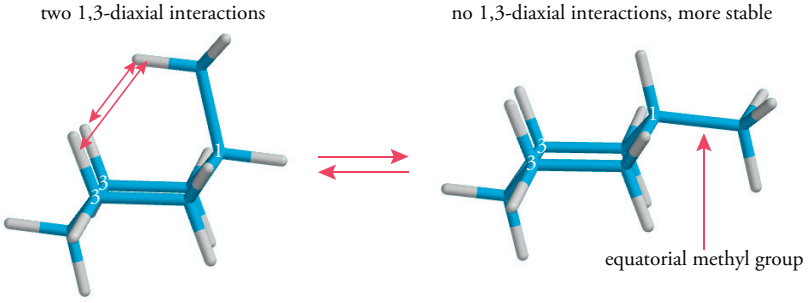
An axial methyl group is at a 60° dihedral angle with respect to the methylene groups at C-3 and C-5. This interaction is equivalent to two gauche butane interactions. Sighting down the C-1 to C-6 bond shows the eclipsing of the methyl group by the C-5 axial hydrogen atom.

two identical 1-3-diaxial interactions, equivalent to gauche butane

Look along the C-1 to C-6 bond to see the eclipsed, gauche butane interaction.



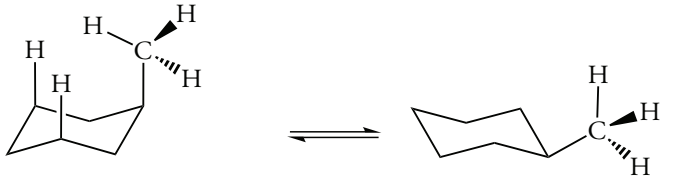
methylcyclohexane (axial conformation)



The conformation with an axial methyl group is less stable than the conformation with an equatorial methyl group because an axial methyl group experiences steric strain from axial hydrogen atoms at C-3 and C-5. This 1,3-diaxial strain is analogous to the steric repulsion between two methyl groups in the gauche conformation of butane. The same relationship occurs twice in the axial conformation of methylcyclohexane (Figure 4.15). When we examine the C-1 to C-2 bond, we see that the methyl group is at a 60° dihedral angle to C-3. A similar relationship exists between the methyl group and C-5 when the view is along the C-1 to C-6 bond. In the equatorial conformation, the methyl group is *anti* to both C-3 and C-5. Therefore, the steric strain for the axial conformation of methylcyclohexane is twice that of the gauche interaction of butane or $2 \times 3.8 = 7.6$ kJ mole^{-1}.

Table 4.6
Conformational Preferences of Groups

Group	*Strain energy (kJ mole^{-1})*
CN	0.8
F	1.0
Cl	2.8
OH	4.2
CH_3	7.6
CH_3—CH_2	8.0
$(CH_3)_2CH$	9.2
$(CH_3)_3C$	22
CO_2H	5.8



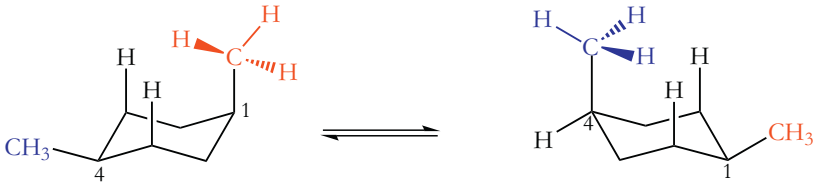
The conformational properties of other substituted cyclohexanes are similar. That is, the conformation with an equatorial substituent is always more stable than the conformation with an axial one. The conversion of an equatorial to an axial conformation is an unfavorable process. The energy difference depends upon the identity of the substituent and is called its **conformational preference**. A list of these energy differences is given in Table 4.6. The conformational preference of a substituent on a cyclohexane ring—that is, the magnitude of the 1,3-diaxial interaction—reflects its interaction with the cyclohexane ring. The conformational preferences of a methyl group, hydroxyl group, and fluorine atom decrease in the order CH_3 > OH > F. This trend reflects in part the decrease in atomic radii from left to right in the periodic table. The conformational preferences of methyl, ethyl, isopropyl, and *t*-butyl decrease in the order $(CH_3)_3C > (CH_3)_2CH > CH_3$—$CH_2 > CH_3$. The trend reflects the ease with which the alkyl group can be oriented in an equatorial site compared to an axial site. This trend parallels the "size" of the alkyl group, which corresponds to its van der Waals radius.

4.9 DISUBSTITUTED CYCLOHEXANES

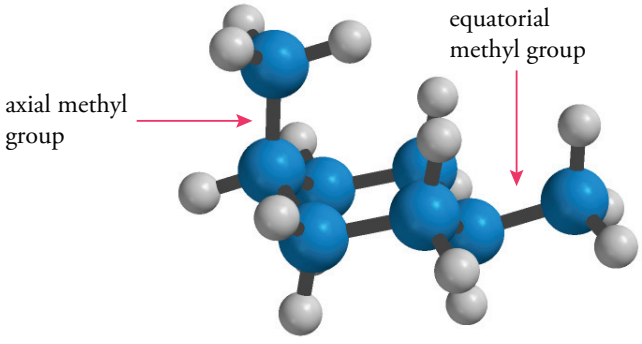
In monosubstituted cyclohexanes, the steric strain and the resulting preference for the equatorial position over the axial position result from the interaction of the substituent with the axial atoms of the ring. In disubstituted cyclohexanes, we have to consider both the inherent steric strain for each individual substituent and any interactions that may occur between the substituents.

cis- and *trans*-1,4-Dimethylcyclohexanes

We'll start with compounds in which the substituents do not interact with one another. This situation occurs in *cis*- and *trans*-1,4-dimethylcyclohexane. The two methyl groups in the *cis* isomer are on the same side of the ring. We can place both substituents on the "top" of the ring. In the following chair conformation, the "up" position at the C(1) atom is axial; the "up" position at the C-4 atom is equatorial. This conformation can convert to another conformation by a ring flip, which changes the C-1 methyl from axial to equatorial and the C-4 methyl group from equatorial to axial.



cis-1,4-dimethylcyclohexane

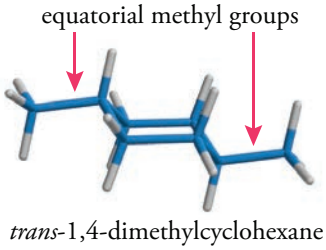


cis-1,4-dimethylcyclohexane

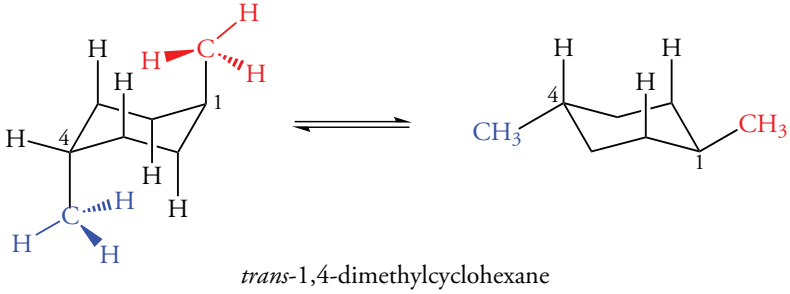
This conformational change does not alter the *cis* relationship of the methyl groups. Moreover, the two conformations are equivalent because each one has an equatorial and an axial methyl group. The steric energy of the *cis* isomer is 7.6 kJ mole^{-1}, like that of the axial conformation of methylcyclohexane.

Because *cis*-1,4-dimethylcyclohexane has an axial methyl group in both of its chair conformations, and because *trans*-1,4-dimethylcyclohexane can exist in a conformation in which both methyl groups are equatorial, the *trans* isomer is more stable than the *cis* isomer. The two geometric isomers differ in energy by 7.6 kJ mole^{-1} . This energy difference is due solely to the axial methyl group of the *cis* isomer.

Now let's consider *trans*-1,4-dimethylcyclohexane. The *trans* isomer has the two methyl groups on the opposite sides of the ring. Let's place the methyl group at the C-1 atom on the "top" of the ring, which corresponds to an axial position. The methyl group at the C-4 atom must then be placed on the "bottom" of the ring, also an axial position. A diaxial arrangement of methyl groups results in a situation that clearly has considerable steric strain.



trans-1,4-dimethylcyclohexane
(diequatorial methyl groups)



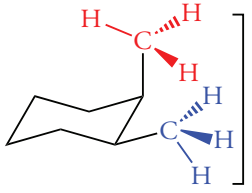
trans-1,4-dimethylcyclohexane

The steric strain of the diaxial conformation is twice that of the axial conformation of methyl-cyclohexane or 2 × 7.6 = 15.2 kJ mole^{-1}. However, interconversion of this conformation by a ring flip changes both axial methyl groups into equatorial methyl groups. The steric energy of this conformation is zero, like the equatorial conformation of methylcyclohexane. Thus, the diaxial conformation is 15.2 kJ mole^{-1} less stable than the diequatorial conformation. Because of this energy difference, approximately 99.5% of the compound exists in the diequatorial conformation at 25 °C.

Because *cis*-1,4-dimethylcyclohexane has an axial methyl group in both of its chair conformations, and because *trans*-1,4-dimethylcyclohexane can exist in a conformation in which both methyl groups are equatorial, the *trans* isomer is more stable than the *cis* isomer. The two geometric isomers differ in energy by 7.6 kJ mole^{-1}. This energy difference is due solely to the axial methyl group of the *cis* isomer.

cis- and *trans*-1,2-Dimethylcyclohexanes

Now let's consider the steric strain of 1,2-dimethylcyclohexane. To do this, we will have to consider both the inherent steric strain for each individual substituent and an interaction between the substituents because they are close to each other. The two methyl groups in *cis*-1,2-dimethylcyclohexane are on the same side of the ring. We can place both substituents on the "top" of the ring. In the following chair conformation, the "up" position at C-1 is axial and the "up" position at C-2 is equatorial. These conformations interconvert by a ring flip that changes the axial methyl at C-1 to an equatorial methyl and the equatorial methyl at C-2 to an axial methyl. The interaction between the methyl groups is equivalent to a gauche butane interaction.



cis-1,2-dimethylcyclohexane

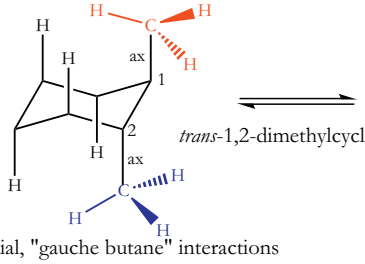


cis-1,2-dimethylcyclohexane

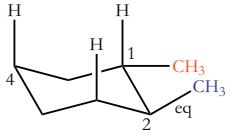
Flipping a cyclohexane ring does not alter the *cis* relationship of the methyl groups. The two conformations are equivalent because each one has an equatorial and an axial methyl group. An axial methyl group contributes 7.6 kJ mole^{-1} to the steric energy of the *cis* isomer, the same as for the axial conformation of methylcyclohexane. However, both conformations also have a gauche butane interaction between the two methyl groups. Thus, the total steric energy is 11.4 kJ mole^{-1}.

The two methyl groups in *trans*-1,2-dimethylcyclohexane are on the opposite sides of the ring. As we did for the *cis* isomer, let's place the methyl group at the C-1 atom on the "top" of the ring, which corresponds to an axial position. Then, the methyl group at the C-2 atom must be placed on the "bottom" of the ring, which is also an axial position. The steric strain of two axial methyl groups is 2(7.6 kJ mole^{-1}) = 15.2 kJ mole^{-1}.

two 1-3 diaxial, "gauche butane" interactions



trans-1,2-dimethylcyclohexane

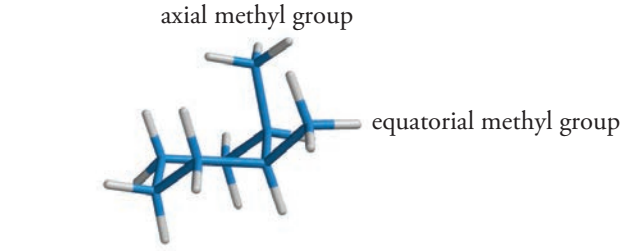


one 1-3 diaxial, "gauche butane" interaction

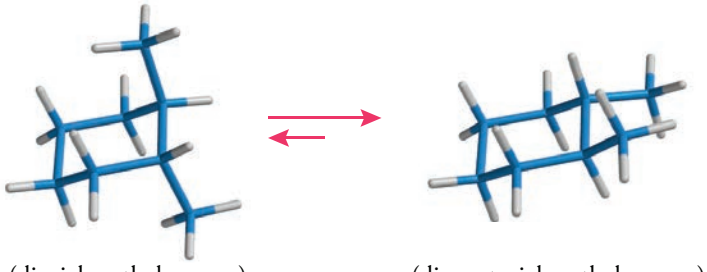
two 1-3 diaxial, "gauche butane" interactions

However, interconversion of this conformation by a ring flip changes both axial methyl groups into equatorial methyl groups. Although the 1,3-diaxial interactions are eliminated, a gauche butane interaction between the two methyl groups results. The steric strain of the diequatorial conformation is 3.8 kJ mole^{-1}. Thus, the diequatorial conformation is more stable than the diaxial conformation by 11.4 kJ mole^{-1}.

Because *cis*-1,2-dimethylcyclohexane has an axial methyl group in both of its chair conformations, and because *trans*-1,2-dimethylcyclohexane can exist in a diequatorial conformation, the *trans* isomer is more stable than the *cis* isomer.



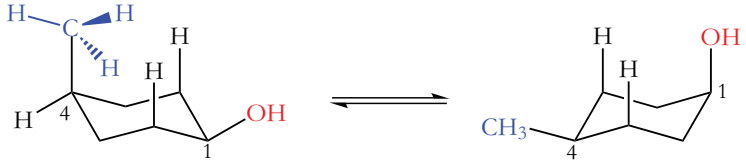
cis-1,2-dimethylcyclohexane



trans-1,2-dimethylcyclohexane

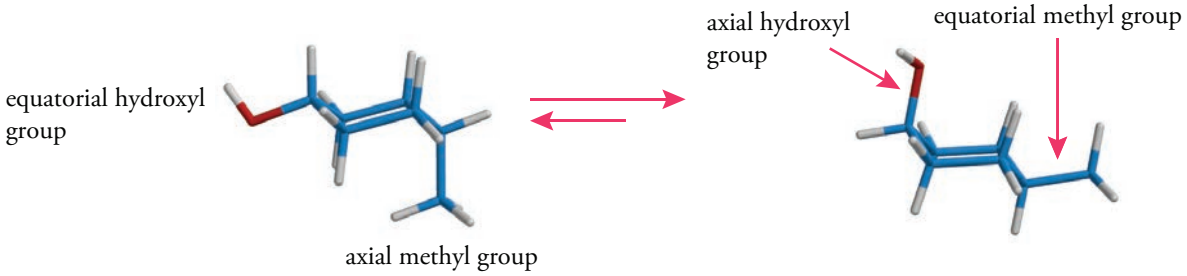
Compounds with Two Different Substituents

We can calculate the steric energy of the conformations of cyclohexanes substituted with two different substituents using the same techniques described above. For example, consider the two conformations of *cis*-4-methylcyclohexanol.



20% 80%

In the conformation on the right, the methyl group is equatorial and has no steric strain, but the steric strain of the axial hydroxyl group is 4.2 kJ mole^{-1}. In the conformation on the left, the strain energy of the methyl group is 7.6 kJ mole^{-1}, and the equatorial hydroxyl group has no steric strain. The energy difference for the interconversion of the two conformations equals the difference between their steric strain energies. The conformation on the left is more stable by 3.4 kJ mole^{-1}. At 298 K, 80% of the conformational mixture exists in the conformation that has an axial hydroxyl group and an equatorial methyl group.



Conformations of *cis*-4-methylcyclohexanol

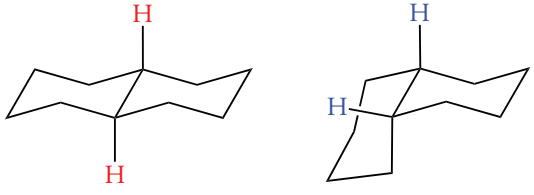
Problem 4.18

Draw the chair conformations of *cis*-1-chloro-4-methylcyclohexane and determine the most stable conformation. Use the data in Table 4.6 to determine the energy difference for the two conformations.

4.10 POLYCYCLIC MOLECULES

cis- and *trans*-Decalin

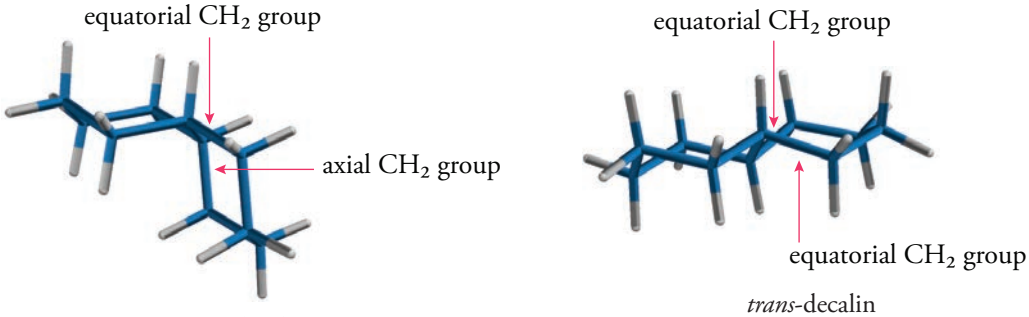
We can extend the analysis of monocyclic ring compounds to **polycyclic compounds**—that is, compounds with more than one ring. Let's look at the two isomeric bicyclo[4.4.0]decanes, which are commonly called *decalins*. These structural units are incorporated in steroids, an important class of biomolecules. Geometric isomerism exists in these compounds because the ring junction can be either *cis* or *trans*. The decalin ring junction can have hydrogen atoms on the same side or opposite sides. When they are on the same side, the molecule is *cis*-decalin. When they are on opposite sides, the molecule is *trans*-decalin. The two compounds are not different conformations. They cannot interconvert unless a carbon–carbon bond or a carbon–hydrogen bond is broken at the points of fusion.



trans-decalin *cis*-decalin

trans-Decalin is relatively rigid. Neither of its rings can "flip." If either ring were to flip, the CH_2 groups bonded to the fusion site would be transformed from a diequatorial into a diaxial arrangement. Of course, the diaxial arrangement is less stable but also, unlike the methyl groups in 1,2-dimethylcyclohexane, the two CH_2 groups must remain linked in a ring. The remaining CH_2—CH_2 unit of the ring cannot "reach" and cover the distance from one axial CH_2 unit to the other axial CH_2 unit. Therefore, this conformation is impossible.

cis-Decalin is relatively flexible. A flip of one ring causes a change in the location of the two CH_2 groups bonded to it. Analogous to *cis*-1,2-dimethylcyclohexane, the axial CH_2 unit is changed into an equatorial CH_2 and vice versa. Hence, the two conformations have the same energy.

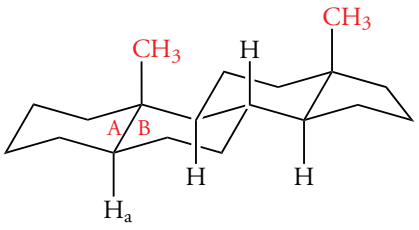


cis-decalin *trans*-decalin

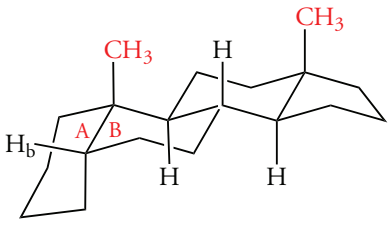
When a decalin ring is linked to substituents, they can be either axial or equatorial. The spatial location of the substituent cannot be changed in *trans*-decalin because the ring system does not flip. However, a substituted *cis*-decalin can exist in two conformations whose energies are not equal.

The Steroid Ring System

Steroids, many of which are hormones, are fused tetracyclic compounds with three six-membered rings and a five-membered ring. The six-membered rings of the carbon skeleton are designated as A, B, C. The five-membered ring is designated as D. In most steroids, the ring junctions are all *trans*, so ring flipping does not occur. *cis*-Decalin is conformationally mobile and undergoes a ring flip. However, a comparable process is not possible in steroids where the A/B junction is *cis*. The B/C ring junction provides a rigid *trans* junction that immobilizes the B ring.

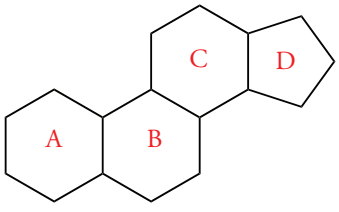


trans (A/B) ring junction

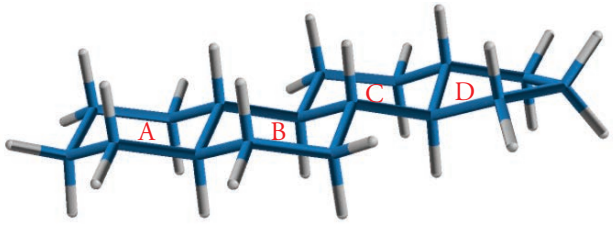


cis (A/B) ring junction

Because the steroid ring system is rigid, functional groups bonded to ring atoms have well-defined positions. Substituents below the plane of the ring are designated as α; those above the plane of the ring are β. We recall that "down" and "up" in substituted cyclohexane compounds are not synonymous with equatorial and axial. For the same reasons, this method of nomenclature for steroids does not indicate whether the substituent is equatorial or axial.



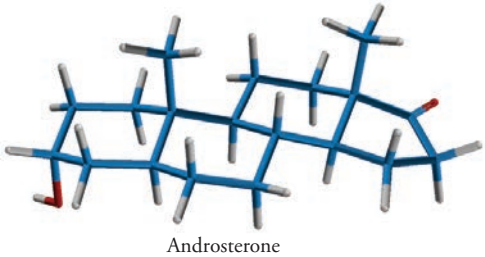
The steroid ring system



Conformation of the steroid ring system

Human Physiological Effects of Steroids

The equatorial and axial locations of functional groups in steroids control the reactivity of these compounds. Androsterone provides an example. It is one of the male sex hormones known as androgens (Figure 4.16). Androsterone has high physiological activity. Both the position of the hydroxyl group and the configuration of the A/B ring junction are important for this activity. The hydroxyl group at C-3 in androsterone is α; it is axial. Epiandrosterone is an isomer with a β hydroxyl group (equatorial). This isomer has much less physiological activity. In the 5β-androsterone, the A/B ring junction is *cis* and the hydroxyl group is equatorial. This compound has no physiological activity. The activity of these three compounds depends on the spatial arrangement of the hydroxyl group and the keto group on the D ring. This stereochemistry determines whether or not a given steroid binds to a specific receptor.



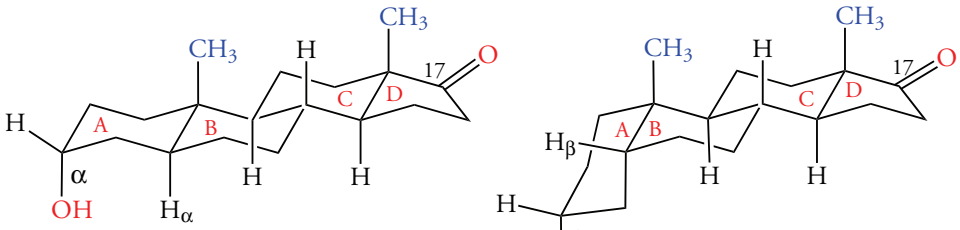
Androsterone

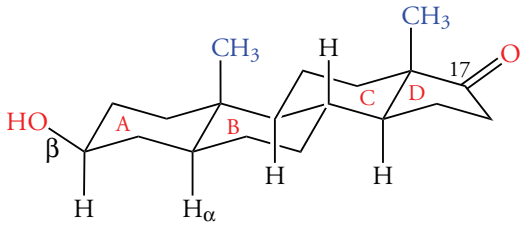
4.11 PHYSICAL PROPERTIES OF ALKANES

van der Waals Forces (London Forces)

The electrons in nonpolar molecules such as alkanes are distributed more or less uniformly throughout the molecule. However, when molecules come close to one another, as they do in the liquid state, electrons in one molecule can become transiently polarized by electrons in a neighboring molecule, resulting in a nonuniform distribution of electrons. One molecule induces a temporary dipole in the other (Figure 4.17). The induced dipoles interact by weak attractive forces called **van der Waals forces** or **London forces**.

Figure 4.16
Structure and Androgen Activity

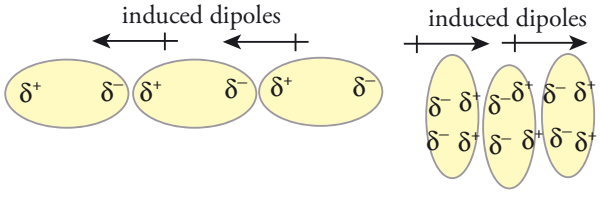




epiandrosterone (reduced activity)

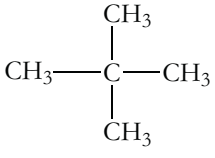
Figure 4.17
van der Waals Forces

(a) The approach of one nonpolar molecule induces a transient dipole in its neighbor "end-to-end." (b) Several nonpolar molecules interacting side-by-side by van der Walls interactions.



Boiling Points of Alkanes

van der Waals forces depend on molecular surface area. For example, the boiling points of pentane and hexane are 36 and 69 °C, respectively. These two nonpolar molecules contain the same types of atoms, but different numbers of atoms. The van der Waals forces are stronger in hexane than in pentane because hexane has a larger surface area to interact with neighboring molecules. The stronger intermolecular attraction holds molecules together more tightly, decreasing the vapor pressure of hexane and giving it a higher boiling point than pentane.

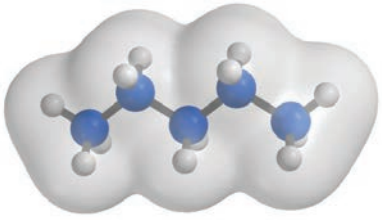


neopentane
bp –10 °C

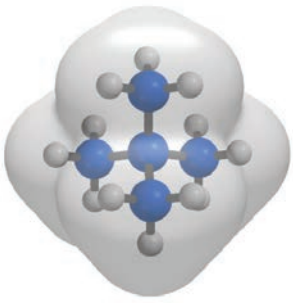
$CH_3CH_2CH_2CH_2CH3$	$CH_3CH_2CH_2CH_2CH_2CH_3$
pentane	hexane
b.p. 36 °C	b.p. 69 °C

van der Waals forces also depend on molecular shape. For example, 2,2-dimethylpropane (neopentane) has a lower boiling point than pentane. Neopentane is more spherical than pentane; therefore, it has less surface area than the more cylindrical pentane molecule. As a consequence, the van der Waals forces are smaller in neopentane, and its boiling point is lower.

In general, the boiling points of isomeric alkanes are related to their shapes. Increased branching results in more compact molecules with smaller surface areas. A smaller surface area results in less contact among adjacent molecules and smaller van der Waals forces. For any group of isomeric alkanes, the most branched isomer has the lowest boiling point. The normal alkane has the highest boiling point.



n-pentane



neopentane

Solubility of Alkanes

Alkanes are not soluble in water, which is highly polar. The two substances do not meet the criterion of solubility, namely, that "like dissolves like." Water molecules are too strongly attracted to one another by hydrogen bonds to allow nonpolar alkanes to slip between them and dissolve.

Alkanes are solvents for nonpolar organic materials such as fats and oils. Alkane vapors, such as those of gasoline, cause severe damage to lung tissue by dissolving the fatty material in cell membranes. Body oils maintain the "moisture" of human skin. Long-term contact between low-molecular-weight alkanes and skin removes skin oils and can cause soreness and blisters. For this reason, contact with alkane solvents such as paint thinner or paint remover should be avoided.

Densities of Alkanes

Alkanes have densities between 0.6 and 0.8 g/cm^3, so they are less dense than water. Thus gasoline, which is largely a mixture of alkanes, is less dense than water and floats on water. Pure alkanes are colorless, tasteless, and nearly odorless. However, gasoline has an odor and some color because dyes are added to gasoline by refiners to indicate its source and composition. Gasoline also contains compounds containing benzene rings, which have characteristic, unpleasant odors. Table 4.7 lists the physical properties of some common alkanes and cycloalkanes.

Table 4.7
Physical Properties of Alkanes and Cycloalkanes

Hydrocarbon	*Boiling Point (°C)*	*Density (g/mL)*
Methane	–164.0	0.678
Ethane	–88.6	0.691
Propane	42.1	0.690
Butane	–0.5	0.711
Pentane	36.1	0.6262
Hexane	68.9	0.6603
Heptane	98.4	0.6837
Octane	125.7	0.7025
Decane	150.8	0.7176
Cyclopropane	–32.7	(gas at 20 °C)
Cyclobutane	12	(gas at 20 °C)
Cyclopentane	49.3	0.7457
Cyclohexane	80.7	0.7786
Cycloheptane	110.5	0.8098
Cyclooctane	148.5	0.8349

4.12 STABILITIES OF ALKYL RADICALS

Bond Dissociation Energies of Alkanes

In Section 3.7, we discussed bond dissociation energies for small molecules such as methane and ethane. Now we will extend that discussion to more complex alkanes. Much of the chemical reactivity of hydrocarbons is associated with the carbon–hydrogen bond. The bond dissociation energy, $\Delta H°$, of the C—H bond of methane is 438 kJ mole^{-1}. In Section 3.7, we saw that this bond dissociation energy is given by the $\Delta H°$ for the following reaction. When we refer to bond dissociation energies, we use the term DH°

$$CH_3{-}H \longrightarrow CH_3\cdot + \cdot H \qquad \Delta H° = 438 \text{ kJ mole}^{-1}$$

A species with an unpaired electron, such as $CH_3\cdot$, is called a **radical**. The strength of a C—H bond in an alkane or cycloalkane depends upon the stability of the radical produced in the dissociation reaction. The strength of the C—H bond depends upon the structure of the hydrocarbon. Table 4.8 lists the variation of C—H bond strengths with structure. The energy required to cleave the R—H bond homolytically to give a free radical, R·, decreases in the order

$$CH_3{-}H > \text{primary C—H} > \text{secondary C—H} > \text{tertiary C —H}$$

This order reflects the stability of the radical products. Table 4.8 also lists the strengths of C —CH_3 bonds. These radicals follow the same order of stability. This is not surprising since in each case a primary, secondary, or tertiary radical is produced, and the methyl radical is the same in all these cases.

Table 4.8
Bond Dissociation Energies of Alkanes

Bond	*DH° (kJ mol^{-1})*	*Bond*	*DH° (kJ mol^{-1})*
$CH_3{-}H$	438	$CH_3{-}CH_3$	368
$CH_3CH_2{-}H$	422	$CH_3CH_2{-}CH_3$	356
$CH_3CH_2CH_2{-}H$	422	$(CH_3)_2CH{-}CH_3$	351
$(CH_3)_2CH{-}H$	410	$(CH_3)_3C{-}CH_3$	335
$(CH_3)_3C{-}H$	401		

Table 4.8 shows that replacing a hydrogen with a carbon increases the stability of a radical. Thus, the radical produced from methane is less substituted than the primary radical generated from ethane. The C—H bond dissociation energy of ethane is 422 kJ mole^{-1}.

$$CH_3CH_2{-}H \longrightarrow CH_3CH_2\cdot + \cdot H \qquad DH° = 422 \text{ kJ mole}^{-1}$$

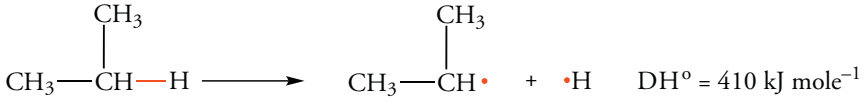
ethyl radical

The methyl and ethyl radicals are electron-deficient species that have a carbon atom with only seven electrons in its valence shell. The DH° for the C—H bond of ethane is smaller than that for the C—H bond of methane because it is stabilized by the inductive effect of the CH_3 group bonded to the radical center.

If alkyl groups stabilize a free radical by an electron-donating inductive effect, then we should see a difference in the DH° values for the two different C—H bonds in propane since one is to a primary carbon and the other to a secondary carbon. And that is exactly what we see.

$$CH_3CH_2CH_2{-}H \longrightarrow CH_3CH_2CH_2\cdot + \cdot H \qquad DH° = 422 \text{ kJ mole}^{-1}$$

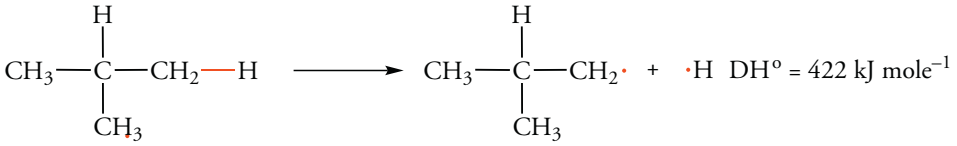
n-propyl radical



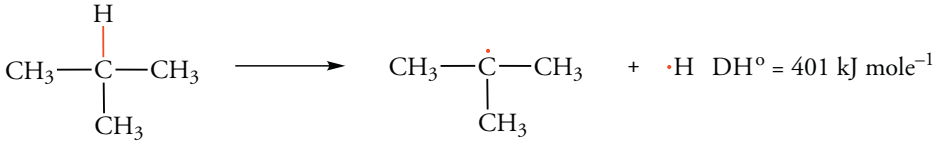
*iso*propyl radical

The DH° values for the primary C—H bonds of propane and ethane are the same, which means that the stabilities of the primary propyl radical and the ethyl radical are the same. This shows that a methyl group and an ethyl group have the same effect on the stability of the radical. Either group counts as an alkyl group. In contrast, the DH° for the secondary C—H bond of propane is smaller, reflecting the greater stability of the secondary radical, which has two electron-releasing alkyl groups bonded to the electron-deficient center. The isomeric propyl and isopropyl radicals differ in energy by 12 kJ mole^{-1} (Figure 4.18).

Now let's compare the DH° values for the two nonequivalent C—H bonds in 2-methylpropane. Cleavage of the C-1 to H bond yields the isobutyl radical, a primary radical. Cleavage of the C-2 to H bond yields a tertiary *tert*-butyl radical.



*iso*butyl radical (1°)



tert-butyl radical (3°)

The DH° is the same for primary C—H bonds of 2-methylpropane, propane, and ethane. The DH° for the tertiary C—H bond of 2-methylpropane is smaller. Therefore, the tertiary radical, which has three alkyl groups bonded to the electron-deficient center, is more stable (Figure 5.18). The isomeric isobutyl and *tert*-butyl radicals differ in energy by 21 kJ mole^{-1}.

Based on the bond dissociation energy data for the simple alkanes, we conclude that the C—H bond energy depends on whether the carbon atom is primary, secondary, or tertiary and *not* on the particular alkane in which it is found. The bond dissociation energy reflects the stabilities of the radical products, which increase in the same order as carbocations.

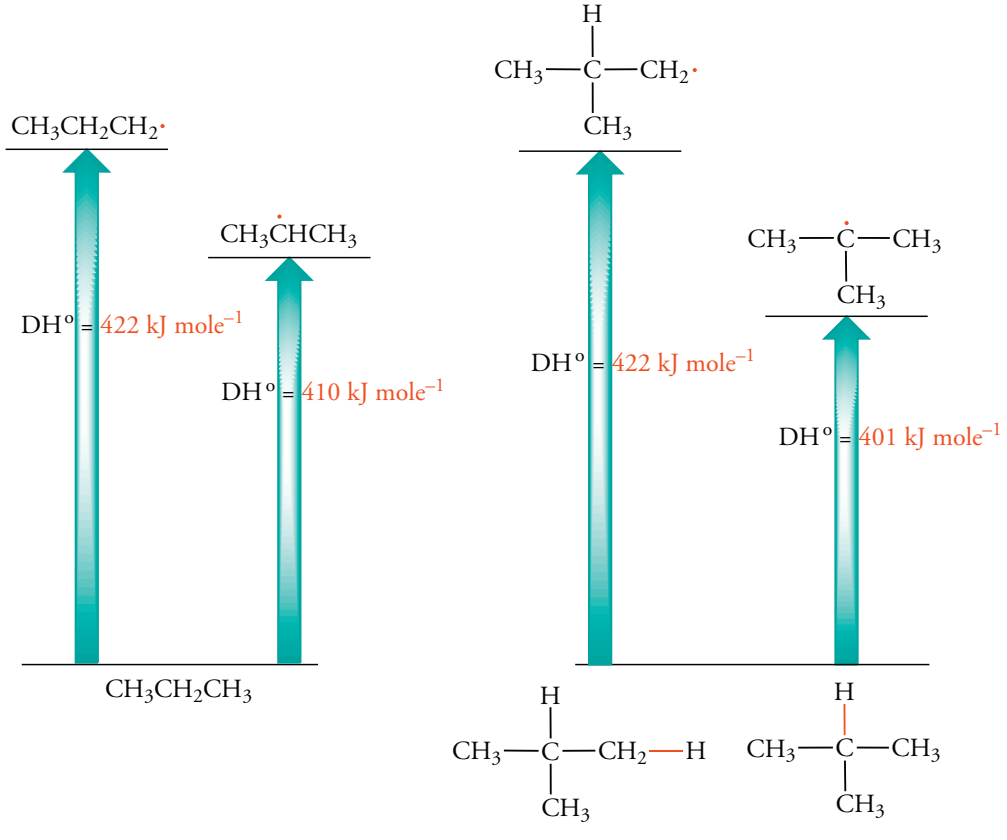
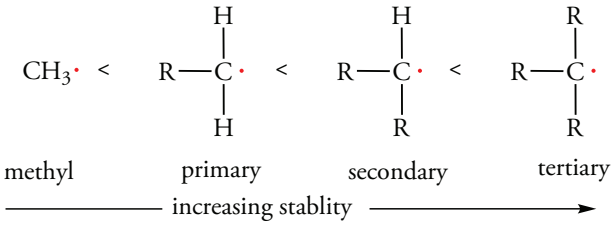


Figure 4.18
Relative Stabilities of Alkyl Radicals
(a) A secondary isopropyl radical is more stable than a primary *n*-propyl radical by 12 kJ mole^{-1}.
(b) A *tert*-butyl radical is 9 kJ mole^{-1} more stable than a secondary isopropyl radical, but the stabilities of the primary *n*-propyl and isobutyl radicals are the same.



Problem 4.19

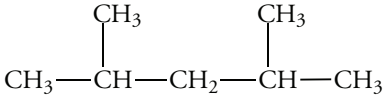
Write the structures of all the possible radicals originating from dissociation of C—H bonds of 2-methylbutane. Estimate the dissociation energy for the formation of each radical.

Problem 4.20

How many radicals can result by cleavage of the C—H bonds of 2,4-dimethylpentane? Which has the smallest bond dissociation energy?

Sample Solution

There are four CH_3 groups, two CH groups, and one CH_2 group in the molecule.



The four methyl groups are located in structurally equivalent positions and give only one primary free radical by cleavage of a carbon–hydrogen bond. Cleavage of a carbon–hydrogen bond of the single CH_2 group gives a secondary free radical. The two CH groups are structurally equivalent, and cleavage of either carbon–hydrogen bond gives a tertiary free radical. This bond has the lowest bond dissociation.

Problem 4.21

Write the structures of all possible radicals formed by dissociation of a C—H bond in pentane. Estimate the C—H bond dissociation energy for the formation of each radical.

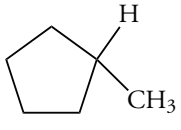
Problem 4.22

Explain why four isomeric radicals result from dissociation of a C—H bond in methylcyclopentane, but only one from cyclohexane.

Sample Solution

Dissociation of any of the three hydrogen atoms of the methyl group of methylcyclopentane gives a primary radical. A tertiary radical results from dissociation of the C-1 hydrogen atom. Dissociation of either of the two hydrogen atoms at C-2 gives the same secondary radical. The fourth radical, which is also secondary, results from removal of either of the two hydrogen atoms at C-3.

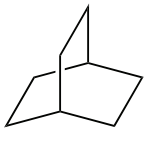
Cyclohexane is a symmetrical compound. All six carbon atoms are equivalent. Dissociation of either of the two hydrogen atoms of any CH_2 groups yields a secondary cyclohexyl radical.



methylcyclopentane

Problem 4.23

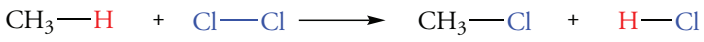
Explain why only two isomeric radicals result from removal of a hydrogen atom from bicyclo[2.2.2]octane.



bicyclo[2.2.2]octane

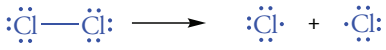
4.13 CHLORINATION OF AN ALKANE—A RADICAL REACTION

Now let's consider a reaction in which bonds break homolytically to give radicals that combine to form a new molecule. When radicals combine, the process is called **homogenic** bond formation. Methane reacts with chlorine gas at elevated temperatures or in the presence of ultraviolet light as an energy source. In this reaction, a chlorine atom replaces a hydrogen atom.

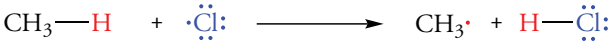


The mechanism of this reaction requires several steps.

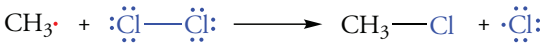
Step 1. **Initiation**. A chlorine molecule absorbs energy, from either ultraviolet light or high temperatures, and the Cl—Cl bond breaks homolytically to give two chlorine atoms. They are electron-deficient, highly reactive radicals. This step starts the reaction and is called the initiation step.



Step 2. **Propagation.** A chlorine atom abstracts a hydrogen atom from methane, breaking a C—H bond and making an H—Cl bond. This step, which continues the reaction by generating a new radical, is called a propagation step.

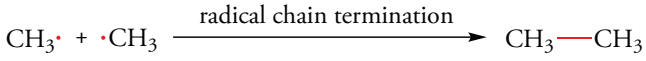


Step 3. **Propagation.** A Cl—Cl bond breaks and a C—Cl bond forms. A radical reacts and another radical forms. This is also a propagation step.



The propagation steps, 2 and 3, repeat because one radical generates another in this sequence of reactions. The process continues as long as radicals and a supply of both reactants are present. Therefore, only a few chlorine atoms are required to initiate the reaction.

Any time two radicals recombine, the chain stops. These are termination steps. Since the concentration of radicals is much less than that of either methane or Cl_2, termination steps are relatively rare. One of the termination steps is mechanistically important: the reaction mixture always contains a small amount of ethane, and this only could have occurred if the reaction had proceeded by way of a methyl radical intermediate.

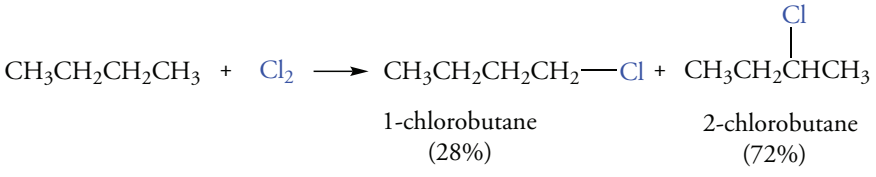


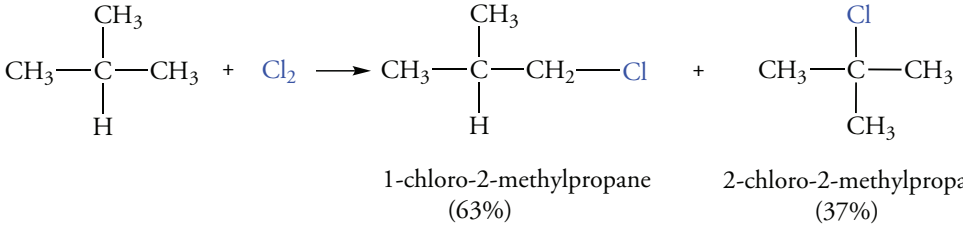
Problem 4.24

Bromine reacts with ethane by a free radical mechanism. Write the steps of this mechanism.

Regioselectivity of Alkane Halogenation

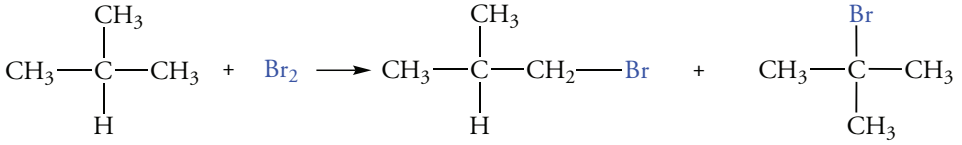
The chlorination of higher-molecular-weight alkanes yields a mixture of isomeric monochlorinated products. For example, the chlorination of butane or 2-methyl-propane, which have nonequivalent hydrogen atoms, yields significant amounts of isomeric monochlorinated derivatives.





If one of several possible isomers predominates, a reaction is said to be **regioselective**. The data for the chlorination of butane and 2-methylpropane indicate that the chlorination of alkanes is not very regioselective. In fact, there doesn't appear to be a simple explanation for the product distribution in these chlorination reactions. For example, in the chlorination of butane, the major product, 2-chlorobutane, arises when a chlorine atom replaces a secondary hydrogen atom rather than a primary hydrogen atom. However, in the case of 2-methylpropane, the major product, 1-chloro-2-methylpropane, arises when a chlorine atom replaces a primary hydrogen atom rather than a tertiary hydrogen atom.

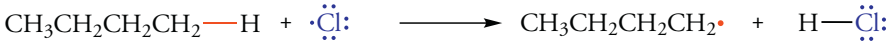
In contrast to chlorination, the bromination of alkanes is highly regioselective. For example, in the photochemical bromination of 2-methylpropane, more than 99% of the product results from substitution of bromine for the tertiary hydrogen atom.



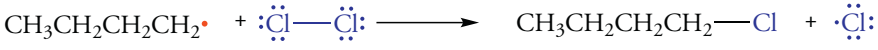
1-bromo-2-methylpropane (1%) 2-bromo-2-methylpropane (99%)

The halogenation of an alkane occurs by a free radical mechanism. The first step is the formation of a halogen radical, which subsequently abstracts a hydrogen atom from the alkane. These steps yield a carbon radical, which reacts with the halogen molecule to give a halogenated product.

Let's consider the chlorination of butane again. If the propagation step generates a primary radical, the product is a primary halide. Thus, the *n*-butyl radical gives 1-chlorobutane.

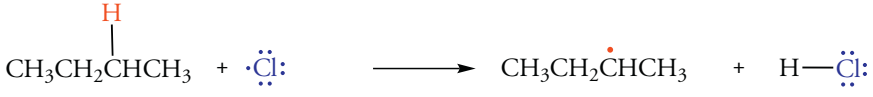


n-butyl radical



1-chlorobutane

If the propagation step generates a secondary radical, the product is a secondary halide. Thus, the *sec*-butyl radical gives 2-chlorobutane.



sec-butyl radical



2-chlorobutane

Now that we understand the origin of the products, we can ask why the reaction of butane with chlorine yields 1-chlorobutane and 2-chlorobutane in the ratio 28:72 (~1:3). Butane has six primary hydrogen atoms and four secondary hydrogen atoms, so there are six ways to form the butyl radical and four ways to form the *sec*-butyl radical. If the primary and secondary hydrogen atoms of butane reacted at the same rate, the ratio of 1-chlorobutane to 2-chlorobutane would be 6:4, but it isn't.

We know that a secondary radical is more stable than a primary radical. The product distribution reflects this difference. *The rate of formation of the radical determines the product distribution.* The secondary radical is more stable, and it forms at a faster rate. Therefore, the major product is derived from the secondary radical.

A similar question arises from the product distribution data for the chlorination of 2-methylpropane. If the primary and tertiary hydrogen atoms of 2-methylpropane reacted at the same rate, the ratio of products formed would be 9:1, but 99% of the products are derived from the most stable tertiary radical. The larger than expected quantity of 2-chloro-2-methylpropane means that the *tert*-butyl radical forms much faster than the primary isobutyl radical.

Reactivity and Statistical Factors

Let's consider the chlorination of butane again in greater detail. We see that there are four ways to get 2-chlorobutane and six ways to obtain 1-chlorobutane. The ratio of 2-chlorobutane to 1-chlorobutane therefore equals the relative rate of abstraction of a secondary hydrogen atom times 4 divided by the relative rate of abstraction of a primary hydrogen atom times 6.

$$\frac{\%\text{ 2-chlorobutane}}{\%\text{ 1-chlorobutane}} = \frac{(\text{rate of } 2^\circ \text{ H abstraction}) \times 4 \text{ atoms}}{(\text{rate of } 1^\circ \text{ H abstraction}) \times 6 \text{ atoms}}$$

$$\frac{\text{rate of } 2^\circ \text{ H abstraction}}{\text{rate of } 1^\circ \text{ H abstraction}} = \frac{\%\text{ 2-chlorobutane} \times 6 \text{ atoms}}{\%\text{ 1-chlorobutane} \times 4 \text{ atoms}} = \frac{72 \times 6}{28 \times 4} = \frac{3.9}{1}$$

Hence, 2-chlorobutane forms in preference to 1-chlorobutane because a single secondary hydrogen atom is abstracted 3.9 times as rapidly as a single primary hydrogen atom.

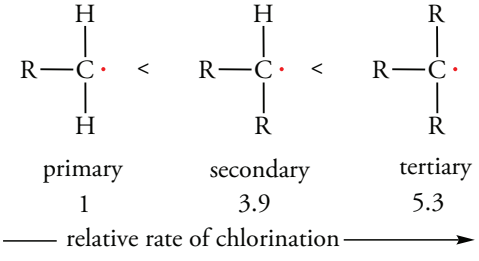
A similar analysis for the chlorination of 2-methylpropane illustrates the reactivity per hydrogen atom even more dramatically. Recall that the primary product predominates in a 63:37 percent ratio.

$$\frac{\%\text{ 2-chloro-2-methylpropane}}{\%\text{ 1-chloro-2-methylpropane}} = \frac{(\text{rate of } 3^\circ \text{ H abstraction}) \times 1 \text{ atom}}{(\text{rate of } 1^\circ \text{ H abstraction}) \times 9 \text{ atoms}}$$

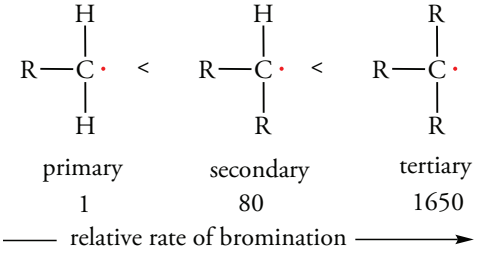
$$\frac{\text{rate of } 3^\circ \text{ H abstraction}}{\text{rate of } 1^\circ \text{ H abstraction}} = \frac{\%\text{ 2-chloro-2-methylpropane} \times 9 \text{ atoms}}{\%\text{ 1-chloro-2-methylpropane} \times 1 \text{ atoms}} = \frac{37 \times 9}{63 \times 1} = \frac{5.3}{1}$$

In this case, the major product does not result from abstraction of the more reactive hydrogen atom. A tertiary hydrogen atom is abstracted at a faster rate than a single primary hydrogen atom, but more primary product forms because there are enough primary hydrogen atoms to offset the difference in relative reactivities.

The order of reactivity per hydrogen atom in the chlorination of alkanes illustrates the low regioselectivity of the reaction.

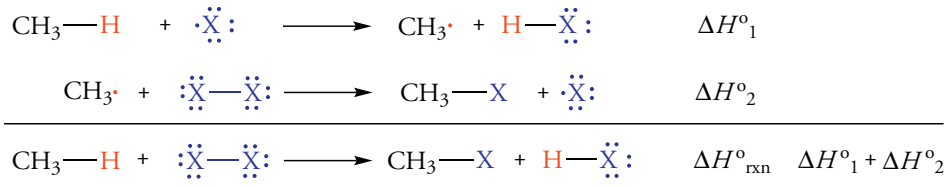


In contrast to chlorination, which is not very regioselective, the bromination of alkanes is highly regioselective. We saw that the bromination of 2-methylpropane yields 2-bromo-2-methylpropane as the major product, even though there are nine primary hydrogen atoms and only one tertiary hydrogen atom. Based on data for a variety of structures, the range of reactivities of tertiary, secondary, and primary hydrogen atoms with bromine is found to be much greater than for the reaction with chlorine.

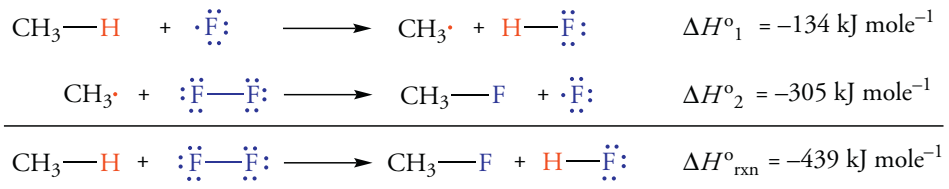


Enthalpy Changes for Halogenation Reactions

In Section 3.7, we discussed the chlorination of methane. Now we'll return to that reaction and consider it in a more general way and from a different perspective. We will consider the enthalpy changes that accompany the various propagation steps in the reaction. We will examine the enthalpy change for each step, and see how it contributes to the overall enthalpy change.

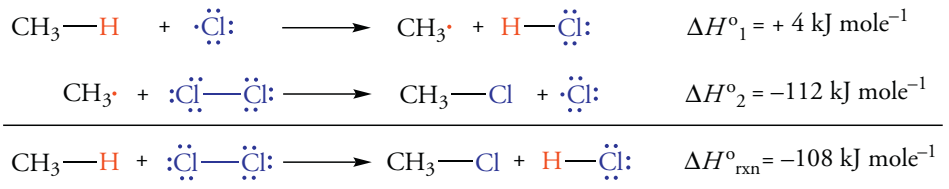


First, we'll consider the fluorination of methane and the enthalpy changes associated with the two propagation steps.



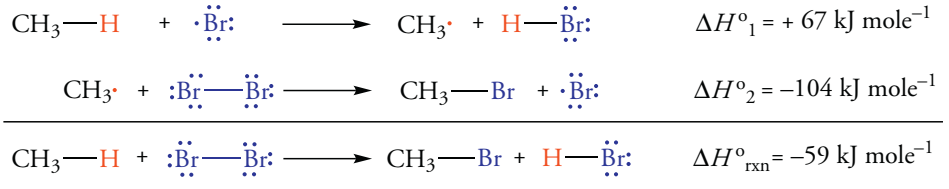
The propagation steps for fluorination are highly exothermic, and the reaction is difficult to control. The large quantity of heat released during the reaction causes the reaction temperature to rise, which in turn increases the rate of the reaction. As a consequence, the reaction may lead to an explosion.

When we turn to chlorination, we find that the first propagation step is very slightly endothermic. The second step is exothermic, but less so than the second step in fluorination.

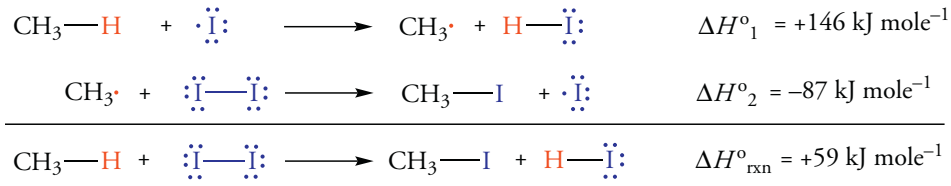


The net reaction is exothermic, but the enthalpy change is less than for fluorination. Chlorination reactions can be more easily controlled than fluorination, so free radical chlorination is an important industrial process.

When we examine the enthalpy changes for the propagation steps in the bromination of methane, we find that the first step is now even more endothermic than the comparable step for chlorination. The overall process is exothermic only because the second step is exothermic.



For iodination, we find that the first step is so endothermic that the overall reaction is endothermic even though the second step is exothermic.



The data tell us that the total energy change, ΔH°_{rxn}, in halogenation of methane decreases in the order

$$F_2 > Cl_2 > Br_2 > I_2$$

This order of halogen reactivity with methane is primarily controlled by the magnitude of the ΔH° for the exothermic propagation step in which the halogen atom abstracts a hydrogen atom. Furthermore, the enthalpy change for this propagation step parallels the strength of the hydrogen–halogen bond. When the H —X bond is strong, as in H—F, this step is highly exothermic. When the H—X is weak, as in H—I, this step is highly endothermic.

Activation Energy for Halogenation

In the preceding discussion, we considered the enthalpy changes for the propagation steps of free radical halogenation. We did not consider the activation energies for these steps, although we implicitly assumed that the rates of reaction are related to the enthalpy change for the reaction. Free radical halogenation is a multistep reaction. Each step has a characteristic activation energy that controls the rate of reaction for that step. The overall rate of the reaction is controlled by the step with the highest activation energy. This is the *rate-determining step* for the reaction.

We know that the enthalpy change for the first propagation step in halogenation is always less exothermic than the enthalpy change for the second step. This step is rate-determining. The second step, in which the methyl radical reacts with the halogen, is quite exothermic and has a very low activation energy (less than 1 kJ mole^{-1}).

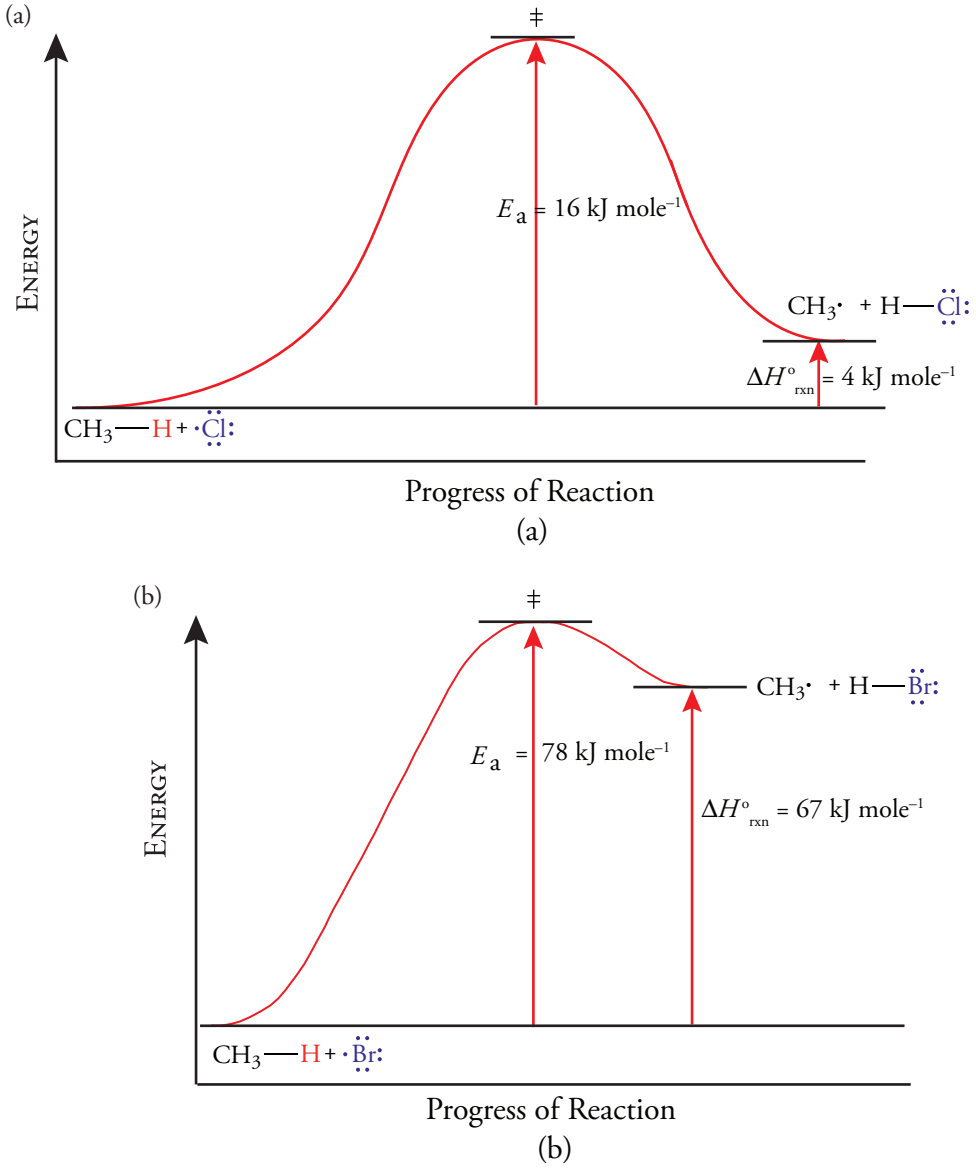


Figure 4.19
Potential Energy Diagrams for Halogenation Reactions
The energy of activation for the abstraction of a hydrogen atom by a chlorine atom (a) is smaller than the energy of activation for the abstraction of a hydrogen atom by a bromine atom (b).

Reactivity and Selectivity

We know that bromine is less reactive than chlorine in the rate-determining step of halogenation of methane. We also recall that bromine is more selective than chlorine. Both the rate of reaction and the selectivity of free radical halogenation are related to the first propagation step, so let's look at the relationship between reactivity and selectivity in terms of the structure of the transition states for chlorination and bromination.

Because the first propagation step of the chlorination reaction is very slightly endothermic, the transition state is only moderately past the "center" of the reaction coordinate axis. In contrast, the transition state for the more endothermic bromination reaction is farther along the reaction coordinate axis (Figure 4.19b). What does this information tell us about the structure of the transition states for the two reactions? We recall that the Hammond postulate states that the structures of transition states most closely resemble those species that are most similar in energy (Section 3.11). Thus, the structure of the transition state for an exothermic process is more reactant-like, or "early," and the structure of the transition state for an endothermic process is more product-like or "late."

The first propagation step for the chlorination reaction is very slightly endothermic. Thus, the position of the transition state along the reaction coordinate is a bit past the midpoint (Figure 4.20). The extent to which the C—H bond is broken and the extent to which the H—Cl bond is formed are comparable because the C—H and H—Cl bond dissociation energies are similar.

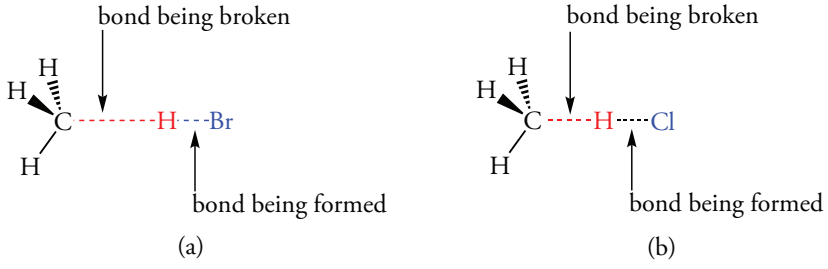


Figure 4.20
Transition State Structures for Halogenation Reactions

(a)In the transition state for abstraction of hydrogen by a bromine atom, the C—H bond is mostly broken and the H—Br bond is mostly formed.
(b) In the transition state for abstraction of hydrogen by a chlorine atom, the C—H bond is broken to a lesser degree and the H—Cl bond is only partially formed.

The first propagation step for the bromination of methane is strongly endothermic, so the transition state is more product-like. The C—H bond is broken to a significant extent, and the H—Br bond is more strongly formed (Figure 4.20).

How does the degree of bond breaking in the transition state affect the selectivity of the reagent? In the less reactive bromination reaction, the transition state for the first propagation step is more product-like and resembles the radical product. Thus, the ease with which the C—H bond is broken reflects the effect of alkyl groups on the stability of the radical. The reaction then shows a selectivity that reflects the stability of the radical product. In the chlorination reaction, the transition state is more reactant-like, and the alkyl group has not developed much radical character. Hence, the type of C—H bond—primary, secondary, or tertiary—has little effect on the reaction, and low selectivity is the result.

Throughout our study of organic reactions, we will find that, for structurally similar reactions, the more reactive reagent is less selective. Many factors account for this selectivity, including inductive, resonance, and steric effects. Regardless of the factors that influence the rate, the less reactive reagent has a more fully developed transition state (more like the products), and the role of structural features in stabilizing the transition state becomes more important.

Hyperconjugation

We have seen that increasing the substitution around a radical is a stabilizing influence. We called this an *inductive effect*, which means that the alkyl substituent donates electron density to the electron-deficient radical center. We often say that inductive effects are "through-bond" effects, as if the bond were a "wire" of sorts through which electron density can be transferred. Let's consider the *tert*-butyl radical. It is very nearly planar, and it has a half-filled 2p orbital on the tertiary carbon.

Hyperconjugation is the result of partial overlap of the sigma bonding orbital of the C—H of the carbon atom adjacent to the electron-deficient radical center with the half-filled 2p orbital (Figure 4.21). The electrons of the sigma bond are partially *delocalized* to the electron-deficient center. As a consequence, the radical is stabilized. Increasing the number of possible C—H bonds of the carbon atoms adjacent to the electron-deficient center provides increased stability of the radical.

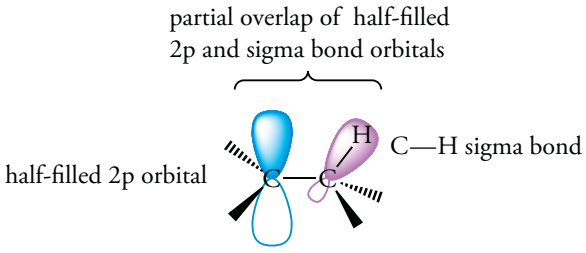


Figure 4.21
Hyperconjugation
A carbon radical is stabilized by overlap of the sigma orbital of a C—H bond on an adjacent carbon with the half-filled 2p orbital at the radical center. This phenomenon is called hyperconjugation.

EXERCISES

Molecular Formulas

4.1 Does each of the following molecular formulas for an acyclic hydrocarbon represent a saturated compound?
(a) C_6H_{12} (b) C_5H_{12} (c) C8H_{16} (d) C10H_{22}.

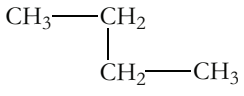
4.2 Can each of the following formulas correspond to an actual acyclic or cyclic molecule?
(a) C_6H_{14} (b) $C_{10}H_{23}$ (c) C_7H_{14} (d) C_5H_{14}

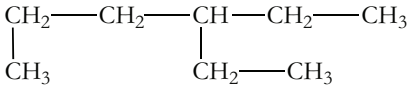
4.3 Beeswax contains approximately 10% hentriacontane, a normal alkane with 31 carbon atoms. What is the molecular formula of hentriacontane? Write a completely condensed formula of hentriacontane.

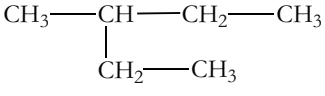
4.4 Hectane is a normal alkane with 100 carbon atoms. What is the molecular formula of hectane? Write a completely condensed formula of hectane.

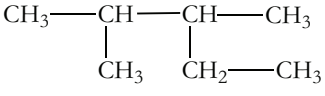
Structural Formulas

4.5 Redraw each of the following so that the longest continuous chain is written horizontally.

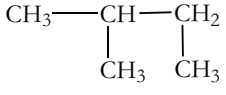
(a) 

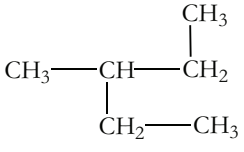
(b) 

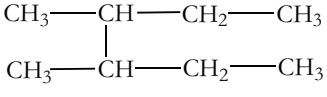
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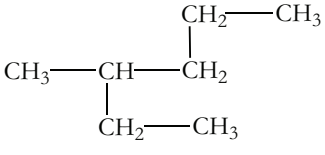
(d) 

4.6 Redraw each of the following so that the longest continuous chain is written horizontally.

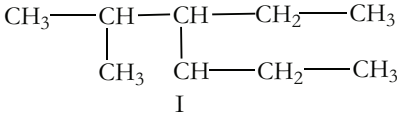
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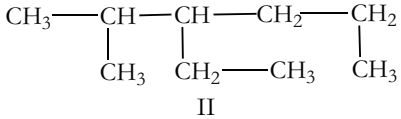
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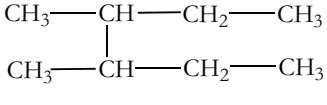
4.7 Which of the following structures represent the same compound?



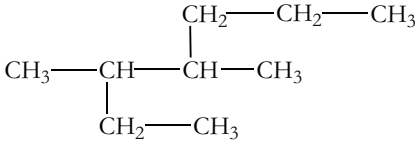
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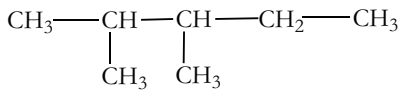


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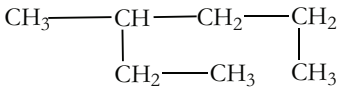


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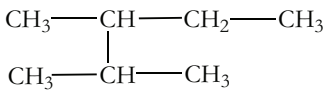
4.8 Which of the following structures represent the same compound?



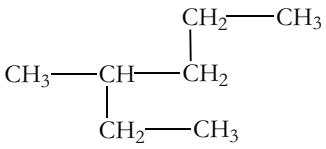
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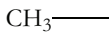
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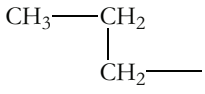


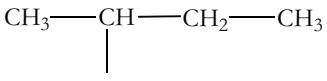
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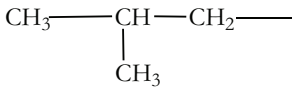
Alkyl Groups

4.9 What is the common name for each of the following alkyl groups?

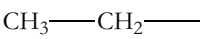
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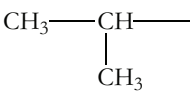
(b) 

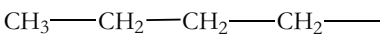
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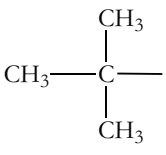
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4.10 What is the common name for each of the following alkyl groups?

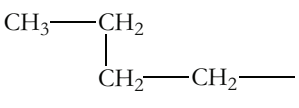
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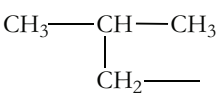
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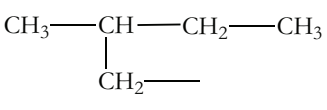
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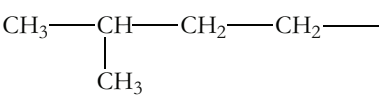
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4.11 What is the common name for each of the following alkyl groups?

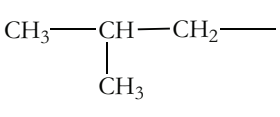
(a) 

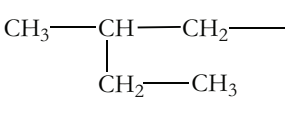
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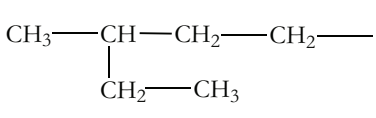
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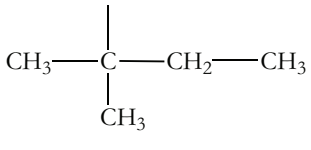
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4.12 What is the IUPAC name for each of the following alkyl groups?

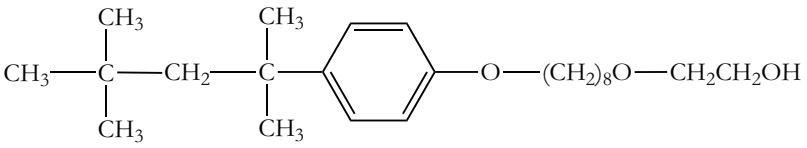
(a) 

(b) 

(c) 

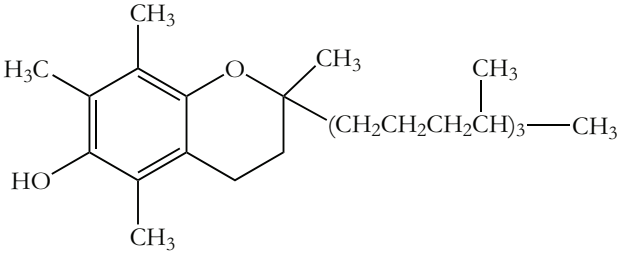
(d) 

4.13 The spermicide octoxynol-9 is used in diverse contraceptive products. Name the alkyl group to the left of the benzene ring.



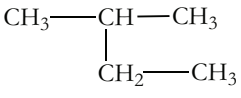
octoxynol-9

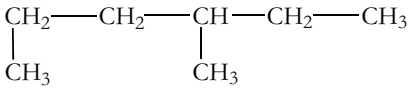
4.14 The name vitamin E actually refers to a series of closely related compounds called tocopherols. Name the complex alkyl group present in α-tocopherol.

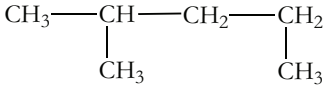


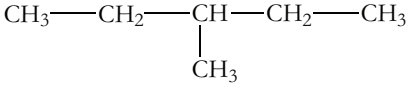
Nomenclature of Alkanes

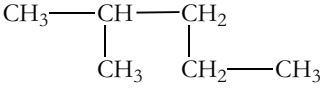
4.15 Give the IUPAC name for each of the following compounds.

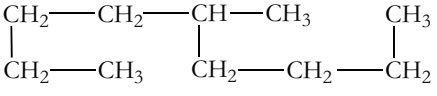
(a) 

(b) 

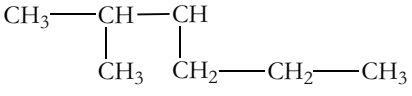
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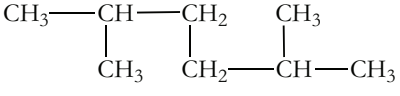
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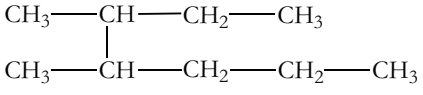
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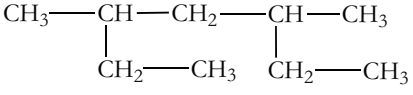
(f) 

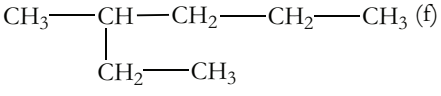
4.16 Give the IUPAC name for each of the following compounds.

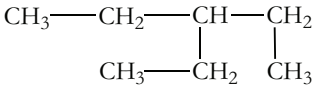
(a) 

(b) 

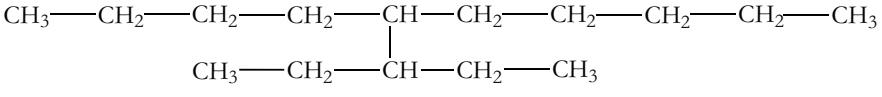
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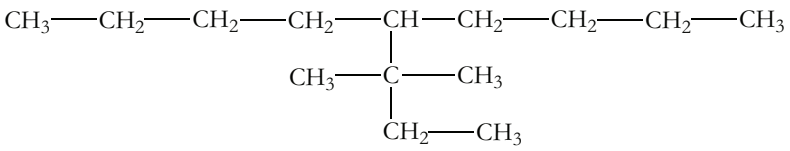
(e) 

(f) 

4.17 Give the IUPAC name for the following compound.



4.18 Give the IUPAC name for the following compound.



4.19 Write the structural formula for each of the following compounds.
(a) 3-methylpentane (b) 3,4-dimethylhexane (c) 2,2,3-trimethylpentane
(d) 4-ethylheptane (e) 2,3,4,5-tetramethylhexane

4.20 Write the structural formula for each of the following compounds.
(a) 2-methylpentane (b) 3-ethylhexane (c) 2,2,4-trimethylhexane
(d) 2,4-dimethylheptane (e) 2,2,3,3-tetramethylpentane

4.21 Write the structural formula for each of the following compounds.
(a) 4-(1-methylethyl)heptane (b) 5-(1,1-dimethylethyl)nonane
(c) 5-(1-methylpropyl)decane

4.22 Write the structural formula for each of the following compounds.
(a) 5-(2-methylpropyl)nonane (b) 4-butyl nonane (c) 5-(2,2-dimethylpropyl)decane

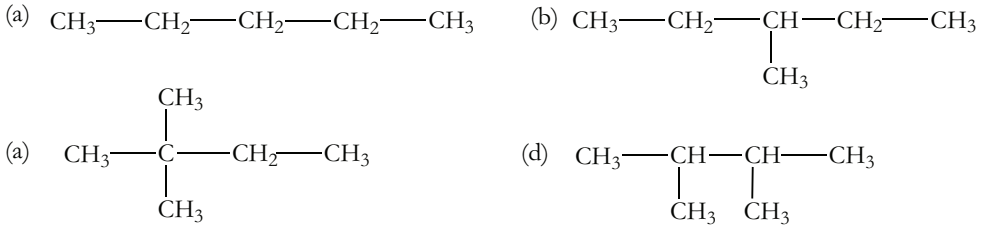
Isomers

4.23 There are nine isomeric C_7H_{16} compounds. Name the isomers that have a single methyl group as a branch.

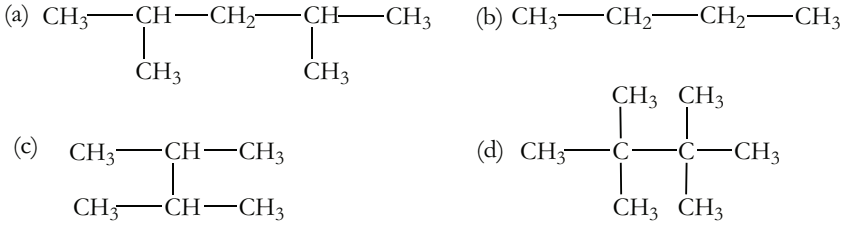
4.24 There are nine isomeric C_7H_{16} compounds. Name the isomers that have two methyl groups as branches and are named as dimethyl-substituted pentanes.

Classification of Carbon Atoms

4.25 Classify each carbon atom in the following compounds as primary, secondary, or tertiary.



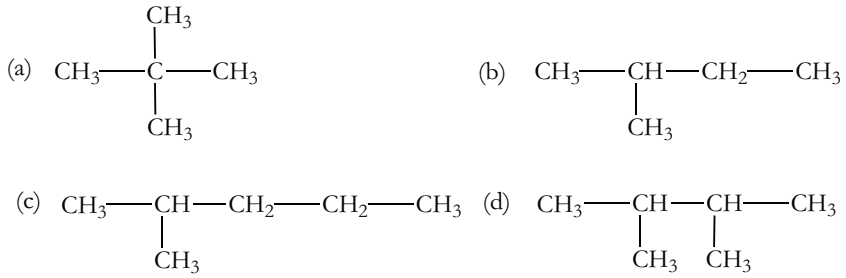
4.26 Classify each carbon atom in the following compounds as primary, secondary, or tertiary.



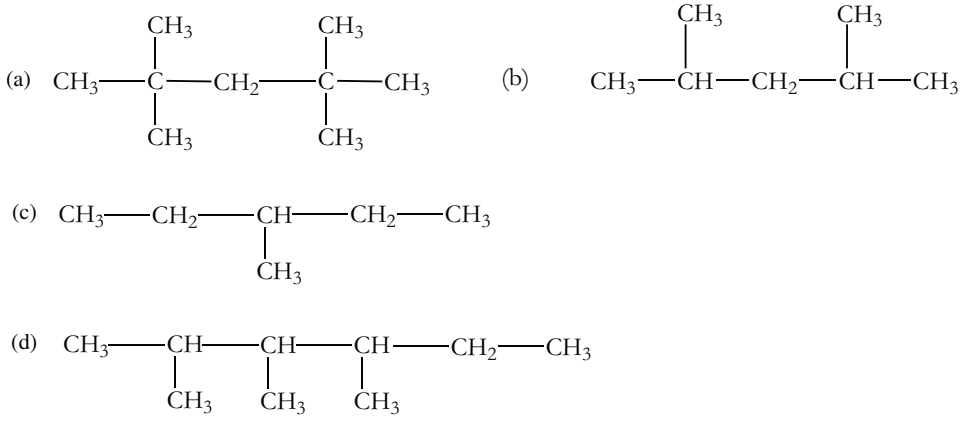
4.27 Draw the structure of a compound with molecular formula C_5H_{12} that has one quaternary and four primary carbon atoms.

4.28 Draw the structure of a compound with molecular formula C_6H_{14} that has two tertiary and four primary carbon atoms.

4.29 Determine the number of primary, secondary, tertiary, and quaternary carbon atoms in each of the following compounds.



4.30 Determine the number of primary, secondary, tertiary, and quaternary carbon atoms in each of the following compounds.

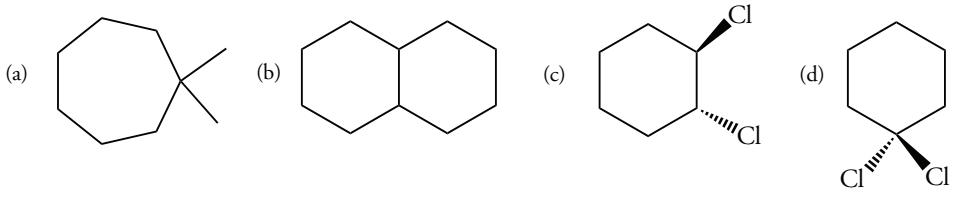


Cycloalkanes

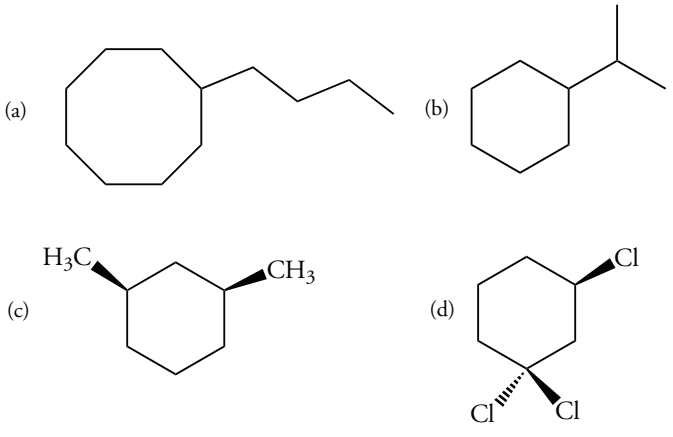
4.31 Write condensed planar formulas for each of the following compounds.
(a) chlorocyclopropane (b) 1,1-dimethylcyclobutane (c) cyclooctane

4.32 Write condensed planar formulas for each of the following compounds.
(a) bromocyclobutane (b) 1,1-dichlorocyclopropane (c) cyclopentane

4.33 Name each of the following compounds.



4.34 Name each of the following compounds.

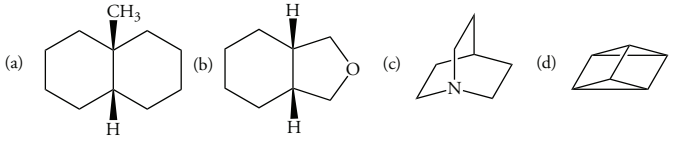


4.35 A saturated refrigerant has the molecular formula C_4F_8. Draw structural formulas for two possible isomers of this compound.

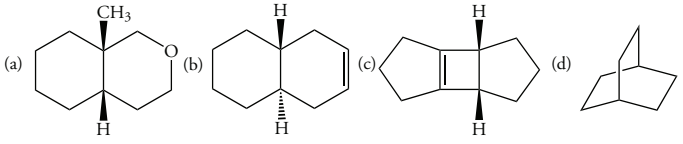
4.36 How many isomeric saturated hydrocarbons have the molecular formula C_5H_{10}?

Bicyclic compounds

4.37 What is the molecular formula of each of the following compounds?

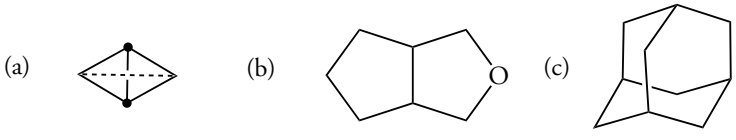


4.38 What is the molecular formula of each of the following compounds?

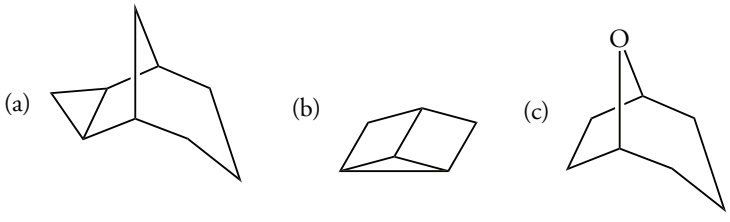


Polycyclic compounds

4.39 How many rings are present in each of the following polycyclic compounds?



4.40 How many rings are present in each of the following polycyclic compounds?



Properties of Hydrocarbons

4.41 Which of the isomeric C_8H_{18} compounds has the highest boiling point? Which has the lowest boiling point?

4.42 The boiling point of methylcyclopentane is lower than the boiling point of cyclohexane. Suggest a reason why.

Newman Projection Formulas of alkanes

4.43 Draw the Newman projection of the staggered conformation of 2,2-dimethylpropane around the C-1 to C-2 bond.

4.44 Draw the Newman projections of the two possible staggered conformations of 2,3-dimethylbutane around the C-2 to C-3 bond.

4.45 Draw the Newman projections of the two possible staggered conformations of 2-methylbutane around the C-2 to C-3 bond. Which is the more stable?

4.46 Draw the Newman projections of the two possible staggered conformations of 2,2-dimethylpentane around the C-3 to C-4 bond. Which is the more stable?

Stabilities of Acyclic Conformations

4.47 Do you expect the barrier to rotation around the central bond for $CH_3—CH_2—SiH_2—CH_3$ to be smaller or larger than the barrier to rotation for butane? Why?

4.48 Draw a potential energy diagram for rotation around the C-2 to C-3 bond of 2,2-dimethylbutane.

4.49 Draw a potential energy diagram for rotation around the C-2 to C-3 bond of 2-methylbutane.

4.50 2-Chloroethanol ($ClCH_2CH_2OH$) is most stable in the gauche conformation. Suggest a reason for this fact.

4.51 1-Chloropropane is most stable in the gauche conformation. What does this fact indicate about the interaction of chlorine and a methyl group in this compound?

4.52 Draw the two staggered conformations of 1,2-dichloroethane. Which of the conformations has a dipole moment? The dipole moment of 1,2-dichloroethane is 1.1 D. Does this fact provide any information about the composition of the mixture of conformations?

4.53 Ethylene glycol ($HOCH_2CH_2OH$) forms intramolecular hydrogen bonds. Does this fact provide any information about the composition of the mixture of conformations?

Conformations of Cyclohexanes

4.54 Draw the most stable conformation of the equatorial form of methylcyclohexane showing the relationship of the methyl hydrogen atoms to the hydrogen atom at C-1.

4.55 Draw the most stable conformation of the axial form of methylcyclohexane showing the relationship of the methyl hydrogen atoms to C-2 and C-6.

4.56 Draw the most stable chair conformation of each of the following compounds.
(a) *trans*-l-fluoro-3-methylcyclohexane (b) *trans*-l-*tert*-butyl-3-methylcyclohexane
(c) *trans*-1,2-dimethylcyclohexane

4.57 Draw the most stable chair conformation of each of the following compounds.
(a) *cis*-1,1,4-trimethylcyclohexane (b) *trans*-1,1,3-trimethylcyclohexane
(c) *cis*-1-fluoro-4-ethylcyclohexane

4.58 Why is the steric strain caused by the *tert*-butyl group so different from those of methyl, ethyl, and isopropyl groups?

4.59 Within experimental error, the steric strain caused by a bromine atom is the same as that of a chlorine atom. Taking into account the "size" of the atoms and the length of the carbon–halogen bond, explain this data.

4.60 *cis*-1,3-Cyclohexanediol is most stable in a diaxial conformation. Suggest a reason for this "unusual" stability.

4.61 *trans*-1,3-Di-*tert*-butylcyclohexane exists in a twist boat conformation, rather than a chair conformation. Why?

4.62 The diaxial conformation of *cis*-1,3-dimethylcyclohexane is 23 kJ $mole^{-1}$ less stable than the diequatorial conformation. Why is this value larger than twice the steric strain of a methyl group?

4.63 The diaxial conformation of *cis*-l-chloro-3-methylcyclohexane is 16 kJ $mole^{-1}$ less stable than the diequatorial conformation. Why is this value larger than the sum of the steric strains of a chlorine atom and a methyl group?

Bicyclic compounds

4.64 An isomerization equilibrium between *cis*-decalin and *trans*-decalin can be established by heating the mixture to about 300 °C in the presence of a palladium catalyst. The *trans* isomer predominates. Why is the *trans* isomer more stable than the *cis* isomer?

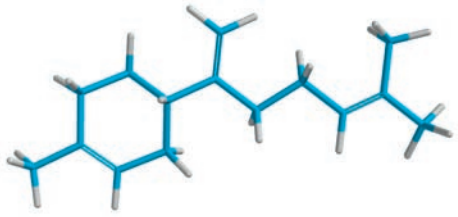
Steroids

4.65 Examine the structure of an A/B (*trans*) steroid skeleton and determine whether each of the following is in an equatorial or axial location.
(a) a 2α hydroxyl group (b) a 3α chlorine atom (c) a 6α amino (—NH2) group
(d) an 11β bromine atom (e) a 12β cyano group

4.66 Examine the structure of an A/B (*trans*) steroid skeleton and determine whether each of the following is in an equatorial or axial location.
(a) a 1β hydroxyl group (b) a 3α chlorine atom (c) a 6α amino (—NH_2) group
(d) an 11α bromine atom (e) a 12α cyano group

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5 Alkenes
Structures and Properties



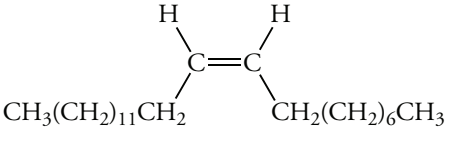
β-Bisabolene (a pheromone of the male Caribbean fruit fly)

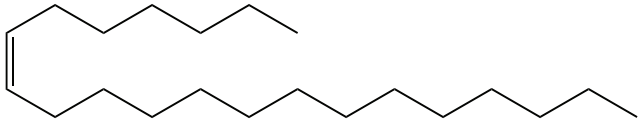
5.1 ALKENES

Organic compounds containing one or more carbon–carbon multiple bonds have fewer hydrogen atoms than structurally related alkanes or cycloalkanes. For this reason, these compounds are said to be **unsaturated**. In this chapter, we focus on one group of unsaturated compounds, the **alkenes**. An alkene must contain at least one carbon–carbon double bond. We recall that a double bond contains both a carbon–carbon σ bond and a π bond that forms from 2p orbitals on adjacent carbon atoms overlapping "side by side." We also recall that the carbon atoms in a σ bond of an alkene are sp^2 hybridized (Section 1.15).

Alkenes and their chemical cousins, the cycloalkenes, are very common in nature. Alkenes have many biological functions. They occur in fats and oils, some vitamins, some are hormones, and others act as pheromones. Ethene is the simplest hormone. It is produced in small amounts in many fruits and stimulates ripening. Ethene has an important commercial application in the food industry. Ripened fruit does not travel well, so growers pick their fruit while it is still green. Unripened fruit is shipped to a warehouse, where it is exposed to ethene. To avoid ripening during transport, the fruit is stored in ventilated containers. This decreases the concentration of ethene and retards ripening. Some fruits can be ripened in the home by placing them in a partially enclosed container that allows some buildup of ethene in the air around the fruit. Fruit that has started to ripen helps to ripen the remaining fruit.

A more complex alkene, called muscalure, is a pheromone secreted by the common housefly (*Musca domestica*). Muscalure, an unbranched alkene containing 23 carbon atoms, is released by the female to attract males. Muscalure has been synthesized in the laboratory and can be used to lure male flies to traps.





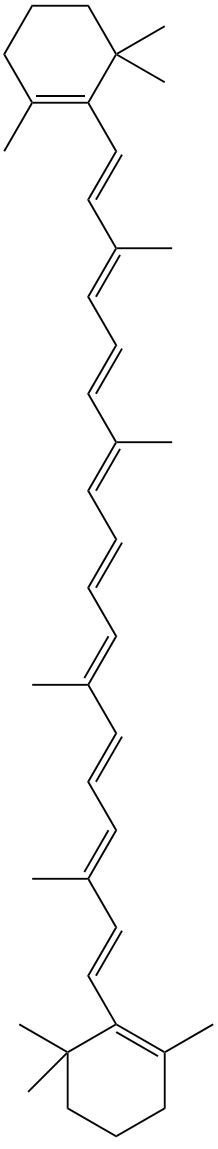
muscalure

Some alkenes, called polyenes, contain two or more carbon–carbon double bonds. Alkenes with two, three, and four double bonds are called dienes, trienes, and tetraenes, respectively. Multiple double bonds are present in polyunsaturated compounds called oils. These substances are esters that contain several carbon–carbon double bonds. Polyunsaturated compounds are common in nature. For example, linolenic acid is a triene that is present as an ester in some polyunsaturated oils. Arachidonic acid, a tetraene, is a precursor to physiologically active molecules called prostaglandins.

$CH_3CH_2CH{=}CH{-}CH_2CH{=}CH{-}CH_2CH{=}CH(CH_2)_3CO_2H$

linolenic acid

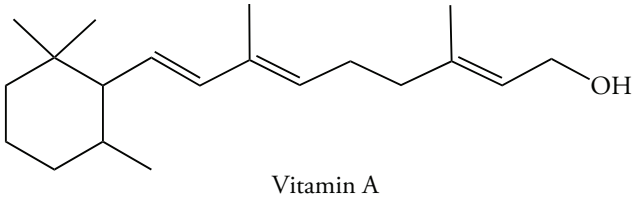
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00005-X
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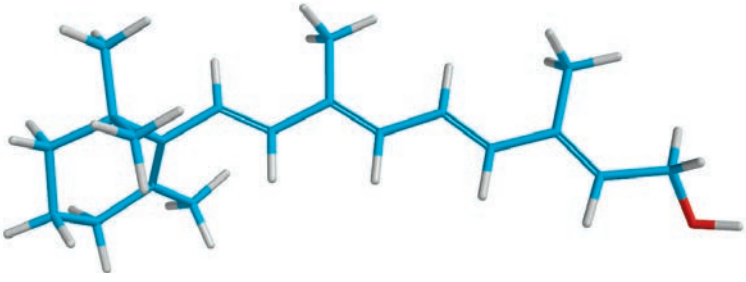
β-carotene

$CH_3(CH_2)_4CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}CH{=}CH{-}CH_2(CH_2)_3CO_2H$
arachidonic acid

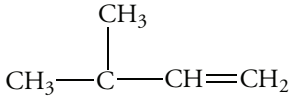
β-Carotene, found in carrots, and vitamin A, which is derived from β-carotene, are polyunsaturated alkenes. β-Carotene is converted to vitamin A in mammals by an enzyme-catalyzed reaction that oxidizes β-carotene into two molecules of vitamin A, which is essential for night vision. It combines with a protein called opsin to give rhodopsin, a retinal pigment that allows vision at very low light levels.



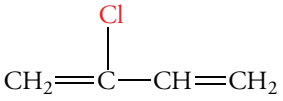
Vitamin A



β-Carotene and vitamin A contain double bonds separated from one another by one single bond. We say that the single and double bonds are "alternating." The alternation of single and double bonds is called conjugation. Therefore, both β-carotene and vitamin A are **conjugated polyenes**. Some industrial products are derived from conjugated dienes. Natural rubber is a polymer of isoprene. The synthetic rubbers called neoprenes are produced from chloroprene.



isoprene



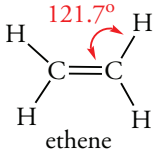
chloroprene

The reactions of conjugated compounds differ from compounds containing double bonds separated by two or more single bonds. The chemistry of conjugated dienes and other more complex conjugated compounds will be discussed in Chapter 12 after we have established a foundation for the typical reactions of alkenes.

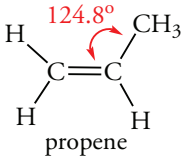
The IUPAC names of alkenes use the suffix *-ene*. Alkynes, which are also unsaturated because they contain one or more carbon–carbon triple bonds, will be discussed in Chapter 7. Unsaturated compounds that contain a benzene ring or structural units that resemble a benzene ring are aromatic hydrocarbons. They will be discussed in Chapter 13.

5.2 STRUCTURE AND BONDING OF ALKENES

The simplest alkene, C_2H_4, commonly called ethylene, has the IUPAC name ethene. Its structure is shown in Figure 5.1. Alkenes contain trigonal planar sp^2-hybridized carbon atoms. Therefore, the bond angles around the sp^2-hybridized carbon atoms should ideally be 120°. The bond angles of alkenes are typically within a few degrees of this value. For example, the H—C=C bond angle in ethene is 121.7°. The C—C=C bond angle of propene is 124.8°.

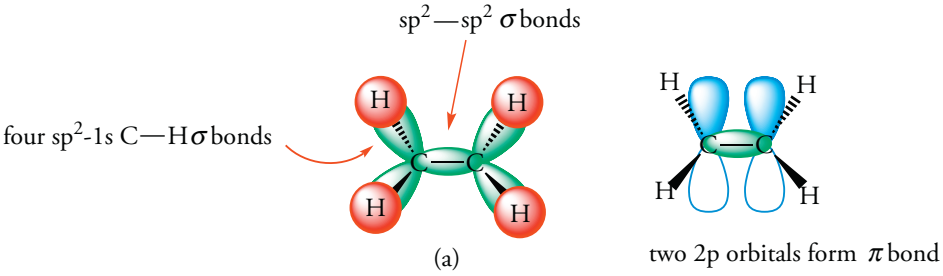


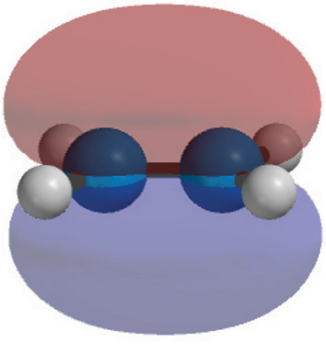
ethene



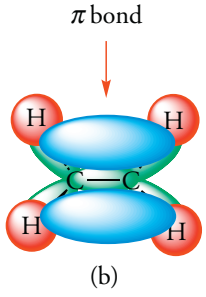
propene

Figure 5.1 Structure of Ethene
(a) The π bond is formed by sideways overlap of the parallel 2p orbitals of adjacent carbon atoms. Carbon forms sigma bonds with sp^2 hybrid orbitals. (b) Schematic diagram of bonding in ethene. (c) The highest occupied molecular orbital of ethene is the π bond.





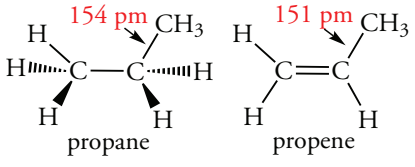
(c) The π bond of ethene



An sp^2 hybrid orbital has 33% s character, whereas an sp^3 hybrid orbital has 25% s character. As the percent s character of a hybrid orbital increases, the electrons are held closer to the nucleus. The increase in percent s character of the s bonds of ethene has an important effect on its bond length and bond energy, as we will see in the next section.

Bond Lengths and Bond Energies

The length of a bond between carbon and another atom is shorter for a carbon atom with sp^2 hybrid orbitals than for a carbon atom with sp^3 hybrid orbitals. For example, the C—H bond lengths in ethene and ethane are 107 pm and 109 pm, respectively. The C—H bond energies of ethene and ethane are 451 and 22 kJ $mole^{-1}$, respectively.



The carbon–carbon bond lengths of ethene and ethane are 133 pm and 154 pm, respectively. The shorter bond length of ethene is partly due to the sp^2 hybridization of the orbitals used to form the carbon–carbon σ bond. Based on the decrease in bond length caused by one sp^2-hybridized carbon atom in propene (3 pm), we could predict that the length of a σ bond between two sp^2-hybridized carbon atoms would be about 148 pm. The actual bond length is much shorter, only 133 pm. Thus, the most important contribution to the decrease in the carbon–carbon bond length of ethene is from the increased number of bonds joining the carbon atoms.

The C=C bond energy of ethene is 605 kJ $mole^{-1}$. The C—C bond energy of ethane is 368 kJ $mole^{-1}$. How can we apportion the contributions of the σ and π bonds to the total bond energy? The σ bond energy in ethene should be somewhat larger than the σ bond energy of ethane because both carbon atoms in ethene are sp^2 hybridized. However, using 368 kJ $mole^{-1}$ as an estimate for the σ bond energy of ethene, the portion of the double bond energy attributed to the σ bond would be 237 kJ $mole^{-1}$. We conclude that the π bond is substantially weaker than the σ bond (Table 5.1).

Table 5.1
Bond Lengths and Bond Strengths in Alkanes Versus Alkenes

Bond	*Bond Length (pm)*	*DH° kJ mole^{-1}*
CH_3—CH_3 (sp^3 — sp^3)	154	347
CH_2=CH_2 (sp^2 — sp^2)	133	610
CH_2=CH—CH_3	151	121
CH_3CH_2—H	109	422
CH_2=CH—H	107	452

Classification of Alkenes

Alkyl groups bonded to the sp^2-hybridized carbon atoms of alkenes affect the stability of the double bond. The chemical reactivity of alkenes also is often affected by the number of alkyl groups bonded to the sp^2-hybridized carbon atoms. Thus, it is useful to classify alkenes by the number of alkyl groups attached to the C=C structural unit. This feature is called the **degree of substitution**. An alkene that has a single alkyl group attached to the sp^2-hybridized carbon atom of the double bond is **monosubstituted.** An alkene whose double bond is at the end of a chain of carbon atoms is also sometimes called a **terminal alkene**. Alkenes that have two, three, and four alkyl groups bonded to the carbon atoms of the double bond are **disubstituted**, **trisubstituted**, and **tetrasubstituted**, respectively.

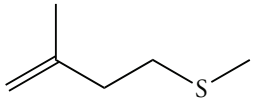
monosubstituted: $RCH=CH_2$
disubstituted: $RCH=CHR$ or $R_2C=CH$
trisubstituted: $R_2C=CHR$
tetrasubstituted: $R_2C=CR_2$

Problem 5.1

The C—Cl bond energy in chloroethane is 341 kJ mole^{-1}; for chloroethene (CH_2=CHCl), it is 368 kJ mole^{-1}. Why is the bond in chloroethene stronger? The C—Cl bond length in chloroethane is 178 pm. Explain whether you expect the C—Cl bond length in vinyl chloride to be longer or shorter than the C—Cl bond in chloroethane.

Problem 5.2

The urine of the red fox contains a scent marker that is an unsaturated thioether. Classify the degree of substitution of the double bond of the scent marker.

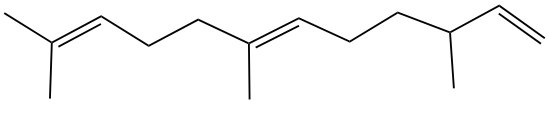


Sample Solution

The compound contains a terminal double bond. The terminal carbon atom has two hydrogen atoms bonded to it. The other carbon atom of the double bond is bonded to a CH_2 group and a CH_2 unit. Thus, the compound contains a disubstituted double bond.

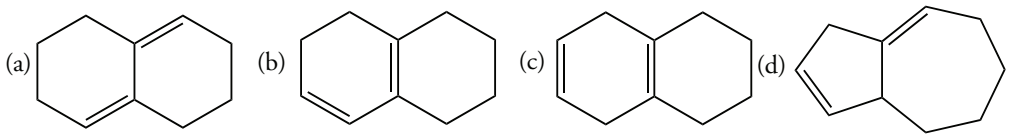
Problem 5.3

Classify each of the three double bonds of farnesene, a compound found in the waxy coating of apples.



Problem 5.4

Classify each double bond in the following isomeric dienes. Which compounds contain conjugated double bonds?



5.3 UNSATURATION NUMBER

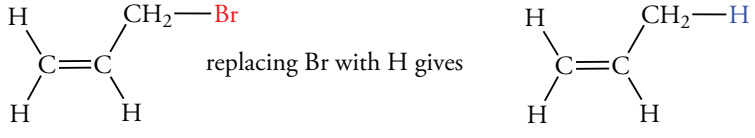
A double bond decreases the number of hydrogen atoms in a molecule by two compared to the corresponding alkane. The general formula of a noncyclic alkene is C_nH_{2n}, compared to the alkane general formula C_nH_{2n+2}. (Alkynes have four fewer hydrogen atoms than alkanes because they have one more π bond than alkenes.) We recall that each ring of a cyclic compound also decreases the number of hydrogen atoms by two. Thus, the molecular formula of an organic compound tells us the combined number of π bonds and rings. We arrive at this information by calculating the **unsaturation number**, which equals the number of π bonds and rings. This is done in three steps.

1. Determine the number of hydrogen atoms in an alkane with the same number of carbon atoms.
2. Subtract the actual number of hydrogen atoms in the compound from the number in the alkane.
3. Divide the difference by two to obtain the degree of unsaturation, or unsaturation number.

The following formula gives the numerical result.

$$\text{unsaturation number} = \frac{[2(\text{number of carbon atoms}) + 2] - [(\text{number of H atoms})]}{2}$$

The unsaturation number can be calculated for molecules containing atoms other than carbon. Because a halogen atom is monovalent, it is regarded as a replacement for hydrogen. Add the number of halogen atoms and hydrogen atoms and then use that quantity in place of the number of hydrogen atoms in the formula. For example, the molecular formula of 3-bromo-1-propene is C_3H_5Br. To calculate the unsaturation number, use a molecular formula with hydrogen replacing bromine, giving C_3H_6.



3-bromo-1-propene propene

The unsaturation number of 3-bromo-1-propene, obtained by substitution into the above formula, is 1.

$$\text{unsaturation number} = \frac{[\,2(3) + 2\,] - 6}{2} = 1$$

We can also calculate the unsaturation number for compounds that contain divalent oxygen atoms. Oxygen atoms are not involved in calculating the degree of unsaturation because they can be "removed" from a structure without changing the number of bonds to hydrogen. For example, when we mentally remove the oxygen atom from dimethyl ether and form a carbon—carbon bond to give ethane, there is no change in the number of hydrogen atoms. Similarly, we can mentally remove the oxygen atom from ethanol and form a carbon—hydrogen bond to give ethane. Thus, dimethyl ether and ethanol have the same degree of unsaturation as ethane.

$CH_3—O—CH_3$ removing oxygen gives $CH_3—CH_3$
dimethyl ether

$CH_3—CH_2—OH$ removing oxygen gives $CH_3—CH_2—H$
ethanol

The formula for determining the unsaturation number of nitrogen-containing compounds is modified for the number of bonds that nitrogen forms. Nitrogen compounds have one more hydrogen atom (per nitrogen atom) than a hydrocarbon with an equal number of carbon atoms. Compare the number of hydrogen atoms in ethane and aminoethane (ethylamine).

$CH_3—CH_2—NH_2$
aminoethane (C_2H_7N)

$CH_3—CH_2—H$
ethane (C_2H_6)

We can easily modify the formula to calculate the degree of unsaturation to include the effect of the number of nitrogen atoms.

$$\text{unsaturation number} = \frac{[2(\text{number of carbon atoms}) + 2] - [(\text{number of H atoms})] + (\text{number of N atoms}) - (\text{number of H atoms})}{2}$$

Problem 5.5

Caryophyllene, which is responsible for the odor of oil of cloves, contains 15 carbon atoms. The compound has two rings and two double bonds. What is the molecular formula of caryophyllene?

Sample Solution

For n = 15, the number of hydrogen atoms for a saturated compound without rings is 32. Each ring and each double bond result in a reduction of two hydrogen atoms. Thus the total number of hydrogen atoms is:

number of hydrogen atoms = 32 – 2(no. of rings) – 2(no. of double bonds) = 32 – 2(2) – 2(2) = 24

The molecular formula is $C_{15}H_{24}$.

Problem 5.6

Based on its location in the periodic table, how should sulfur be treated in the calculation of the degree of unsaturation of a sulfur-containing organic compound?

Problem 5.7

Calculate the unsaturation number for each of the following compounds.

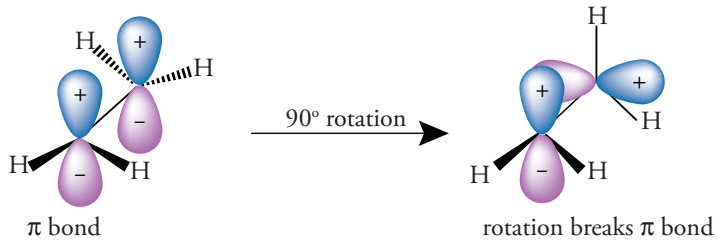
(a) $C_{10}H_{16}$ (b) $C_8H_{10}Br_2$ (c) $C_6H_6O_3$ (d) $C_5H_6N_2$

5.4 GEOMETRIC ISOMERISM

We know that free rotation around carbon—carbon single bonds is fast at room temperature (Section 4.11). Therefore, alkanes can exist in many conformations. Free rotation does not occur around the carbon–carbon double bond of an alkene at room temperature because of its π bond, which forms by side-by-side overlap of two 2p orbitals. About 240 kJ $mole^{-1}$ is required to break a π bond (Figure 5.2). This quantity is the difference between the bond dissociation energies of a carbon–carbon double bond and a carbon–carbon single bond.

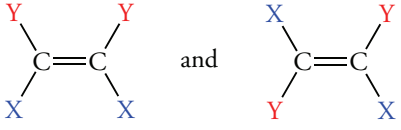
Figure 5.2 Rotation About the π Bond

For rotation to occur about a carbon–carbon double bond, the π bond must break. Loss of overlap between parallel 2p orbitals requires about 240 kJ mole^{-1}.



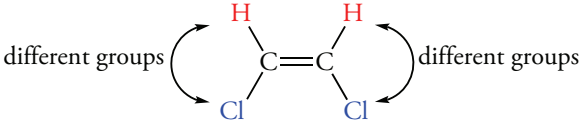
Alkenes with the same molecular formula and the same connectivity of atoms can exist as **stereoisomers**. These isomers differ because groups bonded to the double bond have different spatial arrangements with respect to each other. We call these compounds **geometric isomers.** Geometric isomers have different **configurations**.

Consider an alkene whose formula is CXY=CXY. We can draw the structural formula in two ways.



These two structures represent different molecules (Figure 5.3). In the structure on the left, two X groups are on the same "side" of the molecule. This is the *cis* isomer. In the structure on the right, the X groups are on opposite "sides" of the molecule. It is called the *trans* isomer.

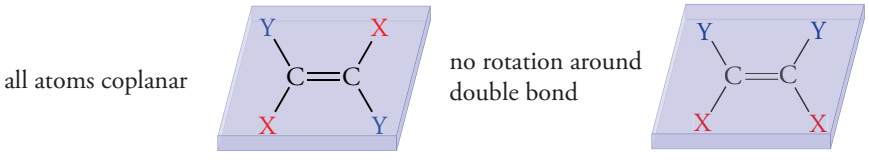
Cis and *trans* isomers are possible only if an alkene has two different atoms or groups of atoms attached to each double-bonded carbon atom. For example, in 1,2-dichloroethene, each unsaturated carbon atom has a chlorine atom and a hydrogen atom attached to it. These groups are different, and both *cis* and *trans* isomers are possible.



1,2-dichloroethene

Figure 5.3 Geometric Isomers of Alkenes

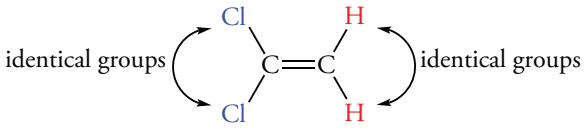
All six atoms lie in the same plane. In the *cis* isomer, two "X" and "Y" groups lie on the same side of the double bond. In the *trans* isomer, "X" and "Y" groups lie on opposite sides of the double bond. They do not interconvert because rotation around the π bond does not occur.



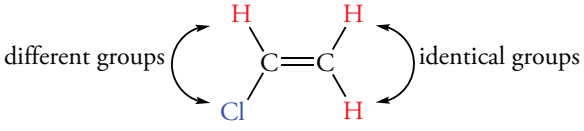
trans geometric isomer

cis geometric isomer

If one of the unsaturated carbon atoms is attached to two identical groups, *cis–trans* isomerism is not possible. For example, neither chloroethene nor 1,1-dichloroethene can exist as *cis* and *trans* geometric isomers.

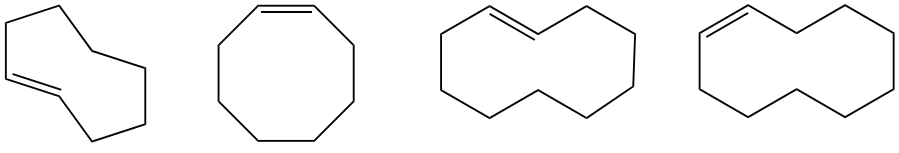


1,1-dichloroethene



chloroethene

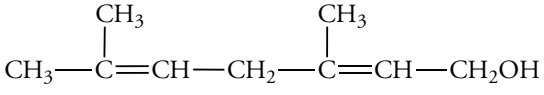
Cycloalkenes in small- and medium-sized ring compounds have *cis* configurations. There are not enough carbon atoms within the ring to bridge the two carbon atoms of the double bond in the *trans* configuration without introducing considerable strain energy. However, both *cis*- and *trans*-cyclooctene are stable compounds at room temperature. The *cis* isomer is more stable than the *trans* isomer by approximately 40 kJ $mole^{-1}$. With an increasing number of CH_2 groups to span the two carbon atoms of the double bond, the strain of the *trans* isomer becomes less severe. For example, the isomeric cyclododecenes are of comparable stability.



trans-cyclooctene *cis*-cyclooctene *trans*-cyclodecene *cis*-cyclodecene

Problem 5.8

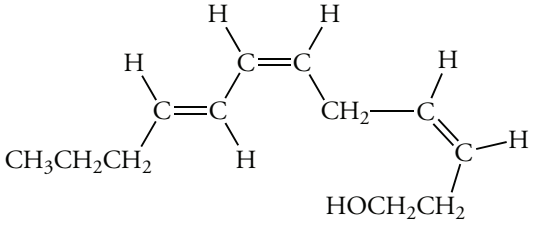
Is *cis–trans* isomerism possible around either of the double bonds of geraniol, a natural oil?



geraniol

Problem 5.9

Determine the *cis–trans* geometry around the double bonds in the following compound, a trail pheromone of termites. (The chain is numbered starting from the carbon atom with the hydroxyl group.) How many geometric isomers are possible for the structure?



5.5 E,Z NOMENCLATURE OF GEOMETRICAL ISOMERS

In the previous section, we applied the terms *cis* and *trans* to describe the relationship of two substituents in the disubstituted alkene 1,2-dichloroethene. This type of nomenclature can easily be used for any disubstituted alkenes. Two examples are *cis*-2-butene and *trans*-2-butene.

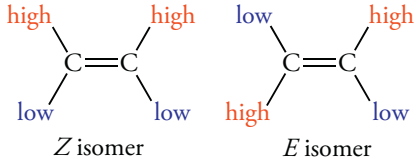


cis-2-butene *trans*-2-butene

However, the *cis* and *trans* notation does not describe isomeric trisubstituted and tetrasubstituted alkenes because there is no longer a simple reference giving the relationship of groups to one another. For example, even the following relatively simple compounds cannot be designated as *cis* and *trans* isomers.



We can distinguish the above isomers and all other tri- and tetrasubstituted alkenes by the ***E,Z* system** of configurational nomenclature. The *E,Z* system uses **sequence rules** to assign priorities to the groups bonded to the atoms of the double bond of any alkene. The two groups bonded to each sp^2-hybridized carbon atom are designated low priority and high priority. If the higher priority groups on each carbon atom are on the same side of the double bond, the alkene is the *Z* isomer (German *zusammen*, together). If the higher priority groups on each carbon atom are on opposite sides of the double bond, the alkene is the *E* isomer (German *entgegen*, opposite).

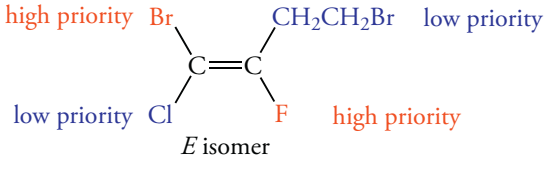


Sequence Rules

To decide whether a group has a high or a low priority, we use a set of rules proposed by Cahn, Ingold, and Prelog in 1964.

1. If two atoms with different atomic numbers *are directly bonded* to a double bond, the atom with the higher atomic number receives a higher priority.

The priority order of some common elements is Br > Cl > F > O > N > C> ^{2}H > H. Applying these priorities to the following alkene, which contains several halogen atoms, allows us to make the *E,Z* assignment. The priority ^{2}H > H tells us that if two isotopes are possible, the one with the higher mass has the higher priority.



The atomic number of bromine is greater than that of chlorine. Therefore, bromine has a higher priority than chlorine. A fluorine atom has a higher priority than a CH_2CH_2Br group, although the reason for this assignment may not be immediately obvious. The priority of a group depends on the atomic number of the atom *directly bonded* to the carbon atom of the double bond. In this case, we have to compare carbon to fluorine. Because fluorine has a higher atomic number than carbon, it has the higher priority.

2. If the atoms directly attached to the carbon atom of the double bond have the same atomic number, consider the second, third, and farther atoms until a difference is found. Then apply rule 1.

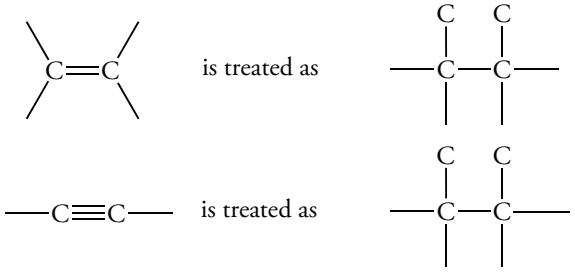
The difference between an ethyl and a methyl group illustrates this rule. They are equivalent at the first directly bonded atom: a carbon atom in each case. The carbon atom of a methyl group is bonded to three hydrogen atoms. The carbon of the ethyl group is bonded to another carbon atom and two hydrogen atoms. Thus, the ethyl group has a higher priority than a methyl group since C > H.

Sometimes the point of first difference is at some distance from the sp^2-hybridized carbon atom. The difference between a $—CH_2CH_2OH$ group and an *n*-propyl group illustrates rule 2. They are equivalent at the directly bonded atom. They are also identical at the second atom. A difference is not found until the third atom. Because oxygen has a higher priority than carbon, the $—CH_2CH_2OH$ group has a higher priority than an *n*-propyl group.

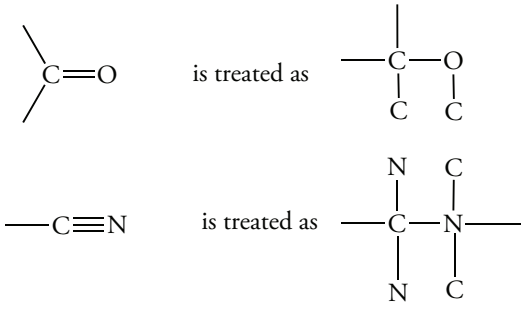
If the first point of difference is not the type of atom, but rather the number of those atoms, then the group with the greater number of high-priority atoms is assigned the higher priority. Based on this consideration, the order of alkyl groups is *tert*-butyl > isopropyl > ethyl > methyl.

The third rule of assigning priorities of groups deals with multiple bonded atoms.

3. A multiple bond is considered equivalent to the same number of single bonds to like atoms. Thus, a double bond is counted as two single bonds for both of the atoms in the double bond. The same principle is used for a triple bond.

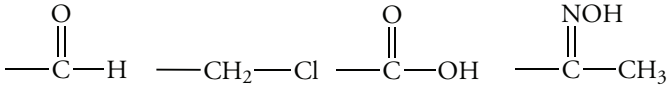


Multiple bonds to atoms other than carbon are also "doubled" or "tripled." For example, a carbonyl group is considered a carbon atom with two single bonds to oxygen atoms, but also an oxygen atom bonded to two carbon atoms. A cyano group is considered a carbon atom with three single bonds to a nitrogen atom and also as a nitrogen atom bonded to three carbon atoms.



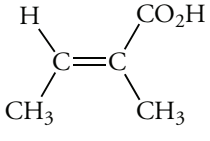
Problem 5.10

Rank the following sets of substituents in order of increasing priority according to the Cahn–Ingold–Prelog rules.



Problem 5.11

Tiglic acid, found in some natural oils, has the following structure. Is it an *E* or a *Z* isomer?

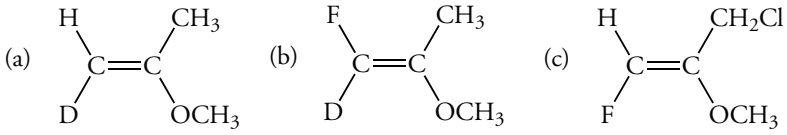


Sample Solution

The methyl group on the carbon atom on the left side of the double bond has a higher priority than the hydrogen atom. However, the methyl group on the right side of the double bond has a lower priority than the CO_2H group. The higher priority groups, CH_3 and CO_2H, are in an *E* arrangement.

Problem 5.12

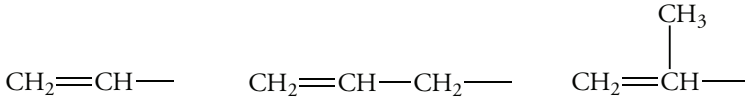
Assign *E* or *Z* to each of the following structures.



5.6 NOMENCLATURE OF ALKENES

Common Names of Alkenyl Groups

As in the nomenclature of alkanes, many groups derived from alkenes have common names. Three of the most often encountered are the vinyl, allyl, and isopropenyl groups.

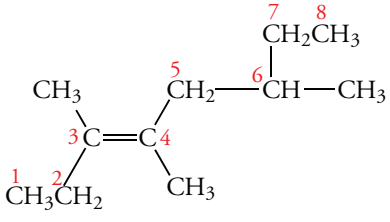


IUPAC Names of Alkenes

The IUPAC rules for naming alkenes are similar to those for alkanes, but the position of the double bond in the chain and the geometric arrangement of substituents around the double bond must be indicated. As in the case of some simple alkyl groups, a few common names are allowed as part of an IUPAC name, including vinyl, allyl, and isopropenyl.

Rule 1

1. The longest continuous chain of carbon atoms that contains the double bond is the parent alkene.



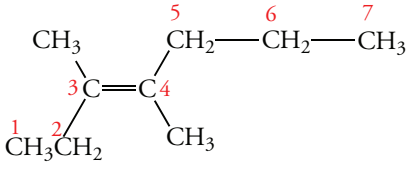
There are eight carbons in this chain, so it is an octene.

Rule 2

2. If the atoms directly attached to the carbon atom of the double bond have the same atomic number, the second, third, and farther atoms are considered until a difference is found. Then apply rule 1.

Rule 3

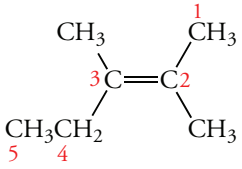
3. Number the carbon atoms in the longest continuous chain starting from the end of the chain nearer the first branch.



This is a substituted 3-heptene, not a substituted 4-heptene.

Rule 4

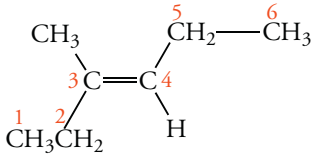
4. Alkyl groups and other substituents are named, and their positions on the chain are identified, according to the numbering established by rule 3. Names and numbers are prefixed to the parent name.



This is 2,3-dimethyl-2-pentene, not 3,4-dimethyl-3-pentene.

Rule 5

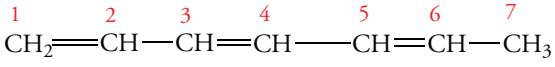
5. If the compound can exist as an *E* or *Z* isomer, the appropriate prefix followed by a hyphen is placed within parentheses in front of the name.



This is (*E*)-3-methyl-3-hexene.

Rule 6

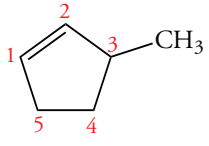
6. If the compound contains more than one double bond, specify the location of each double bond by a number. A prefix to *-ene* indicates the number of double bonds.



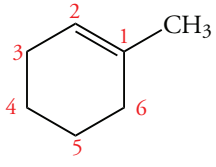
1,3,5-heptatriene

Rule 7

7. Name cycloalkenes by numbering the ring to give the double-bonded carbon atoms the numbers 1 and 2. Choose the direction of numbering so that the first substituent on the ring receives the lower number. The position of the double bond is not given because it is known to be between the C-1 and C-2 atoms.



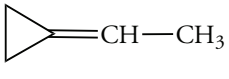
3-methylcyclopentene



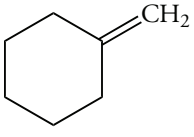
1-methylcyclohexene

Rule 8

8. Compounds with a carbon–carbon double bond positioned between a ring carbon atom and a substituent on the ring are named using **-ylidene** to name the group as a substituent. However, the (=CH_2) group is named methene rather than methylidene.

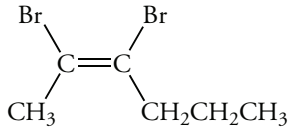


ethylidinecyclopropane



methylenecyclohexane

Problem 5.13
Name the following compound.



Problem 5.14
Draw the structures of the following isomeric compounds.

(a) 1-methyl-1,4-cyclohexadiene
(b) 3-methyl-1,4-cyclohexadiene
(c) 1-methyl-1,3-cyclohexadiene
(d) 2-methyl-1,3-cyclohexadiene
(e) 5-methyl-1,3-cyclohexadiene

Problem 5.15
Draw the structure of each of the following compounds.

(a) (*E*)-1,3-dichloro-2-methy1-3-hexene
(b) 3,3-dimethylcyclohexene
(c) 5-bromo-2,3-dimethyl-2-hexene
(d) (*Z*)-4-bromo-3-methyl-3-heptene

5.7 PHYSICAL PROPERTIES OF ALKENES

Density of Alkenes

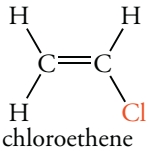
The physical properties of the homologous series of alkenes (C_nH_{2n}) are similar to those of the homologous series of alkanes (C_nH_{2n+2}). Alkenes have densities ranging from 0.6 to 0.8 g cm^{-3} (Table 5.2). Alkenes are either nonpolar or very slightly polar. Thus, they are insoluble in water but soluble in nonpolar solvents such as hexane. They are also soluble in diethyl ether and halogenated solvents.

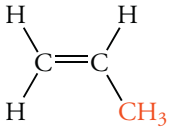
Table 5.2
Densities of Alkenes

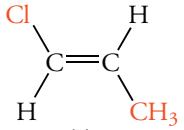
Alkene	*Density d^{20} (g cm^{-1})*
1-Pentene	2.6×10^{-5}
cis-2-pentene	8.5×10^{-5}
trans-2-pentene	2.6×10^{-4}
2-Methyl-2-butene	7.8×10^{-4}
3-Methyl-1-butene	0.648
1-Hexene	0.675
2,3-Dimethyl-2-butene	0.705
1-Heptene	0.698
1-Octene	0.716
1-Nonene	0.731
1-Decene	0.743

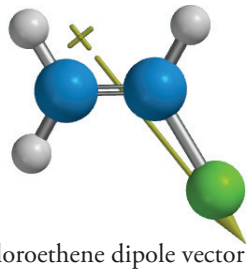
Polarity of Alkenes

Most alkenes are weakly polar. For example, propene has a dipole moment of 0.3 D. The dipole moments of alkenes containing substituents with bond moments of known direction can be used to establish the bond moment for an sp^3–sp^2 carbon—carbon bond. The dipole moment of chloroethene is 1.4 D. Because chlorine is more electronegative than carbon, the chlorine atom has a partial negative charge. The net dipole moment of *trans*-1-chloropropene is 1.7 D. It results from the cumulative effect of the carbon—carbon single bond and the carbon—chlorine bond. Because dipole moment of *trans*-1-chloropropene is larger than that of 1-chloroethene, the two contributing bond moments in *trans*-1-chloropropene reinforce each other.


chloroethene
(1.4 D)


propene
(0.3 D)


trans-1-chloropropene
(1.7 D)


chloroethene dipole vector

Because the bond moments of *trans*-1-chloropropene point in the same direction, the methyl group donates electron density to the sp^2-hybridized carbon atom. We recall that the sp^2-hybridized carbon atom of the double bond has a larger percent s character than the sp^3-hybridized carbon atom of the alkyl group. Thus, the electrons in the σ bond between the methyl group and the double-bonded carbon atom are drawn toward the sp^2-hybridized carbon atom. Other alkyl groups behave similarly.

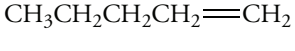
The dipole moments of substituted alkenes depend on the geometric arrangement of the groups. *trans*-2-Butene has no dipole moment because the bond moments of the two bonds to alkyl groups are opposed and cancel. In contrast, the dipole moment of *cis*-2-butene is 0.3 D because the bond moments of the two bonds to the methyl groups do not cancel.

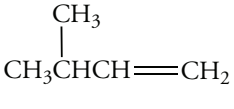
Boiling Points of Alkenes

Alkenes that contain fewer than five carbon atoms are gases at room temperature. The boiling points of the alkenes, like those of alkanes, increase with an increasing number of carbon atoms because the London forces increase (Table 5.3). And, like alkanes, alkenes with branched alkyl groups have lower boiling points. Branched alkenes have more compact structures than the unbranched isomers, and thus less intermolecular contact, which diminishes the intermolecular London forces.

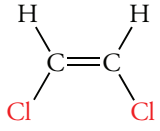
Table 5.3
Boiling Points of Alkenes

Alkene	*Boiling Point (°C)*
Ethene	–103.7
Propene	–47.4
1-Butene	–6.3
2-Methylpropene	–6.9
cis-2-Butene	+3.7
trans-2-Butene	0.9
1-Pentene	30.0
cis-2-Pentene	36.9
trans-2-Pentene	36.4
1-Hexene	63.5
1-Heptene	93
1-Octene	122.5
1-Nonene	146
1-Decene	171

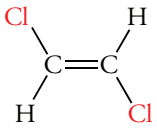

1-pentene
(bp 30 °C)


3-methyl-1-butene
(bp 25 °C)

Because geometric isomers have different polarities, their boiling points differ. For example, the boiling points of *cis*- and *trans*-1,2-dichloroethenes are 60 and 47 °C, respectively. The two C—Cl bond moments of the *trans* isomer cancel each other, so it has no *net* dipole moment. In contrast, the *cis* isomer has a net dipole moment because the two C—Cl bond moments reinforce each other. Therefore, the *cis* isomer is polar and has the higher boiling point.



cis-1,2-chloroethene
(bp 60 °C)



trans-1,2-chlorodichloroethene
(bp 47 °C)

5.8 STABILITY OF ALKENES

The combustion of alkenes is not a synthetic or commercially useful reaction. (We will discuss reactions that partially oxidize alkenes that are synthetically useful in Chapter 6.) However, we recall that we can analyze the heats of combustion to compare the stabilities of isomeric alkanes and cycloalkanes. So it is not so surprising that we can use the heats of combustion of alkenes to compare their stabilities of isomeric alkenes since they form the same number of moles of CO_2 and H_2O. Figure 5.4 compares the heats of combustion of alkenes having the formula C_4H_8. We recall that the more stable compound releases less heat in the combustion reaction.

1-butene < *cis*-2-butene < *trans*-2-butene < 2-methylpropene

——— increasing stability (decreasing ΔH°_c) ⟶

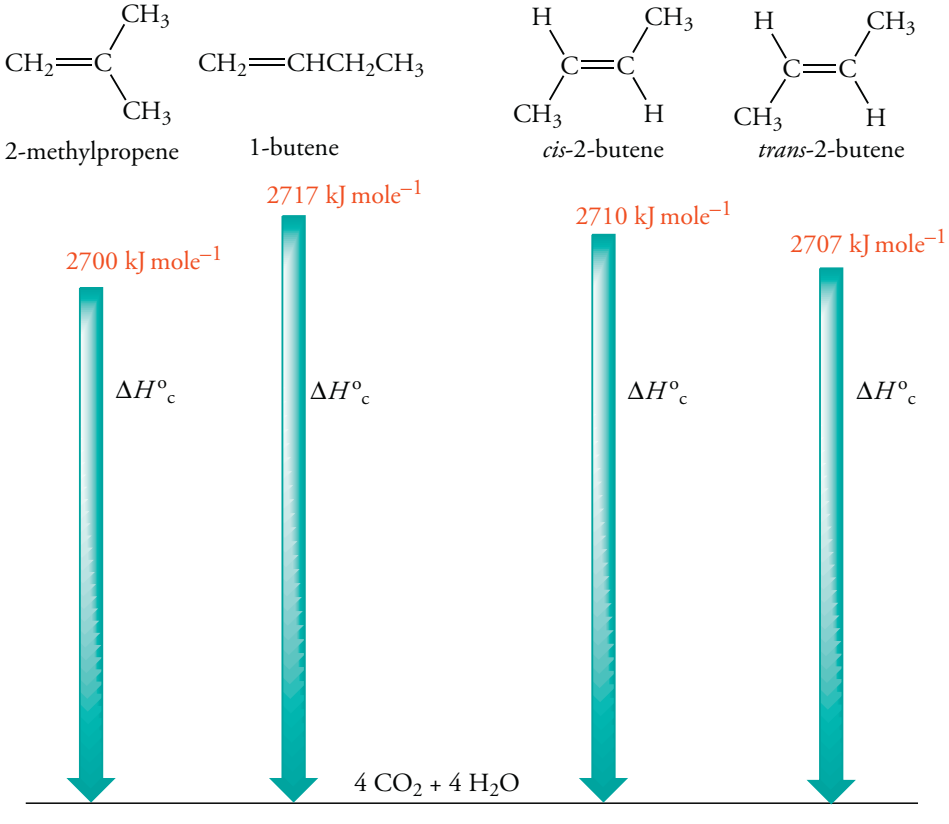
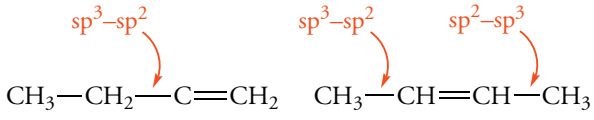


Figure 5.4 Heats of Combustion of Isomeric Butenes
The heats of combustion of the isomeric butenes are plotted on the vertical axis in kJ mole^{-1}. All compounds are at higher energy than the common products, carbon dioxide and water.

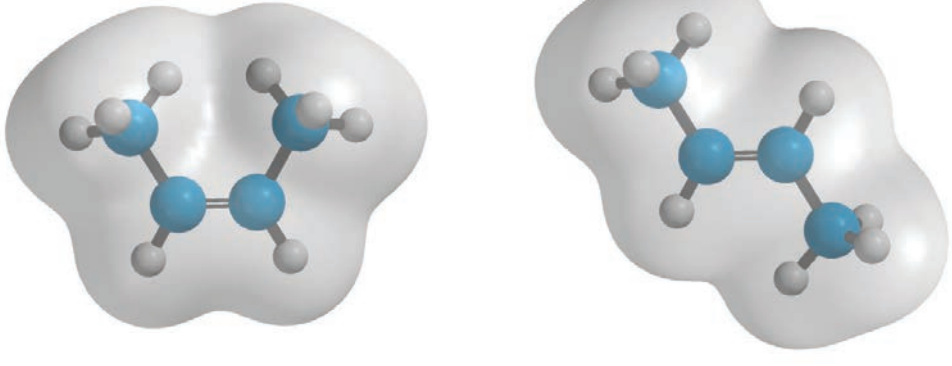
We can explain the relative stabilities of these alkenes using concepts we have already introduced. We recall that a branched alkane is more stable than the isomeric unbranched alkane. For example, 2-methylpropane is more stable than butane. When we examine the relative stabilities of the isomeric C_4H_8 alkenes, we find that the branched isomer is the most stable. However, the principal structural feature that makes one alkene more stable than another isomeric alkene is the degree of substitution. For example, 1-butene, a monosubstituted alkene, is less stable than the disubstituted alkenes *cis*-2-butene and *trans*-2-butene. The sp^3-hybridized carbon atoms of alkyl groups release electron density to the sp^2-hybridized carbon atoms of the alkene. The double bond is stabilized by this effect. The two alkyl groups of *cis*- and *trans*-2-butene release more electron density to the double bond via the two sp^3—sp^2 bonds than the one alkyl group of 1-butene. Of course, 2-methylpropene is also disubstituted, but being branched gives it more stability than *cis*- and *trans*-2-butene.



What is responsible for the difference in the stabilities of *cis*- and *trans*-2-butenes, which have the same carbon skeleton? When we analyze the stabilities of many acyclic alkenes, we find that *trans* alkenes are more stable than *cis* alkenes. This energy difference is the result of a **steric effect**. In a *cis* alkene, two alkyl groups are close enough to each other to generate van der Waals repulsion (Figure 5.5). This steric effect is related to the intramolecular repulsion found in the eclipsed conformation of butane (Section 4.13). The hydrogen atoms of the two methyl groups in *cis*-2-butene are arranged in a 1,6 relationship, and we expect them to be in van der Waals contact. The difference in stabilities of *cis* and *trans* isomers becomes more pronounced as the size of the alkyl groups increases.

Figure 5.5 Steric Effects and Stability of Alkenes
Some of the hydrogen atoms of the two methyl groups in *cis*-2-butene are within their van der Waals radii. These atoms are in a 1,6 relationship, and they sterically interfere with each other. There is no steric effect in the *trans* isomer.

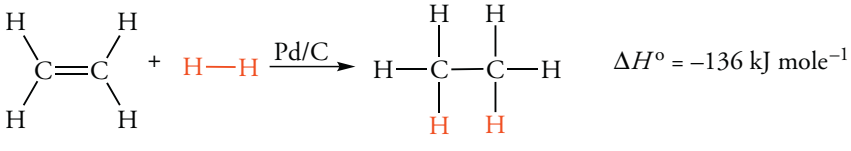
Steric repulsion between methyl groups.



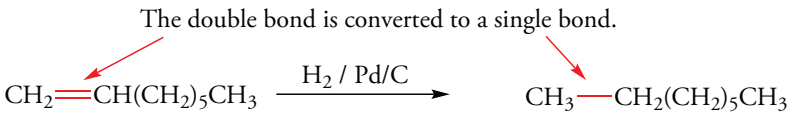
cis-2-butene *trans*-2-butene

5.9 REDUCTION OF ALKENES

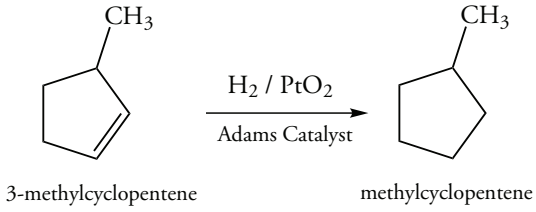
Alkenes and cycloalkenes react with hydrogen gas in an addition reaction to give saturated compounds. In this process, the alkene is reduced. The reaction is called **hydrogenation**. The hydrogenation of an alkene is an exothermic process, but the reaction has a high activation energy, so it occurs slowly even at high temperatures in the absence of a catalyst.



However, the hydrogenation of an alkene, such as 1-octene to octane, occurs rapidly at room temperature in the presence of certain transition metal catalysts. One such catalyst is palladium dispersed on carbon (Pd/C).

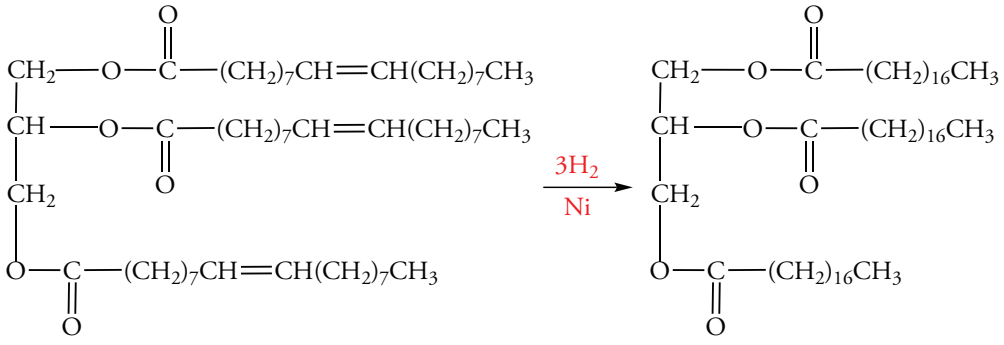


Adams catalyst, PtO_2, is also an effective catalyst for the hydrogenation of alkenes. Under the reaction conditions, hydrogen gas reduces PtO_2 to a finely divided colloidal suspension of platinum metal, which is the active catalyst.



3-methylcyclopentene methylcyclopentene

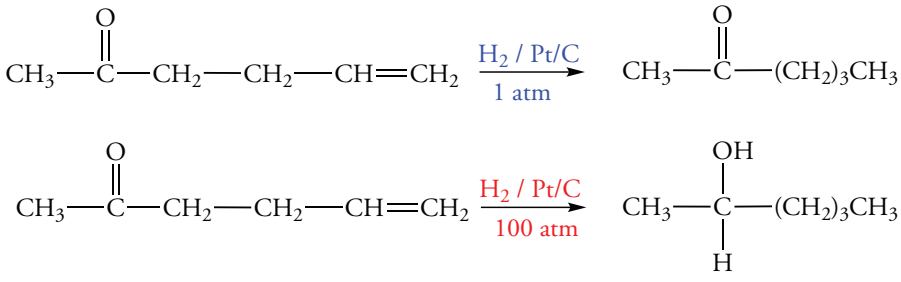
The catalytic hydrogenation of alkenes can also be carried out with a finely dispersed form of nickel known as Raney nickel. It is prepared by treating a nickel–aluminum alloy with aqueous base, which reacts with the aluminum, leaving the finely divided nickel. Hydrogenation reactions using Raney nickel usually require higher temperatures or pressures than those required for palladium or platinum catalysts. However, nickel is less expensive than palladium or platinum, so it is used in industrial processes, such as the conversion of triolein, an oil, into tristearin, a fat.



triolein tristearin

These metal hydrogenation catalysts do not dissolve in organic solvents. The catalytic hydrogenation of alkenes is a heterogeneous reaction, and the solution of the alkene must be stirred or shaken vigorously so that the reactants remain in contact with the dispersed solid phase. Solvents commonly used are ethanol (CH_3CH_2OH) and methanol (CH_3OH).

The conditions used for catalytic hydrogenation of an alkene are too mild to reduce the carbon–oxygen double bond of functional groups such as aldehydes, ketones, carboxylic acids, and esters. Catalytic hydrogenation of alkenes requires an H_2 pressure of only 1 atm, whereas hydrogenation of the carbon–oxygen double bonds of aldehydes or ketones requires pressures in the range of 100 atm. Carboxylic acids or esters react only at very high temperatures.



Regioselectivity of Catalytic Hydrogenation

A reaction that can produce more than one constitutional isomer from a reactant and gives a predominance of one product is said to be **regioselective**. The hydrogenation reaction, for example, is regioselective. The rate of catalytic hydrogenation of alkenes depends on the degree of substitution of the double bond. Hydrogenation of monosubstituted and disubstituted alkenes at room temperature occurs rapidly under 1 atm pressure of hydrogen. The hydrogenation of trisubstituted alkenes is slower and usually requires higher temperatures and higher pressures of hydrogen. Tetrasubstituted double bonds are extremely difficult to hydrogenate. The order of reactivity is

monosubstituted > disubstituted > trisubstituted > tetrasubstituted

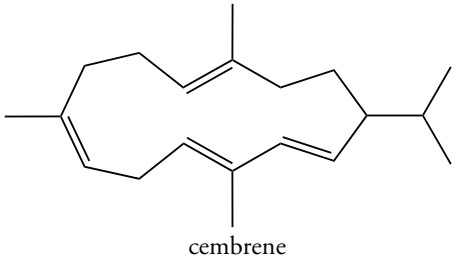
These differences in reaction rate make it possible to hydrogenate one double bond regioselectively in a compound with two or more double bonds if their substitution patterns differ substantially. For example, a monosubstituted double bond can be selectively hydrogenated in a compound that also has a trisubstituted or tetrasubstituted double bond. The solution of an alkene must be stirred or shaken so that the alkene will remain in contact with the dispersed solid metal phase in catalytic hydrogenation. The method is widely used because it is easy to isolate the product. The catalyst can be removed by filtration and the solvent evaporated to yield the reduced product.

Homogeneous Catalytic Hydrogenation

Several homogeneous hydrogenation catalysts have been developed. They cause faster hydrogenation because the reagents remain in continuous contact within the solution. One widely used homogeneous catalyst is $[(C_6H_5)_3P]_3RhClH$, known as the **Wilkinson catalyst**. It does not reduce other functional groups with π bonds such as carbonyl groups, nitro groups ($—NO_2$), and cyano groups ($—C{\equiv}N$) under the conditions that reduce alkenes. The most important feature of the Wilkinson catalyst is its regioselectivity. Monosubstituted double bonds can easily be hydrogenated in the presence of disubstituted double bonds.

Problem 5.16

How many moles of hydrogen gas will react with cembrene, which is present in pine oil? What is the molecular formula of the product?



cembrene

Sample Solution

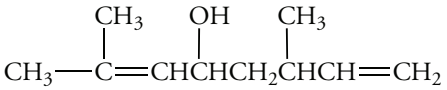
Four moles of hydrogen gas react with the four double bonds. The resulting compound has 14 carbon atoms in the ring, 3 methyl groups and an isopropyl group for a total of 20 carbon atoms. Because there is a single ring, the unsaturation number is 1, and the number of hydrogen atoms must be two fewer than the number contained in an alkane. For 20 (n) carbon atoms of an alkane, there are 42 ($2n + 2$) hydrogen atoms. For the monocyclic compound, there are 40 hydrogen atoms. The molecular formula is $C_{20}H_{40}$.

Problem 5.17

Explain why acetic acid (CH_3CO_2H) and ethyl acetate ($CH_3CO_2CH_2CH_3$) can be used as solvents for catalytic hydrogenation of alkenes.

Problem 5.18

Write the structure obtained by hydrogenation of ipsdienol, a pheromone of the Norwegian spruce beetle, using one equivalent of hydrogen gas and the Wilkinson catalyst.



Problem 5.19

A mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene is obtained in the commercial dimerization of 2-methylpropene. Hydrogenation of the mixture gives a single product. Draw the structures of the alkenes and the product. Explain why a single product forms.

Problem 5.20

Squalene, an intermediate in the biosynthesis of steroids, has the molecular formula $C_{30}H_{50}$. Hydrogenation yields a compound with molecular formula $C_{30}H_{62}$. What is the unsaturation number of squalene? Does the compound contain any rings?

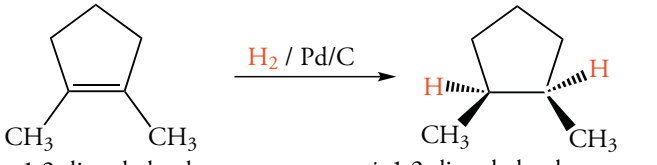
5.10 MECHANISM OF CATALYTIC HYDROGENATION

The heterogeneous catalytic hydrogenation of alkenes occurs in a series of steps in which hydrogen and the alkene bond to the surface of the metal. In the first step, hydrogen gas is adsorbed onto the surface of the metal catalyst and the H—H bond is broken. Then, the alkene forms a complex with the metal in which the π electrons form a coordinate covalent bond with the vacant orbitals of the metal. In subsequent steps, hydrogen atoms add to the carbon atoms of the double bond—probably one atom at a time. The alkene remains attached to the metal surface until both hydrogen atoms are added. Then, the reduced product is released.

Stereochemistry of Hydrogenation

The stereochemistry of hydrogenation cannot be determined by studying the reactions of acyclic alkenes such as 1-octene. The product of the hydrogenation of 1-octene is octane, a conformationally flexible molecule. When octene is converted to octane, the hydrogen atoms have added to adjacent carbon atoms, but we cannot tell how the individual atoms approached the plane of the alkene molecule. However, the stereochemistry of hydrogenation *can* be determined with cycloalkenes.

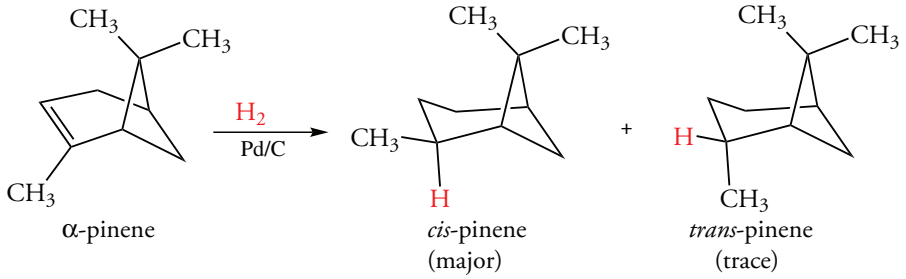
The hydrogenation of 1,2-dimethylcyclopentene produces *cis*-1,2-dimethylcyclopentane. Therefore, hydrogenation of an alkene occurs by the addition of two hydrogen atoms to the same side of the plane of the double bond. The process is called ***syn* addition**. *Syn* addition can only occur if the cycloalkene remains attached to the metal surface, allowing the two hydrogen atoms to add to the same side of the double bond.



1,2-dimethylcyclopentene — *cis*-1,2-dimethylcyclopentane

Stereoselectivity of Hydrogenation

Although catalytic hydrogenation occurs by a *syn* addition mechanism, the two faces of the planar double bond are not always equivalent. In such cases, the addition of hydrogen could occur at either of the two faces of a molecule, yielding mixtures of stereoisomers. Hydrogenation is **stereoselective**. That is, one of the two stereoisomers forms in greater amount than the other. For example, *syn* addition of hydrogen to 2,6,6-trimethy1-2-bicyclo13.1.11heptene (α-pinene) is highly stereoselective and gives almost 100% *cis* isomer.

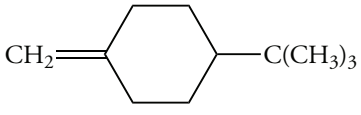


α-pinene *cis*-pinene (major) *trans*-pinene (trace)

The stereoselectivity of the reduction of α-pinene, and other alkenes whose two faces differ, is governed by the steric hindrance that arises when the plane of the alkene approaches the surface of the catalyst. Catalytic hydrogenation occurs at the less hindered face of the reactant. In the case of α-pinene, one of the two methyl groups at the C-6 atom is positioned over the "top" face of the double bond. Thus, the "bottom" face of the double bond is less hindered, and hydrogen adds from that direction. When a hydrogen atom is added from the bottom at the C-2 atom, the methyl group located at that carbon atom is pushed up. In the product, the C-2 methyl group and the C-6 methyl group are on the same side of the six-membered ring, hence the designation *cis*.

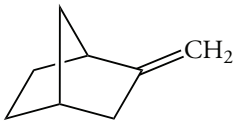
Problem 5.21

Catalytic hydrogenation of the following compound gives a mixture of *cis*- and *trans*-1-*tert*-buty1-4-methylcyclohexanes in a 7:1 ratio. Explain why.



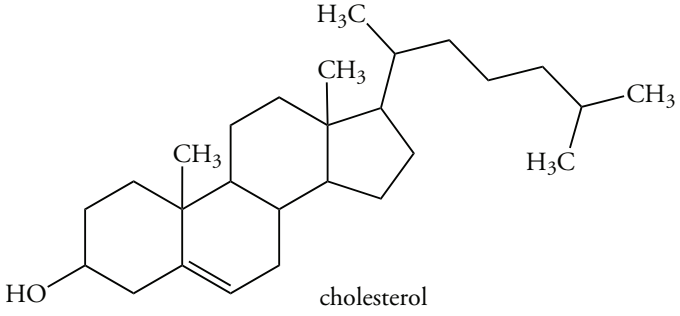
Problem 5.22

Draw the structures of the two products obtained by hydrogenation of the following unsaturated bicyclic compound. Will they be obtained in equal amounts?



Problem 5.23

Predict the stereochemistry of the product obtained by catalytic hydrogenation of cholesterol. The six-membered rings are all in the chair conformation, and the methyl groups at the bridgehead positions are axial. (Refer to Section 4.19 to determine the shape of the steroid.)



cholesterol

5.11 HEATS OF HYDROGENATION OF ALKENES

In the hydrogenation of alkenes, the carbon—carbon π bond and the hydrogen—hydrogen bond of the hydrogen molecule break, and two carbon—hydrogen bonds form. The hydrogenation reaction is exothermic because the two carbon—hydrogen bonds formed are stronger than the combined strengths of the bonds broken. The overall heat evolved for the hydrogenation reaction is usually reported as a positive quantity defined as the heat of hydrogenation ($\Delta H°_{\text{hydrogenation}}$). However, we must remember that $\Delta H°$ for the reaction is negative.

Structural Effects on Heats of Hydrogenation

The relative stabilities of isomeric alkenes such as 1-butene, *cis*-2-butene, and *trans*-2-butene can be analyzed by comparing their heats of hydrogenation. This method is possible because the hydrogenation of these alkenes yields the same product. The heats of hydrogenation of three of the four isomeric C_4H_8 alkenes are shown in Figure 5.6. The more stable compound has the smaller heat of hydrogenation, so we again confirm that the order of increasing stability of the isomers is

1-butene < *cis*-2-butene < *trans*-2-butene

The energy differences as measured by heats of hydrogenation are within the range of experimental error of those obtained from heats of combustion (Section 5.8).

We cannot directly compare the relative stabilities of nonisomeric alkenes by using heats of hydrogenation because such alkenes yield different alkanes. However, as shown in Table 5.4, alkenes with similar structures have similar heats of hydrogenation. The heats of hydrogenation of 1-butene and 1-hexene are the same within the range of experimental error. The heat of hydrogenation of a monosubstituted alkene is approximately 126 kJ mole^{-1}. We saw in Section 5.8 that disubstituted alkenes of the type RCH=CHR are more stable than monosubstituted alkenes. Therefore, they have lower heats of hydrogenation. Furthermore, acyclic *trans* isomers have lower heats of hydrogenation than *cis* isomers. In both classes of alkenes, the heats of hydrogenation are within a narrow range for a variety of alkyl groups. Because $\Delta H°_{\text{hydrogenation}}$ is reported as a positive quantity, the order of heats of hydrogenation of alkenes is

monosubstituted > disubstituted > trisubstituted > tetrasubstituted

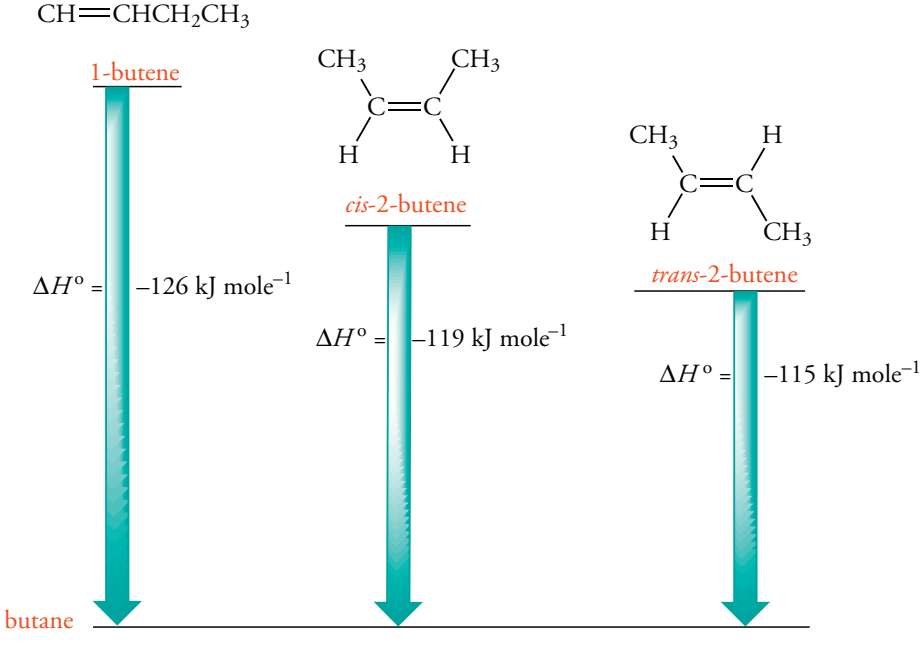


Figure 5.6 Heats of Hydrogenation of Isomeric Butenes
The positions of three isomeric butenes show their relative heats of formation.

Table 5.4
Heats of Hydrogenation of Alkenes

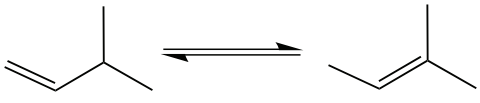
Alkene	$\Delta H^\circ_{hydrogenation}$ *kJ mole*$^{-1}$	*Alkene*	$\Delta H^\circ_{hydrogenation}$ *kJ mole*$^{-1}$
Unsubstituted		*Internal Disubstituted*	
Ethene	136	*cis*-2-butene	119
Monosubstituted		*trans*-2-butene	115
Propene	125	*cis*-2-pentene	117
1-Butene	126	*trans*-2-pentene	114
1-Hexene	126	*cis*-4,5-dimethyl-2-hexene	118
3-Methyl-1-butene	127	*trans*-4,5-dimethyl-2-hexene	113
Terminal disubstituted		*Trisubstituted*	
2-Methylpropene	117	2-Methyl-2-pentene	112
2-Methyl-1-butene	118	2,3-Dimethyl-3-hexene	114
2,3-Dimethyl-1-butene	116	*Tetrasubstituted*	
2,3-Dimethyl-1-hexene	117	2,3-Dimethyl-2-butene	110
		2,3-Dimethyl-2-hexene	106

Problem 5.24

Explain why the stability of 2-methyl-l-propene can be compared to the stability of the isomeric butenes using heat of combustion data, but these stabilities cannot be directly compared using heat of hydrogenation data.

Problem 5.25

The heats of hydrogenation of 3-methyl-1-butene and 2-methyl-2-butene are 127 and 113 kJ mole^{-1}, respectively. Assuming that the following equilibrium reaction can be established, predict the $\Delta H^\circ_{reaction}$.



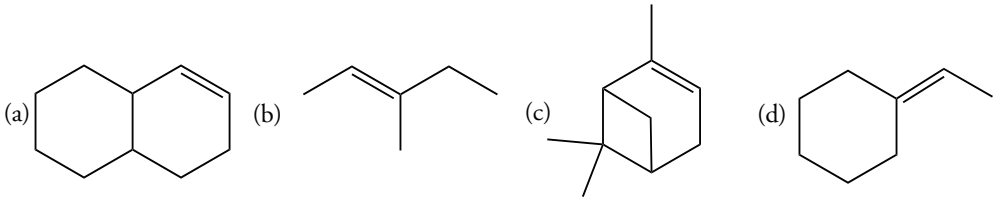
EXERCISES

Molecular Formulas

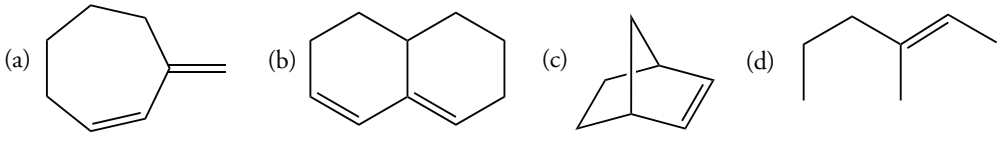
5.1 What is the molecular formula for a compound with each of the following structural features?
(a) six carbon atoms and one double bond
(b) five carbon atoms and two double bonds
(c) seven carbon atoms, a ring, and one double bond

5.2 What is the molecular formula for a compound with each of the following structural features?
(a) four carbon atoms and two double bonds
(b) ten carbon atoms and two rings
(c) ten carbon atoms, two rings, and five double bonds

5.3 Write the molecular formula for each of the following compounds.



5.4 Write the molecular formula for each of the following compounds.



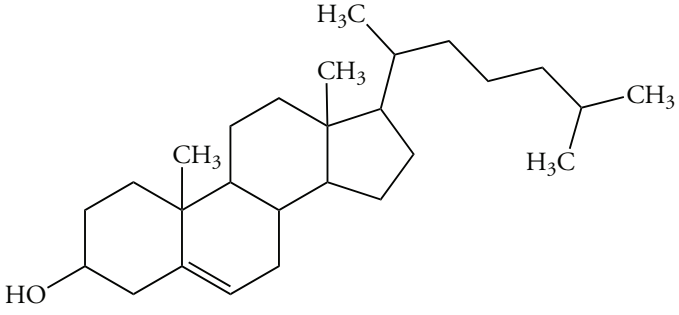
Classification of Alkenes

5.5 Classify each double bond in the alkenes in Exercise 5.3 by its substitution pattern.

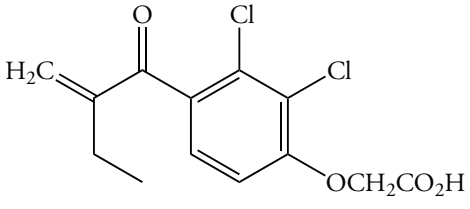
5.6 Classify each double bond in the alkenes in Exercise 5.4 by its substitution pattern.

5.7 Indicate the degree of substitution of the double bond in each of the following compounds.

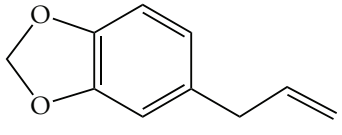
(a) Cholesterol, a steroid



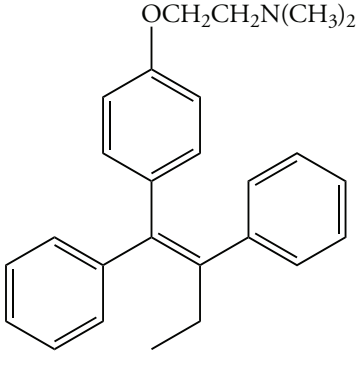
(b) Ethacrynic acid, a diuretic



(c) Saffrole, a carcinogen found in sassafras root

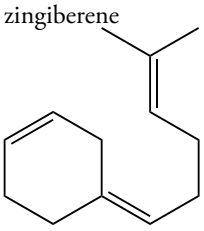


(d) Tamoxifen, a drug used in the treatment of breast cancer

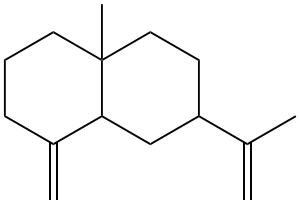


5.8 Indicate the degree of substitution of all double bonds in each of the following compounds, polyenes found in natural oils.

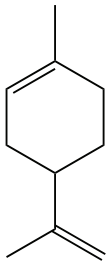
(a) zingiberene



(b) β-selenene



(c) limonene



Unsaturation Number

5.9 Calculate the unsaturation number for each of the following compounds.
(a) camphor, $C_{10}H_{16}O$ (b) nicotine, $C_{10}H_{14}N_2$
(c) vitamin B6, $C_8H_9NO_2$ (d) hexachlorophene, $C_{13}H_6O_2Cl_6$

5.10 Calculate the unsaturation number for each of the following compounds.
(a) β-carotene, $C_{40}H_{56}$ (b) amphetamine, $C_9H_{13}N$ (c) DDT, $C_{11}H_9Cl_5$ (d) aspirin, $C_9H_8O_4$

5.11 Calculate the unsaturation number for each of the following compounds.
(a) vitamin A, $C_{20}H_{30}O$ (b) sucrose, $C_{12}H_{22}O_{11}$ (c) vitamin B2, $C_{17}H_{20}N_4O_6$ (d) saccharin, $C_7H_5NO_3S$

5.12 Calculate the unsaturation number for each of the following compounds.
(a) L-dopa, $C_9H_{11}NO_4$ (b) prontosil, $C_{12}H_{13}N_5O_2S$
(c) testosterone, $C_{19}H_{28}O_2$ (d) phenobarbital, $C_{12}H_{12}N_2O_3$

Geometric Isomers

5.13 Which of the following molecules can exist as *cis* and *trans* isomers?
(a) $CH_3CH{=}CHBr$ (b) $CH_2{=}CHCH_2Br$ (c) $CH_3CH{=}CHCH_2C1$ (d) $(CH_3)_2C{=}CHCH_3$

5.14 Which of the following molecules can exist as *cis* and *trans* isomers?
(a) $CH_3CH{=}CBr_2$ (b) CH=CHCHBr, (c) $CH_3CH{=}CHCHCl_2$ (d) CH,CH,CH=$C(CH_3)_2$

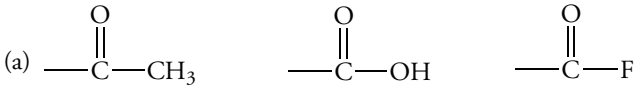
5.15 Which of the following molecules can exist as *cis* and *trans* isomers?
(a) 1-hexene (b) 3-heptene (c) 4-methyl-2-pentene (d) 2-methyl-2-butene

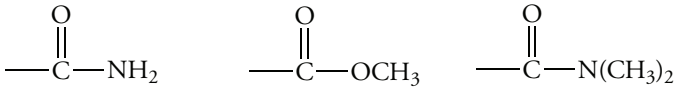
5.16 Which of the following molecules can exist as *cis* and *trans* isomers?
(a) 3-methyl-l-hexene (b) 3-ethyl-3-heptene (c) 2-methyl-2-pentene (d) 3-methyl-2-pentene

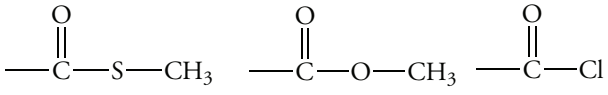
E,Z System of Nomenclature

5.17 Select the group with the highest priority in each of the following sets.
(a) $—CH(CH_3)_2$ $—CHClCH_3$, $—CH_2CH_2Br$
(b) $—CH_2CH{=}CH_2$, $—CH_2CH(CH_3)_2$, $—CH_2C{\equiv}CH$
(c) $—OCH_3$, $—N(CH_3)_2$, $—C(CH_3)_3$

5.18 Select the group with the highest priority in each of the following sets.

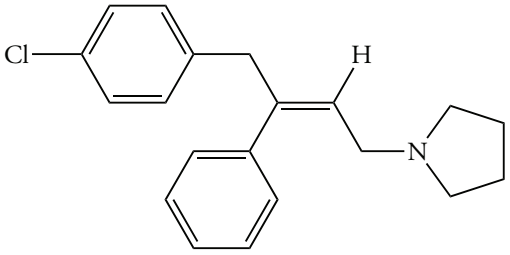
(a) 

(b) 

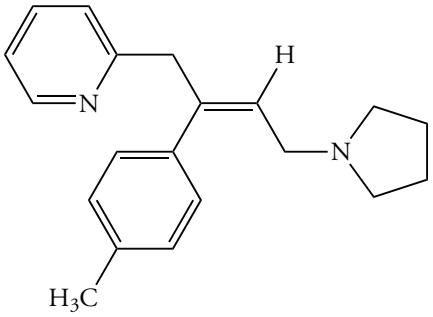
(c) 

5.19 Assign the *E* or *Z* configuration to each of the following antihistamines.

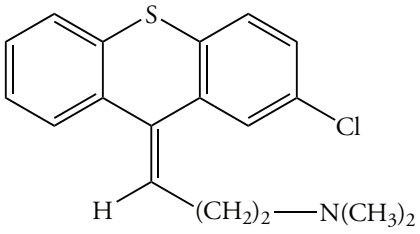
(a) pyrrobutamine



(b) triprolidine

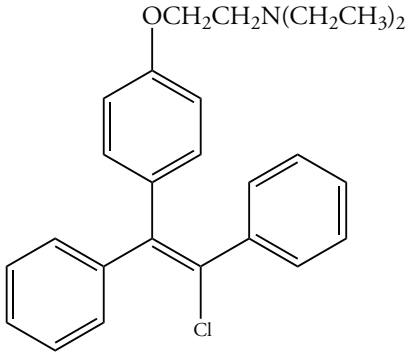


(c) chloroprothixene

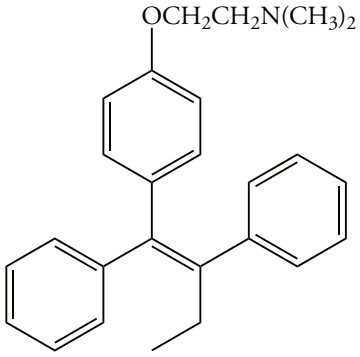


5.20 Assign the *E* or *Z* configuration to each of the following hormone antagonists used to control cancer.

(a) Chlomiphene



(b) Tamoxifen



5.21 Draw the structural formula for each of the following pheromones with the indicated configuration.

(a) sex pheromone of Mediterranean fruit fly, *E* isomer

$CH_3CH_2CH{=}CH(CH_2)_4CH_2OH$

(b) sex pheromone of honey bee, *E* isomer

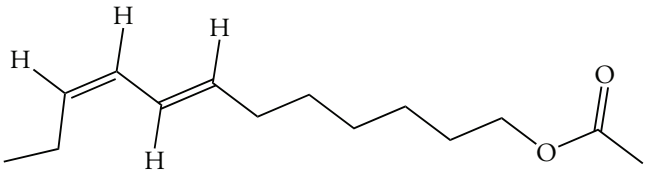
$CH_3CO(CH_2)_4CH_2CH{=}CHCO_2H$

(c) defense pheromone of termite, *E* isomer

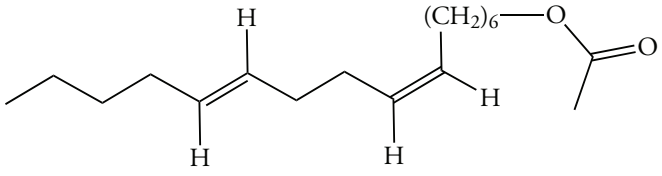
$CH_3(CH_2)_{12}CH{=}CHNO_2$

5.22 Assign the configuration at all double bonds where geometrical isomerism is possible in each of the following sex pheromones.

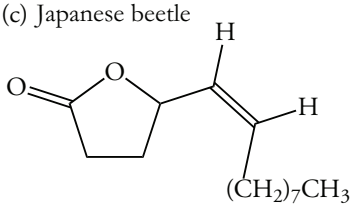
(a) European vine moth



(b) pink bollworm moth

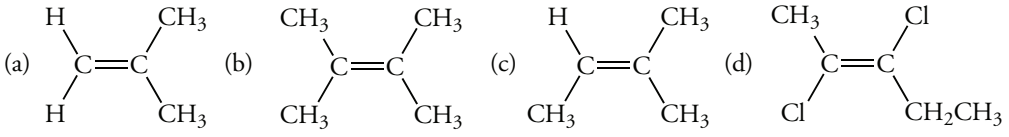


(c) Japanese beetle

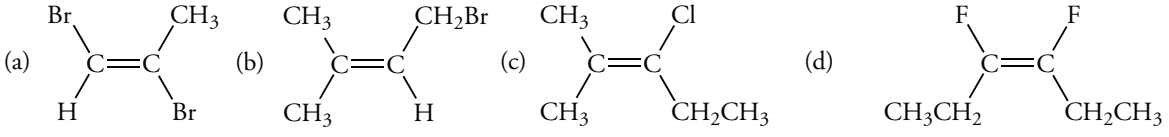


Nomenclature of Alkenes

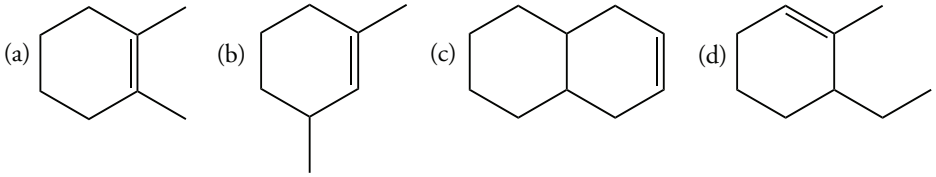
5.23 Name each of the following compounds.



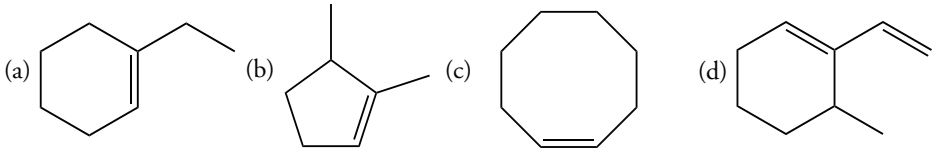
5.24 Name each of the following compounds.



5.25 Name each of the following compounds.



5.26 Name each of the following compounds.



5.27 Draw a structural formula for each of the following compounds.
(a) 2-methyl-2-pentene (b) 1-hexene
(c) (*Z*)-2-methyl-3-hexene (d) (*E*)-5-methyl-2-hexene

5.28 Draw a structural formula for each of the following compounds.
(a) (*E*)-1-chloropropene (b) (*Z*)-2,3-dichloro-2-butene
(c) 3-chloropropene (d) 4-chloro-2,4-dimethyl-2-hexene

5.29 Draw a structural formula for each of the following compounds.
(a) cyclohexene (b) 1-methylcyclopentene
(c) 1,2-dibromocyclohexene (d) 4,4-dimethylcyclohexene

5.30 Draw a structural formula for each of the following compounds.
(a) cyclopentene (b) 3-methylcyclohexene
(c) 1,3-dibromocyclopentene (d) 3,3-dichlorocyclopentene

Physical Properties

5.31 The dipole moment of hexane is 0.09 D, but the dipole moment of 1-hexene is 0.4 D. Explain the reason for the difference.

5.32 Which isomer of 2-butene has the larger dipole moment?

5.33 The dipole moment of 2-methylpropene is 0.5 D, but the dipole moment of 1-butene is 0.3 D. Explain why these values differ.

5.34 The dipole moment of chloroethene is 1.4 D. Predict the dipole moment of *cis*-1,2-dichloroethene.

5.35 *cis*-1-Bromopropene has a higher boiling point than *cis*-1-chloropropene but has the smaller dipole moment. Explain why.

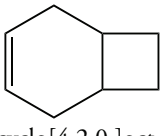
5.36 The boiling points of 1-hexene and 2,3-dimethyl-2-butene are 63.5 and 73 °C, respectively. Suggest a reason for this difference.

Heats of Combustion of Alkenes

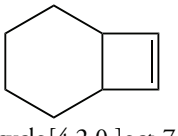
5.37 The difference between the heats of combustion of *cis*- and *trans*-2-butenes is about 4.2 kJ mole^{-1}, but the difference between those of *cis*- and *trans*-4,4-dimethyl-2-pentenes is about 16 kJ mole^{-1}. Explain why these two values differ significantly.

5.38 The difference between the heats of combustion of *cis*- and *trans*-2,2,5,5-tetramethyl-3-hexenes is about 40 kJ mole^{-1}. Explain this very large difference.

5.39 Which of the following two isomers should have the larger heat of combustion? Explain why.

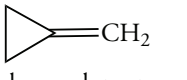


bicyclo[4.2.0.]oct-3-ene
I

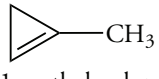


bicyclo[4.2.0.]oct-7-ene
II

5.40 Although 1-methylcyclopropene is a trisubstituted alkene and methenecyclopropane is a disubstituted alkene, the heat of combustion of 1-methycyclopropene is larger by about 42 kJ mole^{-1}. Explain why.



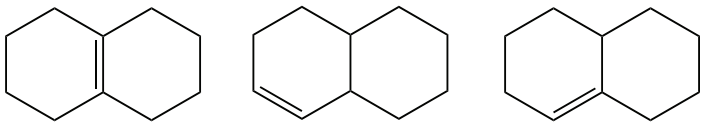
methylenecyclopropane



1-methylcyclopropene

5.41 Arrange the following compounds in order of increasing heats of combustion: 3-methyl-1-butene, 2-methyl-1-butene, 2-methyl-2-butene.

5.42 Arrange the following compounds in order of increasing heats of combustion.



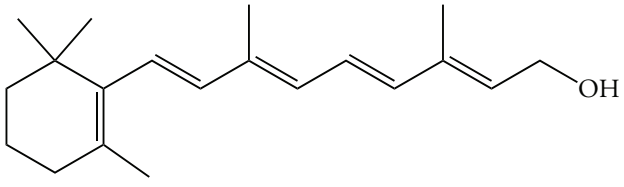
I II III

Hydrogenation of Alkenes

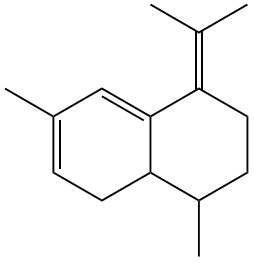
5.43 How many moles of hydrogen gas will react at atmospheric pressure with each of the following compounds?
(a) 1,4-cyclooctadiene (b) 4-vinylcyclohexene
(c) 2,4-dimethy1-1,4-pentadiene (d) 2-methyl-1,3-cyclohexadiene

5.44 How many moles of hydrogen gas will react at atmospheric pressure with each of the following compounds?

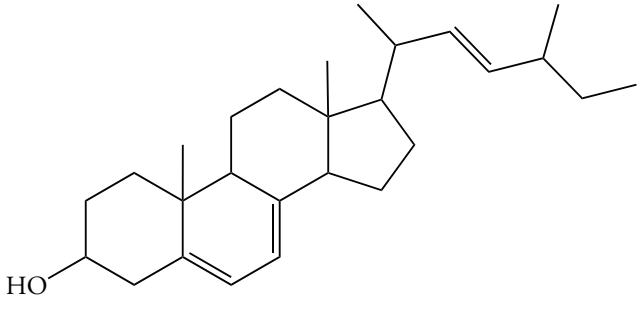
(a) Vitamin A, contained in freshwater fish



(b) zingiberene, found in oil of ginger



(c) ergosterol, a form of vitamin D

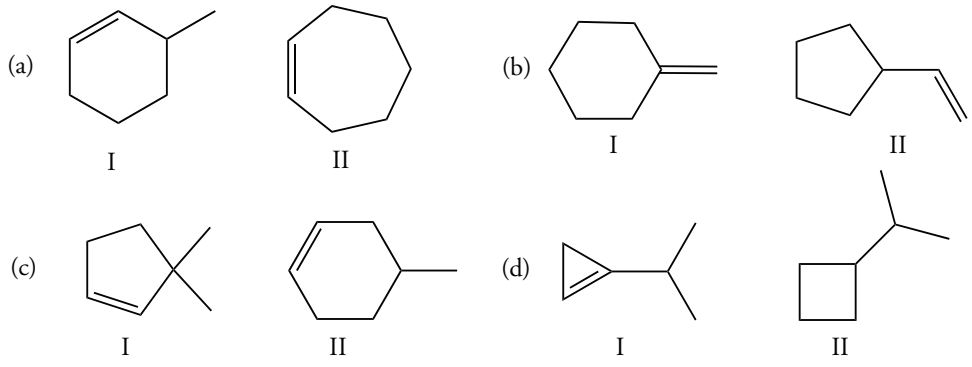


5.45 Oil of marjoram contains α-terpinene, whose molecular formula is $C_{10}H_{16}$. Hydrogenation using the Adams catalyst yields $C_{10}H_{20}$. How many double bonds and how many rings does the α-terpinene contain?

5.46 The wax found on apples contains α-farnesene, whose molecular formula is $C_{15}H_{26}$. Hydrogenation using palladium on charcoal yields $C_{15}H_{32}$. How many double bonds and how many rings does α-farnesene contain?

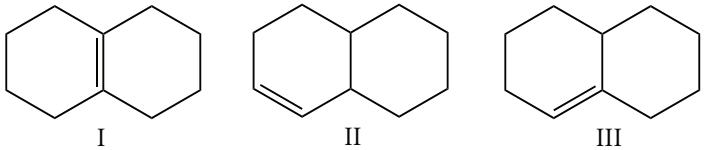
Hydrogenation of Alkenes

5.47 Consider each compound of the following pairs of isomeric hydrocarbons and determine whether or not there should be a substantial difference in their heats of hydrogenation. Explain why. Indicate the compound with the higher heat of hydrogenation where possible.

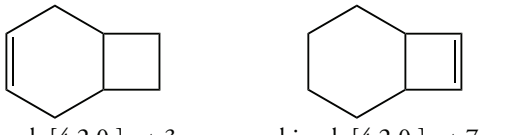


5.48 There are three isomeric methylcyclopentenes. Which compound has the smallest heat of hydrogenation?

5.49 There are three isomeric methylcyclopentenes. Which compound has the smallest heat of hydrogenation?



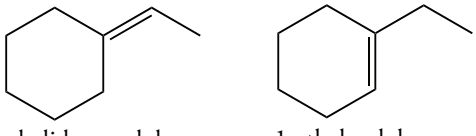
5.50 The standard heat of hydrogenation of of bicyclo[4.2.0]oct-7-ene is larger than that of the isomeric bicyclo[4.2.0]oct-3-ene. Based on this information, which compound is more stable? What feature of the structures of the two compounds is responsible for this difference in stability?



bicyclo[4.2.0.]oct-3-ene
I

bicyclo[4.2.0.]oct-7-ene
II

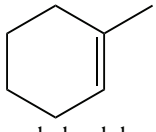
5.51 Although ethylidenecyclohexane and 1-ethylcyclohexene are both trisubstituted alkenes, the latter compound predominates in an equilibrium reaction. Based on this information, which compound has the larger heat of hydrogenation?



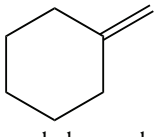
1-ethylidenecyclohexane

1-ethylcyclohexene

5.52 The data given in Exercise 5.51 explain the observation that isomers with double bonds within rings (endocyclic) are more stable than isomers with double bonds between a carbon in the ring and a carbon outside the ring (exocyclic). Explain why the heats of hydrogenation of 1-methylcyclohexane and methenecyclohexane, which are –107 and –116 kJ mole^{-1}, respectively, cannot be used to support this generalization.

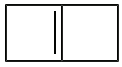


1-methylcyclohexene

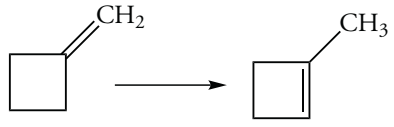


methylenecyclohexane

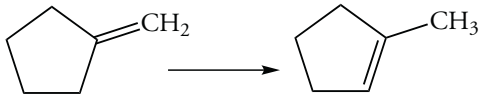
5.53 The heat of hydrogenation of the bicyclic hydrocarbon shown below is approximately 270 kJ mole^{-1}. Why is this value so much larger than those listed in Table 5.3 for alkenes?



5.54 Explain why the $\Delta H°_{reaction}$ for the following two isomerization reactions is negative. Why is the $\Delta H°_{reaction}$ for the second reaction more negative than for the first reaction?



$\Delta H°_{rxn} = -3.7$ kJ mole^{-1}



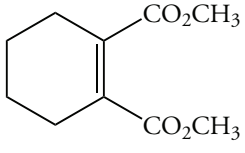
$\Delta H°_{rxn} = -16.2$ kJ mole^{-1}

5.55 The difference between the heats of hydrogenation of (*E*)- and (*Z*)-4,4-dimethyl-2-pentenes is approximately 14.6 kJ mole^{-1}. Compare this difference with the difference between the heats of hydrogenation of (*E*)- and (*Z*)-2-butenes. Why do the two values differ?.

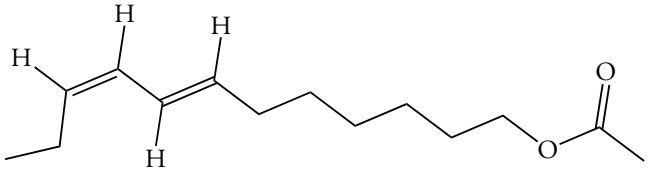
5.56 The heats of hydrogenation of the geometric isomers of 2,2,5,5-tetramethyl-3-hexene differ by 39 kJ mole^{-1}. Explain why this difference is so large compared to other geometric isomers.

Stereochemistry and Stereoselectivity of Hydrogenation

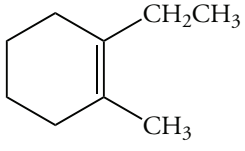
5.57 Write the structure of the product obtained by hydrogenating the following diester using PtO_2 and hydrogen gas at atmospheric pressure.



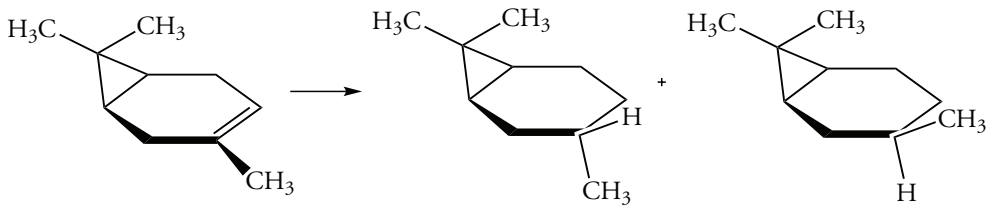
5.58 Write the product obtained by the catalytic hydrogenation of the sex pheromone of the European vine moth at atmospheric pressure using PtO_2 and hydrogen gas.



5.59 Deuterium gas can be used to form deuterated compounds using the Adams catalyst. The reaction proceeds by the same mechanism as for hydrogenation. Write the product of the reaction of 1-ethyl-2-methylcyclohexene with D_2.

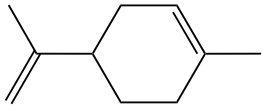


5.60 Which of the two isomeric caranes is the major product of the hydrogenation of 3-carene using the Adams catalyst?



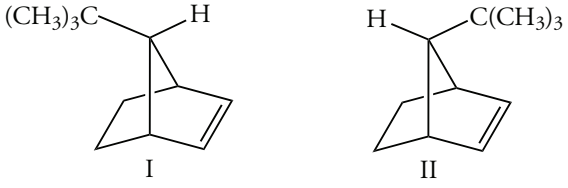
3-carene

5.61 Which of the double bonds of limonene is hydrogenated at the faster rate? Comment on the likelihood that selective hydrogenation may occur.



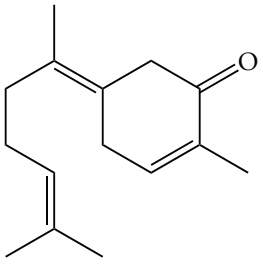
limonene

5.62 Explain why the hydrogenation of compound I occurs at a faster rate that the hydrogenation of compound II.



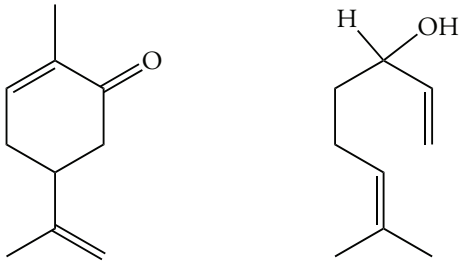
I II

5.63 Evaluate the degree of substitution of the double bonds of bisabolene and determine whether stereoselective reduction of a double bond is possible.



bisabolene

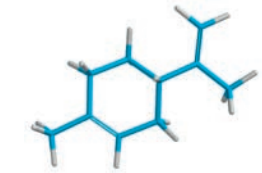
5.64 Write the structure of the product obtained by catalytic reduction of each of the following compounds using the Wilkinson catalyst and one molar equivalent of hydrogen gas.



carvone linalool

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6 Alkenes: Addition Reactions



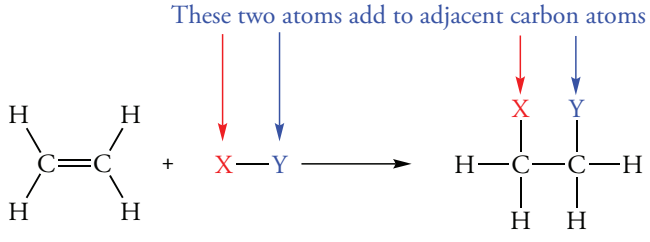
Limonene (a compound with the aroma of oranges)

Until now, we have focused largely on the structures of organic molecules and the effect of structure on physical properties, including bond length, bond strengths, and molecular geometry. In this chapter and for the rest of the text, we will consider the reactions of functional groups. When we consider a chemical reaction, we would like to know both *what* products form and *how* the products form. Therefore, we will focus upon the *mechanism* of each reaction as a way to enhance understanding.

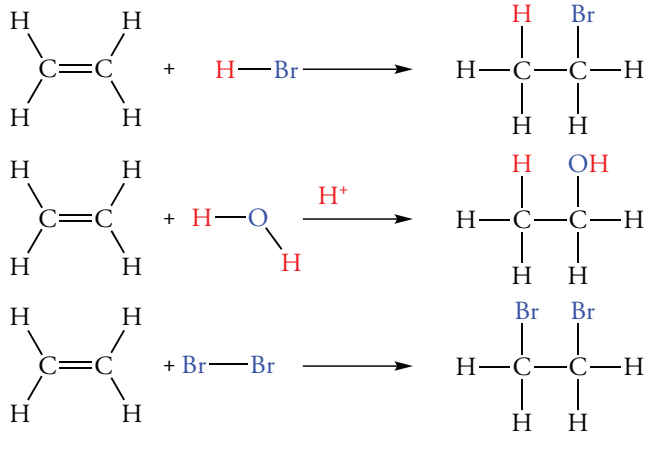
Most of the time we will begin with a general overview, then we will provide a few simple examples. After that, we will gradually increase the structural complexity and the mechanistic subtleties to gain an overall picture of each class of reactions. In short, we will look at patterns. *Pattern recognition* is one of the keys to learning organic chemistry.

6.1 Characteristics of Addition Reactions

The π bonds of alkenes characteristically undergo addition reactions, yielding saturated compounds. For example, the π bond of ethene reacts with a general reagent, X —Y, by the following equation.



Specific examples of the addition reaction with ethylene include the following.



In each case, two atoms or groups of atoms add to adjacent atoms of the π bond. This is a common characteristic of addition reactions, which occur by a variety of mechanisms, depending on the reagent.

In this chapter, we will first consider reagents such as HBr, H_2O, and Br_2, which all react with π bonds by multistep mechanisms involving electrophilic species. Then, we will consider reactions of the double bond with reducing and oxidizing agents. These reactions occur by concerted mechanisms. In the last section of the chapter, we will introduce a powerful synthetic reaction called the Grubbs reaction.

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Stereochemistry of Addition Reactions

The sp^2-hybridized carbon atoms of an alkene and the atoms directly bonded to them are coplanar. Adding two groups X and Y (or identical groups such as X and X) to the carbon atoms of the double bond can occur in either of two ways. Addition to the same face is ***syn* addition**. Addition to the opposite face is ***anti* addition** (Figure 6.1). The stereochemistry of addition reactions can be easily demonstrated using cycloalkenes such as cyclohexene. If the general reaction of cyclohexene with X—Y occurs with *syn* addition, a *cis* compound is produced. *Anti* addition produces the *trans* isomer.

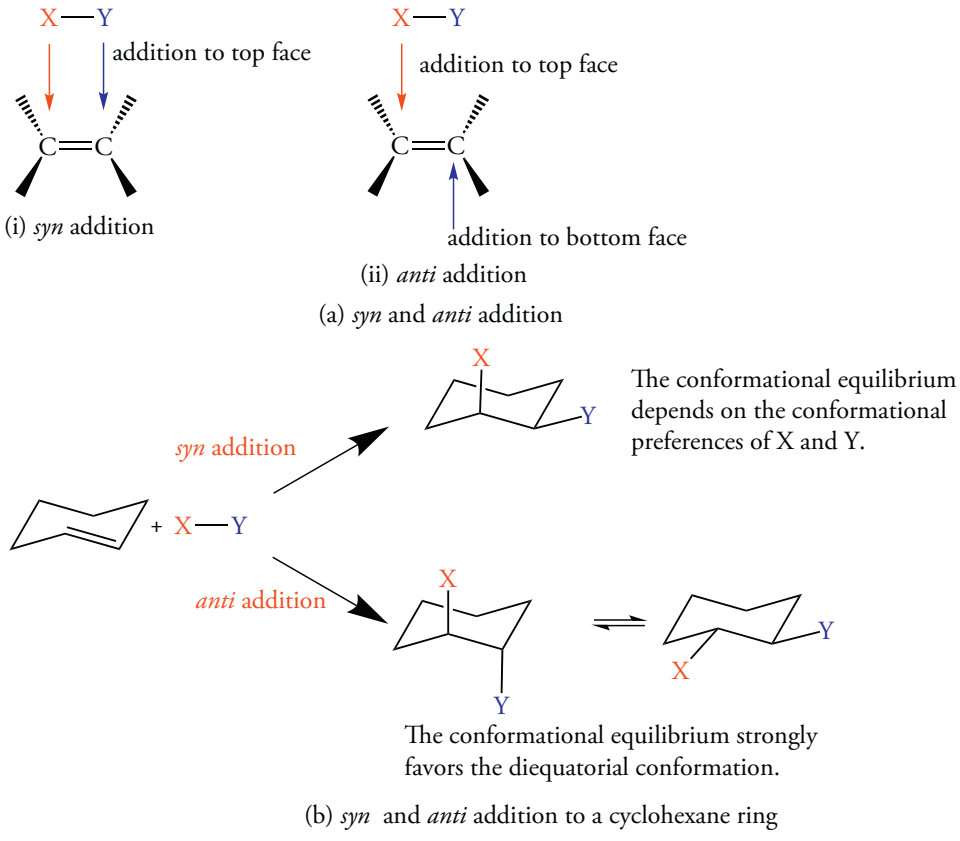
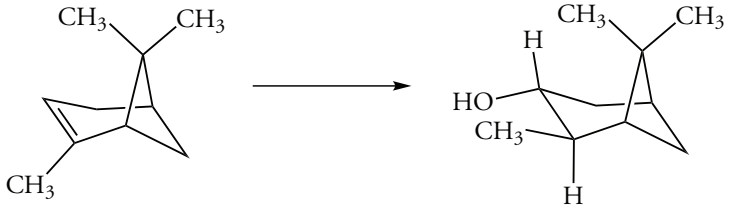


Figure 6.1 *Syn* and *Anti* Addition to Alkenes

The two possible modes of addition of a reagent X—Y to an alkene are shown in (a). In *syn* addition, both groups add to the same side or face of the molecule. In *anti* addition, the groups add to the opposite faces of the molecule. The consequences of *syn* and *anti* additions are shown in (b). Geometric isomers can result from the addition of a reagent X—Y to the double bond of a cycloalkene. *Syn* addition produces a *cis* product, whereas *anti* addition produces a *trans* product.

Problem 6.1

In hydroboration–oxidation, a reaction sequence used to synthesize alcohols, α-pinene is converted to the alcohol shown below. What molecule has been added to the alkene? What is the stereochemistry of the addition reaction?

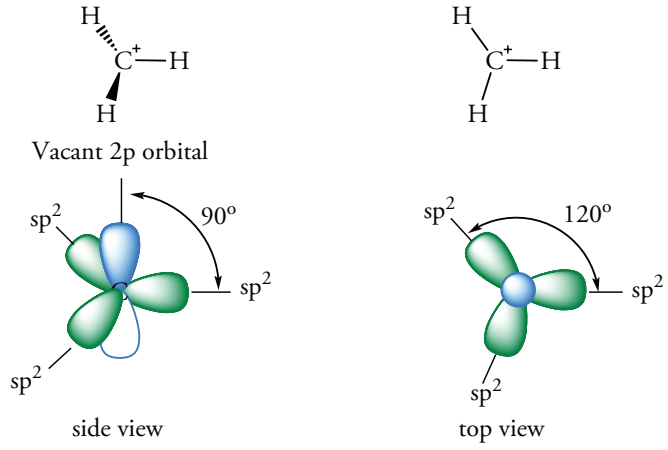


Carbocations in Addition Reactions

We will encounter several reactions in this chapter that proceed by a carbocation intermediate. We recall that the simplest carbocation, the methyl cation (CH_3^+), is a representative of the structure of carbocations. Its three bonding pairs of electrons are located in a trigonal planar arrangement in which the carbon atom is sp^2 hybridized (Figure 6.2). The fourth orbital of carbon is an empty 2p orbital that is perpendicular to the plane of the three sp^2 orbitals. Because carbocation is planar, attack of a nucleophile on the positively charged carbon to form a bond can occur with equal probability from the top or bottom face of the intermediate. Therefore, *reactions in which a carbocation forms will not proceed by exclusive syn or anti addition.*

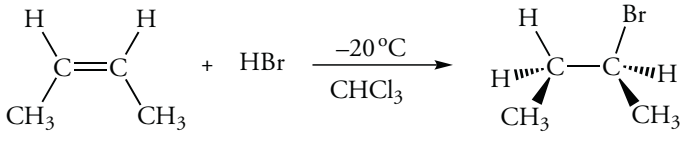
Figure 6.2 Structure and Hybridization of the Methyl Carbocation

The methyl carbocation has an sp^2 hybridized carbon. The H—C—H bond angles are 120°, and the carbon atom has a vacant 2p orbital that isperpendicular to the plane of the four atoms.

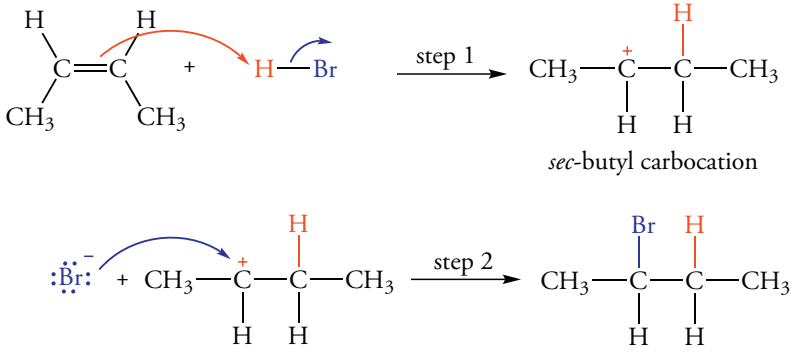


6.2 ADDITION OF HYDROGEN HALIDES TO ALKENES

In Section 6.1, we saw that HBr adds to ethene to give bromoethane. Next, let's consider the addition reaction of HBr to a symmetrical alkene such as *cis*-2-butene. Only one product is possible because the two carbon atoms of the double bond are equivalent.

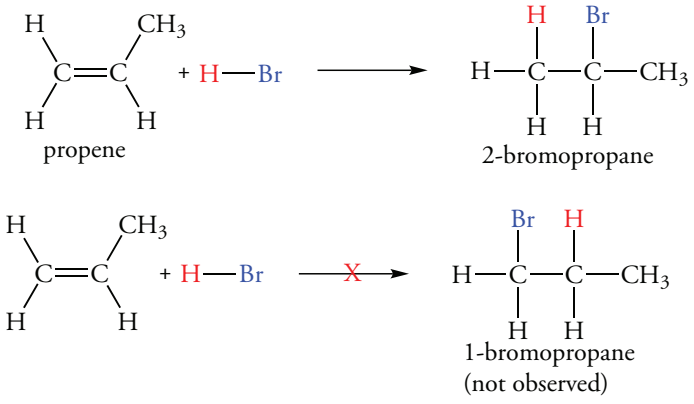


The order of reactivity of hydrogen halides with alkenes is HI > HBr > HCl, which corresponds to the order of decreasing acidity. The reaction is an **electrophilic addition**, in which the proton is the electrophile. The alkene, a Lewis base, accepts a proton from the acid and forms a carbocation. Then, the nucleophilic halide ion reacts with the carbocation to form the addition product.



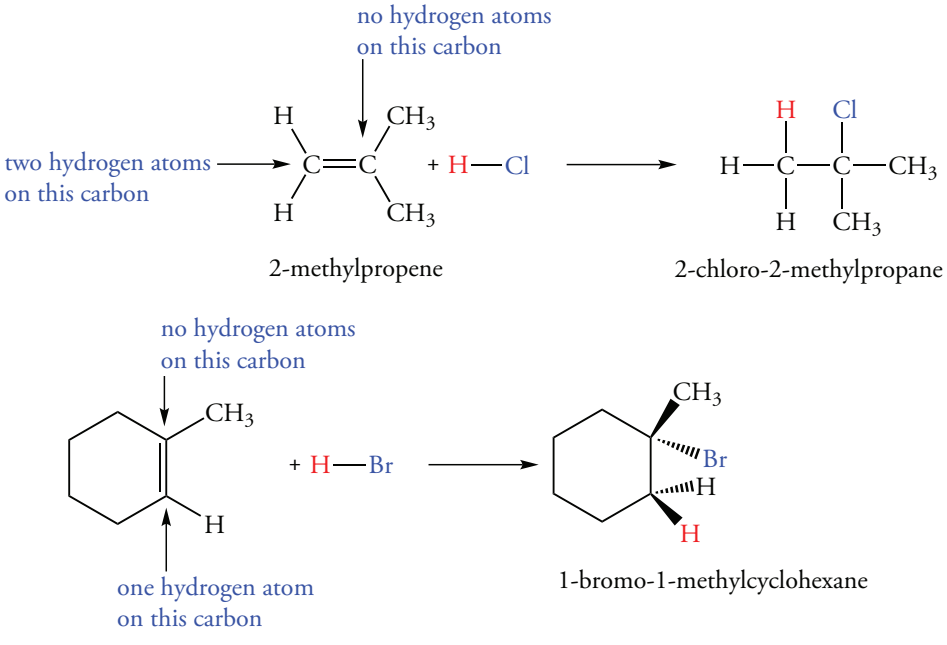
Regiospecificity of Hydrogen Halide Addition

Two products could conceivably result from the addition of HBr to an unsymmetrical alkene, but only one is formed. For example, addition of HBr to propene could yield either 1-bromopropane or 2-bromopropane, but only the latter forms. Thus, the addition of an HBr to an alkene is **regiospecific**.



Markovnikov's Rule

In 1870, the Russian chemist Vladimir Markovnikov observed that reagents add to unsymmetrical alkenes in a specific way. **Markovnikov's rule** states that a molecule of the general formula HX adds to a double bond so that the hydrogen atom forms a bond to the unsaturated carbon atom with the largest number of *directly bonded* hydrogen atoms. This is the less substituted double-bonded carbon atom. The addition reactions of HCl with 2-methylpropene and 1-methylcyclohexene with HBr are two examples of Markovnikov's rule.

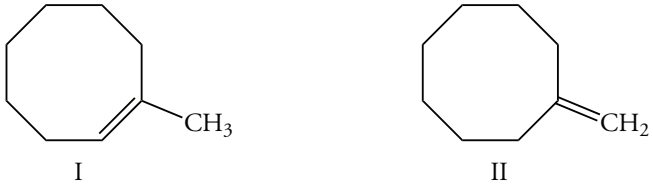


Problem 6.2

Predict the product(s) formed when HCl adds to each of the following.
(a) 2-methyl-2-butene (b) (*Z*)-2-butene (c) (*E*)-2-pentene

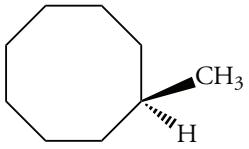
Problem 6.3

(a) Name each of the following compounds. (b) Predict the product of the addition reaction of HBr with each compound.



Sample Solution

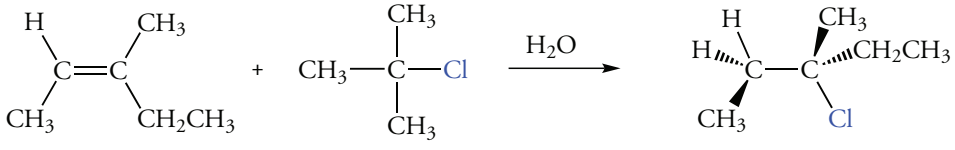
Compound I is 1-methylcyclooctene. One hydrogen atom is bonded at C-2 and none at C-1. Thus, hydrogen adds at C-2 and bromine at C-1. Compound II is methylenecyclooctene. There are two hydrogen atoms at the methylene carbon and none at C-1. Thus, hydrogen adds at the methylene carbon atom and bromine adds at C-1. The product, 1-bromo-1-methylcyclooctane, is the same for both compounds.



1-bromo-1-methylcyclooctene

Synthesis of Alkyl Chlorides

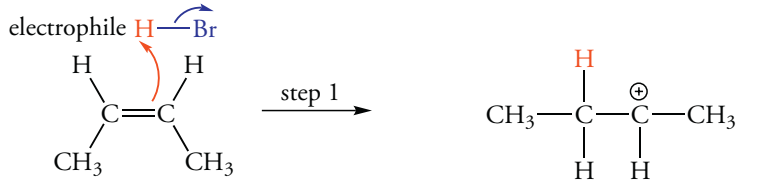
The synthesis of alkyl chlorides by adding HCl to an alkene illustrates the mechanistic features of the reaction, but alkenes react very slowly with HCl. This difficulty can be avoided by changing the reactions conditions. When an alkene is treated with trimethylsilyl chloride, $(CH_3)_3CCl$, and water, HCl rapidly adds across the double bond giving a high yield of product. The reaction follows Markovnikov's rule.



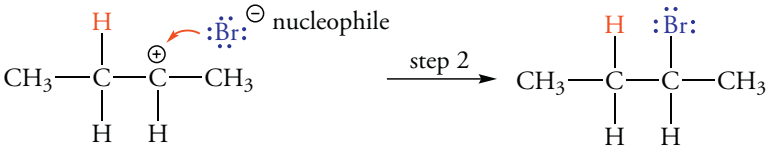
trimethylsilyl chloride

6.3 THE MECHANISTIC BASIS OF MARKOVNIKOV'S RULE

Markovnikov's rule is explained by the mechanism of the reaction. Consider the reaction of propene with HBr. The π electrons in propene act as a Lewis base, and react with a proton, which is an electrophile. This first step is written with a curved arrow to show the "movement" of two electrons in the π bond to form a σ bond to the proton. The resulting intermediate is a *sec*-butyl carbocation.

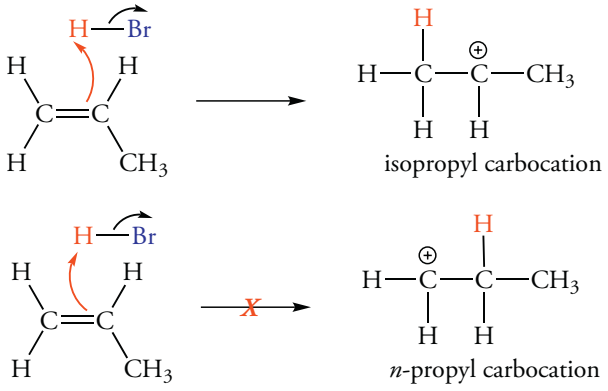


sec-butyl carbocation



In the second step of the addition reaction, the *sec*-butyl carbocation, which has a vacant 2p orbital, acts as a Lewis acid. It accepts an electron pair from the nucleophilic bromide ion. This mechanism accounts for the product predicted by Markovnikov's rule.

The reaction of propene with HBr is shown below. In this case, two different carbocations are possible: If the hydrogen atom had bonded to C-2, a primary, *n*-propyl carbocation would have formed; if the hydrogen bonds to C-3 of propene, a secondary, isopropyl carbocation forms. Since a secondary carbocation is more stable than a primary carbocation, only 2-bromoproane forms.



The isopropyl carbocation has the positive charge on a secondary carbon atom. The *n*-propyl carbocation has the positive charge on a primary carbon atom. The isopropyl carbocation forms, rather than the *n*-propyl cation, because the larger number of alkyl groups attached to a positively charged carbon atom help to stabilize the charge.

The order of carbocation stability explains Markovnikov's rule. Addition of the electrophile to the less substituted double bonded carbon atom gives the more stable carbocation. The formation of the more stable carbocation controls the product formed.

Hammond Postulate and Electrophilic Addition

The regioselectivity in addition of hydrogen halides to alkenes results from the difference in the transition state energies of two competing reactions. We recall that, according to Hammond's postulate, the structure of a transition state resembles that of an intermediate with similar energy (Section 3.17).

The formation of a carbocation by protonation of an alkene is an endothermic process. Thus, the structure of the transition state resembles the intermediate carbocation (Figure 6.3). When a proton reacts with the π bond of an alkene, the π electrons form a σ bond to hydrogen, and the other carbon atom gains a positive charge. Because alkyl groups stabilize carbocations, we can conclude that they also affect the energy of the transition states leading to these intermediates. Increasing the number of alkyl groups present on the carbon atoms of the original double bond decreases the energy barrier for formation of the transition state leading to the carbocation. Therefore, more highly substituted carbocations form faster than less substituted carbocations. The energy barrier for the second step, the reaction of halide ion with the carbocation, is smaller than the energy barrier for the first step. Hence, the rate of the second step does not contribute to the regiospecificity of the reaction.

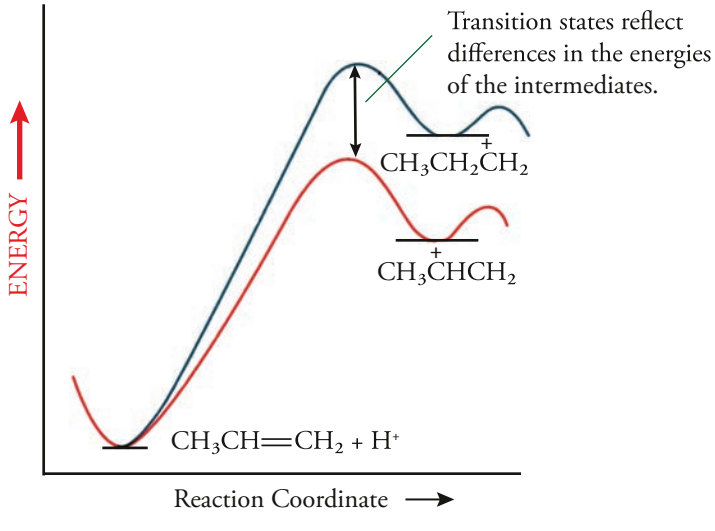


Figure 6.3 Reaction Coordinate Diagrams for Electrophilic Addition Reactions
The transition state that leads to the less stable primary carbocation is of higher energy than the transition state that leads to the more stable secondary carbocation. Subsequent reaction of either carbocation with a nucleophile occurs rapidly.

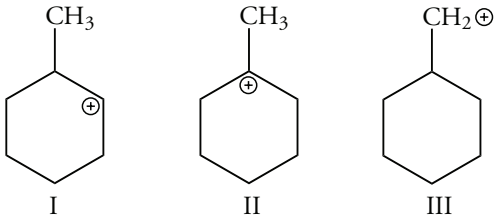
Problem 6.4

Write the structure of the carbocation formed in the addition reaction of HBr with each of the following alkenes.

(a) 1-methylcyclohexene (b) (*Z*)-2-butene (c) 4-methyl-1-pentene

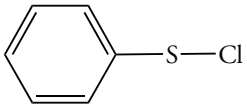
Problem 6.5

Rank the following carbocations in order of their stabilities.



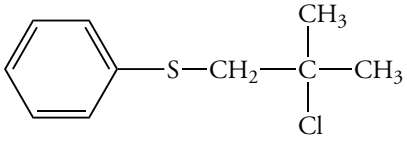
Problem 6.6

Reaction of either 1-butene or 2-butene with HBr gives the same product, 2-bromobutane. The reaction of 1-butene is faster than the reaction of 2-butene, even though both reactions proceed via a common carbocation intermediate. What is responsible for the difference in the rates?



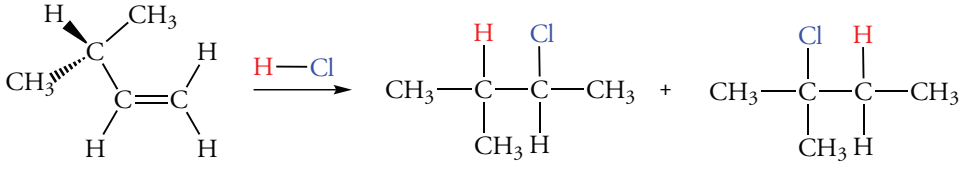
Sample Solution

Chlorine is located to the right of sulfur in period 3 of the periodic table. Thus, chlorine is more electronegative than sulfur. The electrophile is predicted to be a positively charged sulfur species resulting from heterolytic cleavage of the sulfur–chlorine bond. The electrophile adds to C-1 of 2-methyl-1-propene to give a tertiary carbocation, which then reacts with the nucleophilic chloride ion. The product is shown below.



6.4 CARBOCATION REARRANGEMENT REACTIONS

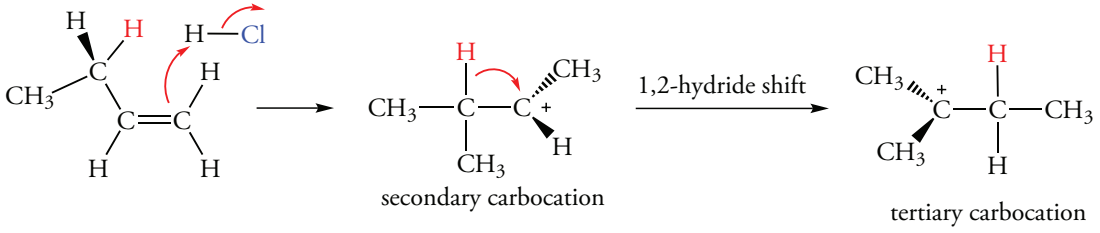
Markovnikov's rule allows us to predict the products of most addition reactions, but constitutional isomers form in some reactions. For example, the addition of HCl to 3-methyl-1-butene gives not only the expected product, 2-chloro-3-methylbutane, but also 2-chloro-2-methylbutane. What is the origin of this second, apparently unexpected product? The answer is: the carbocation formed in the first step of the reaction subsequently rearranges to a more stable species, which then reacts with chloride.



2-chloro-3-methylbutane
40%
(expected product)

2-chloro-2-methylbutane
60%
(rearranged product)

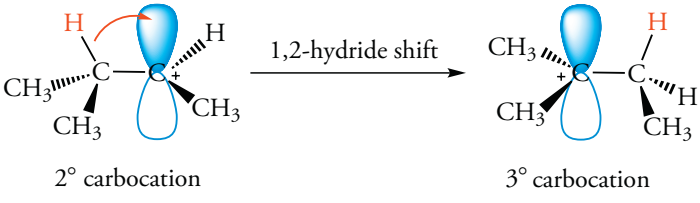
The expected product forms from the reaction of the nucleophilic chloride ion with the secondary cation that forms when a proton adds to the double bond by Markovnikov addition. The isomeric product forms when a nucleophilic chloride ion reacts with a tertiary carbocation. This carbocation forms when the hydrogen atom at C-3 moves, with its bonding pair of electrons, to the adjacent secondary carbocation center (Figure 6.4). This rearrangement is called a **1,2-hydride shift** because a hydride ion (H^-) moves between adjacent carbon atoms.



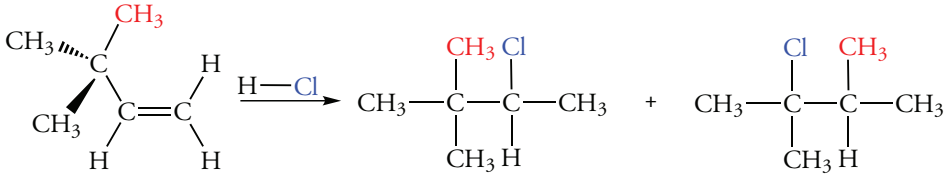
The 1,2-hydride shift converts the secondary carbocation into a more stable tertiary carbocation. The tertiary carbocation reacts with chloride ion to produce the isomeric rearranged product. Some of the secondary carbocation also reacts with chloride ion without rearranging to give the expected product. The relative amounts of rearranged and unrearranged products depend on how efficiently the carbocation is captured by the nucleophile versus the rate of the rearrangement process.

Figure 6.4 Rearrangement of a Carbocation by a 1,2-Hydride Shift

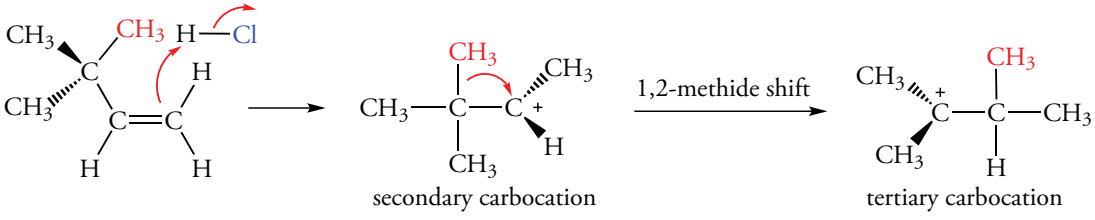
The bonding pair of electrons of the migrating group, a hydride anion, must be coplanar with the vacant 2p orbital of the carbocation for migration to occur.



A rearrangement analogous to a hydride shift occurs when an alkyl group moves, with its bonding electron pair, to an adjacent carbon atom. This type of rearrangement occurs when a more stable carbocation intermediate is produced. The reaction of 3,3-dimethyl-1-butene with HCl gives us an example of this type of rearrangement.



Adding a proton to the less substituted carbon atom of the double bond (Markovnikov's rule again) gives a secondary carbocation. This secondary carbocation reacts with the nucleophilic chloride ion to give the expected product. The rearranged product forms by reaction of chloride ion with a tertiary carbocation that forms by a shift of a methyl group, with its bonding pair of electrons, from the quaternary center to the adjacent secondary carbocation center. This rearrangement is called a **1,2-methide shift** because a CH_3 unit moves between adjacent carbon atoms.



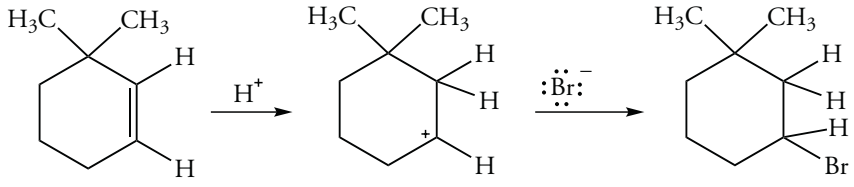
As a result of this shift, a secondary carbocation is converted into a more stable tertiary carbocation. The tertiary carbocation reacts with chloride ion to produce the rearranged product. Some of the secondary carbocation also reacts with a chloride ion without rearranging to give the expected product. We can say, however, that when we consider carbocation chemistry we should more or less "expect the unexpected."

Problem 6.7

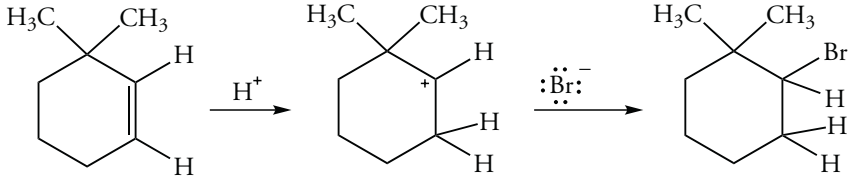
Write the structures of all of the possible addition products of 3,3-dimethylcyclohexene with HBr.

Sample Solution

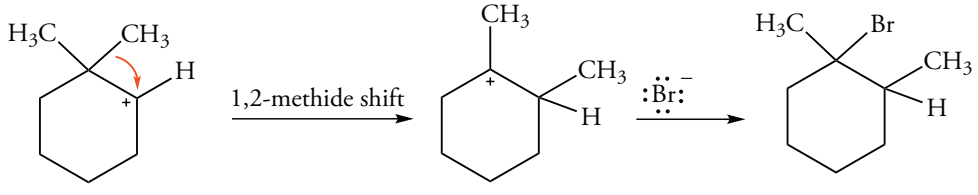
Both carbon atoms of the double bond are bonded to one carbon atom and a hydrogen atom. Thus, a proton can add to either carbon atom. Adding a proton at C-2 gives a secondary carbocation. Capture of this carbocation by bromide ion yields 1-bromo-3,3-dimethylcyclohexane.



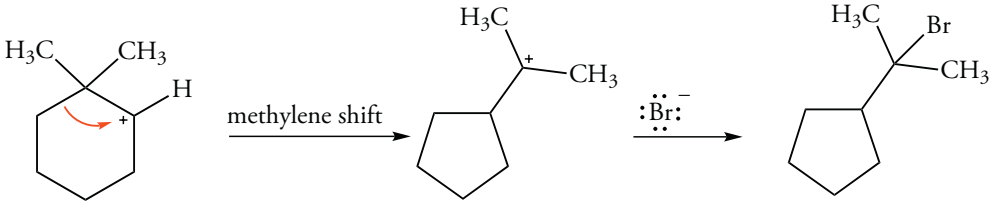
Adding a proton at C-1 gives a secondary carbocation at the original C-2 atom. Capture of the carbocation by bromide ion can give 1-bromo-2,2-dimethylcyclohexane.



However, the secondary carbocation can rearrange to two possible tertiary carbocations. Migration of methyl followed by capture of the carbocation gives 1-bromo-1,2-dimethylcyclohexane.



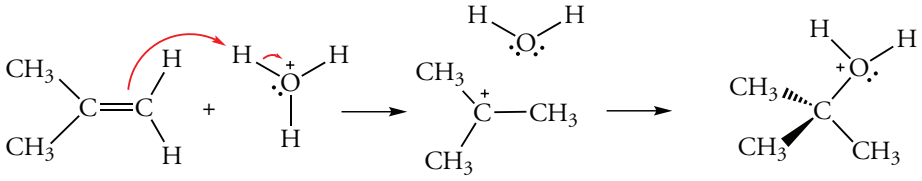
A 1,2-shift of a methylene group of the ring can also occur to give a tertiary carbocation. Capture of the carbocation by bromide gives a product containing a cyclopentane ring.



6.5 HYDRATION OF ALKENES

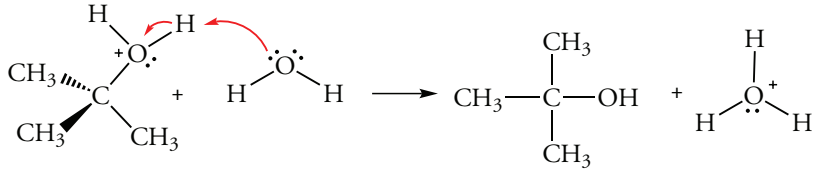
At the beginning of this chapter, we noticed that water can add across the double bond of an alkene to give an alcohol. This is a **hydration** reaction. The reverse reaction is **dehydration**.

Water adds to a π bond in an acidic medium such as aqueous sulfuric acid. A proton is transferred from H_3O^+ to the π bond to give a carbocation, which then reacts with the nucleophilic oxygen atom of water to give an **oxonium ion**.



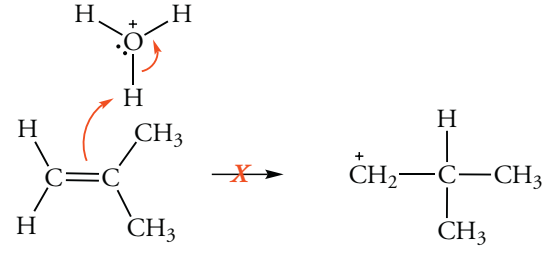
2-methyl-1-propene *tert*-butyl carbocation *tert*-butyl oxonium ion

The *tert*-butyl oxonium ion, which forms in the second step, is the conjugate acid of *tert*-butyl alcohol. The *tert*-butyl oxonium ion transfers a proton to water, regenerating the hydronium ion, the catalyst for the reaction.



tert-butyl oxonium ion *tert*-butyl alcohol

The hydration reaction is regiospecific. It obeys Markovnikov's rule. *tert*-Butyl alcohol forms rather than the isobutyl alcohol that would result from adding a proton to C-2 followed by reaction of water with a carbocation at C-1. Such a process would proceed via a much less stable primary carbocation (the isobutyl cation).

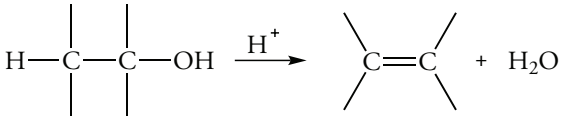


2-methyl-1-propene isobutyl carbocation
(a 1° carbocation, not formed)

The structure of the alkene affects the rate of the hydration reaction. The order of reactivity is 2-methylpropene > propene > ethene. This order reflects the effect of the stability of the carbocation intermediate. 2-Methylpropene reacts faster than propene or ethene because a 3° carbocation forms faster than a secondary or a primary carbocation.

Reversibility of Hydration

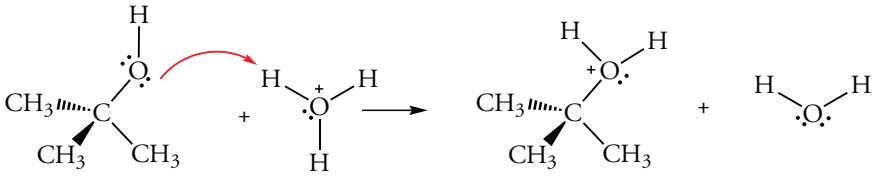
Each step in the hydration of an alkene is reversible, so the entire reaction is reversible. The reverse of the hydration reaction is dehydration, an example of an elimination reaction (Section 3.13).



The direction of the reaction—whether hydration or dehydration occurs—depends upon the concentration of H_2O. If the H_2O concentration is high, as in dilute H_2SO_4, hydration occurs. If the water concentration is low, as in concentrated (about 98%) H_2SO_4, dehydration occurs.

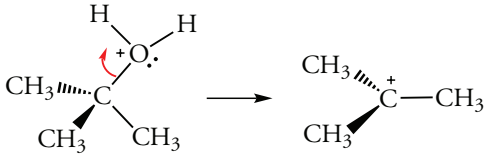
In an equilibrium process, the mechanistic pathways for the forward and reverse reactions are related. This concept is called **the principle of microscopic reversibility**. We can think of this as

follows: the mechanism of a reaction is the *minimum energy*, step-by-step pathway from reactants to products. If this pathway is the lowest energy pathway from left to right (forward), then it *must* be the minimum energy pathway for the reverse reaction (right to left). Thus, to write the mechanism for dehydration, start with the last step of the hydration mechanism and proceed "backward" to the second, and then the first step. When the reactions are written in the reverse direction, the reactants become products and the products become reactants. For the dehydration of an alcohol, the three steps are shown below.

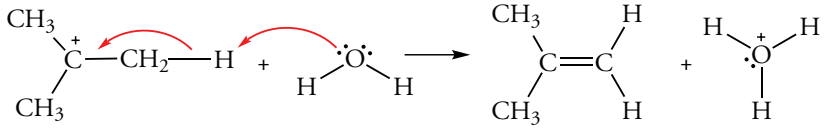


tert-butyl alcohol

tert-butyl oxonium ion

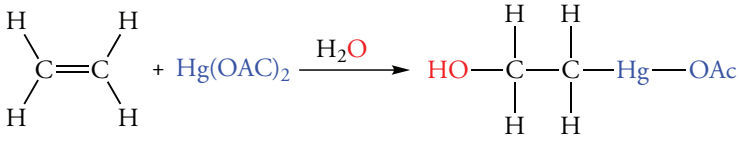


tert-butyl carbocation



Problem 6.8

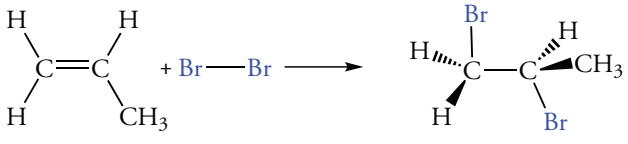
One of the steps in the indirect hydration of alkenes (Section 16.8) is the electrophilic addition of mercuric acetate, $Hg(OAc)_2$ —a covalent compound—according to the following equation. What is the electrophile? Predict the structure of the product of the reaction of mercuric acetate with 2-methyl-l-propene,



6.6 ADDITION OF HALOGENS

We saw earlier that halogens add across the double bond of an alkene to give 1,2-dihalo compounds. In this section, we will consider the addition of chlorine, bromine, and bromine in water, a reaction that produces a halohydrin; that is, a compound with a halogen on one carbon and an hydroxyl group on the adjacent carbon.

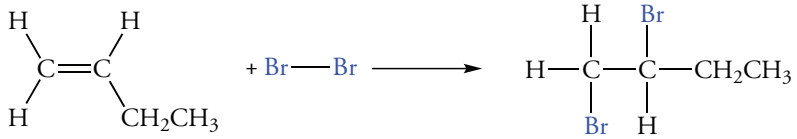
The reaction of an alkene with Br_2 or Cl_2 occurs rapidly at room temperature. The reaction is usually carried out in carbon tetrachloride or methylene chloride as solvent. The product is called a **vicinal** (Latin, *vicinalis*, neighboring) dihalide. Only one product forms.



propene

1,2-dibromopropane

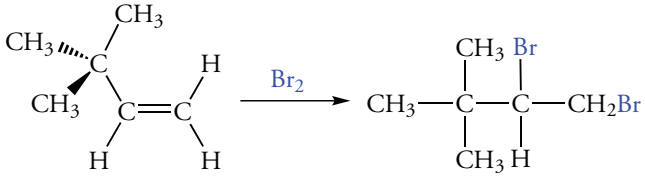
We can easily see the evidence for the addition of bromine to an alkene. Bromine is red-orange. It reacts with alkenes to give a colorless product. Hence, the disappearance of the red-orange color of bromine can be used to determine if a compound is unsaturated. If the bromine color disappears when Br_2 is added to a compound, the compound is unsaturated.



1-butene (colorless) (red-orange) 1,2-dibromobutane (colorless)

Chlorine also adds to a carbon–carbon double bond, but iodine is not sufficiently reactive to give a good yield of addition product. The reaction of alkenes with fluorine is too reactive to control, and several competing reactions also occur if fluorine is used.

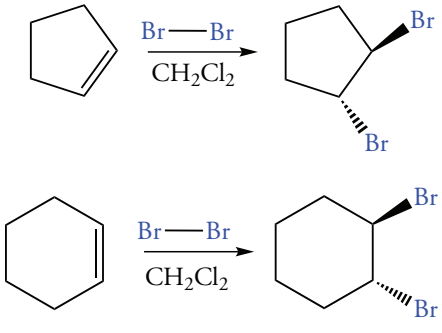
Rearrangement reactions seldom occur when halogens add to alkenes. We recall that water adds to 3,3-dimethyl-1-butene to give a rearranged product as well as the expected product. In contrast, bromine reacts with this alkene to give a single product. This fact suggests that a carbocation similar to that formed in the addition reactions we discussed previously is not formed in the addition of bromine.



3,3-dimethyl-1-butene (no rearranged products)

Stereochemistry of Halogen Addition

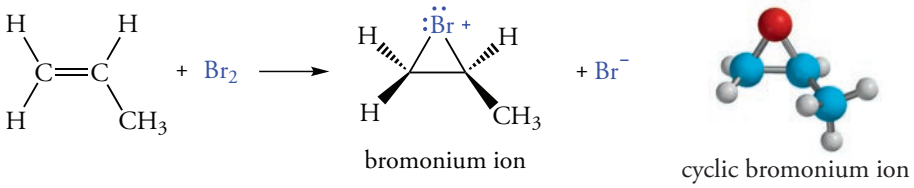
The addition of bromine to cycloalkenes can potentially form two stereoisomeric vicinal dibromides. However, only the *trans* isomer forms. The reaction is stereospecific. The stereochemistry of the products indicates that the halogen atoms bond from opposite faces of the double bond.



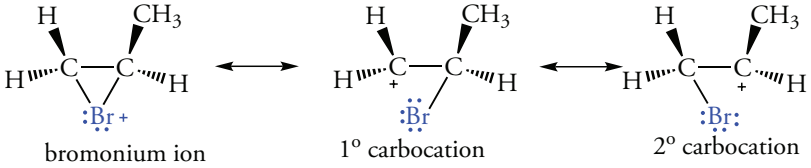
Mechanism of Halogen Addition

The rate of addition of bromine to alkenes is strongly affected by the degree of substitution of the C=C unit. Alkyl groups increase the rate of the reaction. The relative rates of addition of bromine to ethene, propene, and 2-methylpropene are 1, 60, and 5.5×10^3, respectively. Because alkyl groups can donate electrons and stabilize a positive charge, the transition state must have carbocation character. Increasing the number of alkyl groups lowers the energy barrier.

The absence of rearrangement and the *anti* stereochemistry of the addition product must be accommodated in a proposed mechanism for the addition of a halogen to an alkene involving a carbocation intermediate. The first step of the reaction mechanism is the electrophilic addition of bromine to the π bond to give a three-membered ring called a **cyclic bromonium ion**.



Although the three-membered ring is strained, all atoms have a Lewis octet of electrons. This is a more stable arrangement than an electron-deficient carbocation. The bromine atom bears most of the charge in the bridged ion. However, as shown in the contributing resonance structures, some positive charge is located on the carbon atoms. This charge is stabilized by groups that lower the energy barrier to its formation. The location of most of the positive charge on bromine rather than carbon explains why rearrangement reactions do not occur.



The cyclic bromonium ion reacts stereospecifically with a nucleophilic bromide ion, as indicated by the formation of *trans*-1,2-dibromocyclopentane from the addition of bromine to cyclopentene. The bromonium ion intermediate has a bromine atom bonded to one face of the molecule.

Nucleophilic attack by bromide ion at a carbon atom of the three-membered ring breaks one of the carbon–bromine bonds of the cyclic intermediate (Figure 6.5). Because the bromine atom in the three-membered ring of the intermediate "shields" one face of the alkene, the bromide ion can attack only at the opposite face and gives only an *anti* addition product.

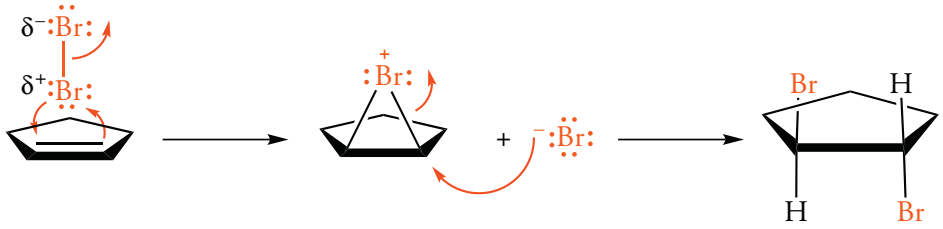
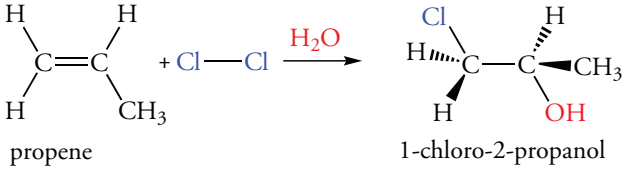


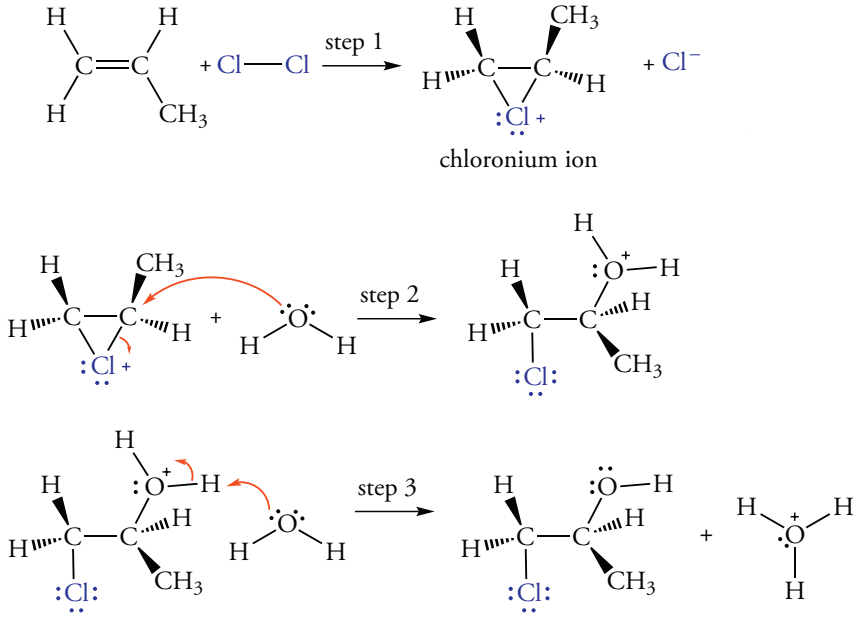
Figure 6.5 Mechanism of Bromine Addition

The π electrons of the alkene act as a nucleophile to displace bromide ion from bromine. The resulting cyclic bromonium ion can be viewed as the addition of Br^+ to the double bond. Bromine has two covalent bonds and a formal 1+ charge in this intermediate. Attack of the nucleophilic bromide ion occurs from the opposite face because the bromine atom that is already there blocks approach from the same face.

Formation of Halohydrins

An aqueous solution of bromine or chlorine reacts with alkenes to form addition products called halohydrins. These compounds have a halogen and a hydroxyl group on adjacent carbon atoms. The reaction of aqueous chlorine with propene is shown below.





Problem 6.9

Give the structure of the product formed when 2-methyl-1-butene reacts with bromine in aqueous solution.

Problem 6.10

Give the structure of the product formed when cyclopentene reacts with chlorine in aqueous solution. What is the stereochemistry of the product?

6.7 ADDITION OF CARBENES

A **carbene** is a divalent carbon species with six electrons in its valence shell and the formula R_2C:. The groups bonded to the carbon atom may be hydrogen, alkyl groups, aryl groups, or other atoms such as halogens. The structure of a carbene such as dichlorocarbene resembles that of a carbocation (Figure 6.6). Its carbon atom is sp^2-hybridized, with an empty p orbital perpendicular to the plane containing the sp^2-hybridized orbitals. Two of the sp^2-hybridized orbitals are bonded to the two chlorine atoms. The remaining sp^2-hybridized orbital has an unshared pair of electrons.

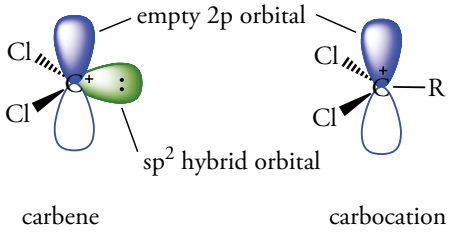
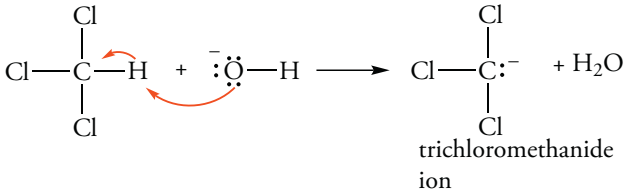


Figure 6.6 Structure of a Carbene Compared to a Carbocation

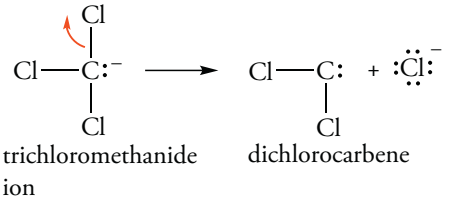
Carbenes have a formal charge of zero because the unshared electron pair in the sp^2-hybridized orbital "belongs" to the carbon atom. Like a carbocation, a carbene is a highly reactive, electrophilic intermediate because it has only six electrons in its valence shell.

Formation of Dichlorocarbene

Dichlorocarbene (Cl_2C) can be made from chloroform ($CHCl_3$), and a strong base such as *tert*-butoxide, $(CH_3)_3CO^-$ or potassium hydroxide. Chloroform has three electronegative chlorine atoms, which inductively withdraw electron density from the carbon atom. Thus, the hydrogen atom of $CHCl_3$ is much more acidic than the hydrogen atom of an alkane. The base removes a proton from $CHCl_3$, leaving the electron pair with the carbon atom. The product is a carbanion, the trichloromethanide ion.



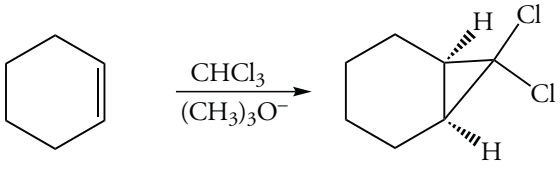
The trichloromethanide ion loses a chloride ion to form dichlorocarbene, which is electrically neutral. Note that the electrons of the C —Cl bond leave with the chloride ion.



The sum of the two steps corresponds to an elimination reaction. The loss of two atoms or groups of atoms from the same carbon atom is called an α elimination reaction.

Stereospecificity of Carbene Addition Reaction

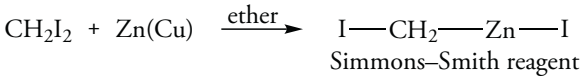
Carbenes are highly reactive intermediates that cannot be isolated, so they are generated in the presence of a selected reactant. When dichlorocarbene forms in the presence of an alkene, the electrophilic carbene reacts with the double bond of the alkene to form a cyclopropane.



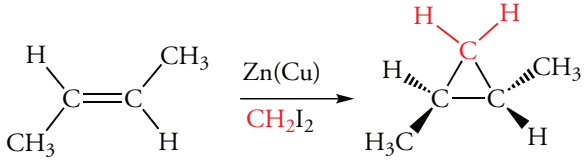
We won't discuss the mechanistic details of the addition of a carbene to an alkene since it would require a detailed consideration of molecular theory. However, we note that a pair of electrons of the π bond and the unshared pair of electrons of the carbene provide the four electrons required to form two C–C bonds of the cyclopropane ring. The reaction shown for cyclohexene and dichlorocarbene is stereospecific. Even with acyclic alkenes, *cis* alkenes yield *cis*-substituted cyclopropanes and *trans* alkenes yield *trans*-substituted cyclopropanes.

Carbenoid Species

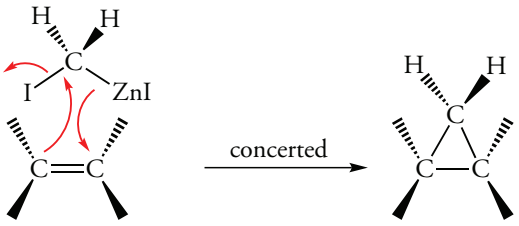
Methylene ($:CH_2$), the simplest carbene, can be prepared by decomposition of the highly toxic and explosive reagent diazomethane (CH_2N_2). However, more easily used reagents have been developed that, while they do not produce methylene directly, function as methylene transfer agents. They are called **carbenoid** species because they react like carbenes. Iodomethylzinc iodide, known as the Simmons–Smith reagent, is a carbenoid. In the Simmons–Smith method, diiodomethane reacts with a zinc–copper alloy to produce an intermediate I—CH_2Zn—I compound.



The Simmons–Smith reagent transfers a CH_2 unit to the alkene in a stereospecific reaction. For example, *trans*-2-butene reacts with the Simmons–Smith reagent to give only *trans*-1,2-dimethy-l-cyclopropane.



The transition state for the reaction of an alkene with the Simmons–Smith reagent results from a concerted transfer of a methylene unit from the iodomethylzinc iodide.



Problem 6.11

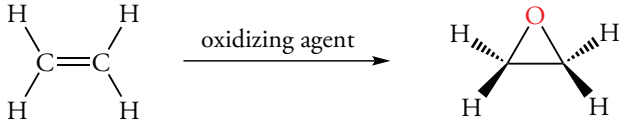
Write the expected product of the reaction of *trans*-2-butene with $CHBr_3$ and potassium *tert*-butoxide. Write the mechanism for the formation of the expected intermediate.

Problem 6.12

1,1-Diiodoethane and Zn(Cu) react with cyclohexene to give a mixture of two isomers with the formula C_8H_{14}. (a) What are their structures. (b) Why does one isomer predominate?

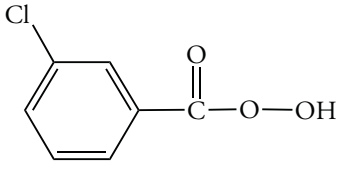
6.8 EPOXIDATION OF ALKENES

The addition of an oxygen atom to an alkene to give a three-membered cyclic ether, called an **epoxide**, is an oxidation reaction because the oxygen content of the molecule increases. We will discuss the preparation and reactions of epoxides in much greater detail in Chapter 17.



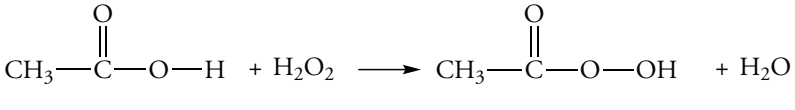
ethylene oxide

Epoxides have a strained three-membered ring, but they are easily prepared by an epoxidation reaction using peroxy acids (RCO_3H) such as peroxyacetic acid or *m*-chloroperbenzoic acid (*m*CPBA), as the oxidizing agent.



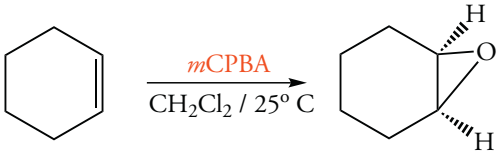
m-chloroperbenzoic acid (*m*CPBA)

Peroxyacetic acid in acetic acid is used in industrial epoxidation reactions. Peroxyacetic acid is produced from the reaction of hydrogen peroxide with acetic acid.

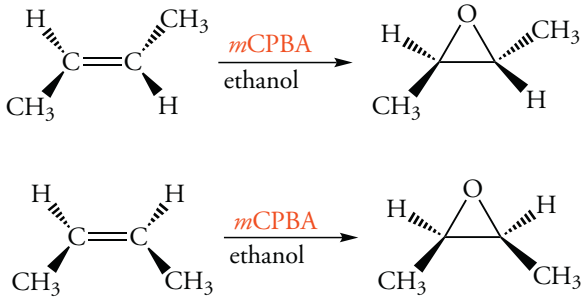


peroxyacetic acid

m-Chloroperoxybenzoic acid (*m*CPBA) is used to prepare smaller amounts of epoxides in the laboratory.



In the epoxidation of alkenes with peroxy acids, the stereochemistry of the groups bonded to the double-bonded carbon atoms is retained. The reaction is stereospecific, as we see in the following deuterium-substituted compounds. Groups that are *cis* in the alkene are *cis* in the epoxide, and groups that are *trans* in the alkene remain *trans* in the epoxide.



Mechanism of Epoxidation

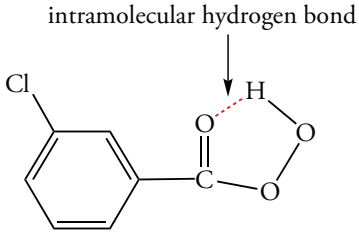
The mechanism of epoxidation is based on (1) the stereochemistry of the addition product and (2) the effect of substituents on the rate of reaction. Alkyl groups increase the rate of reaction. The order of reactivity for some representative alkenes is given below.

	$CH_2{=}CH_2$	<	$CH_3{-}CH{=}CH_2$	<	$(CH_3)_2CH{=}CH_2$
relative rate of epoxidation	1		22		4.8×10^2

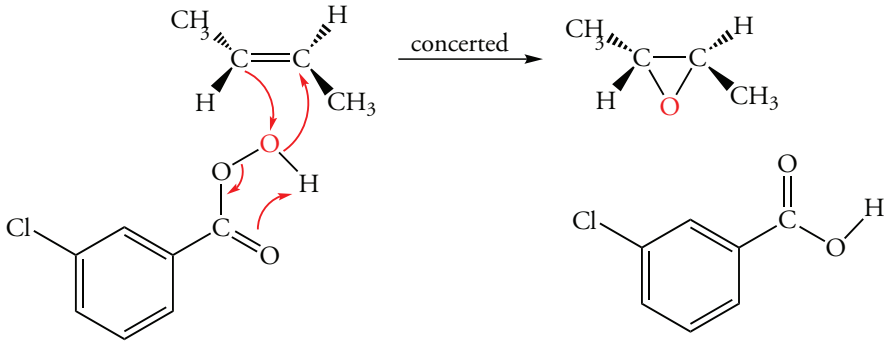
This order of reactivity indicates that some positive charge is developed at a carbon atom in the transition state. Because alkyl groups release electron density, the energy barrier is smaller in the more substituted alkene. The alkene develops a partial positive charge when electrons of the π bond are polarized toward the oxygen atom provided by the peroxy acid. In fact, the rates of the representative alkenes toward peroxy acids resemble the rates for the addition of bromine to alkenes.

	$CH_2{=}CH_2$	<	$CH_3{-}CH{=}CH_2$	<	$(CH_3)_2CH{=}CH_2$
relative rate of bromination	1		60		5.5×10^3

When *m*-chloroperoxybenzoic acid dissolves in CH_2C1_2, it forms an intramolecular hydrogen bond between its hydroxyl hydrogen atom and carbonyl oxygen atom.

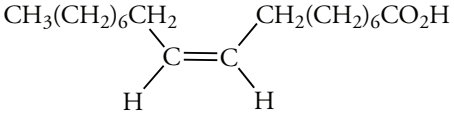


The oxygen–oxygen bond has a low bond energy. The peroxidic oxygen atom bonded to the hydrogen atom is transferred to the alkene in the reaction. This oxygen atom forms a bond with the electron pair of the alkene π bond. The electron pair required for the second carbon–oxygen bond of the epoxide is derived from the O—H bond of the peroxy acid. This electron pair is released as the hydrogen atom is simultaneously transferred to the carbonyl oxygen atom of the peroxy acid.



Problem 6.13

Microbial oxidation of oleic acid yields an epoxide. Write the structure of the product.

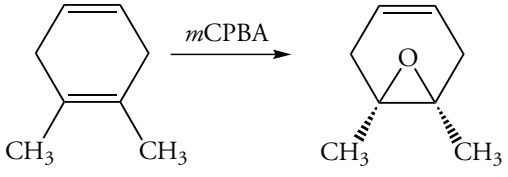


Problem 6.14

Write the structure of the epoxidation product of 1,2-dimethy1-1,4-cyclohexadiene obtained by reaction with *m*CPBA.

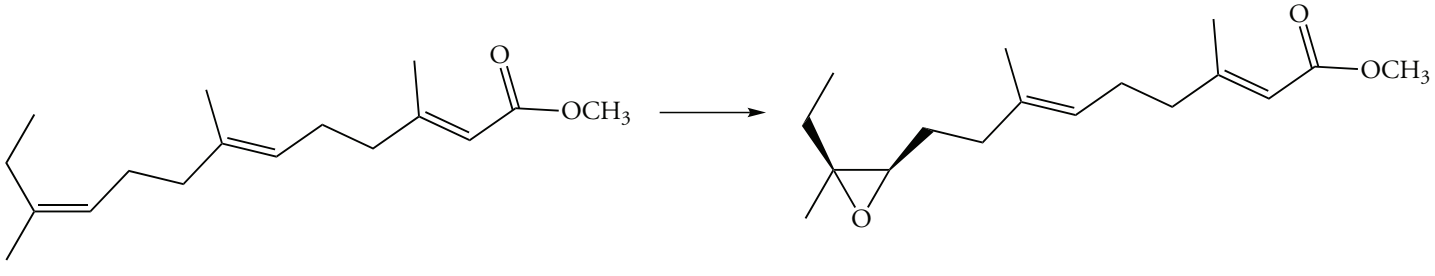
Sample Solution

The compound has a disubstituted and a tetrasubstituted double bond. The rate of epoxidation at the tetrasubstituted bond is greater than that at the disubstituted double bond. The product of the reaction is shown below.



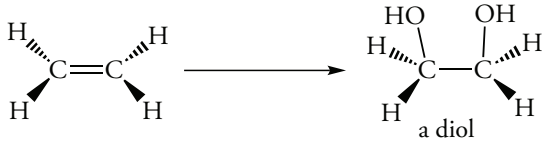
Problem 6.15

Epoxidation of the following compound in a laboratory synthesis gives a 40% yield of the juvenile hormone of insects. Explain why only a 40% yield is obtained.



6.9 DIHYDROXYLATIN OF ALKENES

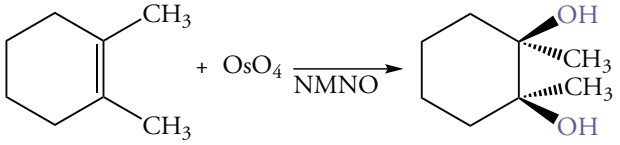
The dihydroxylation of an alkene occurs by adding one hydroxyl group to each of the two alkene carbon atoms. Because two oxygen atoms and two hydrogen atoms are incorporated in the product, the net result is oxidation.

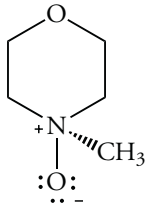


The products of dihydroxylation are **vicinal diols**, commonly called **glycols**. They are made with osmium tetraoxide (OsO_4) as the oxidizing agent.

Dihydroxylation with Osmium Tetraoxide

The oxidation of alkenes with osmium tetraoxide gives excellent yields of vicinal diols. However, this reagent is both expensive and highly toxic. Therefore, it is used only in small-scale laboratory syntheses, not in industrial processes. Osmium tetraoxide can, however, be used in a catalytic process in which the oxidizing agent is recycled. For example, hydrogen peroxide can be used to oxidize the reduced osmium back to osmium tetraoxide, which continues to oxidize the alkene to a diol. This process allows the reaction to be carried out with only a small amount of the toxic OsO_4. A similar result can be obtained with *N*-methylmorpholine-*N*-oxide (NMNO).



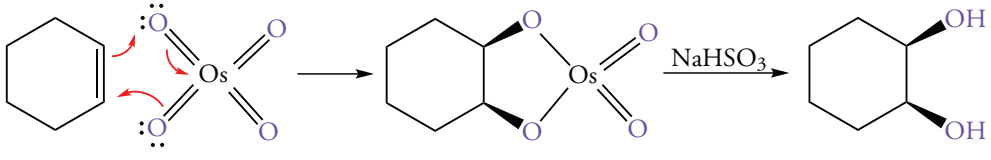


N-methylmorpholine-*N*-oxide (NMNO)
(regenerates OsO_4)

The above reaction shows that the oxygen atoms add to the same face of the double bond. Thus, OsO_4 forms vicinal diols by *syn* addition.

Mechanism of *Syn* Dihydroxylation

Permanganate ion adds to the double bond of an alkene by a cyclic mechanism in which the two carbon–oxygen bonds form simultaneously. The resulting cyclic osmate ester has the oxygen atoms bonded to the same face of the original double bond. Then, the osmium–oxygen bonds of the reactive intermediate are hydrolyzed to form the diol.



Problem 6.16

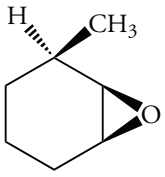
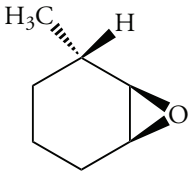
Write the product of the reaction of potassium permanganate with 1-methylcyclohexene under basic conditions.

Problem 6.17

The microbe *Pseudomonas putida* oxidizes 3-methylcyclohexene to produce two epoxides via a *syn* addition mechanism. Write the structures of the two products.

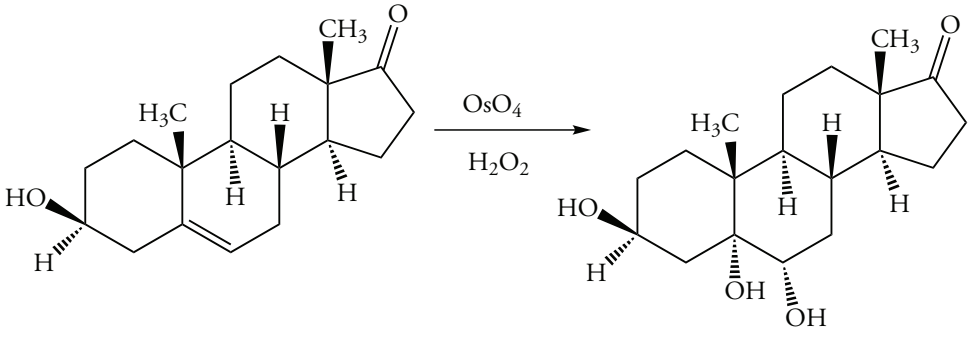
Sample Solution

The oxygen transferred to the double bond can approach from the same side of the ring as the methyl group or the opposite side to give two stereoisomeric products. The epoxide ring may be either *cis* or *trans* to the methyl group in the product.

Problem 6.18

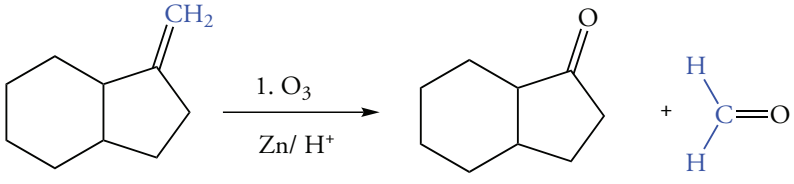
Dihydroxylation of the following steroid gives only the indicated product. Based on the mechanism of the reaction, and the stereochemistry of the product, explain why only one diol forms.



6.10 OZONOLYSIS OF ALKENES

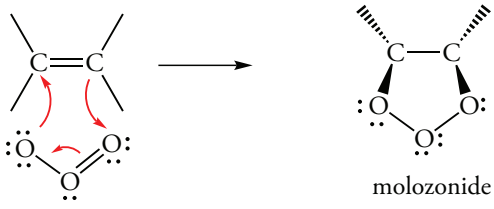
In both epoxidation and dihydroxylation reactions, oxidation occurs at the carbon atoms of the original double bond, but the hydrocarbon skeleton remains intact. Now we consider a reaction in which the products are more highly oxidized. In this reaction, called **ozonolysis,** the carbon–carbon double bond is cleaved to produce carbonyl compounds.

Alkenes react rapidly with ozone (O_3) even at –78 °C. Ozone is produced in the laboratory by a device called an *ozonator*, which forms ozone by passing oxygen gas through an arc discharge. As the ozone forms, oxygen gas containing a few percent ozone is passed through an inert solvent, such as dichloromethane, that contains the alkene. After the reaction is complete, the solution is worked up under reductive conditions such as zinc in acetic acid.



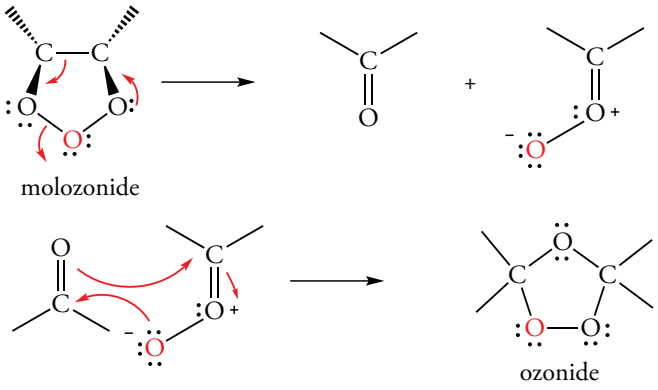
Mechanism of Ozonolysis

Ozonolysis occurs in several steps. First, an unstable intermediate, called a *molozonide*, forms by a cyclic concerted addition of the terminal oxygen atoms of ozone to the π bond of the alkene. This step requires a total of three electron pair shifts, as shown below.



molozonide

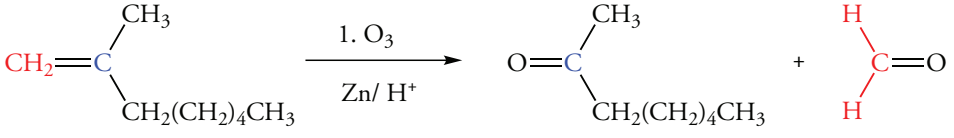
In subsequent steps, the molozonide rapidly rearranges when the π bond of the alkene and an O—O peroxide bond break. The fragments then recombine to give an *ozonide*. The individual fragments are reoriented to illustrate the addition reaction in the second step, which is shown below.



The molozonide has two weak peroxide bonds, but the ozonide has only one. This difference accounts for the direction of the reaction. The rearrangement of the molozonide is exothermic. However, ozonides are explosively unstable compounds. For that reason, the reaction mixture is maintained at low temperatures and immediately reduced or oxidized after the reaction is complete.

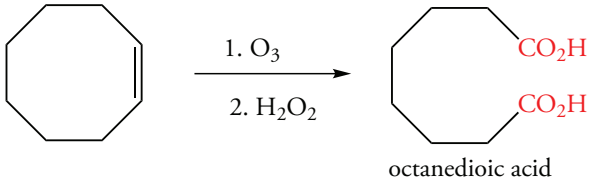
Reductive and Oxidative Workup

The ozonolysis reaction mixture is treated with reducing agents such as zinc metal and aqueous acetic acid or dimethyl sulfide. When zinc is used, the by-product is zinc oxide. When dimethyl sulfide is the reducing agent, dimethyl sulfoxide, $(CH_3)_2SO$, is a by-product. In each case, the reducing agent removes one of the oxygen atoms of the ozonide. The other two oxygen atoms of the ozonide are found as carbonyl oxygen atoms in the product as aldehydes or ketones.

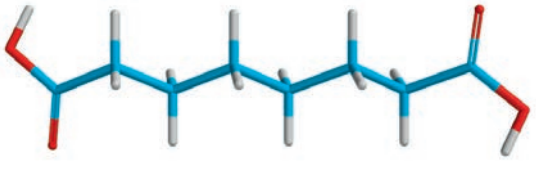


2-methyl-1-octene 2-octanone formaldehyde

If the ozonolysis reaction mixture is treated with an oxidizing agent such as hydrogen peroxide, carboxylic acids rather than aldehydes are produced. For example, the ozonolysis of cyclooctene with an oxidative workup yields octanedioic acid (suberic acid). This compound is one of several dicarboxylic acids excreted in large amounts by persons suffering from diabetes.



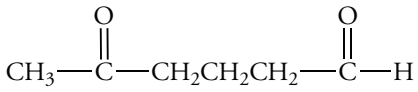
octanedioic acid
(suberic acid)



The choice of reducing or oxidizing workup depends on the goal of the synthesis, which may be to prepare aldehydes (or ketones) or carboxylic acids.

Problem 6.19

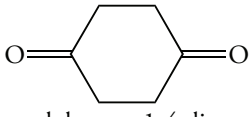
A hydrocarbon of molecular formula C_6H_{10} reacts with ozone followed by treatment with zinc and acetic acid to give 5-ketohexanal. Draw the structure of the hydrocarbon.



5-ketohexanal

Problem 6.20

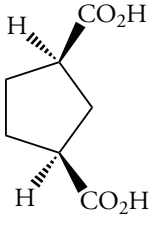
A hydrocarbon of molecular formula C_8H_{12} reacts with O_3 followed by workup with $(CH_3)_2S$ to give formaldehyde and cyclohexane-1,4-dione. Draw the structure of the hydrocarbon.



cyclohexane-1-4-dione

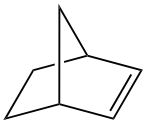
Problem 6.21

A hydrocarbon of molecular formula C_7H_{10} reacts with O_3 followed by an oxidative workup to give only the following dicarboxylic acid. Draw the structure of the hydrocarbon.



Sample Solution

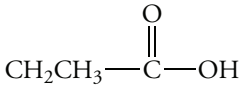
If both oxidative fragments are contained within a single molecule, the original compound must have been a cycloalkene. Joining the two carbon atoms of the carboxyl groups by a carbon–carbon double bond generates another ring. The original compound is bicyclic, bicyclo[2.2.1]heptene.



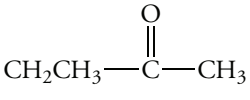
bicyclo[2.2.1]heptene

Problem 6.22

A hydrocarbon of molecular formula C_7H_{14} reacts with O_3 followed by an oxidative workup to give propanoic acid and 2-butanone. Does this information unambiguously establish the structure of the hydrocarbon?



propanoic acid

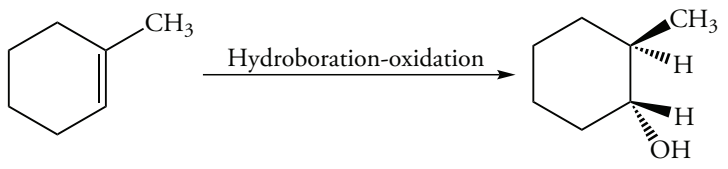


2-butanone

EXERCISES

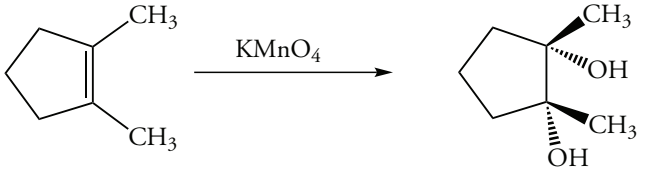
Syn–Anti Addition

6.1 The indirect hydration of an alkene using a procedure called hydroboration–oxidation transforms 1-methylcyclohexene into *trans*-2-methylcyclohexanol. Describe the stereochemistry of the net addition reaction.



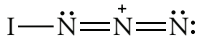
trans-2-methyl-cyclohexanol

6.2 Reaction of 1,2-dimethylcyclopentene with potassium permanganate yields the following compound. What is the stereochemistry of the net addition reaction?

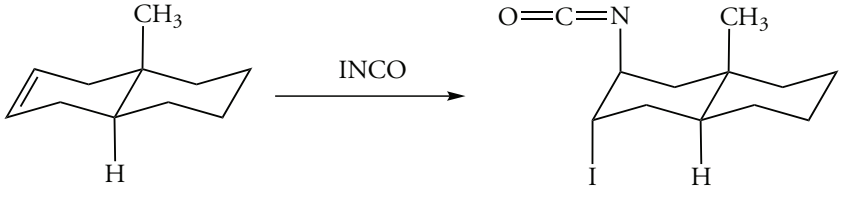


Electrophiles and Markovnikov Addition

6.3 Predict the structure of the addition product of IN_3 and 1-pentene. The mechanism occurs by electrophilic attack followed by capture of the carbocation by a nucleophile. The structure of IN_3 is given below.



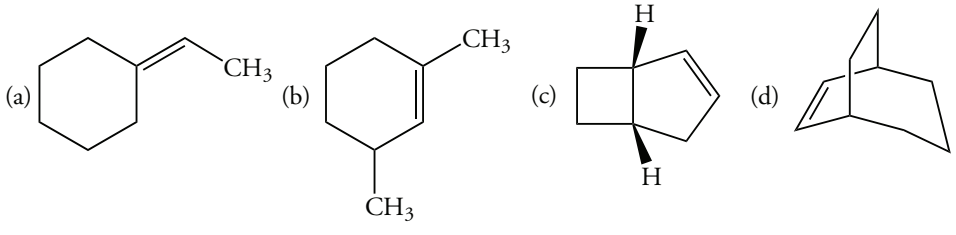
6.4 Based on the information given in the following equation, outline the mechanism of the reaction of the reagent INCO.



6.5 Write the product of the reaction of HBr with each of the following compounds.

(a) 2-methyl-l-butene (b) 2-methyl-2-butene (c) (*Z*)-2-hexene (d) (*E*)-3-methyl-2-pentene

6.6 Write the product of the reaction of HBr with each of the following compounds.



6.7 Reaction of 1,6-dimethylcyclohexene with HBr by an electrophilic addition mechanism yields two products. What are the two compounds?

6.8 Reaction of 1,2-dimethylcyclohexene with HCl by an electrophilic addition mechanism yields two products. What are the two compounds?

6.9 The electrophilic addition of HCl to 3,3,3-trifluoropropene gives 1-chloro-3,3,3-trifluoropropane, an *anti*-Markovnikov addition product. Consider the structure of the intermediate carbocations possible for the two modes of addition and suggest a reason for the observed regioselectivity.

$$CF_3CH{=}CH_2 \xrightarrow{HCl} CF_3CH_2CH_2Cl$$

6.10 The electrophilic addition of HCl to chloroethene yields 1,1-dichloroethane. Based on resonance structures, account for the observed regioselectivity.

6.11 Reaction of 3,3-dimethy1-1-butene with HI gives a mixture of unrearranged product and rearranged product in the ratio 90:10. Account for the difference in this ratio compared to that for addition of HCl (Section 7.4).

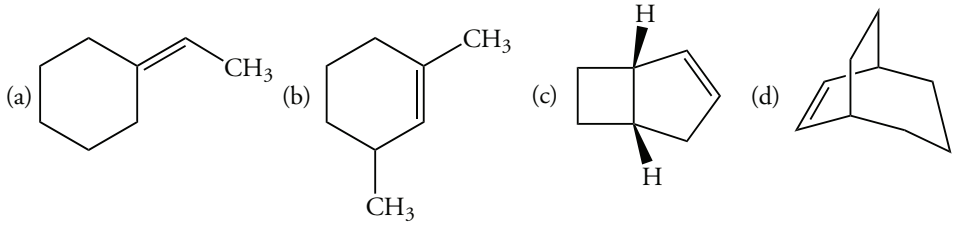
6.12 Reaction of 3,3-dimethyl-l-butene with HBr gives a mixture of two addition products in the ratio 70:30. Based on Exercise 6.11, predict the structures of the two products.

Hydration of Alkenes

6.13 Write the product of hydration of each of the following compounds assuming that no rearrangement occurs.

(a) 2-methyl-l-butene (b) 2-methyl-2-butene (c) (*Z*)-2-hexene (d) (*E*)-3-methyl-2-pentene

6.14 Write the product of hydration of each of the following compounds assuming that no rearrangement occurs.



6.15 Hydration of either 2-methyl-l-butene or 2-methyl-2-butene yields the same alcohol. What is its structure? Explain why the same compound forms from both alkenes.

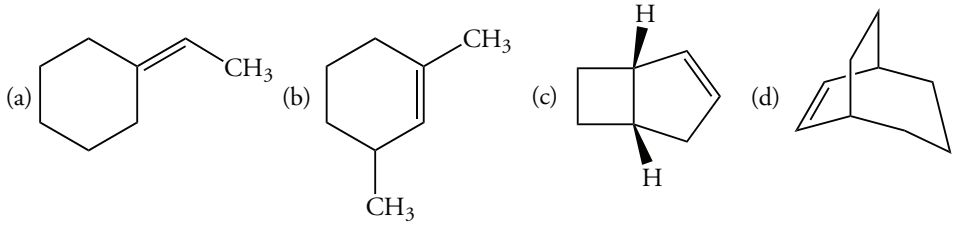
6.16 Hydration of 2,3-dimethyl-2-butene is a slower reaction than the hydration of 2,3-dimethyl-l-butene under the same reaction conditions. Suggest a possible explanation.

Addition of Bromine to Alkenes

6.17 Write the product of the reaction of Br_2 with each of the following compounds.

(a) 2-methyl-l-butene (b) 2-methyl-2-butene (c) (*Z*)-2-hexene (d) (*E*)-3-methyl-2-pentene

6.18 Write the product of the reaction of Br_2 with each of the following compounds.



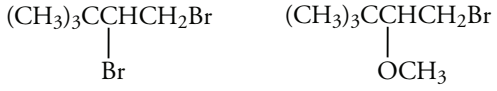
6.19 Reaction of 3-methylcyclohexene with bromine in CCl_4 gives a mixture of two products. Explain why two products result.

6.20 Reaction of 3-bromocyclohexene with HBr gives an "unusual" product, *trans*-1,2-dibromocyclohexane. Explain its origin using an appropriate mechanism and intermediate.

6.21 The reaction of cyclohexene with bromine in water as the solvent yields the alcohol *trans*-2-bromocyclohexanol. Explain why.

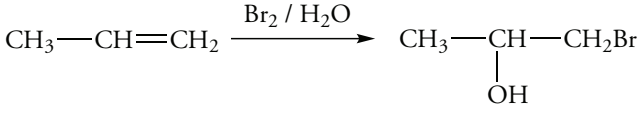
6.22 Reaction of cyclohexene with an aqueous bromine solution saturated with sodium chloride gives a mixture of *trans*-2-bromocyclohexanol and a compound with the molecular formula $C_6H_{10}BrCl$. What is the structure of the latter compound?

6.23 Bromination of 3,3-dimethyl-1-butene in methanol (CH_3OH) gives a mixture of the expected dibromo compound and a bromoether. Explain the origin of the two products.

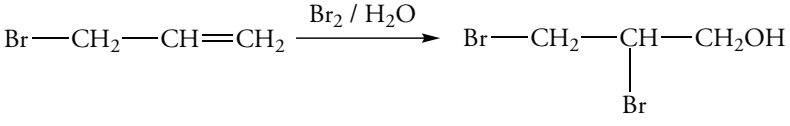


6.24 Based on the information given in Exercise 6.21, predict the structure of the chloroalcohol formed in the reaction of methylenecyclohexane with an aqueous chlorine solution.

6.25 Reaction of propene with aqueous bromine gives the expected product 1-bromo-2-propanol, but reaction of 3-bromo-1-propene with aqueous bromine gives 2,3-dibromo-1-propanol. Suggest a reason for this difference in regioselectivity.

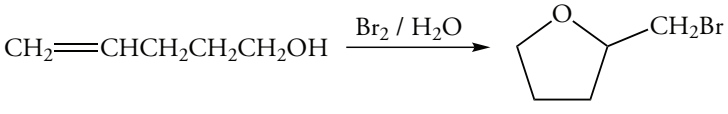


1-bromo-2-propanol



2,3-dibromo-1-propanol

6.26 Reaction of 4-penten-l-ol with aqueous bromine gives the indicated cyclic bromoether. Write a mechanism for its formation.

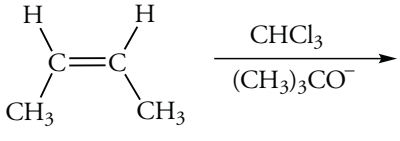


Addition of Carbenes to Alkenes

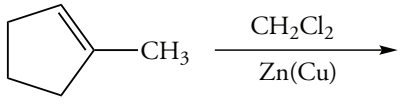
6.27 Chlorocarbene (CHCl) can be produced from dichloromethane using butyl lithium ($CH_3CH_2CH_2CH^{2-}\ Li^+$) but cannot be produced using potassium *tert*-butoxide. Suggest a reason why not.

6.28 Addition of chlorocarbene to *cis*-2-butene gives a mixture of two isomeric compounds. Explain why.

6.29 Write the products of the following reaction.



6.30 Write the products of the following reaction.

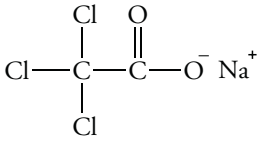


6.31 Based on the stated electrophilicity of dichlorocarbene, predict the relative reactivities of 1-butene and *trans*-2-butene with dichlorocarbene.

6.32 Predict the relative electrophilicities of dichlorocarbene and chlorocarbene.

6.33 Reaction of 1,1-dichloroethane with butyllithium does not give a carbene. Why?

6.34 Based on the electrophilicity of dichlorocarbene, predict the relative reactivities of 1-butene and *trans*-2-butene with dichlorocarbene.

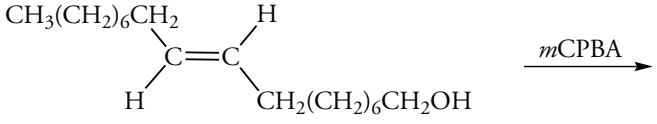


sodium trichloroacetate

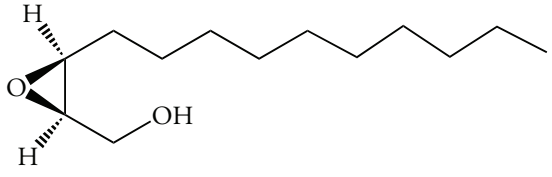
Epoxidation of Alkenes

6.35 Write the structure of the epoxide obtained from the reaction of *trans*-9-octadecen-l-ol with *m*CPBA.

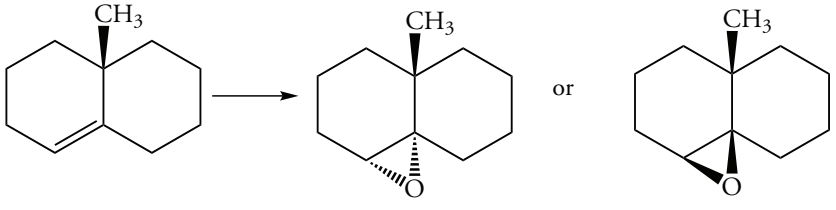
6.36 Write the structure of the epoxide obtained from the reaction of *trans*-9-octadecen-l-ol with *m*CPBA.



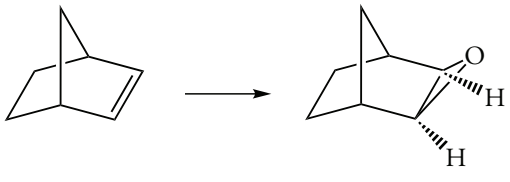
trans-9-octadecene-1-ol



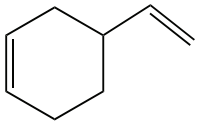
6.37 Predict which of the two isomeric epoxides will be produced from the following bicyclic unsaturated compound.



6.38 Oxidation of bicyclo[2.2.1]hept-2-ene gives the indicated epoxide. Write the structure of an alternative epoxide product and explain why this compound is not produced.



6.39 Write the structure of the epoxide expected from the reaction of the following diene with one molar equivalent of *m*CPBA.



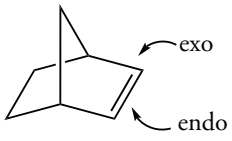
6.40 Arrange the following compounds in order of increasing rate of reaction with *m*CPBA.
I: 5-methyl-1-hexene II: 3-methyl-2-hexene III: 4-methyl-2-hexene IV: 2,3-dimethyl-2-pentene

Dihydroxylation of Alkenes

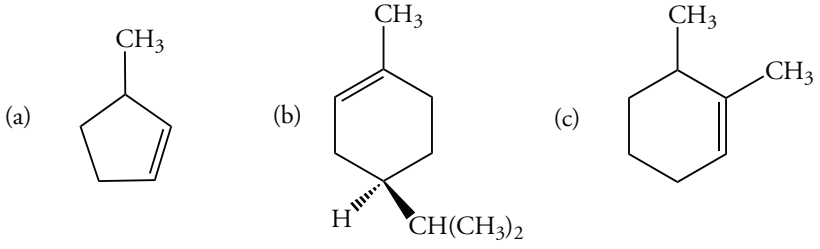
6.41 Describe the observation that is made when *cis*-2-pentene reacts with potassium permanganate. How could this reagent be used to distinguish between the isomers *cis*-2-pentene and cyclopentane?

6.42 Write the product of the reaction of vinylcyclohexane with potassium permanganate.

6.43 The *exo* face of bicyclo[2.2.1]hept-2-ene (norbornene) is less sterically hindered than the *endo* face. Based on this information, write the product of reaction of norbornene with $KMnO_4$.

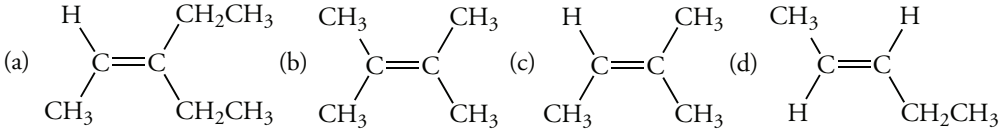


6.44 Write the structure of the diol that forms when OsO_4 reacts with the following alkenes.

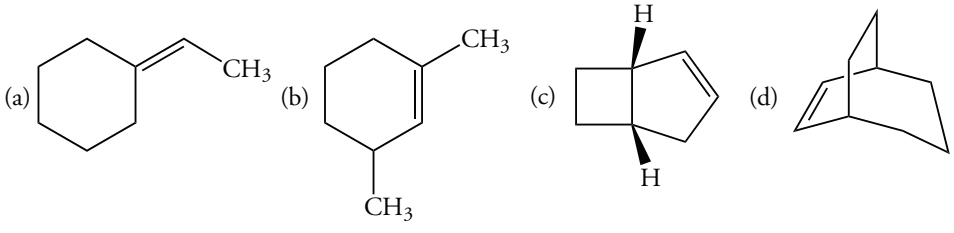


Ozonolysis of Alkenes

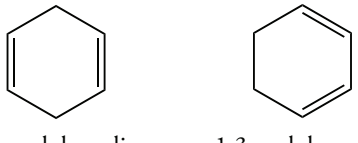
6.45 Write the product(s) of ozonolysis of each of the following compounds under reductive workup conditions.



6.46 Write the product(s) of ozonolysis of each of the following compounds under reductive workup conditions.



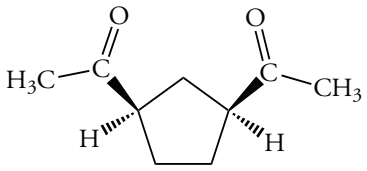
6.47 How can you distinguish between 1,3-cyclohexadiene and 1,4-cyclohexadiene based on their ozonolysis products?



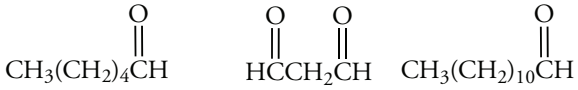
1,4-cyclohexadiene 1,3-cyclohexadiene

6.48 Write the products of ozonolysis using reductive workup conditions for each of the three isomeric methylcyclohexenes and classify the carbonyl group present in each product.

6.49 A hydrocarbon of molecular formula C_9H_{14} is found in sandalwood oil. Ozonolysis of the hydrocarbon followed by oxidative workup gives the following diketone. Draw the structure of the hydrocarbon.



6.50 A hydrocarbon component of a pheromone of a species of moth reacts with ozone followed by reductive workup to give the following compounds. Draw a structure of the hydrocarbon. How many geometric isomers are possible with this structure?



6.51 Two isomeric unsaturated carboxylic acids, oleic acid and elaidic acid, melt at 13 and 45 °C, respectively. Ozonolysis of either compounds under oxidative conditions yields the following two compounds. What are possible structures of the two compounds? Why do they give the same products?



6.52 An unsaturated fatty acid isolated from brain tissue has the molecular formula $C_{24}H_{40}O_2$. Hydrogenation yields an unbranched carboxylic acid with the molecular formula $C_{24}H_{46}O_2$. Ozonolysis of the fatty acid under reductive conditions yields two equivalents of 1,3-propanedial and one equivalent each of hexanal and an aldehydic acid with the formula $C_{12}H_{22}O_3$. Write the structure of the most stable isomer that is most consistent with these data. How many other isomeric compounds are also consistent with the data?

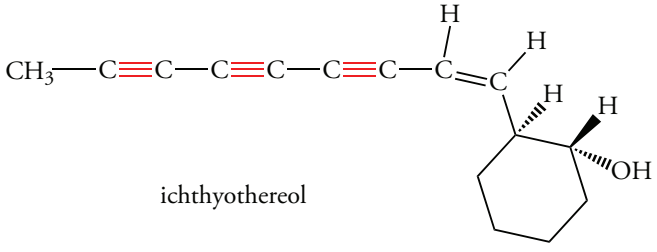


hexanal propanedial

7 ALKYNES

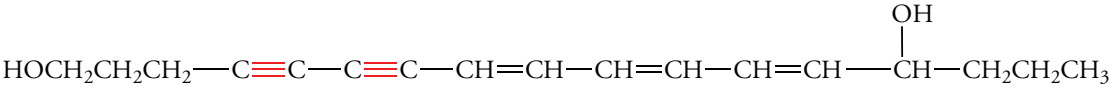
7.1 OCCURRENCE AND USES OF ALKYNES

Many natural products contain alkynes, which contain one or more triple bonds. Many natural alkynes contain several triple bonds and are physiologically active. For example, the skin of a species of frog that lives in the Lower Amazon Basin secretes a mucous membrane irritant that wards off predators. This compound is an alkyne with three triple bonds, a triyne, called ichthyothereol. The Indians of the area coat their arrowheads with the secretion. When the arrow pierces the skin of the prey, the compound acts on the nervous system and causes convulsions.



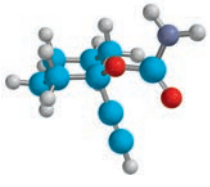
ichthyothereol

Natural products with several triple bonds are also found in plants. Cicutoxin, a poisonous compound contained in water hemlock, is the compound that caused the death of Socrates, who was sentenced to death for allegedly corrupting the morals of Athenian youth—by encouraging them to ask inconvenient questions.

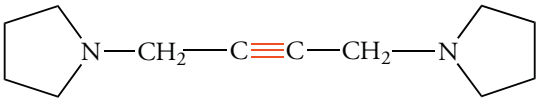


cicutoxin

Some synthetic drugs contain a triple bond. For example, ethinamate is a sedative and hypnotic drug, and tremorine is used to treat Parkinson's disease.



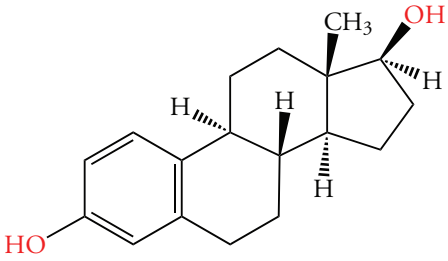
ethinamate



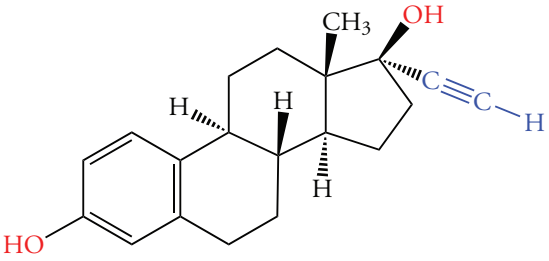
tremorine

Synthetic estrogens such as 17-ethynylestradiol are birth control agents. Estradiol, the female sex hormone, is a secondary alcohol that cannot be administered orally because it would be rapidly oxidized by the liver. The synthetic estrogens contain an ethynyl group (—C≡CH) and are tertiary alcohols that are not oxidized in metabolic reactions. The ethynyl group in these compounds is located so that the hydroxyl group has the same stereochemistry as the natural estradiol.

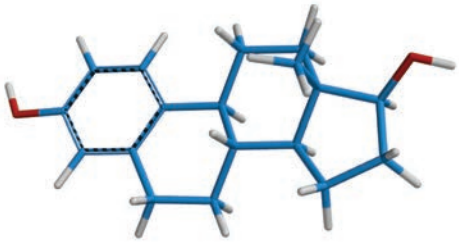
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00007-3
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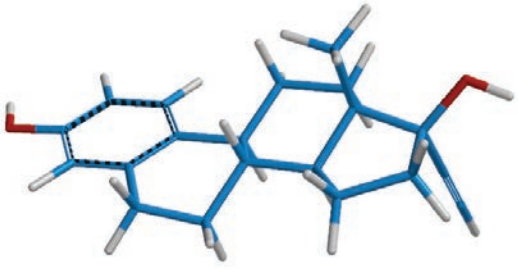
estradiol



17-ethynylestradiol



estradiol



17-ethynylestradiol

7.2 STRUCTURE AND PROPERTIES OF ALKYNES

The simplest alkyne, C_2H_2, is commonly called *acetylene*. Unfortunately, the common name ends in -ene, which suggests that the compound contains a double bond. Such confusion is one reason IUPAC names are so important for clear communication in chemistry. The IUPAC name for C_2H_2 is *ethyne*.

The four atoms of ethyne are collinear. Therefore, each H—C≡C—H bond angle is 180°. In all alkynes, the two triple-bonded carbon atoms and the two atoms directly attached to them are colinear. We described the sp hybridization of the carbon atoms of ethyne in Section 1.17. Figure 7.1 shows the bonding in ethyne.

Classification of Alkynes

The classes of alkynes are more limited than the classes of alkenes because only one alkyl group can bond to each sp-hybridized carbon atom of the triple bond. If one alkyl group is bonded to one of the carbon atoms of the triple bond, the compound is a **monosubstituted alkyne** (R—C≡C—H). This is also called a **terminal alkyne** because the triple bond is at the end of the carbon chain. When alkyl groups are bonded to both carbon atoms of the triple bond, the compound is a **disubstituted**, or an **internal alkyne** (R—C≡C—R).

Hybridization, Bond Length, and Bond Energies in Alkynes

The sp hybrid orbital has 50% s character, which is greater than the 33% and 25% s characters of the sp^2 hybrid orbitals of alkenes and the sp^3 and hybrid orbitals of alkanes. We recall that as the percent s character of hybrid orbitals increases the electrons in the hybrid orbitals are closer to the nucleus. Therefore, the bonding electrons in an sp hybrid orbital of a C—H bond in ethyne are closer to the nucleus than the electrons in the hybrid orbital of the C—H bonds of ethylene or ethane. The greater s character of the sigma bonds of acetylene and alkynes affects their physical properties.

The length of a bond between a carbon atom and another atom is the shortest for a carbon atom with sp hybrid orbitals. The carbon–hydrogen bond lengths for ethyne, ethene, and ethane are 105, 109, and 111 pm, respectively. The C—H bond energy of ethyne is 536 kJ $mole^{-1}$, larger than the 470 kJ $mole^{-1}$ C—H bond energy of ethene and the 422 kJ $mole^{-1}$ C—H bond energy of ethane.

The length of a carbon–carbon sigma bond depends on the hybridization of both carbon atoms. For example, the sp–sp^3 C—C bond of propyne is shorter than both the sp^2–sp^3 C—C bond of propene and the sp^3–sp^3 C—C bond of propane (Table 7.1).

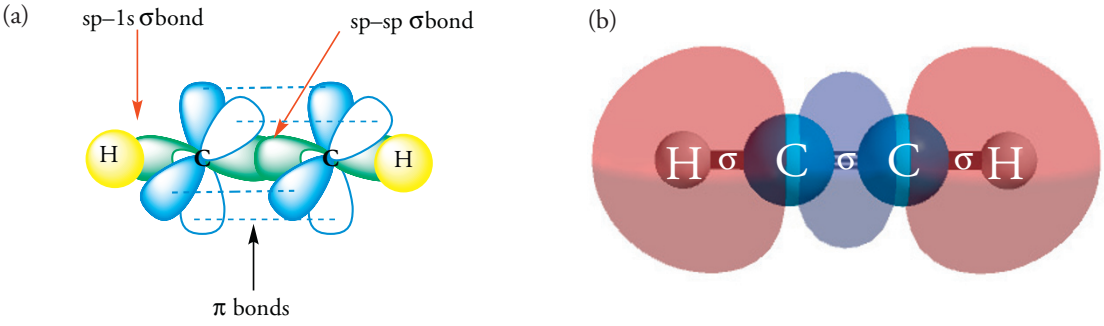
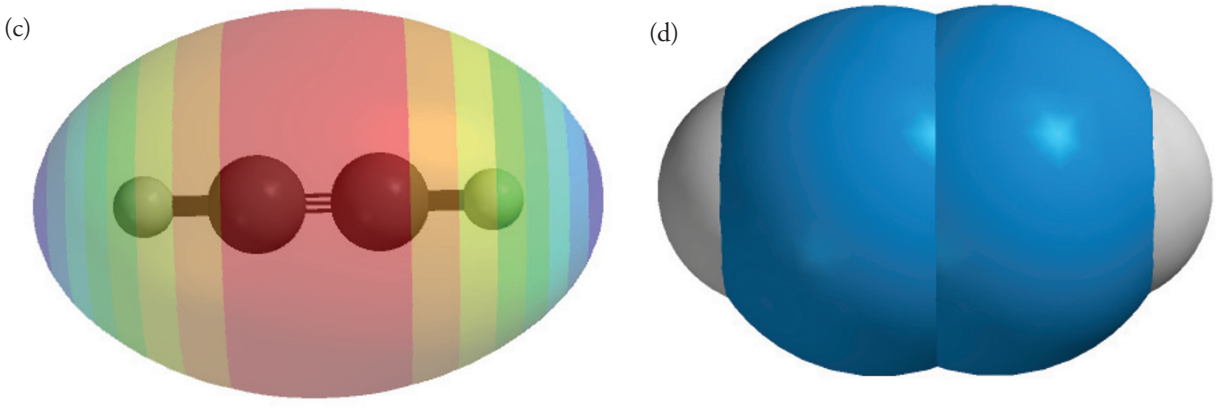


Figure 7.1 Structure and Bonding in Ethyne
(a) Schematic diagram.
(b) Sigma bonds in ethyne.
(c) Electrostatic potential map. We recall that an sp-hybridized carbon is electron-deficient relative to an sp^2- or sp^3-hybridized carbon. The regions of partial positive charge surrounding the carbon atoms is shown in red. The negative end of the C—H dipole is shown in blue.
(d) Space-filling model.

Bonding in ethyne: the carbon–carbon σ bonds are colinear; the π bonds lie above and below, and in front and behind the sigma bonds.



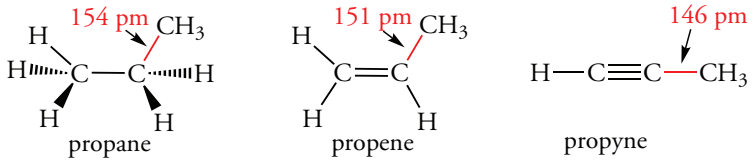


Table 7.1
C—C and C—H Bond Lengths and Bond Strengths in Alkynes, Alkenes, and Alkanes

Compound	*Bond Length (pm)*	*Bond Strength (kJ mole^{-1})*
C≡C—H (ethyne)	105	536
C=C—H (ethene)	109	470
C—H (ethane)	111	422
C≡C (ethyne)	121	820
C=C (ethene)	133	605
C—C (ethane)	154	368

Physical Properties of Alkynes

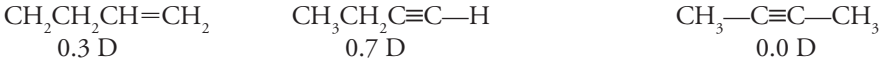
The general molecular formula for alkynes is C_nH_{2n-2} because an alkyne has four fewer hydrogen atoms than an alkane with the same number of carbon atoms. The physical properties of the homologous series of alkynes are similar to those of the homologous series of alkenes (C_nH_{2n}) and alkanes (C_nH_{2n+2}). Unsaturated hydrocarbons are essentially nonpolar.

The members of each series containing fewer than five carbon atoms are gases at room temperature. The boiling points of the alkynes, like those of alkanes and alkenes, increase as the number of carbon atoms increases because the London forces increase (Table 7.2). Branching tends to decrease the boiling point.

Table 7.2
Physical Properties of Alkynes

Compound	*Boiling Point (°C)*	*Density (g/cm³)*
1-Butyne	8.1	0.678
2-Butyne	27	0.091
1-Pentyne	40.2	0.690
2-Pentyne	56.1	0.711
3-Methyl-1-butyne	29	0.666
1-Hexyne	71.3	0.716
2-Hexyne	84	0.732
3-Hexyne	81.5	0.723
4-Methyl-1-pentyne	61.1	0.709
4-Methyl-2-pentyne	72.0	0.716
3,3-Dimethyl-1-butyne	39.5	0.669
1-Heptyne	99.7	0.733
2-Heptyne	112	0.748
3-Heptyne	105.5	0.753
5-Methyl-1-hexyne	92	0.727
5-Methyl-2-hexyne	102	0.738
2-Methyl-3-hexyne	95.2	0.726
4,4-Dimethyl-1-pentyne	76.1	0.714
4,4-Dimethyl-2-pentyne	82.3	0.718
3-Ethyl-1-pentyne	88	0.724

Terminal alkynes have dipole moments that are larger than the dipole moments of terminal alkenes. Disubstituted alkynes with identical or even similar alkyl groups have no dipole moment.

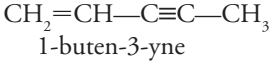


Chemical Properties of Alkynes

We have learned that the π bond of alkenes reacts in characteristic ways with electrophiles, oxidizing agents, and reducing agents. Alkynes, with two π bonds, undergo similar regiospecific reactions. However, both π bonds of alkynes can react, and this means that we have to pay attention to the experimental conditions (Sections 7.6 and 7.7).

1. Do the conditions for adding a reagent to one π bond to give an alkene allow addition to the second π bond?
2. We have to consider the regiospecificity of the addition reactions to the first and second π bonds.
3. We have to learn how to control the stepwise progression of such reactions.
4. Because alkenes can form as either *E* or *Z* isomers, we need to establish the stereospecificity of the first addition reaction.

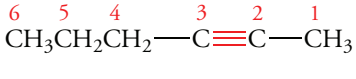
Problem 7.1 Based on hybridization considerations alone, predict the C-2 to C-3 bond length of 1-buten-3-yne.



7.3 IUPAC NAMES OF ALKYNES

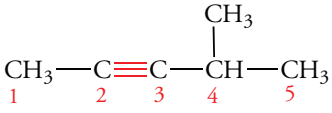
The IUPAC rules for naming alkynes are similar to those for alkenes. As a branching group, the unit —C≡CH is named ethynyl. The next homolog, —CH,—C≡CH, is 2-propynyl; the common name is *propargyl*. The IUPAC rules for alkynes parallel those for alkenes and alkanes.

1. The longest continuous chain that contains the triple bond is the parent.
2. Give the parent the same stem name as an alkane but replace *-ane* with *-yne*.
3. Number the carbon atoms consecutively from the end of the chain nearer the triple bond. Use the number of the first carbon atom with the triple bond as a prefix separated by a hyphen from the parent name.



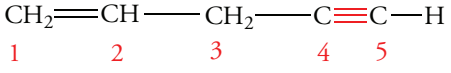
Number this compound from right to left.
It is 2-hexyne.

4. Alkyl groups are named, and their positions on the chain determined, by the numbering established by rule 3.



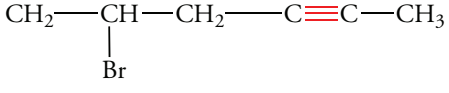
Number this compound from left to right.
It is 4-methyl-2-pentyne.

5. Compounds with multiple triple bonds are diynes, triynes, and so on. Compounds with both double and triple bonds are called *enynes*, *not* ynenes. Start the numbering of compounds with both double and triple bonds from the end nearer the first multiple bond, regardless of type. When a choice is possible, assign double bonds lower numbers than triple bonds.



This is 1-penten-4-yne,
not 4-penten-1-yne

Problem 7.2 Why is 2-bromo-4-hexyne an incorrect name for the following compound? What is the correct IUPAC name?



Sample Solution

The name is incorrect because it is based on using bromine rather than the triple bond to establish the numbering of the carbon chain. Starting from the right carbon atom places the triple bond at C-2. The bromine atom is on C-5, and the correct name is 5-bromo-2-hexyne.

Problem 7.3 1,3,11-Tridecatriene-5,7,9-triyne is a compound found in safflowers and used as a chemical defense against nematode infestations. Write its structure.

Problem 7.4 Write the structure of each of the following compounds.
(a) 1-ethynylcyclohexanol (b) cyclododecyne (c) 4-methyl-1,6-heptadiyne

---

7.4 ACIDITY OF TERMINAL ALKYNES

Terminal alkynes are weak acids, but a very strong base may remove a proton from the terminal carbon atom to give a carbanion called an alkynide ion. The common name for an **alkynide** ion is the **acetylide** ion.



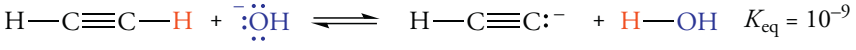
(an alkynide ion)

Formation of a carbanion, the conjugate base of a hydrocarbon, is generally less favorable than the ionization of acids in which a hydrogen atom is bonded to electronegative atoms such as oxygen or nitrogen. Because carbon is less electronegative than these two elements, the pK_a values of hydrocarbons are very small.

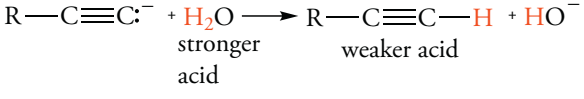
$CH_3—CH_3$	$CH_2=CH_2$	HC≡CH
K_a 10^{-50}	$K_a = 10^{-44}$	K_a 10^{-25}

The C—H acid dissociation constant, K_a, is related to the hybridization of the carbon atom. It increases for carbon atoms in the order $sp^3 < sp^2 < sp$. This order of acidities parallels the percent s character of the hybrid orbitals. Because an sp hybrid orbital has more s character than an sp^2 or sp^3 orbital, its electrons are located closer to the nucleus, and a hydrogen atom bonded to an sp-hybridized carbon atom can be more easily removed as a proton.

Although ethyne and terminal alkynes are much stronger acids than other hydrocarbons, they are still very weak acids. Hydroxide ion is not a strong enough base to convert a terminal alkyne to its conjugate base to any significant degree.



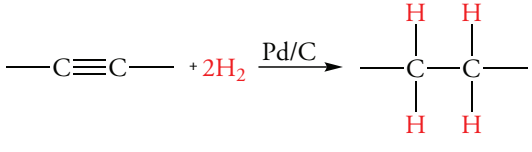
In fact, the conjugate base of an alkyne rapidly and quantitatively converts to the alkyne whenever it reacts with compounds that contain hydroxyl groups (such as water, alcohols, and carboxylic acids).



From the periodic trends of acidity we discussed earlier, we know that an N—H bond is a weaker acid than an O—H bond. Therefore NH_2^-, the conjugate base of ammonia, is a stronger base than OH^-, the conjugate base of water. The K_a of ammonia is 10^{-36}. Thus, amide ion quantitatively removes a proton from a terminal alkyne, whose pK_a value is about 10^{-25}.

7.5 HYDROGENATION OF ALKYNES

Like alkenes, alkynes react with hydrogen gas to give more saturated compounds. Alkynes are quantitatively reduced to alkanes by reaction with two molar equivalents of hydrogen gas in the presence of a palladium catalyst.



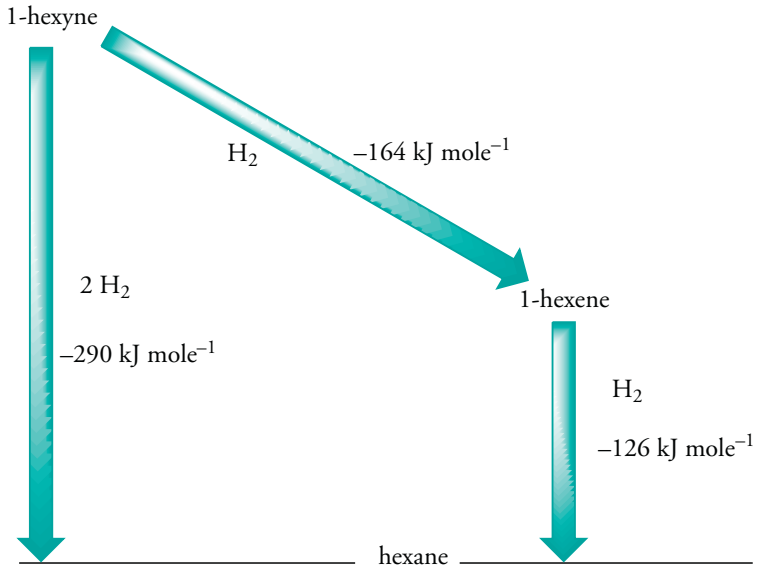
The reaction occurs with stepwise addition of hydrogen to first give an alkene. The second step occurs even faster than the first. Therefore, catalytic hydrogenation with transition metal catalysts cannot be used to partially hydrogenate alkynes and "stop" at an alkene. The hydrogenation goes all the way to the alkane.

In the hydrogenation of alkynes, the two π bonds break, along with the hydrogen—hydrogen bond of two hydrogen molecules. Four carbon—hydrogen bonds form. The hydrogenation reaction is exothermic regardless of the structure of the alkyne because the four carbon—hydrogen bonds that form are stronger than the combined strength of the bonds that break. We recall that the heat evolved for a hydrogenation reaction is reported as a positive quantity called the **heat of hydrogenation** ($\Delta H°_{\text{hydrogenation}}$), but $\Delta H°$ for the reaction is negative (Figure 7.2).

The relative stabilities of the two π bonds of an alkyne can be compared to the single π bond of an alkene. The heat of hydrogenation of 1-hexyne, 290 kJ mol^{-1}, is more than twice the heat of hydrogenation of 1-hexene, 126 kJ mol^{-1}.

$$CH_3(CH_2)_2CH_2{-}C{\equiv}C{-}H \xrightarrow[2H_2]{Pd/C} CH_3(CH_2)_3CH_2{-}CH_3 \quad \Delta H = -290 \text{ kJ mole}^{-1}$$

Figure 7.2 Stability of Alkenes and Alkynes

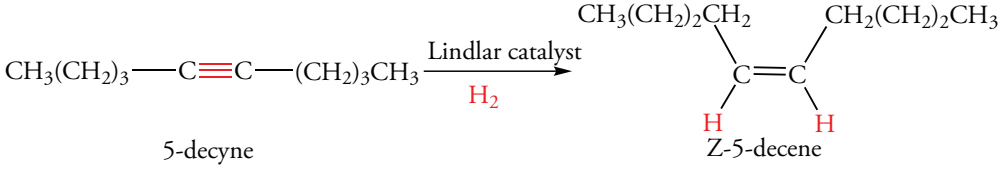


The heat evolved by addition of the first mole of hydrogen to 1-hexyne, 164 kJ $mole^{-1}$, can be determined by taking the difference in the heat of hydrogenation of 1-hexyne (–290 kJ $mole^{-1}$) and 1-hexene (–126 kJ $mole^{-1}$). Thus, the calculated heat of hydrogenation for converting the alkyne to the alkene is –164 kJ $mole^{-1}$.

We find that the first step in the hydrogenation of an alkyne is more exothermic than the hydrogenation of an alkene. Thus, we conclude that the single π bond of an alkene is more stable than either of the two π bonds of an alkyne. The release of electrons from alkyl groups to the unsaturated carbon atoms explains the higher stability of the π bond of alkenes compared to alkynes. The sp-hybridized carbon atoms of alkynes attract electrons more strongly than the sp^2-hybridized carbon atoms of alkenes, but there are fewer alkyl groups available to supply those electrons in alkynes.

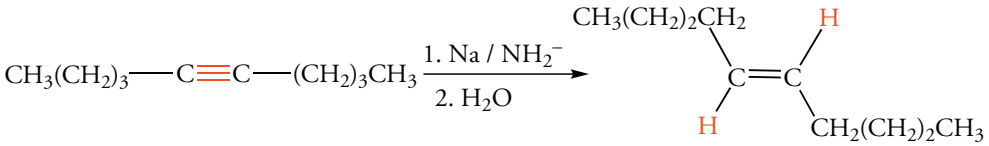
Syn Addition of Hydrogen

The catalytic hydrogenation reaction can be stopped after adding one molar equivalent of hydrogen gas to form an alkene with a modified palladium catalyst. One such palladium catalyst, called the **Lindlar catalyst**, has palladium coated on calcium carbonate that contains a small amount of lead acetate. Hydrogenation of an alkyne using the Lindlar catalyst is stereospecific. *Syn* addition occurs, giving the *Z* (*cis*) isomer. This *syn* addition indicates that the reaction occurs on the surface of the palladium catalyst and that both hydrogen atoms bond on the same "face," while the compound remains bound to the catalyst.



Anti Addition of Hydrogen

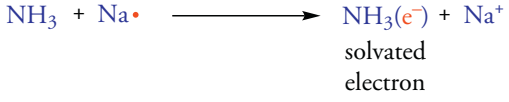
Reduction of an alkyne with sodium metal in liquid ammonia gives an alkene formed by *anti* addition of two hydrogen atoms. The reaction occurs by a very different mechanism than the catalytic hydrogenation reaction.



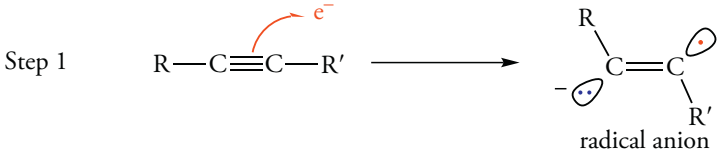
5-decyne (*E*)-5-decene

Mechanism of *Anti* Addition

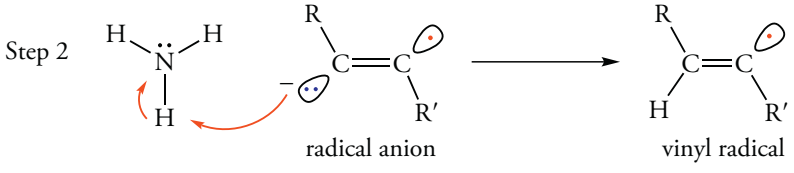
This reaction occurs in four steps: two are electron transfer reactions and two are acid–base reactions. An electron of the alkali metal moves to ammonia to give a "solvated electron," which is the active reducing agent. The formation of this solvated electron causes a deep blue color, cerulean blue, when the metal is placed in ammonia.



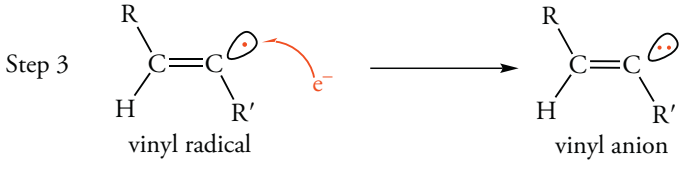
In the first step, an electron adds to a π orbital of the alkyne to form a *radical anion*. The two non-bonded orbitals are shown *trans* to each other. However, the stereochemistry is not critical at this point. Vinyl carbanions are configurationally stable, but vinyl radicals are less so.

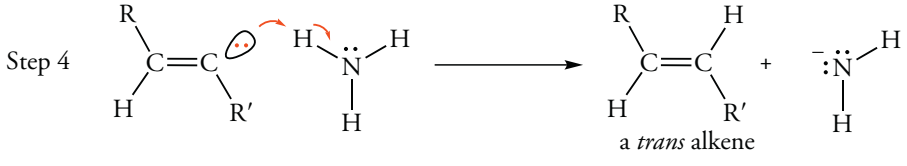


The second step is an acid–base reaction. Because C—H bonds of sp^2-hybridized carbon atoms are less acidic than N—H bonds, the equilibrium lies to the right. At this point, even if the vinyl radical is not configurationally stable, the two alkyl groups are more stable *trans* to each other because steric hindrance would result if they were *cis*.



In the third step, a second electron transfer occurs to form a vinyl anion in which the alkyl groups are *trans*. Finally, in the fourth step, an acid–base reaction occurs to protonate the vinyl anion.

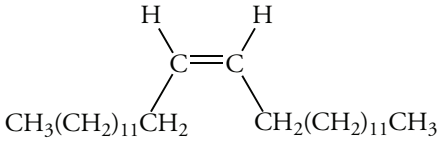




Problem 7.5 The heats of hydrogenation of 1-butyne and 2-butyne are 292 and 274 kJ mole^{-1}, respectively. Which compound is more stable? Why?

Problem 7.6 One of the intermediate compounds in the synthesis of the spruce budworm sex pheromone is (*E*)-11-tetradecen-1-ol. How can this compound be produced from a substituted alkyne? Name the alkyne.

Problem 7.7 The IUPAC name of muscalure, the sex hormone of the housefly, is (*Z*)-9-tricosene. How can this compound be produced from a structurally related alkyne? Name the alkyne.



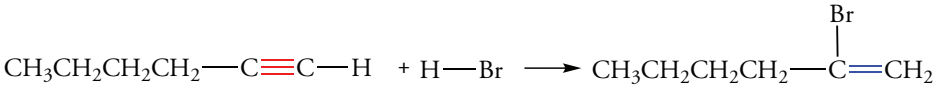
muscalure

7.6 ELECTROPHILIC ADDITION REACTIONS

In Chapter 6, we considered the addition of HBr, Br_2, and H_2O to double bonds. These reagents react with alkenes by common, well-established mechanisms. We will now use this information to consider the addition reactions of alkynes.

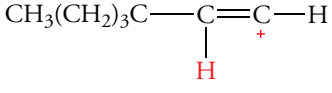
Addition of Hydrogen Halides

Hydrogen bromide adds to alkynes at a slightly slower rate than it adds to alkenes. This regioselective reaction is a Markovnikov addition.

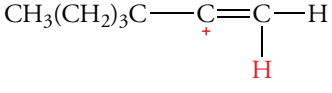


1-hexyne 2-bromo-1-hexene

The reaction occurs when a proton adds to the triple bond to form an *alkenyl carbocation*, which the nucleophilic bromide ion subsequently captures. Of the two possible carbocations, the secondary is more stable than the primary because the secondary carbocation is more highly substituted. The more stable intermediate forms in the rate-determining step of the reaction because it has a lower energy barrier.

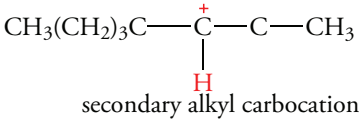


primary alkenyl carbocation (less stable)

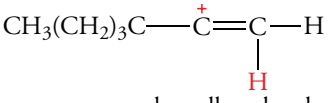


secondary alkenyl carbocation (more stable)

Hydrogen bromide adds to alkynes more slowly than to alkenes. To understand why, consider the carbocations formed in the addition of a proton to 1-hexene and 1-hexyne.



secondary alkyl carbocation (more stable)

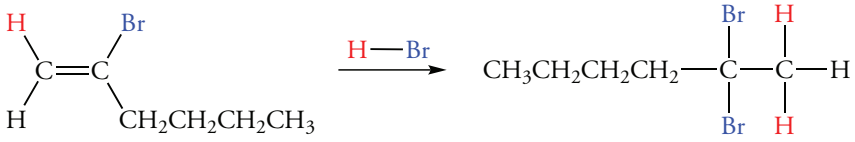


secondary alkenyl carbocation (less stable)

The positive carbon atoms of the alkyl and alkenyl carbocations are sp²- and sp-hybridized, respectively. The sp hybrid orbital is of lower energy than the sp² hybrid orbital. If electrons were present in these orbitals, the ones in the sp hybrid orbital would be more strongly attracted to the carbon atom. Because the carbocation does not have electrons in the hybrid orbital, it requires more energy to form the alkenyl carbocation than the alkyl carbocation. That is, the alkenyl carbocation is less stable than an alkyl carbocation. For this reason, the rate-determining step for forming the alkenyl carbocation is somewhat slower than the step forming the alkyl carbocation.

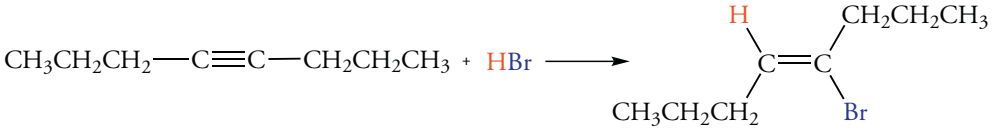
The addition product of one mole of HBr to an alkyne can be isolated because the electron-withdrawing bromine atom diminishes the reactivity of the product toward electrophiles. The electronegative bromine atom withdraws electron density from the π bond of the alkenyl bromide, thereby decreasing the availability of it electrons to electrophiles. Nevertheless, when the alkenyl bromide

does react with a second mole of HBr, the second step is also a regiospecific Markovnikov addition.



Although the bromine atom is electron withdrawing, the secondary carbocation resulting from adding a proton to the C-1 atom is still more stable than the primary carbocation that would result from adding a proton to C-2.

Now let's consider the stereochemistry of the addition of the first mole of HBr. The bromide ion tends to add *trans* to the proton, although the stereoselectivity may be low in some cases.

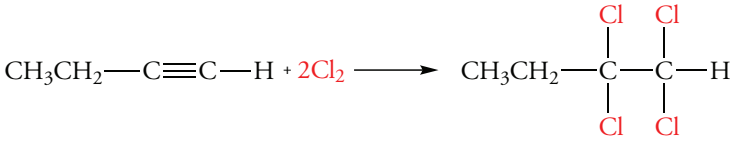


4-octyne (*Z*)-4-bromo-4-octene

Adding excess bromide ion to the reaction mixture tends to increase the percentage of *anti* addition product. The increased stereoselectivity may result from the simultaneous attack of the entering bromide ion on the developing carbocation as the proton is transferred to the π electrons.

Addition of Halogens

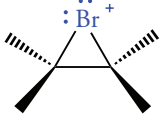
Alkynes react with chlorine or bromine to produce tetrahaloalkanes, which contain two halogen atoms on each of the original carbon atoms of the triple bond. Hence, the reaction consumes two molar equivalents of the halogen. As in alkenes, both chlorine and bromine give halogenated products.



1-butyne 1,1,2,2-tetrachlorobutane

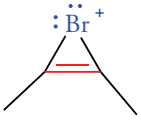
The reaction is much faster for disubstituted alkynes, which form *trans* dibromoalkenes in the first step leading to the terahalogenated product. The model for the stereoselectivity of the addition of bromine to a triple bond is similar to that for the *anti* addition of bromine to a double bond. A cyclic halonium ion forms as an intermediate, and the nucleophilic halide ion attacks the electrophilic carbon atom from the side opposite the bridged halogen atom. The rate of formation of the intermediate is slower for an alkyne because the double bond in the cyclic halonium ion intermediate is highly strained. Because the intermediate is less stable, the transition state also reflects the same ring strain, and the energy barrier for its formation is higher. Therefore, the rate of the reaction is slower for alkynes than for alkenes.

cyclic bromonium ion from alkene addition

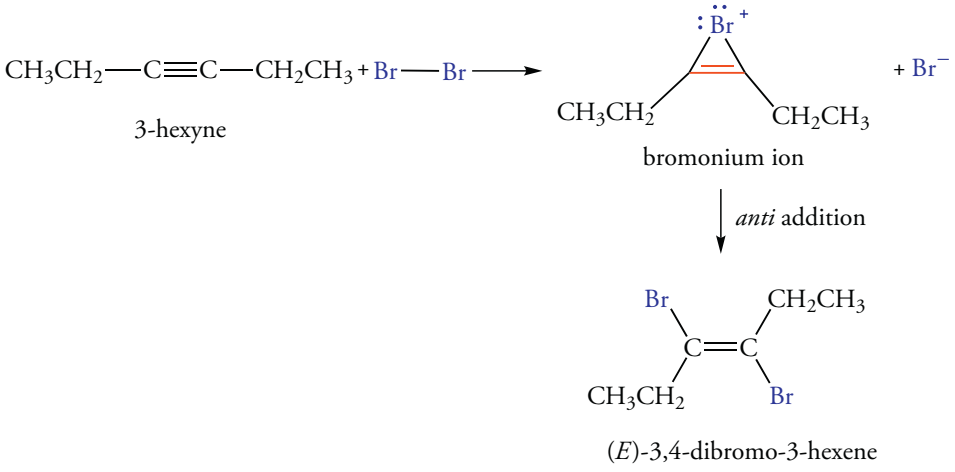


more stable

cyclic bromonium ion from alkyne addition

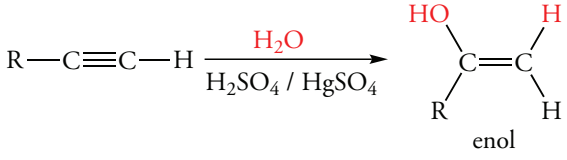


less stable

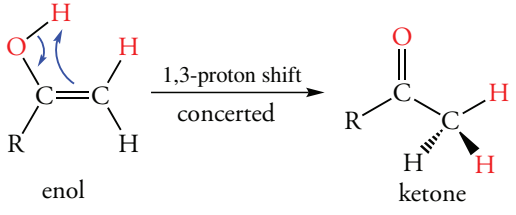


Hydration of Alkynes

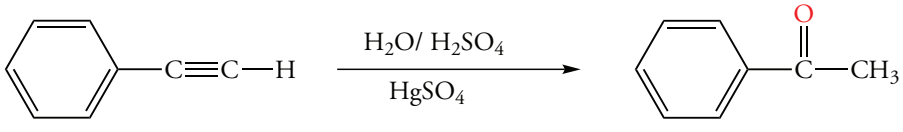
Water adds to one of the π bonds of a triple bond in aqueous sulfuric acid in the presence of mercuric sulfate catalyst. The reaction is regiospecific and occurs by Markovnikov addition. However, the alcohol that forms has its —OH group bonded to the double-bonded carbon atom of an alkene. This type of compound is called an **enol**, a name that includes both the *-ene* suffix of a double bond and the alcohol suffix *-ol*.



Enols are unstable compounds that rapidly rearrange to carbonyl compounds. The conversion of the enol intermediate to a ketone is a rapid, reversible reaction whose equilibrium lies very far on the side of the more stable carbonyl compound. It occurs by a concerted 1,3-proton shift. We will discuss this reaction in much greater detail when we discuss the chemistry of carbonyl compounds.



Thus the product of the hydration of an alkyne is a ketone. The more substituted carbon atom of the alkyne is converted into a carbonyl carbon atom.



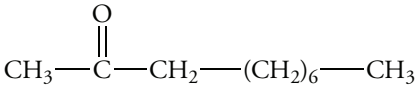
Problem 7.8 Write the structure of the product formed in the reaction of excess chlorine with each of the following compounds.

(a) ethynylcyclohexane (b) propargylcyclopentane (c) 1,5-hexadiyne

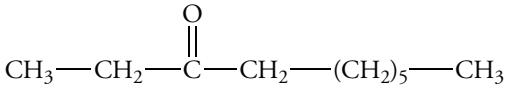
Problem 7.9 Consider the regioselectivity of the hydration of 2-decyne. Write the products of the reaction. Predict the percentage of each compound in the product mixture.

Sample Solution

The initial hydration of an alkyne places the hydroxyl group on the more substituted carbon atom. This carbon atom is the eventual site of the carbonyl group. In 2-decyne, both C-2 and C-3 are substituted to the same degree. C-2 is bonded to a methyl group; C-3 is bonded to a heptyl group. As a consequence, hydration can occur either of two ways, and two products, 2-decanone and 3-decanone, are formed.



2-decanone



3-decanone

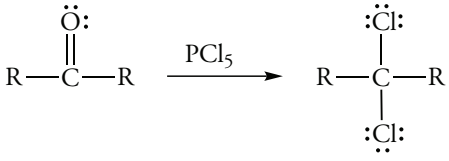
Although the heptyl group is larger than a methyl group, it is a primary alkyl group. Thus, the steric sizes of the heptyl group and the methyl group are not dramatically different. We would expect approximately equal amounts of the two ketones.

7.7 SYNTHESIS OF ALKYNES

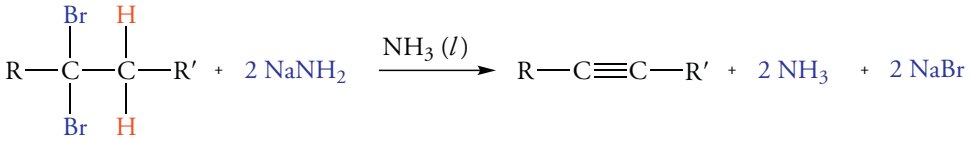
Some synthetic methods introduce the carbon–carbon triple bond by functional group transformations such as the elimination reaction of vicinal dihalides. Other methods construct complex alkynes by forming carbon–carbon single bonds between two molecules, one of which already contains a triple bond. We discuss both synthetic methods in this section.

Elimination Reactions of Dihalides

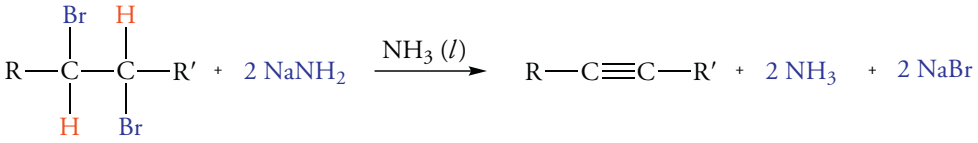
Alkynes can be prepared by elimination reactions under conditions similar to those used to form alkenes. Because an alkyne has two π bonds, two molar equivalents of HX must be eliminated from the starting material. One such suitable reactant is a vicinal dihalide, a compound with halogen atoms on adjacent carbon atoms. We recall that such compounds result from the addition of a halogen to the double bond of an alkene (Section 6.5). A **geminal** dihalide, which has both halogens on the same carbon atom, can also be used to synthesize alkynes. Geminal dichlorides can be made by reaction of phosphorus pentachloride with an aldehyde or ketone.



The synthesis of an alkyne from either a geminal dihalide or a vicinal dihalide requires a strong base to eliminate two moles of hydrogen halide. Two suitable reagents for this reaction are sodium amide in liquid ammonia as the solvent and potassium *tert*-butoxide in dimethyl sulfoxide.

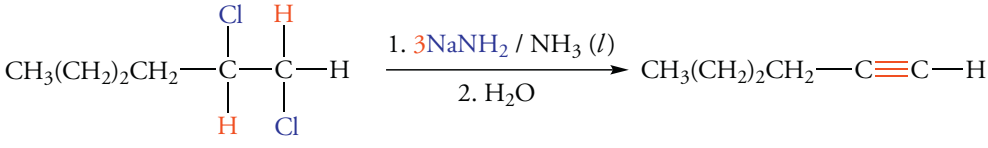


geminal dibromide



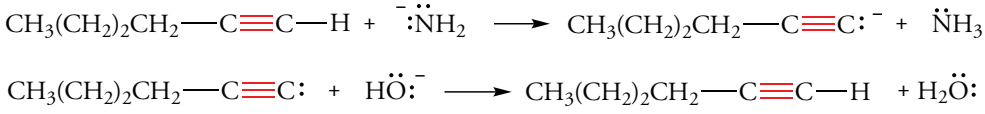
vicinal dibromide

A terminal alkyne can be synthesized from a 1,2-dihalo compound. We recall that this starting material can be synthesized in an addition reaction of a halogen to a monosubstituted (terminal) alkene. For example, adding chlorine to 1-hexene yields 1,2-dichlorohexane. The double dehydrohalogenation of 1,2-dichlorohexane yields 1-hexyne.

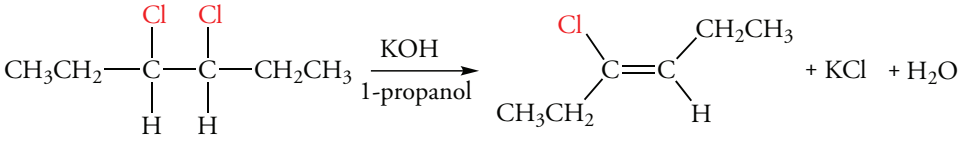


1,2-dichlorohexane 1-hexyne

Note that the synthesis of this terminal alkyne requires a total of *three* equivalents of base. The double dehydrohalogenation itself requires two equivalents. However, a third equivalent is required because, as the alkyne forms, its acidic hydrogen atom reacts with the amide ion to convert the alkyne to its conjugate base. Without the "extra" equivalent of amide ion, the reaction would not go to completion. The water in the workup step acts as an acid to protonate the alkynide and to convert any excess amide ion to ammonia.



The double dehydrohalogenation occurs in two distinct steps. The second is slower than the first. The reaction can be stopped after the first step by using a weak base such as hydroxide if the vinyl halide is the object of the synthesis.



3,4-dichloroexane

Alkylation of Alkynes

Now we will see how to combine smaller structural units, one of which already has a carbon–carbon triple bond, to build an alkyne having a more complex structure.

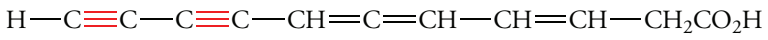
The attachment of an alkyl group to a selected molecular structure is called **alkylation.** We will encounter this method of forming carbon–carbon bonds repeatedly in later chapters dealing with other functional groups. Alkylation is one of the fundamental reactions used to construct complex structures.

The alkylation reaction considered here replaces the hydrogen atom of a terminal alkyne by an alkyl group derived from an alkyl halide. In the first step, the alkynide ion forms. Sodium amide in ammonia is a strong base that quantitatively abstracts protons from C—H bonds of sp-hybridized carbon atoms.

EXERCISES

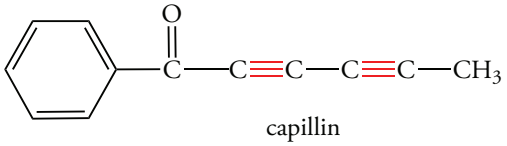
Structures of Alkynes

7.1 What is the molecular formula of each of the following compounds that contain carbon–carbon triple bonds?
(a) mycomycin, an antibiotic



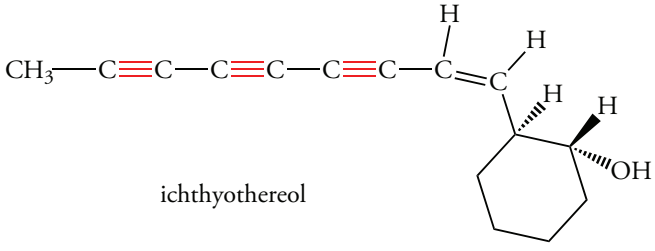
mycomycin

(b) capillin, a skin fungicide



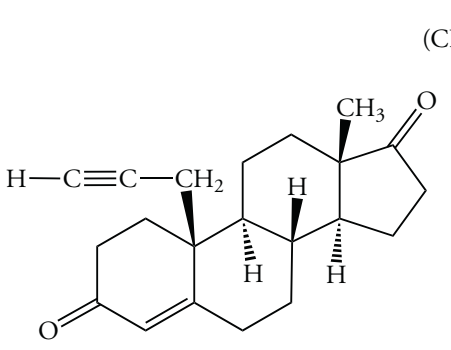
capillin

(c)) ichthyothereol, a convulsant

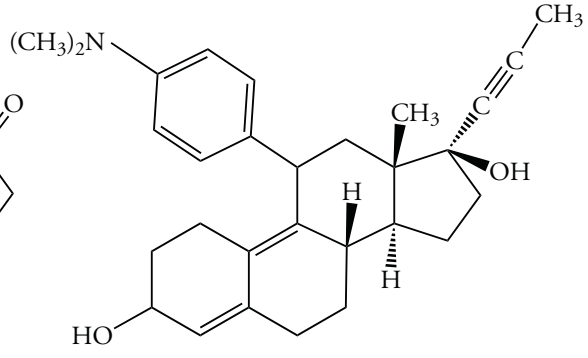


ichthyothereol

7.2 Classify the triple bond in each of the following drugs. MDL 18962 is a drug used in breast cancer therapy. RU 486 is a drug used to induce abortion and may be useful in cancer therapy.



MDL 18962



RU 486

7.3 Write the molecular formula for the compounds with each of the following structural features.
(a) six carbon atoms and one double bond (b) five carbon atoms and two double bonds
(c) seven carbon atoms, a ring, and one double bond (d) four carbon atoms and one triple bond

7.4 What is the molecular formula for the compounds with each of the following structural features?
(a) four carbon atoms and two triple bonds (b) four carbon atoms, a double bond, and a triple bond
(c) ten carbon atoms and two rings (d) ten carbon atoms, two rings, and five double bonds

Properties of Alkynes

7.5 The heats of formation of 1-pentyne and 2-pentyne are 144 and 128.6 kJ mole^{-1}, respectively. Which compound is more stable? Based on this information, which compound has the larger heat of combustion?

7.6 The heats of formation of 1-pentyne and 1,4-pentadiene are 144 and 106 kJ mole^{-1}, respectively. What does this information indicate about the relative stability of a triple bond compared to two double bonds?

7.7 The heats of formation of 1-propyne and 1,2-propadiene (allene) are 185 and 190 kJ mole^{-1}, respectively. Assuming that an equilibrium can be established, which compound would be present in the larger amount?

7.8 Predict the direction of the dipole moment of 1-propyne. Why is its dipole moment larger than that of 1-propene?

7.9 The boiling points of 1-alkynes are higher than those of the 1-alkenes with the same number of carbon atoms. Suggest reasons for this fact.

7.10 The boiling points of 3,3-dimethyl-l-butyne and 1-hexyne are 39.5 °C and 71.3 °C, respectively. Explain why the values are so different for these two isomers.

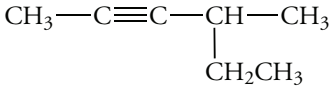
7.11 The boiling points of terminal alkynes are lower than the boiling points of isomeric internal alkynes. Is this fact consistent with the dipole moments of the compounds? If not, what other structural factors might contribute to the difference in the boiling points?

Nomenclature

7.12 Name each of the following compounds.

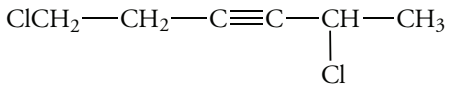
(a) $CH_3CH_2CH_2C{\equiv}CH$

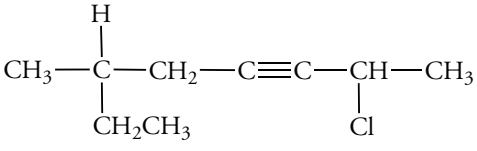
(b) $(CH_3)_3CC{\equiv}CCH_2CH_3$

(c) 

7.13 Name each of the following compounds.

(a) $CH_3CHBrCHBr{-}C{\equiv}C{-}CH_2(CH_2)_2CH_3$

(b) 

(c) 

7.14 Write the structural formula for each of the following compounds.
(a) 2-hexyne (b) 3-methyl-l-pentyne (c) 5-ethyl-3-octyne

7.15 Write the structural formula for each of the following compounds.
(a) 3-heptyne (b) 4-methyl-l-pentyne (c) 5-methyl-3-heptyne

7.16 Write the structural formula for 4-ethynyl-l,5-nonadien-7-yne.

7.17 Write the structural formula for 1-ethyl-3-(2-propynyl)cyclopentene.

7.18 What is the IUPAC name for the group $-C{\equiv}C-CH_3$?

7.19 Which of the drugs listed in Exercise 7.2 contains a propargyl group?

Acidity of Terminal Alkynes

7.20 Diisopropylamide ion $[(CH_3)_2CH]_2N^-$ is a strong base commonly used in organic reactions. Is it expected to be a stronger or weaker base than the amide ion?

7.21 Suggest an experimental procedure to prepare 1-deuterio-l-propyne from propene.

Hydrogenation Reactions

7.22 How many moles of hydrogen gas will react with each of the following compounds?

(a) CH_3=CH=CH—C≡CH (b) HC≡C—C≡C—H

(c) CH_2=CH—C≡C—CH=CH_2 (d) HC≡C—C≡C—C≡CH

7.23 How many moles of hydrogen gas will react with each of the compounds listed in Exercise 7.1?

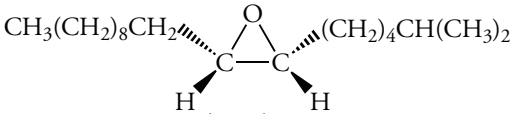
7.24 Which compound should have the larger heat of hydrogenation for the addition of two moles of hydrogen gas, 1-pentyne or 1,4-pentadiene? Why?

7.25 Stearolic acid is converted to oleic acid by hydrogenation using the Lindlar catalyst. Elaidic acid is the product obtained by sodium/ammonia reduction of stearolic acid. Write the structures of oleic and elaidic acids.

$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H$

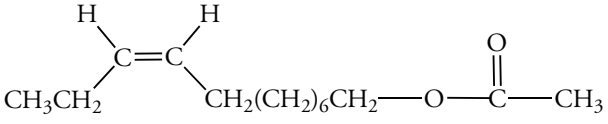
stearolic acid

7.26 Disparlure, the pheromone of the gypsy moth, can be prepared by reduction of an alkyne followed by epoxidation of the alkene. What alkyne is required? What is the configuration of the alkene? What reagents are required for reduction of the alkyne?



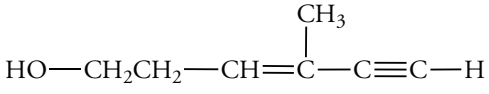
disparlure

7.27 The pheromone of the grape berry moth is indicated below. How could this compound be prepared from a related alkyne. Would the ester functional group be affected by the reaction conditions?

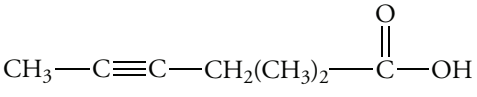


7.28 (*E*)-11-Tetradecen-l-ol is one of the intermediate compounds required to synthesize the sex pheromone of the spruce budworm. How could this compound be prepared from an appropriate alkyne? Would the reaction conditions affect the hydroxyl group?

7.29 Draw the structure of the product of the reaction of the following compound with hydrogen using the Lindlar catalyst.



7.30 Draw the structure of the product of the reaction of the following compound with hydrogen using the Lindlar catalyst.



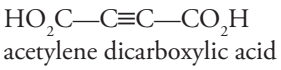
Electrophilic Addition Reactions

7.31 Addition of one mole of HCl to 2-hexyne gives a mixture of two products in approximately equal amounts. Draw their structures.

7.32 Draw the structure of the addition of one mole of DBr to 1-propyne.

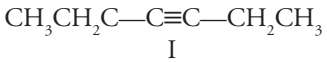
7.33 Predict the product of the addition of one mole of Br_2 to 1-penten-4-yne.

7.34 Draw the structure of the compound resulting from the addition of one molar equivalent of bromine to acetylene dicarboxylic acid. What is the dipole moment of the product?

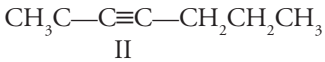


acetylene dicarboxylic acid

7.35 Hydration of one of the following two compounds yields a single ketone product. The other compound yields a mixture of ketones. Which one yields only the single ketone product? Explain why only one product forms.

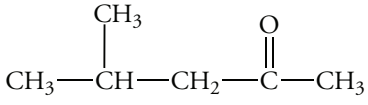


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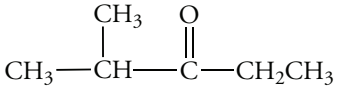


II

7.36 Hydration of 4-methyl-2-pentyne gives the following compounds in the indicated amounts. Suggest a reason for the observed product ratio.



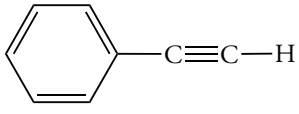
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II

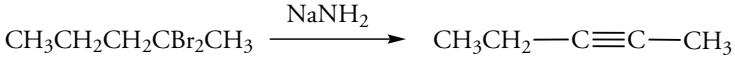
Synthesis of Alkynes

7.37 Write the structure of all compounds that could yield the following alkyne upon dehydrohalogenation.



7.38 Which isomer, 2,2-dibromopentane or 3,3-dibromopentane, would give the better yield of 2-pentyne using sodium amide as the base?

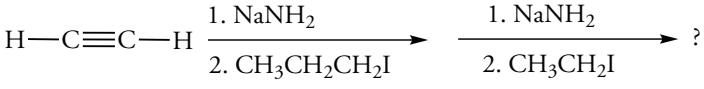
7.39 Would the following reaction provide a good yield of the indicated product? Explain.



7.40 Write the product of the reaction of 1,6-dibromohexane with excess sodium acetylide.

7.41 Predict the product of the reaction of one equivalent of the alkynide of 1-propyne and 1-bromo-5-fluoropentane.

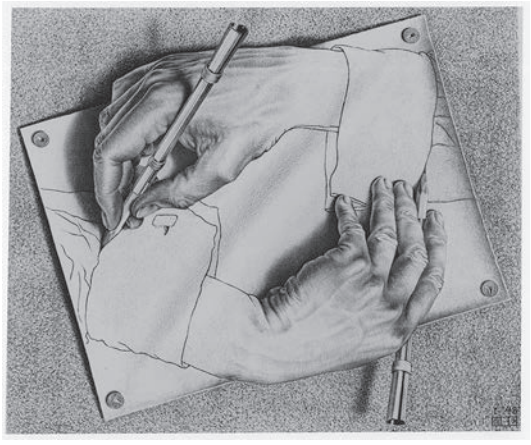
7.42 Draw the structure of the final product of the following series of reactions.



7.43 Outline the steps of a synthesis of 2,2-dimethyl-3-octyne using reactants having no more than six carbon atoms.

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8 STEREOCHEMISTRY



M. C. Escher, Drawing Hands, 1948

8.1 STEREOISOMERS

Molecules that have different arrangements in three-dimensional space are **stereoisomers**. Stereoisomers have different **configurations**. In Chapter 4, we considered the structures of geometric isomers —*E*,*Z* isomers—an important class of stereoisomers that have different configurations. Another type of stereoisomerism, which is based on *mirror image relationships* between molecules, is the subject of this chapter. The mirror image relationships of stereoisomers are not as easily visualized as the relation between geometric isomers, and a bit of practice is likely to be needed before we can "see" their relationship in three-dimensional space. This is a case where molecular models are very handy.

Changes in molecular configuration that occur in a reaction provide a valuable tool for probing many reaction mechanisms. Stereochemistry can also play an important role in organic synthesis since it is not an easy task to synthesize only a "right-handed" or "left-handed" molecule when both could potentially be formed in a chemical reaction. The chemical synthesis of molecules with precisely the right three-dimensional structure is often a huge experimental challenge; in practical terms, "chiral synthesis" is an essential component of virtually all drug synthesis.

A molecule's configuration also plays a major role in its biological function. We will see many examples of stereoisomerism in biological systems in this chapter and beyond.

8.2 MIRROR IMAGE OBJECTS, MIRROR IMAGE MOLECULES, AND CHIRALITY

We are all familiar with mirror image objects. Every object has a mirror image, but this reflected image need not be identical to the actual object. Thus, when we look into a mirror, we see someone who does not actually exist, namely, our mirror image.

A simple wooden chair looks exactly like its mirror image (Figure 8.1a). Similarly, the mirror images of a teacup or a hammer are identical to the objects themselves. When an object and its mirror image are identical, they are *superimposable*. Superimposable objects can be "placed" on each other so that each feature of one object precisely coincides in space with an equivalent feature in the mirror image object.

Some objects cannot be superimposed upon their mirror images: They are *nonsuperimposable*. One example is the sidearm chair shown in Figure 8.1b. When a chair with a "right-handed arm" is reflected in a mirror, it becomes a chair with a "left-handed arm" (Figure 8.1b). We can convince ourselves of this by imagining sitting in the chair or its mirror image. Or, we could stop by a classroom, which usually has chairs for both right- and left-handed persons, and do the experiment.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00008-5
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Figure 8.1 Objects and Their Mirror Images
In (a), the chair and its mirror image are identical. They can be superimposed. In (b), the mirror image, side-arm chairs cannot be superimposed. One chair has a "right-handed" arm, and the other has a "left-handed" arm. (These particular chairs were designed by the renowned woodworker George Nakashima.)

Our hands are related as nonsuperimposable mirror images. We know that we cannot superimpose our hands, as is deftly shown by the M. C. Escher lithograph found at the beginning of this chapter and in Figure 8.2. An object that is not superimposable on its mirror image is **chiral** (Greek *chiron*, hand). Objects such as gloves and shoes also have a "handedness," and they are also chiral. An object that can be superimposed on its mirror image is **achiral**.

We can determine whether or not an object is chiral without trying to superimpose it on its mirror image. If an object has a *plane of symmetry*, it is not chiral. A plane of symmetry bisects an object so that one half is the mirror image of the other half. For example, a cup has a plane of symmetry that divides it so that one half is the mirror image of the other half. The chair in part (a) of Figure 8.3 is achiral because it has a plane of symmetry. *The presence or absence of a plane of symmetry tells us whether an object is chiral or achiral.*

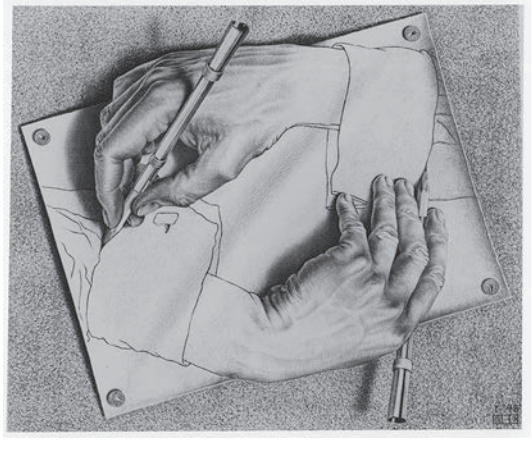


Figure 8.2 Nonsuperimosable Mirror Images
A left and a right hand are nonsuperimposable mirror images. (M.C. Escher's "Drawing Hands" © 2014 The M.C. Escher Company-The Netherlands. All rights reserved. www.mcescher.com)

Chiral Molecules

We can extend the concept of chirality from macroscopic objects to molecules. *A molecule is chiral if it contains at least one carbon atom attached to four different atoms or groups.* Such a carbon atom is a **stereogenic** center. A stereogenic center is sometimes called a **chiral center**, and the carbon atom is sometimes called a **chiral carbon** atom, although it is the molecule that is chiral, not a single carbon atom within it. Most molecules produced in living organisms are chiral, nearly all drugs are chiral, and the synthesis of chiral molecules in the laboratory is a significant part of organic synthesis.

The four atoms or groups at a stereogenic center can be arranged in two ways to give two stereoisomers. The stereoisomers of bromochlorofluoromethane provide an example. Bromochlorofluoromethane does not have a plane of symmetry. Figure 8.3 shows that it can exist as a pair of nonsuperimposable mirror image isomers. Therefore, bromochlorofluoromethane is chiral.

Figure 8.3 Nonsuperimosable Mirror Image Molecules

Bromochlorofluoromethane does not have a plane of symmetry. Therefore, it is chiral, and it exists as a pair of nonsuperimposable mirror image isomers. (a) Schematic diagram; (b) Ball-and-stick molecular models.

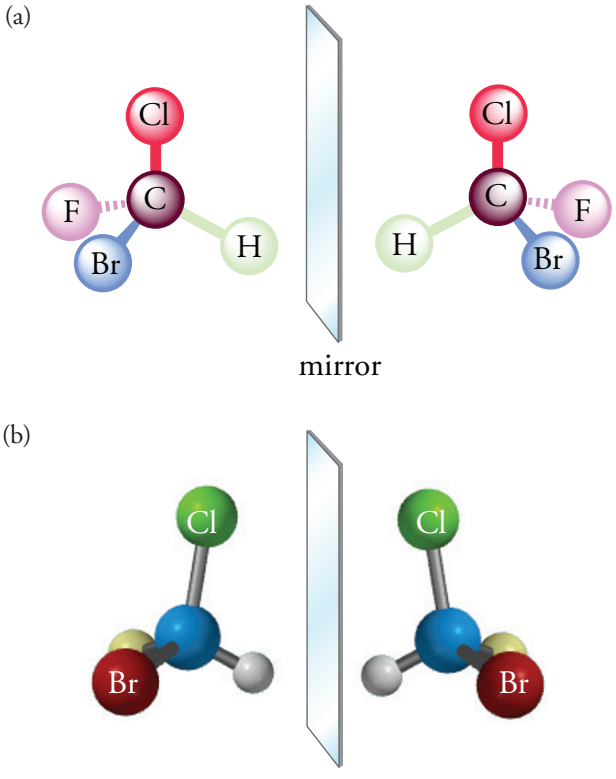


Figure 8.4 Planes of Symmetry in Dichloromethane

Dichloromethane, which has not one, but two planes of symmetry, can be superimposed on its mirror image. It is achiral.

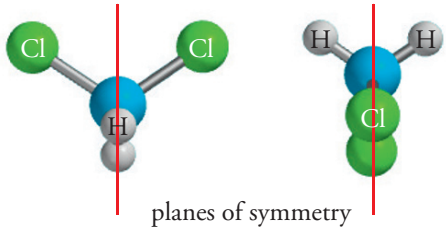
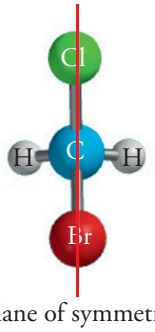


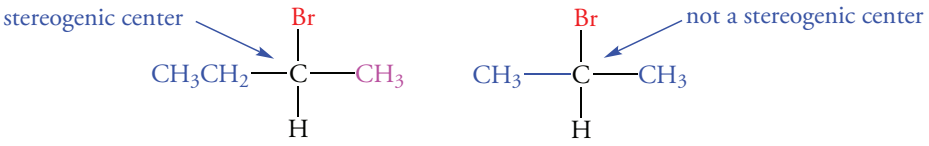
Figure 8.5 Plane of Symmetry in Bromochloromethane

Bromochloromethane has a plane of symmetry, and therefore, it can be superimposed on its mirror image. It is achiral.

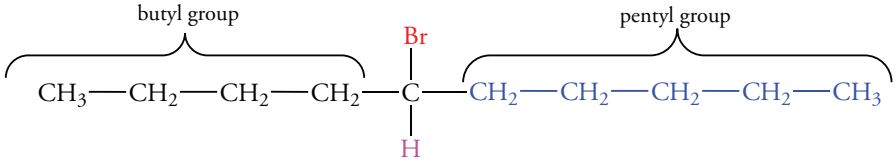


Mirror Image Isomers

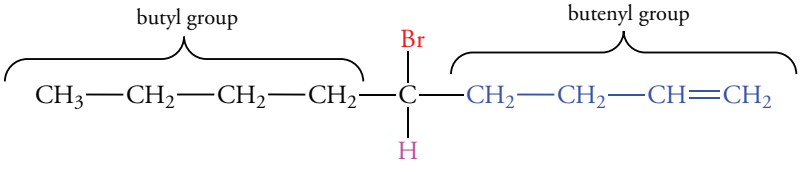
Two stereoisomers related as nonsuperimposable mirror images are called **enantiomers** (Greek *enantios*, opposite + *meros*, part). We can tell that a substance is chiral and predict that two enantiomers exist by identifying the substituents on each carbon atom. A carbon atom with four different substituents is a stereogenic center, and a molecule with a stereogenic center is chiral. It can exist as either of a pair of enantiomers. For example, 2-bromobutane is chiral because C-2 is attached to four different groups (CH_3—, CH_3CH_2—, Br—, and H—). In contrast, no carbon in 2-bromopropane is bonded to four different groups; C-2 is bonded to two methyl groups. Thus, 2-bromopropane is not chiral (Figures 8.4 and 8.5).



The existence of a stereogenic center in a complex molecule may not be immediately apparent. This situation occurs when the groups bonded to a chiral carbon atom differ at sites not immediately adjacent to the stereogenic center. The difference between a methyl group and an ethyl group is readily apparent in 2-bromobutane. However, in some molecules, the difference is less obvious. For example, 5-bromodecane and 5-bromo-1-nonene both have a stereogenic center.



5-bromodecane

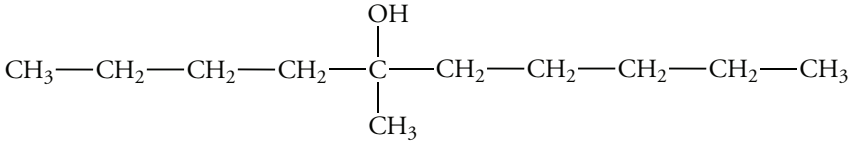


5-bromo-1-nonene

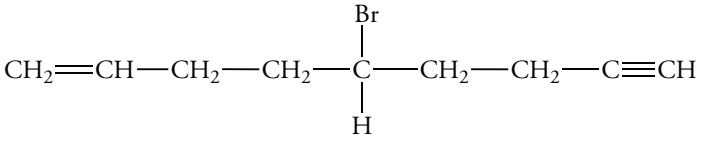
Problem 8.1

Which of the following molecules are chiral? Explain your answer.

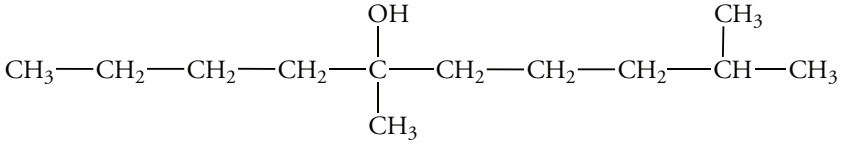
(a)



(b)

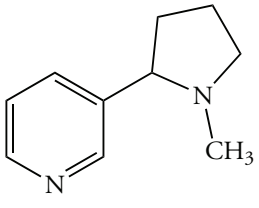


(c)



Problem 8.2

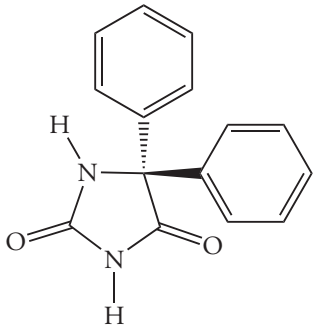
The structure of nicotine is shown below. Is nicotine chiral?



nicotine

Problem 8.3

Phenytoin has anticonvulsant activity. Is phenytoin chiral or achiral? Determine your answer by identifying the number of different groups bonded to its tetrahedral carbon atoms; then determine whether or not it has a plane of symmetry.



phenytoin

Sample Solution

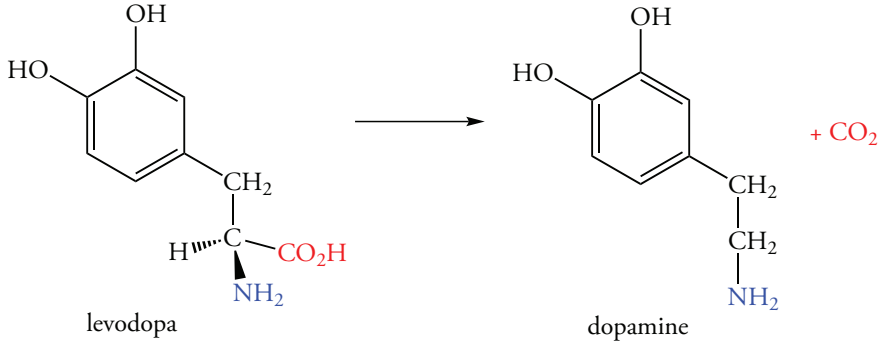
Phenytoin does not contain a carbon bonded to four different groups. It has a plane of symmetry that lies in the plane of the page. One of the benzene rings of phenytoin is above and the other below the symmetry plane. It is achiral.

Properties of Enantiomers

We can regard hands as analogous to the enantiomers of a chiral molecule. Let's consider the interaction of hands with a symmetrical object such as a pair of tweezers. The tweezers are symmetrical. They can be used equally well with either hand because there is no preferred way to pick up or manipulate a pair of tweezers. However, even if blindfolded, we could easily use our hands to distinguish right- and left-handed gloves. Our hands are "a chiral environment," and in this environment, mirror image gloves do not interact with hands in the same way. The right glove will fit only the right hand. *We can distinguish chiral objects only because we are chiral.*

Pairs of enantiomers have the same physical and chemical properties: they have that same heats of formation, density, melting point, and boiling point. They also have the same chemical properties, and undergo the same reactions in an achiral environment. However, enantiomers can be distinguished in a chiral environment. This difference is important in many processes in living cells. Only one of a pair of enantiomers fits into a specific site in a biological molecule such as an enzyme catalyst because the site on the enzyme that binds the enantiomer is chiral. The binding of this enantiomer is **stereospecific**.

An example of a stereospecific process is the conversion of the drug levodopa to dopamine, a neurotransmitter in the brain. Levodopa (or L-dopa), the precursor of dopamine, is administered to treat Parkinson's disease. Levodopa has one chiral carbon atom. Therefore, it exists as either of two enantiomers. Only the enantiomer with the configuration shown below is transformed into dopamine.



levodopa dopamine

The reaction occurs because a stereospecific decarboxylase catalyzes the loss of a carboxyl group by formation of carbon dioxide (decarboxylation). This enzyme has a chiral binding site for levodopa, but it does not bind the enantiomer of levodopa.

8.3 OPTICAL ACTIVITY

Although enantiomers have identical chemical properties in achiral environments, they differ in one important physical property: Enantiomers behave differently toward plane-polarized light. This difference allows us to distinguish a chiral molecule from its enantiomer in the laboratory.

Plane-Polarized Light

A beam of light consists of electromagnetic waves oscillating in an infinite number of planes at right angles to the direction of propagation of the light. When a light beam passes through a polarizing filter, it is converted to *plane-polarized light* whose electromagnetic waves oscillate in a single plane. We are familiar with this phenomenon in everyday life: Plane-polarized light can be produced by certain sunglasses, which reduce glare by acting as a polarizing filter. They partly block horizontally oscillating light reflecting off the surfaces of various objects. Some camera lenses also have polarizing filters to reduce glare in brightly lit photographs.

Plane-polarized light interacts with chiral molecules. This interaction can be measured by an instrument called a **polarimeter** (Figure 8.6). In a polarimeter, light with a single wavelength—that is, *monochromatic light*—passes through a polarizing filter. The polarized light then traverses a tube containing a solution of the compound to be examined. Plane-polarized light is not affected by achiral molecules. However, the plane of polarized light rotates when it is absorbed by chiral molecules. When the plane-polarized light leaves the sample tube, it passes through a second polarizing filter called an analyzer. The analyzer is rotated in either clockwise or counterclockwise direction to match the rotated polarization plane so that it passes through the filter with maximum intensity. An angle, α, is read off the analyzer. This angle is called the *observed optical rotation*, α_{obs}. It equals the angle by which the light has been rotated by the chiral compound. Because chiral molecules rotate plane-polarized light, they are **optically active**. Achiral molecules do not rotate plane-polarized light, so they are **optically inactive**.

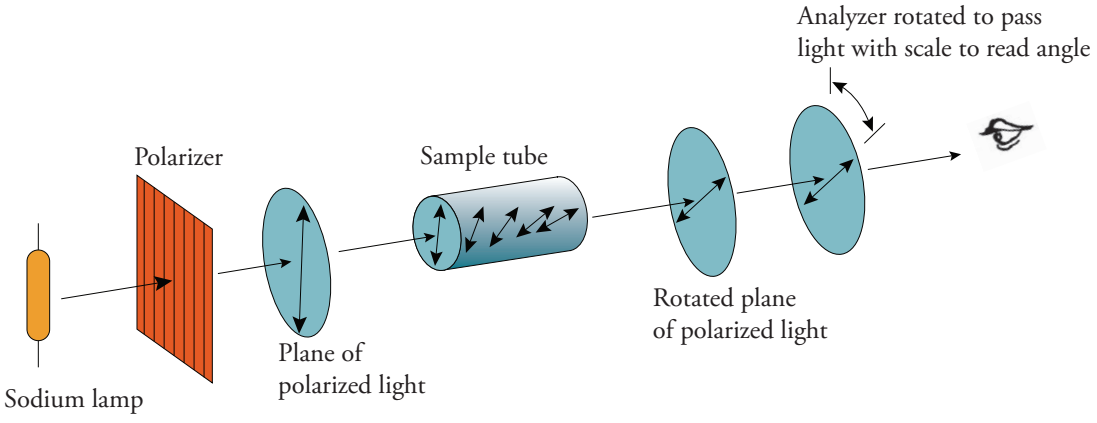


Figure 8.6 Schematic Diagram of a Polarimeter
Plane-polarized light is obtained by passing light through a polarizing filter. Any chiral compound in the sample tube rotates the plane-polarized light. The direction and magnitude of the rotation are determined by rotating the analyzer to allow the light to pass through with maximum brightness. In a modern instrument, this is all done electronically, but the basic principle is the same.

Specific Rotation

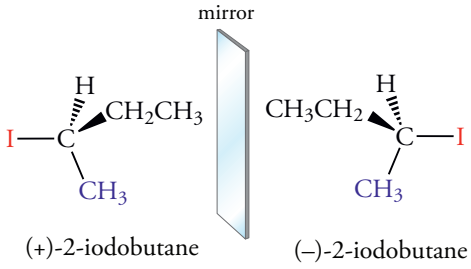
The amount of rotation observed in a polarimeter depends on the structure of the substance and on its concentration. The optical activity of a pure chiral substance is reported as its *specific rotation*, symbolized by $[\alpha]_D$. It is the number of degrees of rotation of a solution at a concentration measured in g mL^{-1} in a tube 1 dm (10 cm) long. The standard conditions selected for polarimetry measurements are 25 °C, and a wavelength of 589 nm. This yellow light is the D line of a sodium vapor lamp.

$$[\alpha]_D = \frac{\alpha_{obs}}{l \times c}$$

If a chiral substance rotates plane-polarized light to the right—that is, in a positive (+) or clockwise direction—the substance is *dextrorotatory* (Latin *dextra*, right). If a chiral substance rotates plane-polarized light to the left—in a negative (–) or counterclockwise direction—the substance is *levorotatory* (Latin

laevus, left). The enantiomers of a chiral substance—called dextrorotatory and levorotatory isomers—rotate polarized light the same number of degrees, but in opposite directions. Therefore, they are sometimes called **optical isomers**.

We often refer to an enantiomer by prefixing the sign of the optical rotation at 589 nm to the name of the compound. For example, one of the enantiomers of 2-iodobutane has $[\alpha]_D = -15.15$. It is called (–)-2-iodobutane. The other enantiomer is (+)-2-iodobutane, $[\alpha]_D = +15.15$.



(+)-2-iodobutane (–)-2-iodobutane

The (+) isomer is sometimes called the *d* form because it is dextrorotatory; the (–) isomer is sometimes called the *l* form because it is levorotatory. Earlier, we encountered levodopa, so named because it is levorotatory. It is also called L-dopa and (–)-dopa. The specific rotation of L-dopa is –13.1°. Table 8.1 lists the specific rotations of some common substances.

Table 8.1
Specific Rotations of Common Compounds

Compound	$[\alpha]_D$
Azidothymidine (AZT)	+99°
Cefotaxin (a cephalosporin)	+55°
Cholesterol	–31.5°
Cocaine	–16°
Codeine	–136°
Epinephrine (adrenaline)	–5.0°
Levodopa	–13.1°
Monosodium glutamate (MSG)	+25.5°
Morphine	–132°
Oxacillin (a penicillin)	+201°
Progesterone	+172°
Sucrose	+66°
Testosterone	+109°

Circularly Polarized Light and Optical Rotation

We have said that chiral molecules cannot be distinguished in a symmetric environment. In the next sentence, we said that chiral molecules interact differently with plane-polarized light. However, by definition, plane-polarized light has a plane of symmetry! Is there not a massive contradiction here? The answer is no because we can interpret plane-polarized light in terms of *circularly polarized light* (Figure 8.7). One form of circularly polarized light has a right-handed helical sense, and the other form has a left-handed helical sense. A helix is a chiral object, and right- and left-handed helices are related as mirror images. If we superimpose the two, we obtain plane-polarized light. So this helicity is "hiding" in plane-polarized light, which has inherent chiral components.

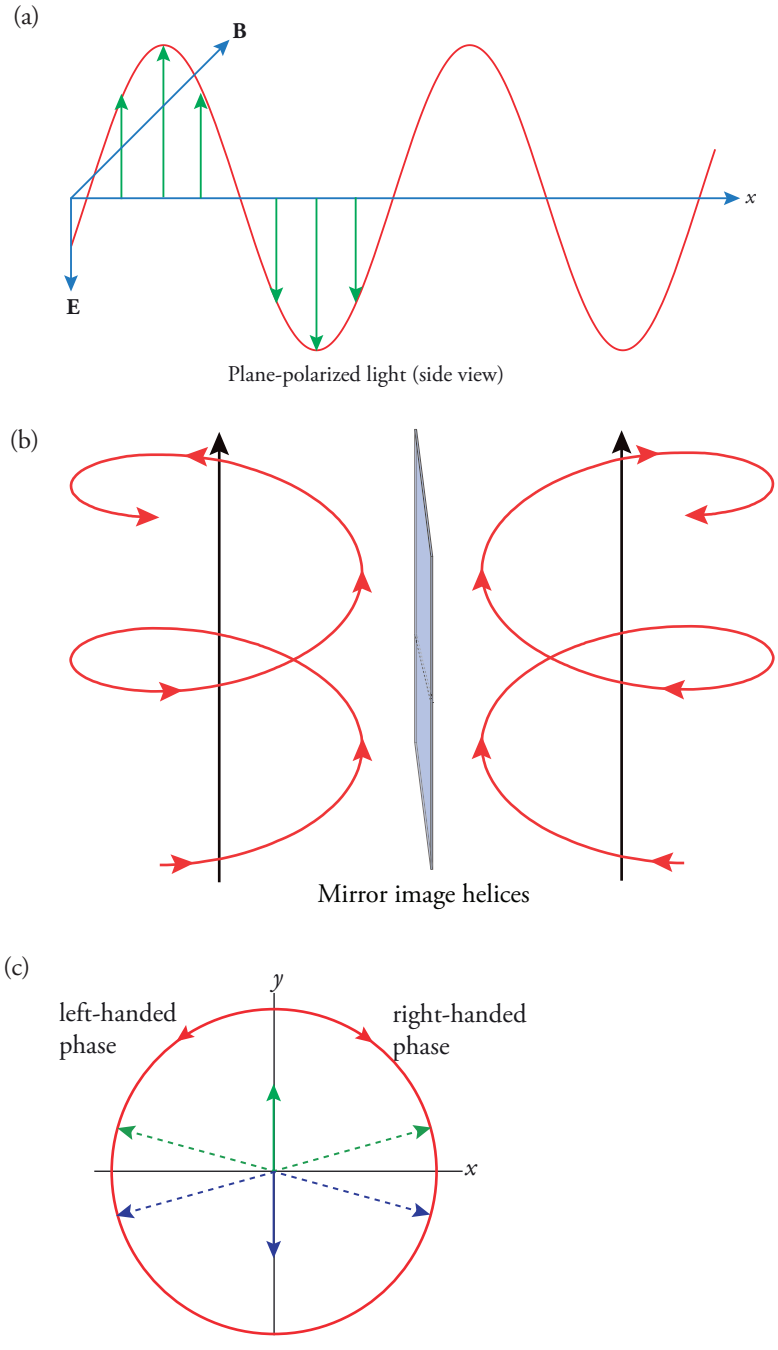


Figure 8.7
Schematic Diagrams of Plane- and Circularly Polarized Light
(a) In plane-polarized light, the electric field vectors of the light all oscillate in a single plane. (b) In circularly polarized light, the electric field vector can rotate in a right-handed (clockwise) or left-handed (counterclockwise) direction. (c) If right-handed and left-handed phases of circularly polarized light are superimposed, the electric field vectors in the $+x$ to $-x$ directions cancel, and the y-components are additive, and directed along the y-axis. The net result is plane-polarized light.

A chiral center is bonded to four different groups, and each of these bonds has an electric field. Therefore, the net electric field around a chiral center is chiral, and it absorbs one phase of circularly polarized light more than the other. As a result, the vectors no longer cancel, and the light is rotated in either a clockwise or counterclockwise direction.

Optical Purity

Most naturally occurring molecules that contain one stereogenic center exist as one enantiomer. Samples that contain only one enantiomeric form are **optically pure**. Naturally occurring cholesterol, for example, exists only as the (–) form. It rotates light in a counterclockwise direction. However, compounds synthesized in the laboratory may not all have the same handedness, and the reaction yields a mixture of two enantiomers.

What is the optical rotation of a mixture of enantiomers, and how is it related to the percentage of each enantiomer in the mixture? When plane-polarized light interacts with a single enantiomer of a chiral molecule, the plane is rotated in one direction. If the plane-polarized light interacts with the other enantiomer, the plane is rotated in an equal and opposite direction. If a solution contains equal amounts of two enantiomers, the clockwise and counterclockwise rotations resulting from all molecules

cancel, and there is no net rotation. Mixtures containing equal amounts of enantiomers are called **racemic mixtures**. A racemic mixture is represented in the name of a compound with a (±) prefix, as in (±)-2-iodobutane. The word "racemic" is derived from the Latin word *racemus*, a cluster of grapes. It is so named because racemic mixtures were first found in tartaric acid, which precipitates from many wines as they age. See Figure 8.13.

Now consider a circumstance in which the percent ratio of a mixture of enantiomers is not 50:50. The percent **enantiomeric excess** of the enantiomer present in the larger amount is calculated as follows.

$$\%\ \text{enantiomeric excess} = \%\ \text{of one enantiomer} - \%\ \text{of other enantiomer} = \text{optical purity}$$

The percent enantiomeric excess is the **optical purity** of the sample. For example, a 60:40 ratio of (+)-2-iodobutane and (–)-2-iodobutane is 20% optically pure. This value indicates that the rotation of the (–) isomer (40% of the total) cancels the rotation of some of the (+) isomer (40% of the total). The remaining 20% of the sample, which is (+)-2-iodobutane, is responsible for the observed rotation, so the sample is 20% optically pure.

$$\text{optical purity} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100\%$$

Problem 8.4

What is $[\alpha]_D$ of the enantiomer of naturally occurring testosterone? (See Table 8.1.) What is the name of this enantiomer?

Problem 8.5

A sample of a solution of 1.5 g of cholic acid, a bile steroid, in 10 mL of alcohol is placed in a 10.0-cm sample tube. The observed rotation is +5.5. Calculate $[\alpha]_D$ for cholic acid.

Problem 8.6

A sample of epinephrine prepared in the laboratory has $\alpha_{obs} = -0.5°$. What is the optical purity of the sample? What is the percentage of each enantiomer in the sample? $[\alpha]_D$ for epinephrine is –5.0°.

Sample Solution

The specific rotation of epinephrine is –5.0°. We calculate the optical purity using the following equation.

$$\text{optical purity} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100\%$$

$$\text{optical purity} = \frac{-0.5}{-5.0} \times 100\% = 10\%$$

The enantiomeric excess is equal to the optical purity. The sum of the two enantiomers is 100%. Let the percent of the enantiomer with the negative optical rotation be x. The percent of the other enantiomer is $100 - x$. Use the following equation and substitute the algebraic quantities.

$\%$ enantiomeric excess = $\%$ of one enantiomer – $\%$ of other enantiomer = optical purity

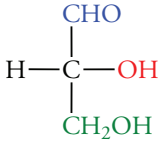
$$10\% = x - (100\% - x)$$

$$x = 55\%$$

Thus, the percentages of the two enantiomers are 55% and 45%.

8.4 FISCHER PROJECTION FORMULAS

Drawing molecules in three dimensions is time consuming. Furthermore, it is not easy to "read" the resulting perspective structural formulas, especially for compounds that contain several chiral centers (Section 8.6). However, the structural formula of a chiral substance can be conveniently drawn as a **Fischer projection**, which was introduced by the German chemist Emil Fischer more than a century ago. The configuration of a chiral substance in a Fischer projection formula is obtained by comparing it to the configuration of a *reference compound* whose common name is glyceraldehyde.



glyceraldehyde

Glyceraldehyde contains a carbon atom bonded to four different groups, so it can exist as either of two enantiomers (Figure 8.8). The enantiomers of glyceraldehyde in a Fischer projection are drawn according to the following conventions:

1. Arrange the carbon chain vertically with the most oxidized group (—CHO in glyceraldehyde) at the "top."
2. Place the carbon atom at the chiral center in the plane of the paper. It is C-2 in glyceraldehyde.
3. Because C-2 is bonded to four groups, the CHO group and the CH_2OH group extend behind the plane of the page, and the hydrogen atom and the hydroxyl group extend up and out of the plane.
4. Project these four groups onto a plane. The carbon atom at the chiral center is usually not shown in this convention. It is located at the point where the bond lines cross. The vertical lines project away from the viewer. The horizontal lines project toward the viewer.

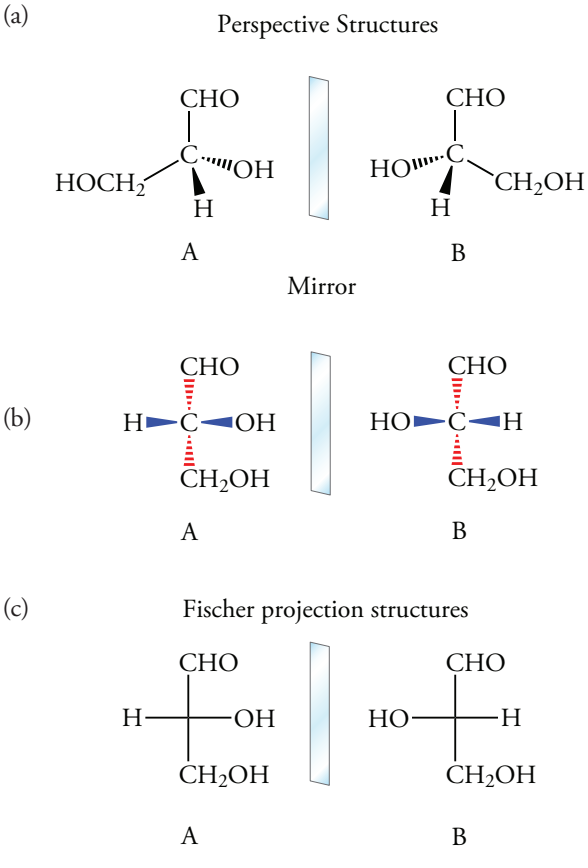
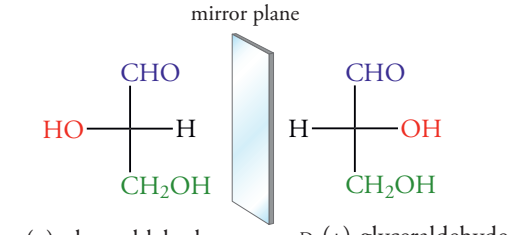


Figure 8.8 Fischer Projection Structures of Glyceraldehyde
(a) Perspective structures of glyceraldehyde. (b) Projection structures. (c) Fisher projection structures of the enantiomers glyceraldehyde. The chiral center is located at the point where the bond lines intersect. The carbon atom is not usually shown. The vertical lines extend away from the viewer, behind the plane of the page; horizontal lines extend toward the viewer, out of the plane of the page, as shown in part (b).

A Fischer projection formula is a two-dimensional representation. It might appear that if we lifted one formula out of the plane and rotated it 180° around the carbon backbone, we would obtain the structure of the enantiomer. However, if this were done for molecule A in Figure 8.8, the carbonyl group and the hydroxymethyl group, originally behind the plane, would be in front of the plane. These groups would not occupy identical positions with respect to the carbonyl group and hydroxymethyl group of molecule B, which are behind the plane. Therefore, to avoid the error of apparently achieving a two-dimensional equivalence of nonequivalent three-dimensional molecules, we *cannot* lift the two-dimensional representations out of the plane of the paper.

Fischer projection formulas can be drawn for any pair of enantiomers. These formulas imply that we know the configuration at the chiral carbon atom. However, the true configuration could not be determined by early chemists because there was no way to determine the arrangement of the atoms in space. Therefore, Fischer arbitrarily assigned a configuration to one member of the enantiomeric pair of

glyceraldehydes. The dextrorotatory enantiomer of glyceraldehyde, which rotates plane-polarized light in a clockwise direction (+13.5°), was assigned to the Fischer projection with the hydroxyl group on the right side. Fischer called the compound D-glyceraldehyde. The mirror image compound, (–)-glyceraldehyde, corresponds to the structure in which the hydroxyl group is on the left. It rotates plane-polarized light in a counterclockwise direction (–13.5°). Fischer called the compound L-glyceraldehyde.



L-(–)-glyceraldehyde
$[\alpha]_D = -13.5°$

D-(+)-glyceraldehyde
$[\alpha]_D = +13.5°$

Fischer projection structures

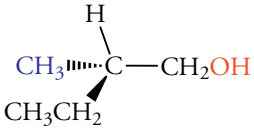
Problem 8.7

Write the Fischer projection formula of each of the following compounds.

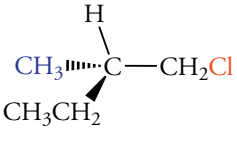
(a) D-lactic acid, $CH_3CH(OH)CO_2H$
(b) L-serine, $HOCH_2CH(NH_2)CO_2H$
(c) D-valine, $(CH_3)_2CHCH(NH_2)CO_2$

8.5 ABSOLUTE CONFIGURATION

We began this chapter by saying that the arrangement of atoms in space determines the configuration of a molecule. When we know the exact positions of these atoms in space, we know the molecule's **absolute configuration**. The absolute configuration of an enantiomer cannot be established by measuring the direction or magnitude of its optical rotation. Optical rotation depends on both the configuration and the identity of the four groups around the central carbon atom. One "left-handed" molecule could be levorotatory, whereas another "left-handed" molecule with different groups could be dextrorotatory. For example, in spite of the similarity of three of the groups (CH_3CH_2, CH_3, and H), the following structures of 2-methyl-1-butanol and l-chloro-2-methylbutane, which have the same configuration, have different directions of optical rotation.



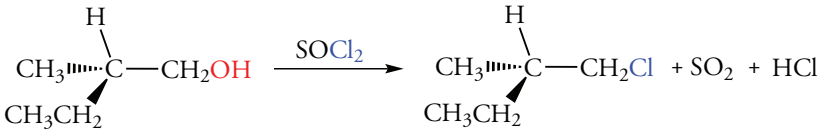
(–)-2-methyl-1-butanol
$[\alpha]_D = -5.8$



(+)-1-chloro-2-methylbutane
$[\alpha]_D = +1.7$

To determine the absolute configuration, we require a method that can specify the positions of all atoms in the molecule. One way to do this is by X-ray crystallography. The absolute configuration of an optically active substance was first determined in 1950. The arrangement of its atoms in space corresponds to the arrangement of atoms in (+)-glyceraldehyde arbitrarily assigned by Fischer. His original choice was correct! As a result, all configurations that had been deduced by using (+)-glyceraldehyde as the reference compound are also correct, and this includes all the amino acids isolated from proteins, all carbohydrates, and many other compounds.

The absolute configuration of a compound can be determined by comparing it to a reference compound of known absolute configuration. This structure proof sometimes requires an elaborate series of reactions. However, the principle is easily illustrated with the conversion of 2-methyl-l-butanol to l-chloro-2-methylbutane. Alcohols can be converted into chloroalkanes by thionyl chloride ($SOCl_2$). The reaction does not affect any of the bonds at the stereogenic center of 2-methyl-l-butanol. Hence, the configuration is unchanged. If the absolute configuration of the alcohol is known, the groups bonded to the stereogenic center in the chloroalkane must be arranged in the same configuration. If the absolute configuration of the alcohol were not known, we would still know that the haloalkane would have the same relative configuration.



R,S Configurations: The Kahn–Ingold–Prelog System of Configurational Nomenclature

The configurations of some molecules, such as amino acids and carbohydrates, can easily be compared to reference compounds such as D-glyceraldehyde. But this procedure is not easily applied to molecules whose structures differ considerably from the reference compound. To circumvent this difficulty, R. S. Kahn, K. C. Ingold, and V. Prelog established a set of rules in 1964 that describe the absolute configuration of any chiral molecule.

The ***R,S* system** of configurational nomenclature for describing absolute configurations is related to the method we described in Chapter 6 to assign the *E,Z* configuration of alkenes. In the *R,S* system, the four groups bonded to each chiral carbon atom are ranked from highest to lowest priority. The highest priority group is assigned the number 1, the lowest priority group is assigned the number 4. Then, the molecule is oriented so that the bond from the carbon atom to the group of lowest priority is arranged directly along our line of sight pointing downward (Figure 8.9). When this has been done, the three higher priority groups point up and lie on the circumference of a circle. (It may help to imagine holding the lowest priority group in your hand like the stem of a flower as you examine the petals.) Consider the path taken as we trace the groups ranked 1–3. In Figure 8.9, this direction is clockwise. Therefore, the configuration is designated *R* (Latin *rectus*, right). If we trace a counterclockwise path from groups ranked 1–3, the configuration is designated *S* (Latin *sinister*, left). Once established, the configuration is designated by the symbol *R* or *S*, within parentheses, as a prefix to the name of the compound.

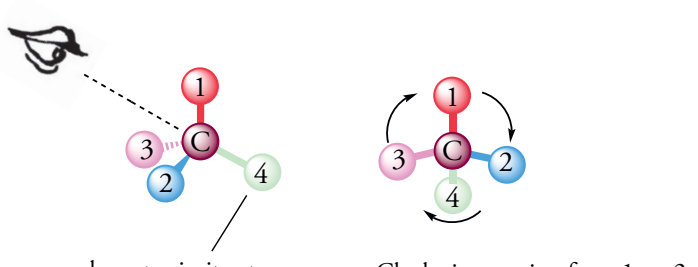


Figure 8.9
Kahn–Ingold–Prelog System of Configurational Nomenclature
Place the lowest priority atom or group away from your eye and view the chiral site along the axis of the carbon bond to the lowest priority group. (The diagram of the eye in this figure is from a drawing in the notebooks of Leonardo da Vinci.)

Priority Rules

The priority rules we defined in Chapter 5 for describing the configuration of geometric isomers also apply to *R,S* configurational nomenclature for chiral compounds.

1. Atoms: Rank the four atoms bonded to a chiral carbon atom in order of decreasing atomic number; the lower the atomic number, the lower the priority. Isotopes are ranked in order of decreasing mass. For example, ^{2}H (deuterium) > ^{1}H.

$$I > Br > Cl > F > O > N > C > {}^{2}H > {}^{1}H$$

highest priority — lowest priority

2. Groups of atoms: If a chiral atom is attached to two or more identical atoms, move down the chain until a difference is encountered. Then apply rule 1. Using this rule, we find that the priority of alkyl groups is

$$(CH_3)_3C\text{—} > (CH_3)_2CH\text{—} > CH_3CH_2\text{—} > CH_3\text{—}$$

3. Multiple bonds: If a group contains a double bond, both atoms are doubled. That is, a double bond is counted as two single bonds to each of the atoms of the double bond. The same principle is used for a triple bond. Thus, the order is

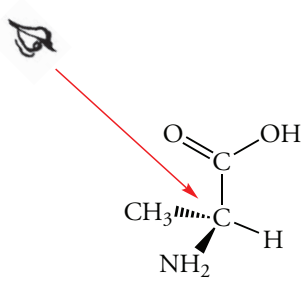
$$HC{\equiv}C{-} > CH_2{=}CH{-} > CH_3CH_2{-}$$

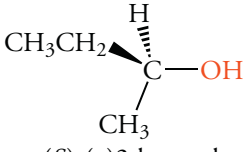
The priority order for common functional groups containing oxygen is

$$-CO_2H \text{ (carboxylic acid)} > -CHO \text{ (aldehyde)} > -CH_2OH \text{ (alcohol)}$$

We can use the *R*,*S* system to describe the configuration of the enantiomers of alanine, which has a chiral center bonded to a hydrogen atom, a methyl group, a carboxylic acid group, and an amino group (NH_2). A perspective drawing of the enantiomer of alanine isolated from proteins is shown below. It has an S configuration.

Look into the molecule toward the lowest priority group, which is hydrogen.



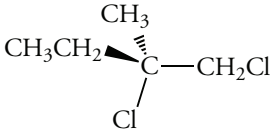


(*S*)-(+)2-butanol

We recall that the direction or magnitude of the optical rotation of a stereoisomer does not determine its absolute configuration. That is, a (+) optical rotation does *not* mean that a molecule has an *R* configuration. For example, the optical rotation of (*S*)-2-butanol is clockwise (+). This isomer is *S*-(+)-2-butanol.

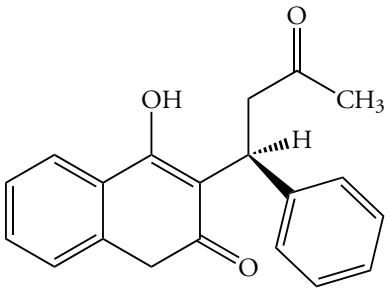
Problem 8.8

What is the configuration of the following stereoisomer of 1,2-dichloro-2-methylbutane?



Problem 8.9

Warfarin is an anticoagulant drug. Warfarin is used both to treat thromboembolic disease and, in larger doses, as a rat poison. Assign its configuration. (The C_6H_5 group, a *phenyl* group, represents a benzene ring bonded at the chiral center.) Assign the configuration of the following stereoisomer of 1,2-dichloro-2-methylbutane.

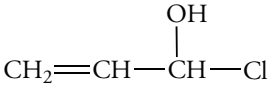


Sample Solution

Warfarin contains only one carbon atom that is attached to four different groups. That carbon atom is bonded to a hydrogen atom, a C_6H_5— group, a CH_2— group, and a fused ring system. The hydrogen atom has priority 4. Which has a higher priority, the benzene ring or the fused ring? The fused ring has a higher priority (1) than the benzene ring (2) because the first point of difference is an oxygen atom in the carbonyl group of the fused ring. Looking into the carbon–hydrogen bond at the chiral center, so that the hydrogen atom points away from us, we trace a counterclockwise path from group 1 to group 2 to group 3. Therefore, this enantiomer of warfarin has an *S* configuration.

Problem 8.10

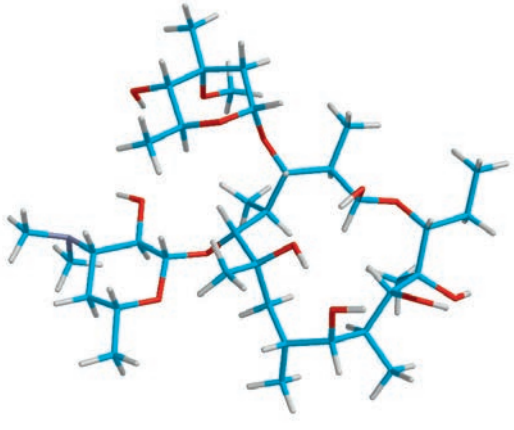
Reduction of (–)-3-buten-2-ol with hydrogen over a palladium catalyst gives (–)-2-butanol. Does the same sign of rotation show that the relative configurations of the two compounds are the same? Based on the mechanism of catalytic hydrogenation, what is the relative configuration of the two compounds? If (–)-3-buten-2-ol has the R configuration, what is the configuration of the product, (–)-2-butanol?



3-buten-2-ol

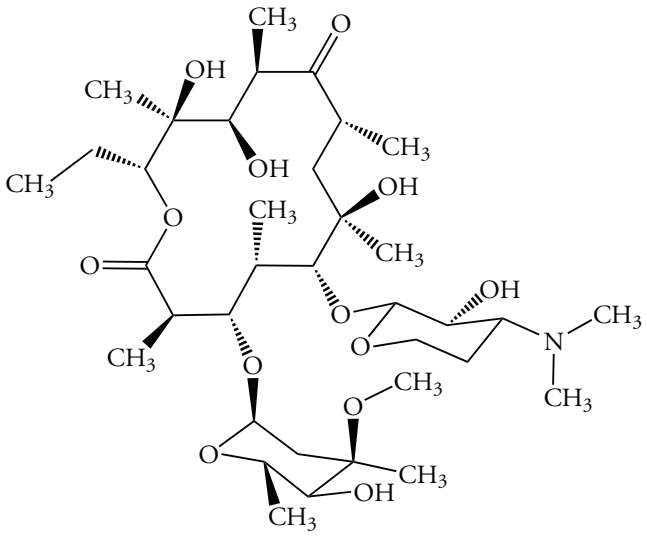
8.6 MOLECULES WITH TWO (OR MORE) STEREOGENIC CENTERS

So far, we have considered molecules that have only one stereogenic center. However, some compounds contain two or more stereogenic centers. For example, the antibiotic erythromycin, which is effective against many bacterial infections, contains 18 chiral centers (Figure 8.10). A molecule with one stereogenic center can exist as either of two enantiomers. How is the number of stereoisomers related to the number of stereogenic centers? What relationships exist between these isomers, and how are their optical rotations related? The answers to these questions depend on the relationship between the groups at each stereogenic center. Are the centers equivalent or nonequivalent? If the chiral carbon atoms are not bonded to identical sets of substituents, the stereogenic centers are **nonequivalent**. In contrast, if the stereogenic centers are bonded to identical sets of substituents, the centers are **equivalent**.



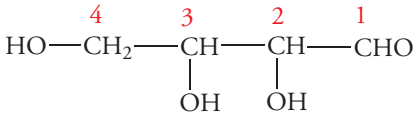
erythromycin A

Figure 8.10
Erythromycin—A Chiral Antibiotic
Erythromycin has 18 chiral centers. Each one is designated with dashed or solid wedge-shaped lines. The hydrogen atoms at the stereogenic centers have been omitted for clarity.



Nonequivalent Stereogenic Centers

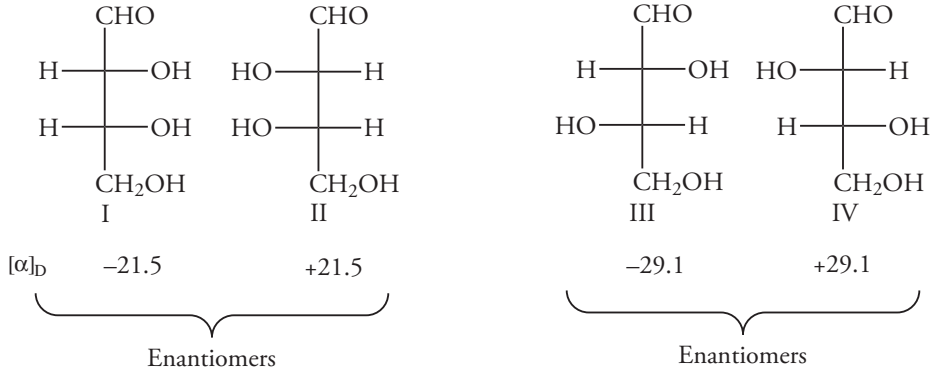
If a molecule contains two or more stereogenic centers, and if they are not bonded to identical groups, the stereogenic centers are nonequivalent. For n nonequivalent centers, the number of stereoisomers equals 2^n. The following example, 2,3,4-trihydroxybutanal, illustrates the general principle.



2,3,4-trihydroxybutanal

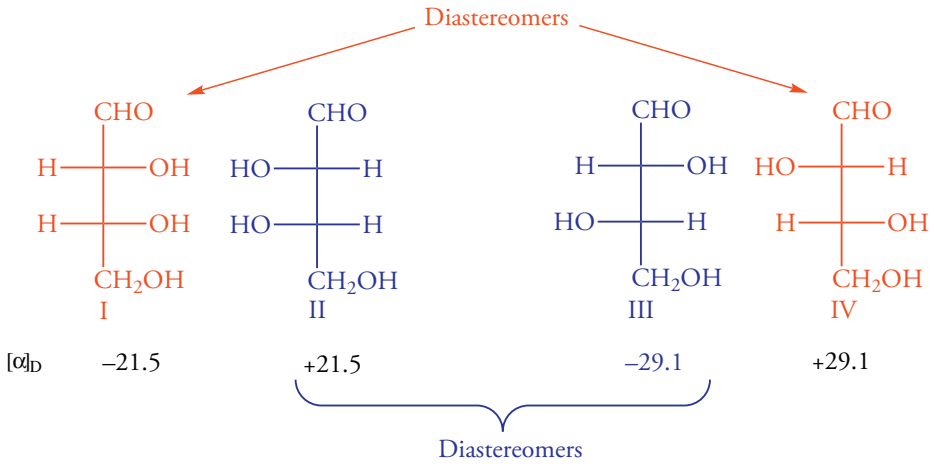
C-2 and C-3 are chiral. They are nonequivalent because they are not bonded to identical groups. Therefore, the configurations at C-2 and at C-3 can be *R* or *S*. Without even drawing the structures, we predict that the four stereoisomers calculated from the 2^n rule can be identified as (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*). Figure 8.11 shows these configurations in Fischer projection formulas.

Figure 8.11
Enantiomers and Diastereomers
A molecule that contains two nonequivalent chiral centers, such as 2,3-4-trihydroxybutanal, can exist as four stereoisomers. They exist as two pairs of enantiomers. Stereoisomers that are not enantiomers are diastereomers.



The relationships between the stereoisomeric 2,3,4-trihydroxybutanals are established with mirror planes. Imagine a mirror placed between I and II. Structures I and II are nonsuperimposable mirror images; they are enantiomers. Structures III and IV are also nonsuperimposable mirror images. Like all enantiomers, they rotate plane-polarized light in equal and opposite directions.

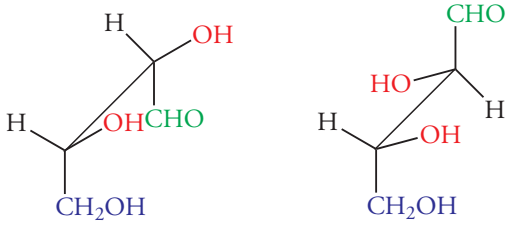
Structures I and III are stereoisomers, but they are not enantiomers. *Stereoisomers that are not enantiomers are called* ***diastereomers***. The pairs II and III, I and IV, and II and IV are diastereomers. In contrast to enantiomers, which have the same chemical and physical properties, diastereomers have different chemical and physical properties. For example, the enantiomers I and II both are liquids at room temperature and are very soluble in ethanol. The enantiomers III and IV both melt at 130 °C and are only slightly soluble in ethanol.



Nomenclature of Diastereomers

The name of a compound with two or more chiral centers contains the configuration of every chiral center. The configuration of each chiral center is indicated by a number that corresponds to its position in the carbon chain and the letter *R* or *S*. Commas separate the configurations. This designation immediately tells us about the relationship between stereoisomers without reference to three-dimensional structures or assignment of the priorities of the groups at the stereogenic centers. Let's consider the four stereoisomers labeled (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*). The enantiomer of the 2*R*,3*R* compound must be the 2*S*,3*S* isomer, which has the opposite configuration at each chiral center. Compounds whose configurations differ at only one of the two chiral centers are diastereomers. For example, the 2*R*,3*R* compound is a diastereomer of the 2*S*,3*R* isomer.

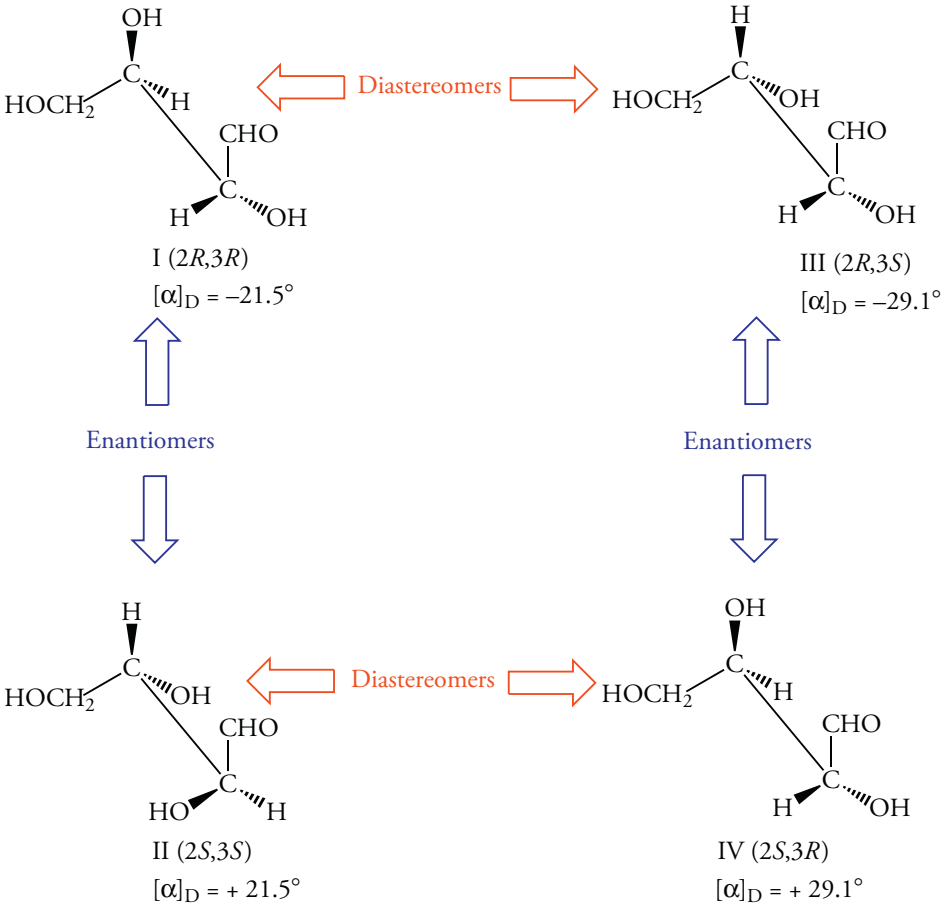
To assign the configurations of the 2,3,4-trihydroxybutanals shown in the Fischer projections in Figure 8.11, we rewrite the structures in three-dimensions. Consider structure I. The CHO and CH_2OH groups are behind the plane of the page. The H and OH groups are in front of the plane of the page. Note that the Fischer projection formula places the carbon chain in an eclipsed conformation. The configuration of each center can be established from this conformation. Their configurations can be also assigned from the more stable, staggered conformation that results from rotation around the C-2 to C-3 bond. Rotating groups around sigma bonds interconverts conformations, but it does *not* change the configuration at any chiral center.



eclipsed conformation staggered conformation

Converting the stereoisomers of 2,3,4-trihydroxybutanal into three-dimensional, staggered conformations gives the structures shown in Figure 8.12. Structure I has the configuration 2*R*,3*R*. Structure II is the mirror image of structure I. If a mirror were placed behind the plane of the page, you would see structure II. Because structures I and II are enantiomers I, we know that the configuration of structure I must be 2*S*,3*S*. The specific rotation of structure I is –21.5°, and the specific rotation of structure of structure II is +21.5°. The common names of structures I and II are (–)-erythrose and (+)-erythrose. The common names for structures III and IV are (–)-threose and (+)-threose. We will encounter erythrose and threose again in Chapter 25 when we discuss carbohydrates.

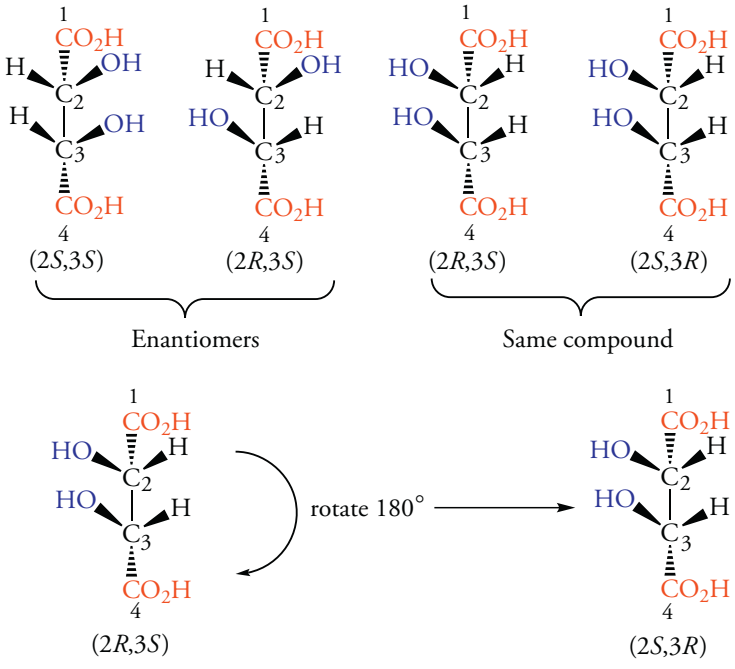
Figure 8.12
Configurations of Enantiomers and Diastereomers



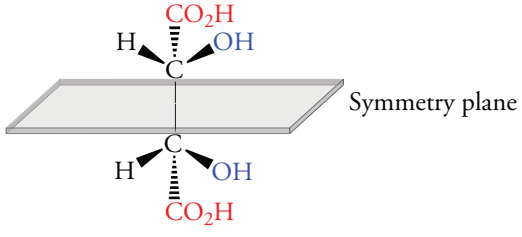
Equivalent Stereogenic Centers

We began our discussion of molecules with two or more stereogenic centers by noting that they chiral could be either equivalent or nonequivalent. Now let's consider compounds with equivalently substituted chiral centers. Examples of equivalent substituted chiral centers are shown in the eclipsed conformations of the tartaric acids (Figure 8.13). In each structure, C-2 and C-3 are connected to four different groups. However, only three stereoisomers exist. Of these, one is optically inactive! The structures labeled (2*S*,3*S*) and (2*R*,3*R*) are enantiomers; therefore, they are optically active. But look at the structures labeled (2*R*,3*S*) and (2*S*,3*R*). Although the structures are drawn as "mirror images," they are superimposable and, in fact, are identical. Thus, the two structures represent the same molecule. We can see this if we rotate the structure on the left in Figure 8.13 by 180° *in the plane of the page*. (Do not lift it out of the page!)

Figure 8.13
Configurations of Optically Active Tartaric Acids and Meso Compounds
Only three stereoisomers exist for tartaric acid because it has two equivalent chiral centers. Two of the stereoisomers are enantiomers. The third has a plane of symmetry, is optically inactive, and is called a *meso* compound, i.e., *meso*-tartaric acid.



Why is one of the stereoisomer of the tartaric acids optically inactive? The structures labeled (2*R*,3*S*) and (2*S*,3*R*) have two equivalent chiral carbon atoms, and each structure has a plane of symmetry. We recall from Section 8.2 that a structure with a plane of symmetry is achiral, and that it is superimposable on its mirror image. In the case of achiral tartaric acid, the plane of symmetry is between C-2 and C-3, so the top half of the molecule is the mirror image of the bottom half.



meso-tartaric acid

Compounds, such as tartaric acid, which have two or more chiral centers, but are nevertheless achiral, are called *meso* compounds (Greek *meso*, middle). *Meso* compounds are not optically active.

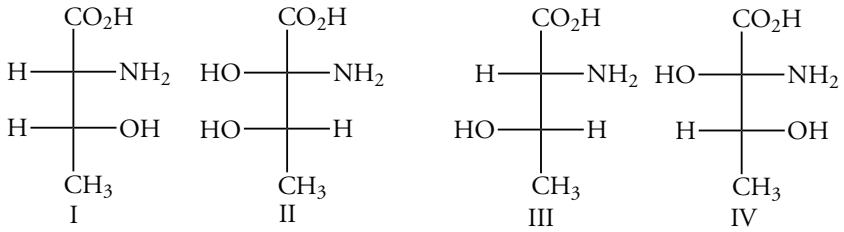
Problem 8.11

Threonine, an amino acid isolated from proteins, has the following condensed molecular formula. Write the Fischer projections of the possible stereoisomers. What is the configuration at each stereogenic center in each stereoisomer?

$$\overset{4}{C}H_3\overset{3}{C}H(OH)\overset{2}{C}H(NH_2)\overset{1}{C}O_2H$$

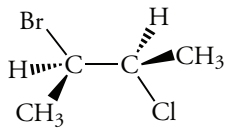
Sample Solution

C-2 and C-3 are each bonded to four different substituents. Therefore, threonine has two chiral centers. Because the chiral centers are nonequivalent, four diastereomers are possible. The Fischer projections are written by placing the carboxyl group at the top of the vertical chain. The amino and hydroxyl groups can be on the right or left sides of the projection formula. The structure of threonine isolated from proteins is given by the Fischer projection at the right. Its configuration is 2*S*,3*R*.

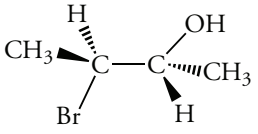


Problem 8.12

Determine the configuration at the stereogenic centers of each of the following structures.



2-bromo-3-chlorobutane



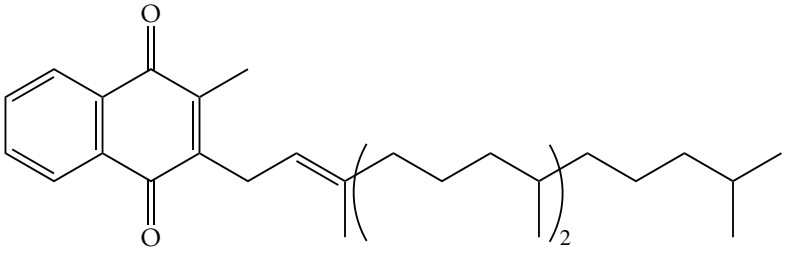
3-bromo-2-butanol

Problem 8.13

Write the Fischer projection formulas of the stereoisomers of 2,3-dibromobutane. What relationship exists between the optical activities of these isomers?

Problem 8.14

Determine the number of chiral centers in vitamin K_1. How many stereoisomers are possible?



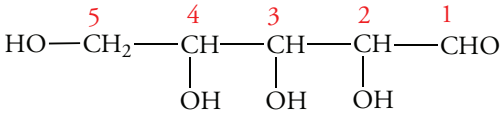
Sample Solution

The carbon atoms in the two rings are not chiral because neither one has a tetrahedral carbon atom. The long alkyl chain contains eight methylene units, none are chiral centers because a carbon atom in a methylene group is bonded to two hydrogen atoms. The tertiary carbon atom near the end of the alkyl chain, which has two methyl groups, is not chiral either.

Next, consider the positions in the middle of the alkyl chain that have methyl group branches. The methyl group on the left is bonded to a double-bonded carbon atom, which does not have four groups bonded to it; therefore, it is not chiral. The next two methyl groups are located on chiral centers. Because there are two chiral carbon atoms, $2^2 = 4$ stereoisomers are possible. These are the two carbons by the right hand of the parenthesis.

Problem 8.15

Using numbers and the symbols *R* and *S*, write the prefix designations of all of the possible stereoisomers of 2,3,4,5-tetrahydroxypentanal.



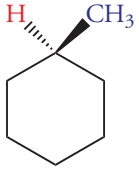
2,3,4,5-tetrahydroxypentanal

8.7 Cyclic Molecules with Stereogenic Centers

Many cyclic compounds have stereogenic centers. We assign their configurations in the same manner we described previously for acyclic compounds.

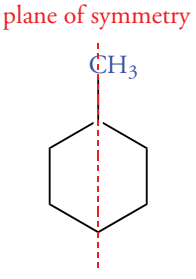
Cyclic Structures with One Stereogenic Center

When a stereogenic center is in a ring, we assign the priorities of the groups bonded to it by treating two "parts" of the ring as groups. First, we examine the atoms in the path around the ring in one direction. Then, we look at the atoms in the path around the ring in the opposite direction. Next, we apply priority rules 1 through 3 (Section 8.5). The structure of methylcyclohexane provides an example.



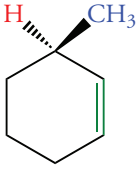
methylcyclohexane

The methyl group and the hydrogen atom at C-1 are two of the required four groups for a stereogenic center. What about the other two groups? C-2 and C-6 are equivalent methylene units by priority rule 1. We apply rule 2 and proceed to the next atom in each path and find that C-3 and C-5 are also equivalent methylene units. Finally, we encounter C-4 from either direction. Thus, C-l is bonded to two equivalent "groups" that are part of the ring itself. Methylcyclohexane has a plane of symmetry containing C-1 and C-4. Since methylcyclohexane has a plane of symmetry, it is achiral.



methylcyclohexane

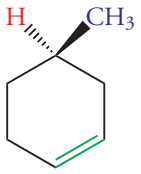
Now consider a compound in which the two paths around the ring are not equivalent. In 3-methylcyclohexene, a methyl group and a hydrogen atom are bonded to C-3. C-2 and C-4 are not equivalent by rule 3. As a result, C-3 of 3-methylcyclohexene is a stereogenic center. The structure of (*R*)-3-methylcyclohexene is shown below. We see that it does not have a plane of symmetry.



3-methylcyclohexene

What is the absolute configuration of this enantiomer of 4-methylcyclohexene? The lowest priority group is the hydrogen atom located behind the plane of the page. Thus, the arrangement of the other three higher priority groups is ideal to assign the configuration. The highest priority group, the sp^2-hybridized carbon atom, is located at the "4 o'clock" position. Priority group 2 is the methylene group of the C-4 atom because it is bonded to another carbon atom. It is located at the "8 o'clock" position. The methyl group is priority group 3 and is located at the "12 o'clock" position. The path traced by the three highest priority groups is clockwise, so the configuration of 4-methylcyclohexene in this structure is *R*.

As in acyclic compounds, differences in the groups can be at some distance from the stereogenic center. The difference in 4-methylcyclohexene is two carbon atoms away from the stereogenic center.



(*R*)-4-methylcyclohexene

Cyclic Structures with Two Stereogenic Centers: Disubstituted Cyclobutanes

As we found when we considered acyclic compounds containing two stereogenic centers, the number of stereoisomers of cyclic compounds depends on whether or not the centers are equivalent. This also true for cyclic compounds. First, we'll examine the isomeric *cis*- and *trans*-1-bromo-2-chlorocyclobutanes (Figure 8.14a). These compounds are diastereomers. The compounds in Figure 8.14 are arranged to demonstrate the mirror image relationship of the two *trans* enantiomers, whose configurations are 1*R*,2*R* and 1*S*,2*S*. There are also two enantiomeric *cis* isomers.

Now consider the consequences of the two equivalent stereogenic centers of 1,2-dibromocyclobutane (Figure 8.14b). There are still two enantiomeric *trans* compounds. However, the *cis* isomer has a plane of symmetry that passes through the C-l to C-2 bond, perpendicular to the plane of the ring. The 1*R*,2*S* and 1*S*,2*R* structures are identical and represent a single *meso* compound.

Cyclic Structures with Two Stereogenic Centers: Dimethyl Cyclohexanes

The relationship between the chiral cyclohexane compounds that we originally called geometric isomers follows from the above discussion of the disubstituted cyclobutanes. Cyclohexane exists in a chair conformation. However, for the purposes of determining stereochemical relationships, a planar structure gives the right answers since we can project the six-membered ring onto a plane without altering the configuration of a chiral center.

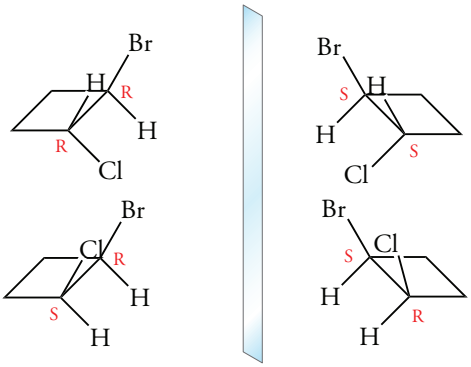
In this section, we will examine only dimethyl cyclohexanes. First, let's examine *cis*- and *trans*-1,4-dimethylcyclohexane (Figure 8.15). These compounds have no stereogenic centers because a symmetry plane passes through C-l and C-4 and cuts through both methyl groups. This plane is more easily seen in the planar projection of these compounds.

cis- and *trans*-1,3-Dimethylcyclohexane each have two stereogenic centers. Because the centers are equivalent, only three stereoisomers exist (Figure 8.16). *cis*-l,3-Dimethylcyclohexane, a *meso* compound, has a symmetry plane that passes through C-2 and C-5. The symmetry plane is easily seen in the planar projection structure. *trans*-l,3-Dimethylcyclohexane has two stereogenic centers and no plane of symmetry. Thus, it exists as two enantiomers.

The *cis*- and *trans*-1,2-dimethylcyclohexanes have two stereogenic centers. The *trans* isomer does not have a plane of symmetry. Thus, it exists as two enantiomers (Figure 8.17). The *cis* isomer is a *meso* compound, but for reasons that are not straightforward. The two chair conformations rapidly interconvert, and they have equal energy. They are enantiomers. Hence, there is no net optical rotation (Figure 8.18). (If chair–chair interconversion were slow—which it is not—the two enantiomers could in principle be separated.)

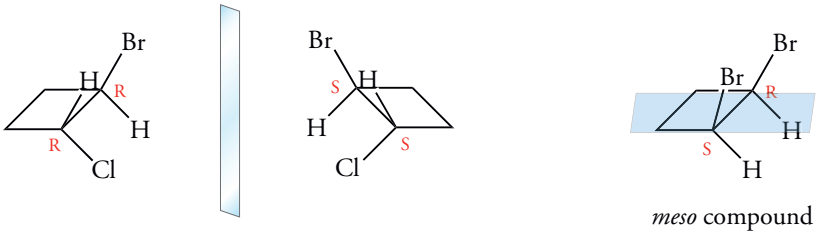
Figure 8.14
Diastereomers of 1,2-Disubstituted Cyclobutanes

(a) A 1,2-disubstituted cyclobutane with two nonequivalent chiral centers has four diastereomers. (b) However, a 1,2-disubstituted cyclobutane with two equivalent chiral centers has only three diastereomers, one of which is a *meso* compound.



Mirror

(a) Diastereomers of 1-bromo-2-chlorocyclobutane

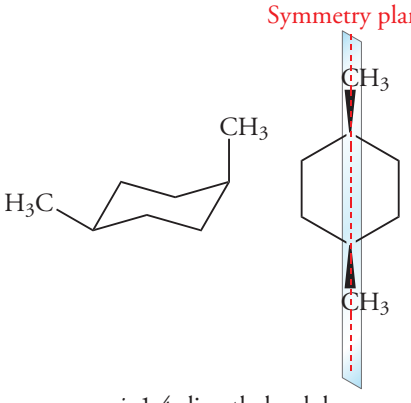


meso compound

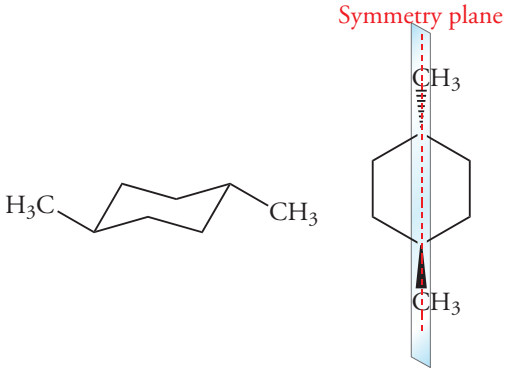
(b) Diastereomers of 1,2-dibromocyclobutane

Figure 8.15
Stereoisomers of 1,4-Dimethylcyclohexane

The *cis* and *trans* isomers of 1,4-dimethylcyclohexane are achiral because each has a plane of symmetry.

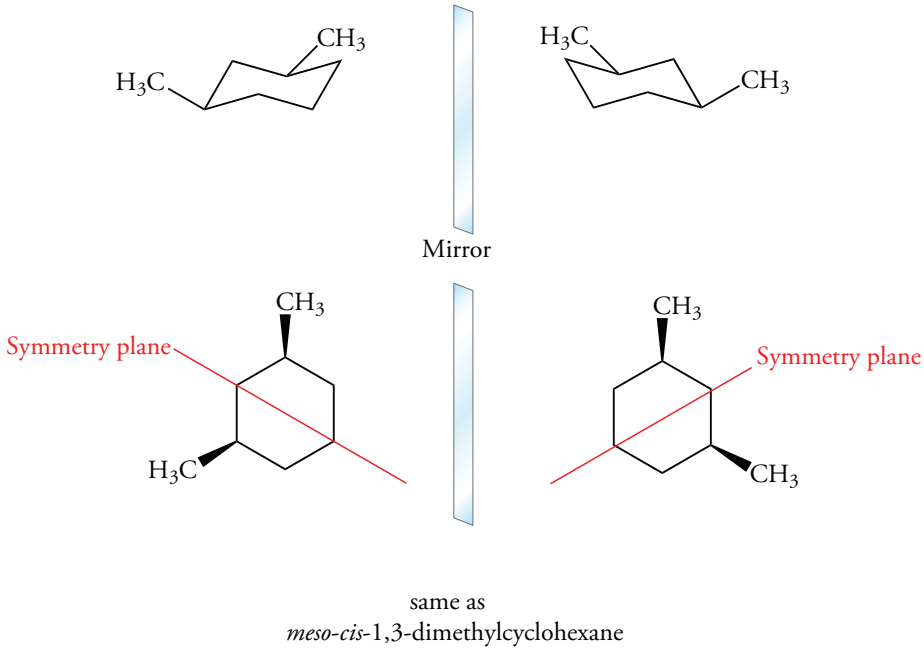


cis-1,4-dimethylcyclohexane

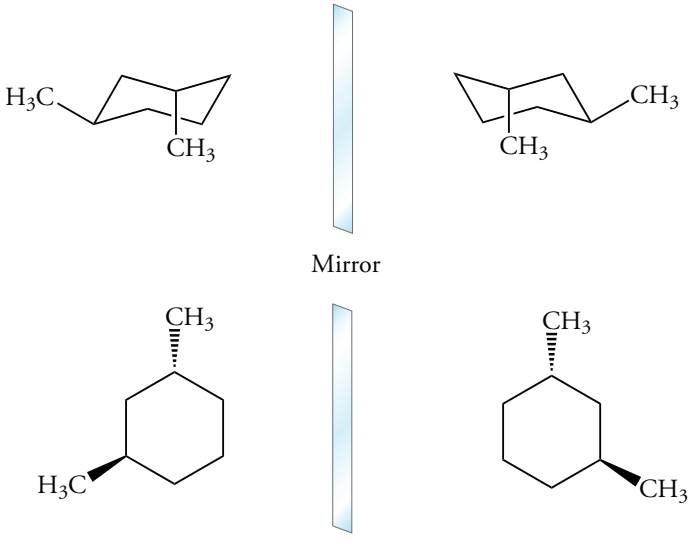


trans-1,4-dimethylcyclohexane

Figure 8.16
Diastereomers of 1,3-Dimethylcyclohexane
cis-1,3-Dimethylcyclohexane is a *meso* compound. It is achiral because it has a plane of symmetry. *trans*-1,3-Dimethylcyclohexane exists as a pair of enantiomers.



same as
meso-cis-1,3-dimethylcyclohexane



enantiomers
trans-1,3-dimethylcyclohexane

Figure 8.17
Enantiomers of *trans*-1,2-Dimethylcyclohexane
trans-1,2-Dimethylcyclohexane exists as a pair of enantiomers. There is no a plane of symmetry.

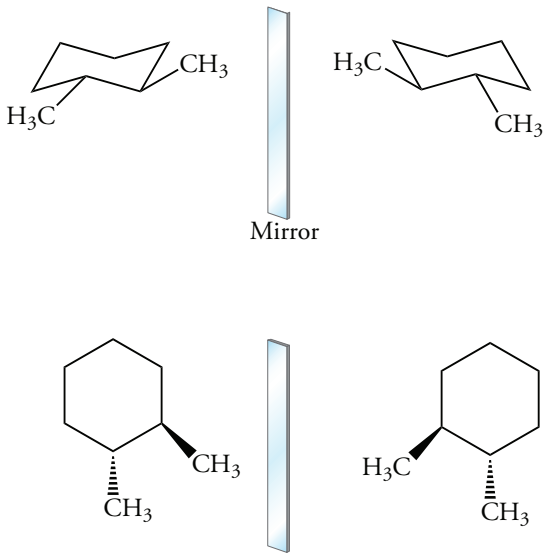
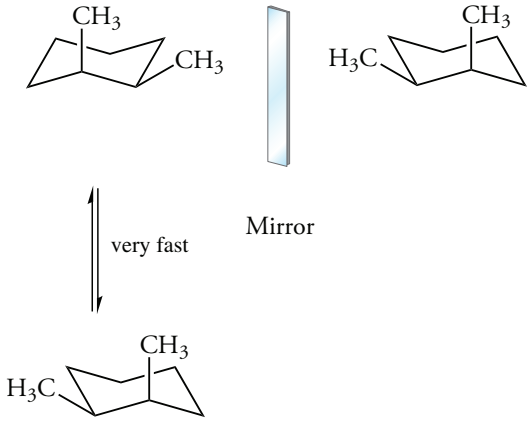
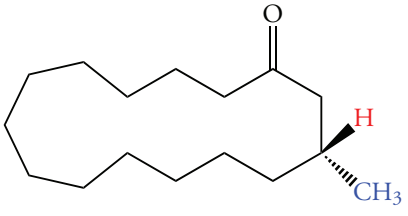


Figure 8.18
***cis*-1,2-Dimethylcyclohexane**
The mirror images of *cis*-1,2-dimethylcyclohexane are not superimposable. However, chair–chair interconversion is very fast, so the enantiomers cannot be separated.



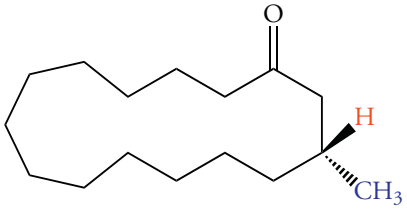
Problem 8.16
What is the absolute configuration of muscone, a compound used in perfumes to provide a musk odor?



muscone

Sample Solution

The stereogenic center is at the branch containing the methyl group. The lowest priority group is a hydrogen atom that points above the plane of the page at the branching carbon atom. The methylene carbon atoms of the ring attached to the branching point both have higher priorities than the methyl group, which is priority (3). The methylene portion of the ring that contains the carbonyl carbon atom has a higher priority than the other methylene portion of the ring. Looking into the C—H from behind the plane of the page, and into the C—H bond, and tracing the other three groups, we move in a clockwise direction. Therefore, muscone has an *R* configuration.



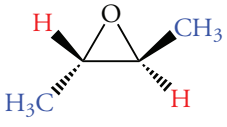
(*R*)-muscone

Problem 8.17

Write the structures of (1*R*,2*S*)- and (1*S*,2*S*)-1-bromo-2-chlorocyclopropane. Which is a *cis* and which is a *trans* isomer? Are the structures enantiomers or diastereomers?

Problem 8.18

Determine the configuration of each stereogenic center in the following *trans*-2,3-dimethyloxirane. Write a structure of its enantiomer.

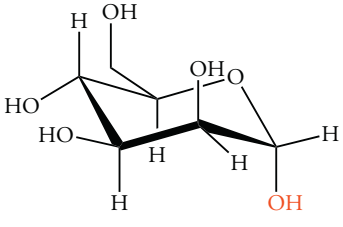


trans-1,2-dimethyloxirane

Chirality and Our Senses of Taste and Smell

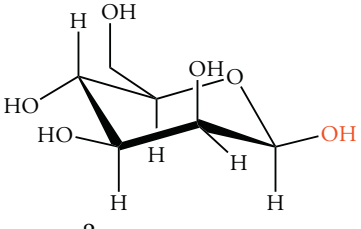
Our senses are sensitive to the configuration of molecules. Both the sense of taste and the sense of smell result from changes induced in a sensory receptor when it binds a specific small molecule (ligand). Ligand binding causes a conformational change that triggers a sequence of events culminating in transmission of a nerve impulse to the brain by sensory neurons. The brain interprets the input from sensory neurons as the "odor" of, say, spearmint.

Diastereomers interact with highly specific sensory receptors. For example, D-mannose, a carbohydrate, exists in two diastereomeric forms that differ in the configuration of a hydroxyl group at one center. The two isomers are designated α and β. The α form tastes sweet, but the β form tastes bitter.



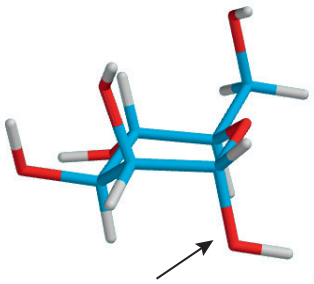
α-D-mannose

(The hydroxy group is axial in the α isomer.)

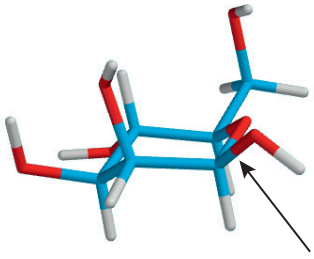


β-D-mannose

(The hydroxy group is equatorial in the β isomer.)

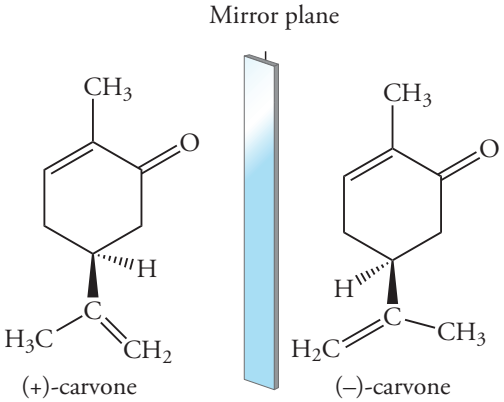


α-D-mannose (axial hydroxyl group)



β-D-mannose (equatorial hydroxyl group)

Sensory receptors also readily distinguish enantiomers. The specificity of response is similar to the relationship between our hands and how they fit into gloves. Because sensory receptors are chiral, they interact stereospecifically with only one of a pair of enantiomers. The two enantiomeric forms of carvone have very different odors. (+)-Carvone is present in spearmint oil, imparting its odor. In contrast, its enantiomer, (–)-carvone, is present in caraway seed. It has the familiar odor associated with rye bread.



(+)-carvone
(spearmint)

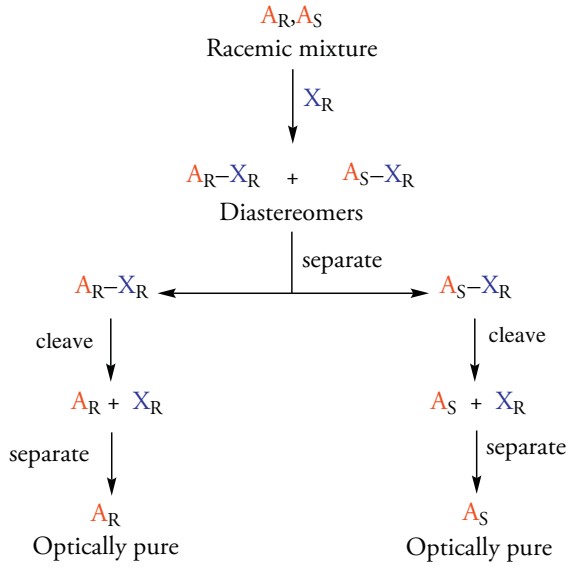
(–)-carvone
(caraway)

8.8 SEPARATION OF ENANTIOMERS

General Principles

Substances with stereogenic centers are invariably found in nature as a single enantiomer. However, as we noted in Section 8.3, compounds with stereogenic centers prepared in the laboratory from achiral starting materials are racemic. We can separate the racemic mixture into pure samples of each enantiomer by indirect methods. Because enantiomers have the same physical properties, such as boiling point or solubility, they cannot be separated by distillation or crystallization. However, enantiomers can be separated by reacting the racemic mixture with another optically pure compound to produce a mixture of diastereomers (Figure 8.19). Because diastereomers have different physical properties, they can often be separated on the basis of solubility differences. Then, each enantiomer is recovered from its diastereomeric derivative by another chemical reaction. The entire process is called **resolution** of enantiomers. The optically pure compound used to form the diastereomeric mixture is called the **resolving agent**.

Figure 8.19
General Method for Resolving Enantiomers

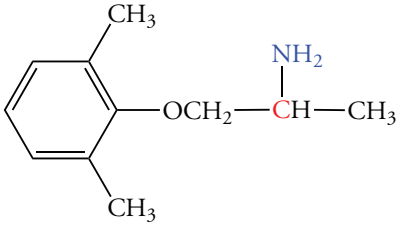


The racemic mixture to be resolved in Figure 8.19 is designated A_R,A_S. The optically active compound selected as the resolving agent is represented X_R. The choice of X_R over X_S is arbitrary in this discussion. The choice we make in the laboratory is based on the configuration of the available resolving agent. The diastereomeric compounds made from the racemic mixture are A_R–X_R and A_S–X_R. After the diastereomers are separated, one or the other or both can be reacted to liberate the pure enantiomers. In practice, only one of the enantiomers is easily obtained. For example, the least soluble diastereomer may crystallize from solution and yield one of the enantiomers in the subsequent step. Because some of the less soluble diastereomer remains in solution with the more soluble diastereomer, it is difficult to obtain the second enantiomer in optically pure form.

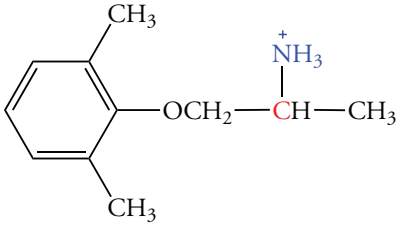
Chiral Chromatography

The method for resolving enantiomers we discussed above illustrates the general principle that the key to the separation of enantiomers is the formation of diastereomers. This can be achieved by **chiral chromatography**, a process in which the column itself contains a chiral ligand. Chiral chromatography depends upon a partition between compounds in the moving phase—the solution of enantiomers passing through the column—and a stationary phase, the chiral column material itself. When a solution of enantiomers passes through the column, the enantiomers bind to the column with different affinities because an (*R*-ligand/*R*-enantiomer) interaction differs from an (*R*-ligand/*S*-enantiomer) interaction.

We will examine the separation of the enantiomers of mexiletine, an antiarrhythmic drug that acts by blocking sodium channels. (–)-*R*-mexiletine is far more potent than its enantiomer, but for a long time, mexiletine has been administered as a racemic mixture. In many cases, if one enantiomer of a drug is effective therapeutically, its enantiomer is either inactive or toxic. Thus, the purification of drug enantiomers is pharmacologically important.



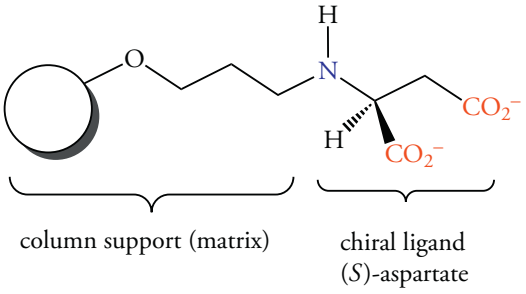
(±)-mexiletine (an antiarrhythmic drug)



conjugate acid of mexiletine (pH 7)

Enantiomers can be separated by high-performance liquid chromatography in which the column material, or matrix, is covalently bonded to a chiral ligand. In this case, the chiral ligand is (*S*)-aspartic acid, an inexpensive, readily available amino acid. At pH 7, the carboxylic acid group of aspartic acid exists as its conjugate base, a carboxylate anion. The amino group is bonded to the column matrix.

At pH 7, the carboxylic acid group of aspartic acid exists as its conjugate base, a carboxylate anion. It is called (*S*)-aspartate. The column matrix itself—covalently bound to (*S*)-aspartate—is the resolving agent.



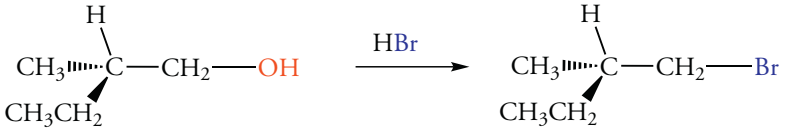
Mexiletine contains an amino group, and at pH 7, it exists as its conjugate acid; that is the amino group is a protonated ammonium ion. When a solution of (±)-mexiletine at pH 7 passes through a column whose chiral ligand is (*S*)-aspartate, ion pairs between the chiral column matrix and the (+) and (–) forms of mexiletine form transiently. The ion pairs are diastereomers, and the mexiletine enantiomers do not have the same affinity for the column. It turns out that (–)-(*R*)-mexiletine binds to the column with lower affinity than its enantiomer, and it emerges from the column (elutes) first. A complete separation of enantiomers is the result.

8.9 CHEMICAL REACTIONS AT STEREOGENIC CENTERS

In this section, we consider some reactions of chiral molecules, which are often highly valuable in the study of reaction mechanisms. They are also of great importance in the study of enzymatic catalysis, since virtually all enzymes react with chiral molecules.

Reactions of Chiral Molecules That Do Not Occur at the Stereogenic Center

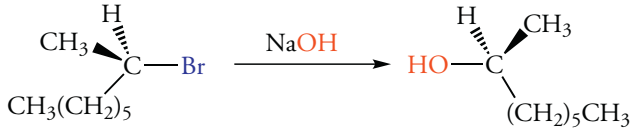
If a reaction of a chiral compound does not form or cleave any bonds to the stereogenic center, then the configuration of the product is the same as that of the reactant. Therefore, we can establish the absolute configuration of particular molecules using reference molecules of known absolute configuration. For example, 2-methyl-l-butanol is converted to 1-bromo-2-methylbutane by HBr. The reaction does not occur at the stereogenic center. Therefore, the *S*-2-methyl-l-butanol yields S-1-bromo-2-methylbutane.



(*S*)-2-methyl-1-butanol (*S*)-1-bromo-2-methylbutanet

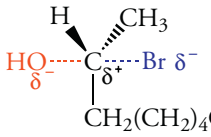
Preview: Stereochemistry of a Substitution Reaction at a Stereogenic Center

In coming chapters, we will devote considerable attention to substitution reactions at sp^3-hybridized carbon atoms. The stereochemical changes that occur in these reactions provide a powerful probe of the reaction mechanisms. For example, the reaction shown below occurs at the stereogenic center of a chiral compound and yields a chiral product. Treating (*R*)-2-bromooctane with sodium hydroxide yields (*S*)-2-octanol. In this reaction, the stereochemistry of the reactant and product are opposite, so the reaction occurs with **inversion of configuration** at the stereogenic site of the substitution reaction.



(*R*)-2-bromooctane (*S*)-2-octanol

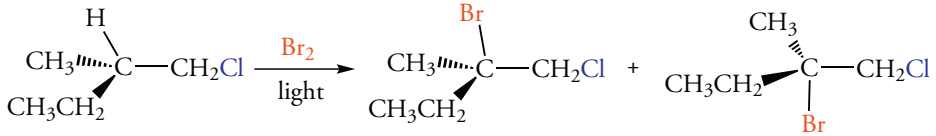
We can account for inversion of configuration by imagining that the hydroxide ion attacks (*R*)-2-bromooctane at the carbon atom from the side opposite the C—Br bond axis. Thus, it is reasonable to propose a linear transition state in which the stereogenic center has partial bonds to both the hydroxide and the bromide ions.



Transition state for inversion of configuration

Stereochemistry of a Free Radical Reaction

A substitution reaction at a stereogenic center can lead to a racemic mixture of products. For example, in the free radical reaction of bromine with (*S*)-1-chloro-2-methylbutane, a bromine atom replaces a hydrogen atom at the tertiary stereogenic center to give a racemic mixture of (*R*)- and (*S*)-2-bromo-l-chloro-2-methylbutane.



(*S*)-1-chloro-2-methylbutane

This experimental result indicates that the free radical intermediate produced in the course of the reaction is achiral. The radical is planar (Figure 8.20). Therefore, reaction of the radical with bromine can occur with equal probability from above or below the plane, giving a 50:50 mixture of enantiomers.

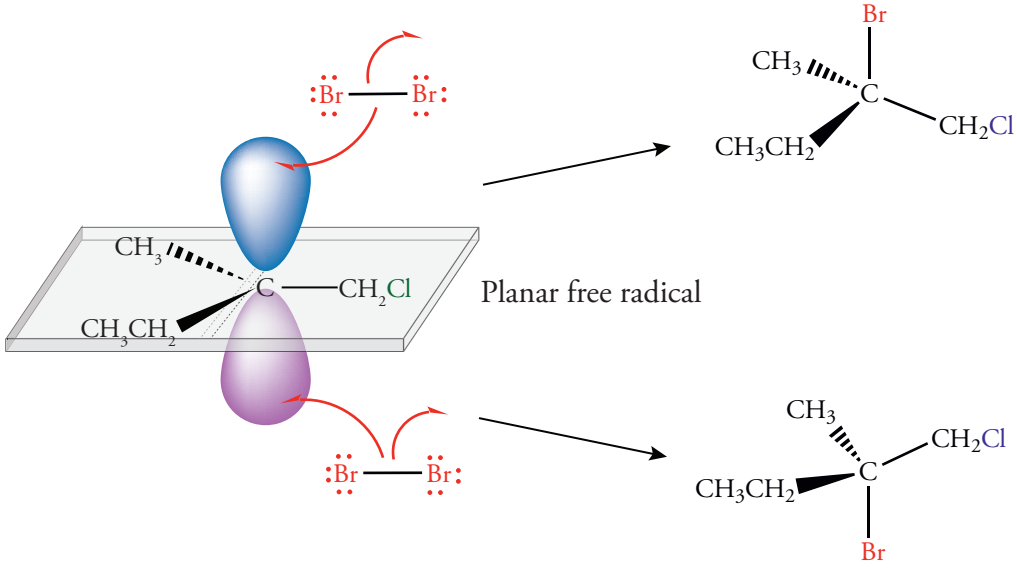


Figure 8.20
Free Radical Reaction at a Stereogenic Center
A free radical intermediate is achiral because it has a plane of symmetry. A bromine molecule can therefore attack with equal probability from above or below the plane to give a 50:50 mixture of enantiomers. The 2p orbital is half-occupied, and there is a 50% probability of finding an electron above or below the nodal plane of the orbital.

Problem 8.19

Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure of the 2-bromo-1-chlorobutane formed. Determine the configuration(s) of the stereogenic center(s). Is the product optically active?

Problem 8.20

Based on the data for the conversion of (*R*)-2-bromooctane into (*S*)-2-octanol using NaOH, predict the product of the reaction of (*S*)-2-bromooctane with NaOH.

Sample Solution

Nucleophilic attack at the side opposite the bond of the displaced leaving group from (*S*)-2-bromooctane gives a product with inversion of configuration. Thus, the enantiomeric *R* compound should react likewise and gives an inverted product, (*S*)-2-octanol.

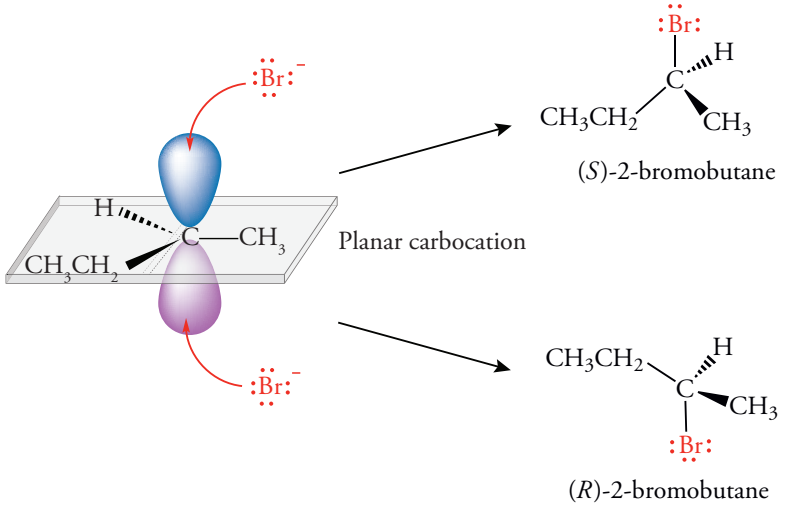
8.10 REACTIONS THAT PRODUCE STEREOGENIC CENTERS

We have studied several reactions that yield products with stereogenic centers from compounds with no stereogenic centers. What prediction can we make about the configuration of the product? The reaction of an achiral radical described previously shows that chiral products cannot form from the reaction of achiral reactants. Molecules with stereogenic centers can form, however, the enantiomers form in equal amounts.

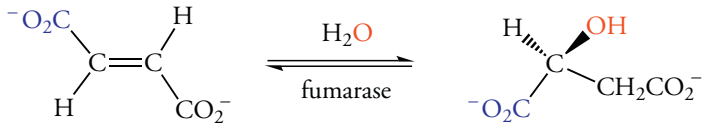
Stereochemistry of Markovnikov Addition to Alkenes

Let's examine the stereochemistry of the addition of HBr to 1-butene to give 2-bromobutane. We know that this is Markovnikov addition. A proton adds to 1-butene at C-1 to give a secondary carbocation. It is achiral because it has a plane of symmetry (Figure 8.21). The carbocation is attacked by the nucleophilic bromide ion with equal probability from the top or bottom side of the planar intermediate. Attack at the top gives the *S* enantiomer, attack at the bottom gives the R enantiomer, and a racemic mixture results.

Figure 8.21
Stereochemistry of Markovnikov Addition of HBr to 1-Butene
A proton adds to the double bond of 1-butene to give an intermediate secondary carbocation. It is achiral because it has a plane of symmetry. Bromide ion can attack with equal probability from the top or the bottom to give a racemic mixture.



Biochemical processes are catalyzed by enzymes that have multiple stereogenic centers and are therefore chiral. Enzymes provide a chiral environment in which to form stereogenic centers. As a consequence, only one enantiomer forms from an enzyme-catalyzed reaction, even if the reactant is achiral. For example, fumaric acid reacts with water in an addition reaction catalyzed by the enzyme fumarase in the citric acid cycle to give only (*S*)-malic acid. We show the carboxylic acids as their conjugate bases because they are ionized at pH 7. These ionic compounds are called "fumarate" and "malate." This reaction converts fumarate to (*S*)-malate.



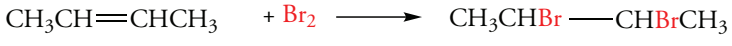
fumarate
(the conjugate base of fumaric acid)

(*S*)-malate
(the conjugate base of (*S*)-malic acid)

Only one enantiomer forms in the reaction, and only the *trans* geometric isomer reacts in the presence of fumarase. The *cis* unsaturated isomer is not converted to a hydrated product by fumarase. In fact, it does not bind to the enzyme at all.

Stereochemistry of Alkene Bromination

We recall that the reaction of bromine with an alkene gives a product with bromine atoms on adjacent carbon atoms (Section 6.6). For example, 2-butene reacts with bromine to give 2,3-dibromobutane. Two equivalently substituted stereogenic centers form in this reaction. There are three stereoisomers for such compounds, a pair of enantiomers and a *meso* compound. Which products would we predict based on the reaction mechanism we discussed in Section 7.6? Put another way, how do the observed products support the proposed mechanism of the reaction?



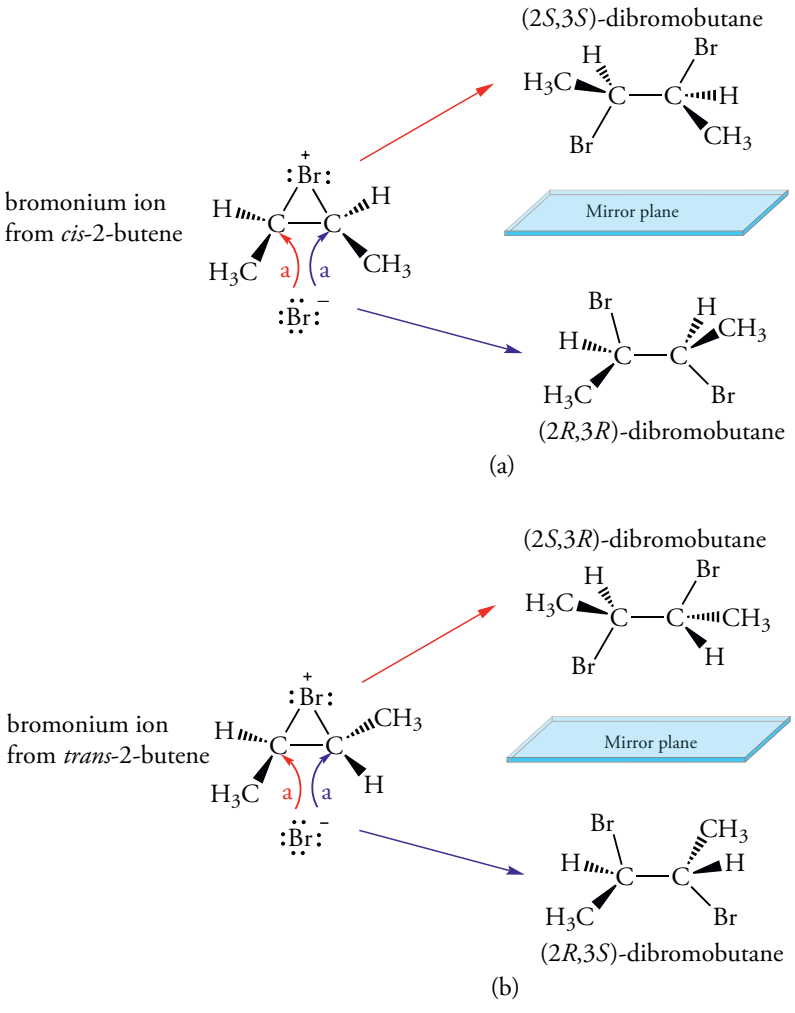
The configuration of the addition product depends on the configuration of the 2-butene, which can be *cis*- or *trans*-, and on the stereochemistry of the *anti* addition reaction that occurs in the second step. Bromine adds to *cis*-2-butene to give a mixture of the enantiomeric (2*R*,3*R*)- and (2*S*,3*S*)-dibromobutanes (Figure 8.22a). Although the bromonium ion could form by attack equally well on the top or bottom, let's examine the intermediate obtained from attack on the top. (The intermediate obtained from attack on the bottom is the same because it is achiral.) Subsequent attack of bromide ion can occur at either the right or the left carbon atom. Attack at the right carbon atom gives the 2*R*,3*R* isomer. Attack at the left carbon atom gives the 2*S*,3*S* isomer. Both paths of attack are equally probable, and a racemic mixture results.

Now let's consider the consequences of formation of the cyclic bromonium ion derived from *trans*-2-butene followed by nucleophilic attack by bromide ion (Figure 8.22b). The bromonium ion results from attack on the top. Bromide ion attacks equally well at the right and left carbon atoms, giving the 2*S*,3*R* and 2*R*,3*S* structures, respectively. This pattern corresponds to two equivalently substituted chiral carbon atoms in a molecule with a plane of symmetry; thus, this isomer corresponds to a single *meso* compound.

We now can confidently accept the mechanism for addition of bromine to alkenes because it agrees with the experimental facts. We have again found that achiral reactants—in this case either *cis*- or *trans*-2-butene and bromine—always form optically inactive products. Remember: the products have two stereogenic centers; the reaction produces either a racemic mixture or a *meso* compound.

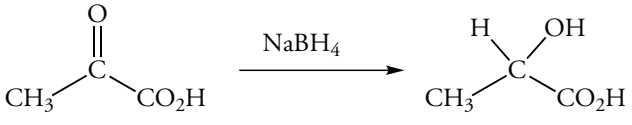
Figure 8.22
Stereochemistry of Bromine Addition to Alkenes

The reaction of bromine with an alkene produces a bromonium ion intermediate. This intermediate reacts with bromide ion in a process that results in net *anti* addition of bromine. The stereochemical consequences for adding bromine to *cis*-2-butene and *trans*-2-butene are different. *cis*-2-Butene yields a pair of enantiomers; *trans*-2-butene yields a *meso* compound.



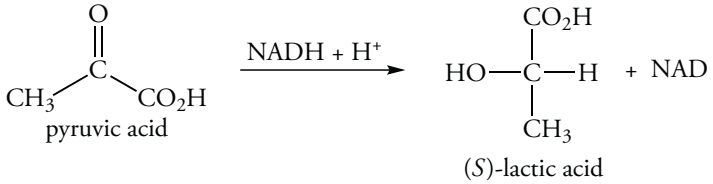
Problem 8.21

Sodium borohydride ($NaBH_4$) reacts with the C-2 carbonyl carbon atom of pyruvic acid to give lactic acid. What is the optical rotation of the product(s)?



Problem 8.22

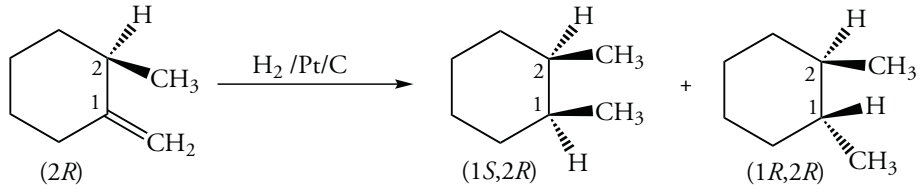
Reduction of pyruvic acid by NADH using the liver enzyme lactate dehydrogenase yields exclusively (*S*)-lactic acid. Write the Fischer projection of this product. Why does only a single product form?



8.11 REACTIONS THAT FORM DIASTEREOMERS

In the previous section, we discussed the formation of compounds with one or two stereogenic centers from achiral reactants. Now, we'll see what happens when a second stereogenic center forms in a chiral molecule. Diastereomers could result. A molecule with one stereogenic site, designated A_R, that forms a second stereogenic site at B within the molecule could give A_RB_R and A_RB_S. We recall that a single enantiomer results when a stereogenic center forms in a molecule in a chiral environment, such that provided by an enzyme. Similarly, a chiral site in a molecule should affect the stereochemistry of the second site when diastereomers form.

In the hydrogenation of an alkene using a transition metal catalyst, the planar molecule binds to the surface of the metal. If the alkene is achiral, the "side" presented to the surface of the metal is not important. The alkene can be hydrogenated from the "top" or "bottom" to give the hydrogenated product. If the alkene contains a chiral carbon atom near the double bond, however, two products are possible. Consider the catalytic hydrogenation of (*R*)-2-methylmethylenecyclohexane. Two stereoisomers, 1*S*,2*R* and 1*R*,2*R*, form, but in unequal amounts. Approximately 70% of the product is the *cis* isomer (1*S*,2*R*).



Because the alkene is chiral, there is a difference between the steric environment of the two faces of the double bond. The methyl group above the plane decreases the probability of hydrogenation from that face of the double bond. Hydrogenation from the less hindered bottom side "pushes" the newly formed methyl group up, and the *cis* isomer results. The two stereoisomers form in unequal amounts as a consequence of the chiral center. The reaction is **stereoselective**.

Similar observations show that one enantiomer reacts with an achiral reagent to give unequal amounts of diastereomeric products. The relative yields of the diastereomers often depend on the structure of the existing stereogenic center and its proximity to the newly formed stereogenic center. Many stereogenic centers are present in an enzyme catalyst. They create a chiral environment, which leads to high stereoselectivity. Usually, only one diastereomer forms in enzyme-catalyzed reactions.

Problem 8.23

Write the structure of the oxirane (epoxide) that forms when (*Z*)-2-butene reacts with *m*-chloroperbenzoic acid. Assign the configurations of the stereogenic centers.

Problem 8.24

Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure(s) of the 2-bromo-3-chlorobutane formed. Assign the configuration of the stereogenic center(s). Is the product optically active?

Problem 8.25

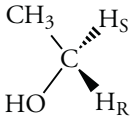
Based on the percent composition of the products for the hydrogenation of 2-methyl-methylenecyclohexane, predict the product(s) of the hydrogenation of 2-*tert*-butylmethylenecyclohexane.

Sample Solution

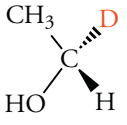
The 2-*tert*-butyl group on the "top" of the molecule decreases the probability of hydrogenation from that face. Hydrogenation tends to occur from the less hindered side and "pushes" the newly formed methyl group up. The methyl and *tert*-butyl groups are *cis*. The *cis*/*trans* ratio is larger than the 70:30 obtained from 2-methylmethylenecyclohexane because the larger *tert*-butyl group hinders attack by hydrogen more than the smaller methyl group.

8.12 PROCHIRAL CENTERS

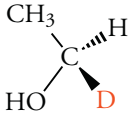
We have seen some examples of biochemical reactions in which an enzyme stereospecifically distinguishes between enantiomers. Enzymes can also distinguish between apparently equivalent groups in achiral substrates. Under such circumstances, the enzyme can generate a chiral center at an atom of an achiral reactant. An atomic center that can become chiral as a result of a stereospecific reaction is called **prochiral**. The methylene group of ethanol provides a simple example. Because the methylene carbon atom is bonded to two hydrogen atoms, it is not a chiral center. Now assume that an enzyme-catalyzed reaction substitutes a deuterium atom for one hydrogen atom. Two enantiomers result. The hydrogen atoms are **enantiotopic** because they are in mirror image environments. We designate these hydrogens H_R and H_S. For example, enantiomeric compounds form if deuterium replaces one hydrogen atom at C-1.



ethanol



(*S*)-1-deuteroethanol

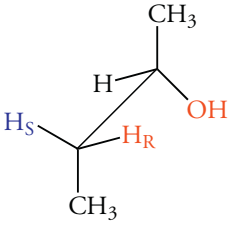


(*R*)-1-deuteroethanol

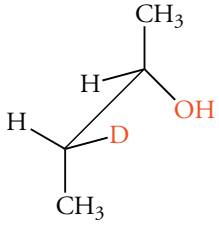
Enantiotopic atoms or groups are designated *pro-R* and *pro-S*. The hydrogen atom behind the page, as shown above, is designated *pro-S* because replacing it with deuterium gives the *S* enantiomer. The hydrogen atom in front of the page is designated *pro-R* because replacing it with deuterium gives the *R* enantiomer. A prochiral center cannot be converted into a single chiral compound by a symmetrical (achiral) reagent. However, the enzymes that catalyze biochemical reactions are chiral. Therefore, enzymes can distinguish between the enantiotopic groups of a prochiral center. Enzymes have specific binding sites into which substrates fit. For a molecule such as ethanol, when the CH_3— and OH— groups "fit" into the enzyme binding site, the prochiral hydrogen atoms are located in different environments of the chiral enzyme. A reaction might occur at one prochiral hydrogen atom, for example, and not at the other.

The concept of prochirality is also important in describing the biochemical reactions of molecules that already have one or more chiral centers. Formation of a second chiral center at an achiral site could lead to a mixture of diastereomers. The two equivalent groups at the achiral site are **diastereotopic**.

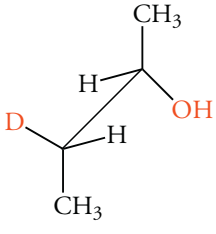
The hydrogen atoms at C-3 of (*R*)-2-butanol are diastereotopic. We can replace either one of them by deuterium. Replacing the C-3 hydrogen atom on the right in the structure gives the *R* configuration. That hydrogen atom is *pro-R*. The diastereomeric 2*R*,3*S* compound results from replacing the C-3 hydrogen atom on the left, which is *pro-S*.



(*R*)-2-butanol

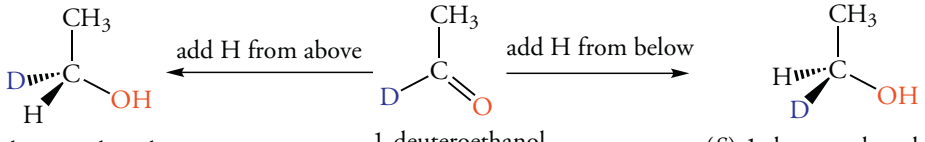


(2*R*,3*R*)



(2*R*,3*S*)

Next we consider a reaction at an sp^2-hybridized carbon atom as it is converted into a product with an sp^3-hybridized carbon atom. Although the trigonal carbon atom of a carbonyl group is not a stereogenic center, reducing that group to an alcohol gives a new stereogenic center. Consider the formation of a C—H bond in the reduction of ethanal that has been deuterated at C-l. Bond formation at one face gives one enantiomer; formation of a C—H bond at the opposite face gives the other enantiomer.



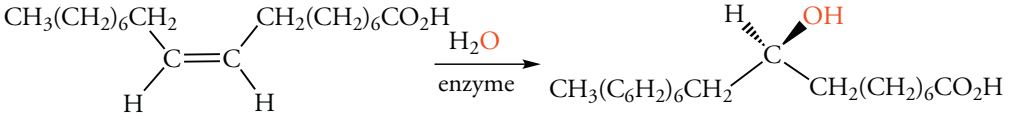
(*R*)-1-deuteroethanol

1-deuteroethanol

(*S*)-1-deuteroethanol

To describe the addition reactions at the two possible faces of planar parts of a molecule, we must be able to distinguish the faces. To do this, consider the sequence of groups bonded to the trigonal atom. If, when viewed from one face, the groups are in a clockwise sequence when arranged by *R*,*S* priority rules, that face is designated *re*. If the sequence of groups is counterclockwise, the face is designated *si*. Viewing ethanal-l-d from above the page as shown above, the face is *si* because the order of the groups O > CH_3 > D is counterclockwise. If a hydrogen adds to the *si* face, pushing the deuterium down, the product is (*R*)-1-deuteroethanol.

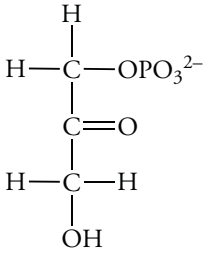
Many biochemical reductions occur at sp^2-hybridized carbon atoms. These reactions yield a single enantiomer. For example, the hydration of oleic acid yields exclusively (*R*)-10-hydroxystearic acid.



oleic acid (*R*)-10-hydroxystearic acid

Problem 8.26

The structure of dihydroxyacetone phosphate, an intermediate in glycolysis, is shown below. Identify the prochiral hydrogen atoms and label them as H_R and H_S.



dihydroxyacetone phosphate

Problem 8.27

In the addition of water to oleic acid in the above example, is the face to which oxygen adds *si* or *re*?

Exercises

Chirality

8.1 Which of the following isomeric methylheptanes has a chiral center?

(a) 2-methylheptane (b) 3-methylheptane (c) 4-methylheptane

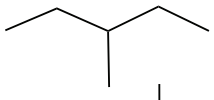
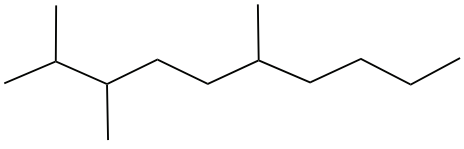
8.2 Which of the following isomeric bromohexanes has a chiral center?

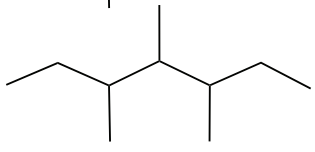
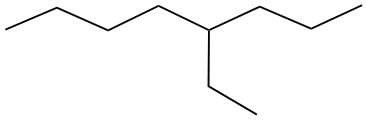
(a) l-bromohexane (b) 2-bromohexane (c) 3-bromohexane

8.3 Which of the compounds with molecular formula $C_5H_{11}Cl$ has a chiral center?

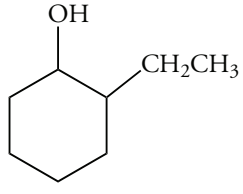
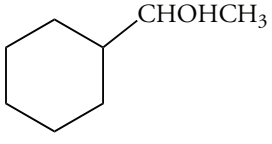
8.4 Which of the compounds with molecular formula $C_3H_5Cl_2$ has a chiral center?

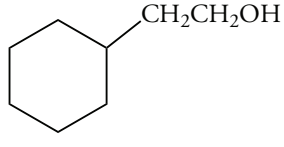
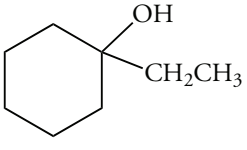
8.5 Which of the following isomeric methylheptanes has a chiral center?

(a)  (b) 

(c)  (d) 

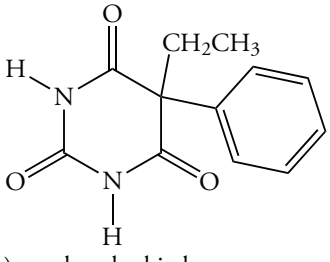
8.6 How many chiral centers does each of the following cyclic compounds have?

(a)  (b) 

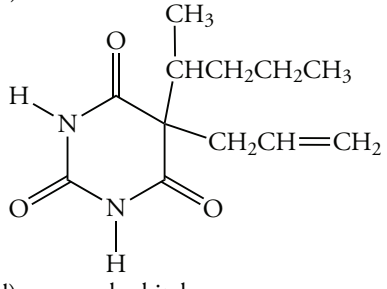
(a)  (d) 

8.7 How many chiral centers does each of the following barbiturates have?

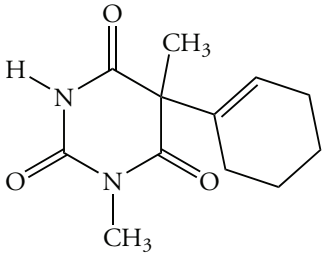
(a) phenobarbital



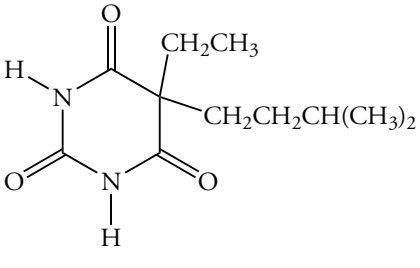
(b) secobarbital



(c) hexobarbital

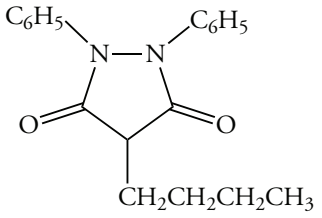


(d) amobarbital

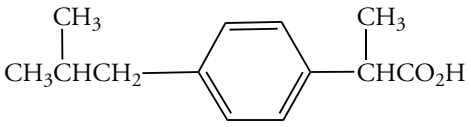


8.8 How many chiral centers does each of the following drugs have?

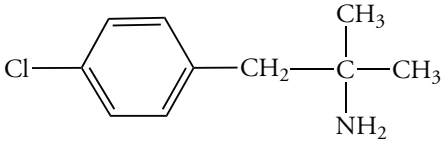
(a) phenylbutazone, used to treat gout



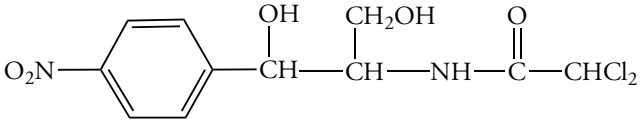
(b) ibuprofen, an analgesic



(c) chlorphentermine, a nervous system stimulent

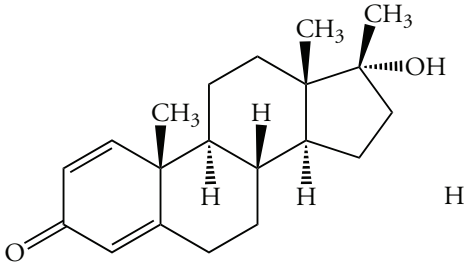


(d) chloramphenicol, an antibiotic

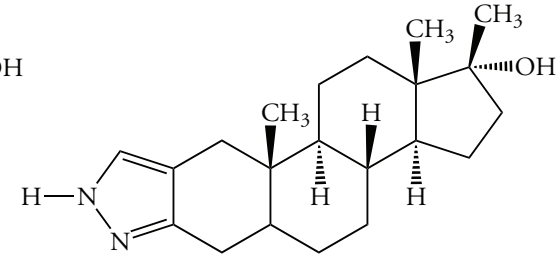


8.9 How many chiral carbon atoms are in each of the following synthetic anabolic steroids?

(a) Dianabol

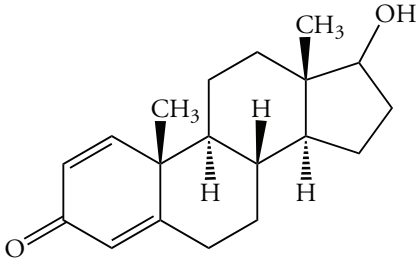


(b) stanozolol

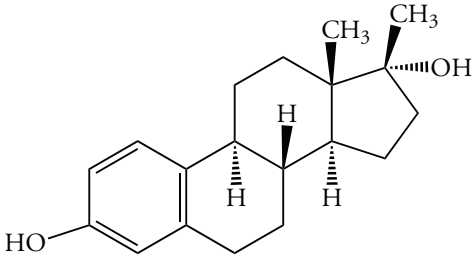


8.10 Determine the number of chiral centers in the male sex hormone testosterone and in the female sex hormone estradiol.

(a) testosterone

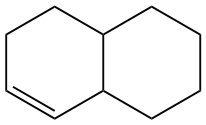


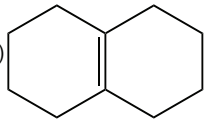
(b) estradiol

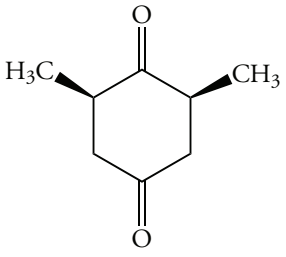


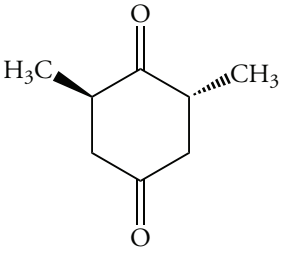
Plane of Symmetry

8.11 Determine whether each of the following compounds has a plane of symmetry.

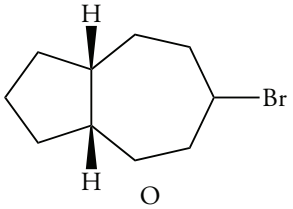
(a) 

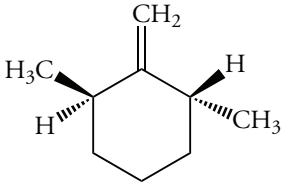
(b) 

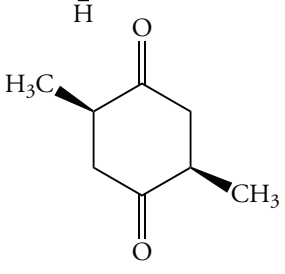
(c) 

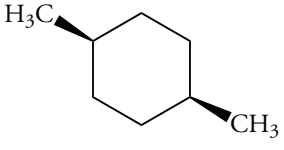
(d) 

8.12 Determine whether each of the following compounds has a plane of symmetry.

(a) 

(b) 

(c) 

(d) 

Optical Activity

8.13 Lactic acid in the blood has a specific rotation of +2.6°. A sample of lactic acid obtained from sour milk has a specific rotation of –2.6°. How do these compounds differ?

8.14 Optically pure (*S*)-(+)-citronellol from citronella oil has a specific rotation of +5.3°. An enantiomer of optically pure (*S*)-(+)-citronellol is obtained from geranium oil. What is its specific rotation?

8.15 The configuration of naturally occurring monosodium glutamate, MSG, which has a specific rotation of +24° is *S*. Is the assignment of configuration based upon the sign of the optical rotation correct?

8.16 Carvone obtained from spearmint oil is the (*R*)-(–) enantiomer. Explain the meaning of both terms within parentheses.

8.17 A solution of 3 g of menthol in 50 mL of ethanol is prepared and a sample is placed in a 10-cm tube. The optical rotation is +3.0. What is the specific rotation of menthol?

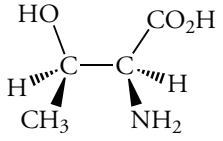
8.18 The specific rotation of (*R*)-2-bromobutane in ethanol is –23.1°. A solution of the compound in a 1-dm tube has $[\alpha]_D$ = 55°. What is the concentration of the compound in grams per 100 mL?

8.19 The specific rotation of (+)-2-butanol as a pure liquid is +13.9°. A synthetic sample of 2-butanol has an optical rotation of –4.5°. What is the composition of the sample?

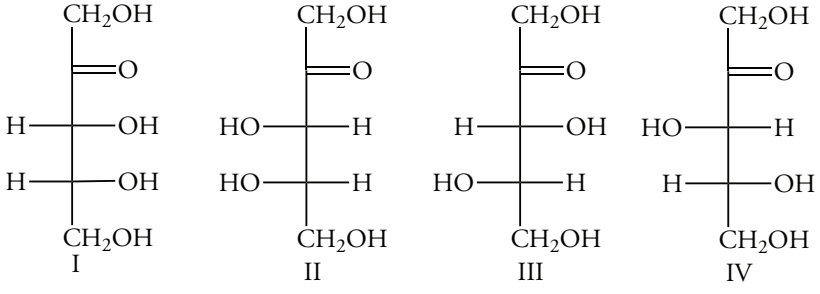
8.20 The specific rotation of the *S* enantiomer of MSG, a flavor enhancer, is +24°. What is the optical purity of a synthetic sample whose α_{obs} is +6°? What are the percentages of the two enantiomers in the sample?

Fischer Projection Formulas

8.21 Draw the Fischer projection formula of the following enantiomer of naturally occurring threonine which is isolated from proteins. Also, draw the Fischer projection formula for the other diastereomers.



8.22 What stereochemical relationship exists between any and all pairs of the following structures of carbohydrates?



Priority Rules

8.23 Arrange the groups in each of the following sets in order of increasing priority.

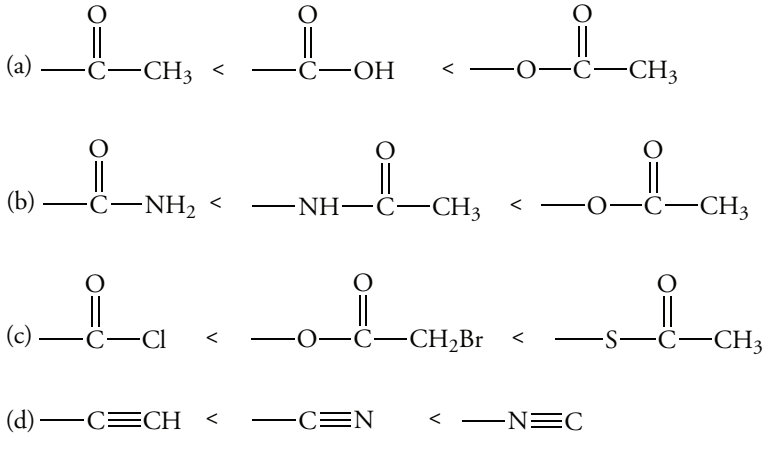
(a) —OH, —SH, —SCH_3, —OCH_3

(b) —CH_2Br, —CH_2Cl, —Cl, —Br

(c) —CH_2—CH=CH_2, —CH_2—O—CH_3, — CH_2—C≡CH, —C≡C—CH_3

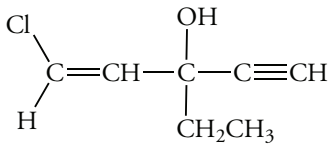
(d) —CH_2CH_3, —CH_2OH, —CH_2CH_2Cl, —OCH_3

8.24 Arrange the groups in each of the following sets in order of increasing priority.

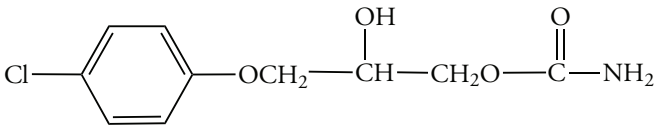


8.25 Examine the chiral carbon atom in each of the following drugs and arrange the groups from low to high priority.

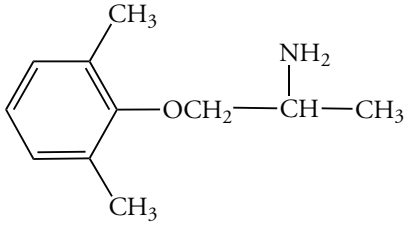
(a) ethchlorvynol, a sedative-hypnotic



(b) chlorphenesin carbamate, a muscle relaxant

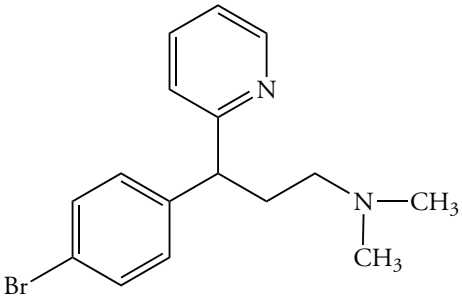


(c) mexiletine, an antiarrhythmic

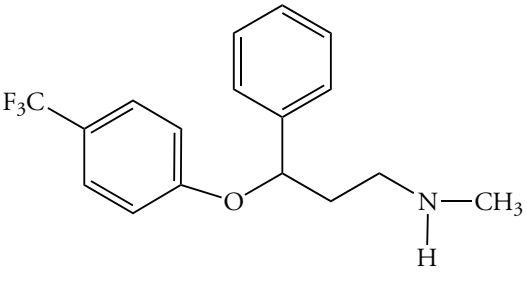


8.26 Examine the chiral carbon atom in each of the following drugs and arrange the groups from low to high priority.

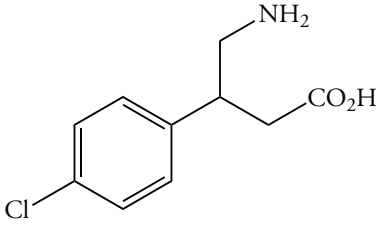
(a) brompheniramine, an antihistamine



(b) fluoxetine, an antidepressant



(c) baclophen, an antispastic



R,S Configuration

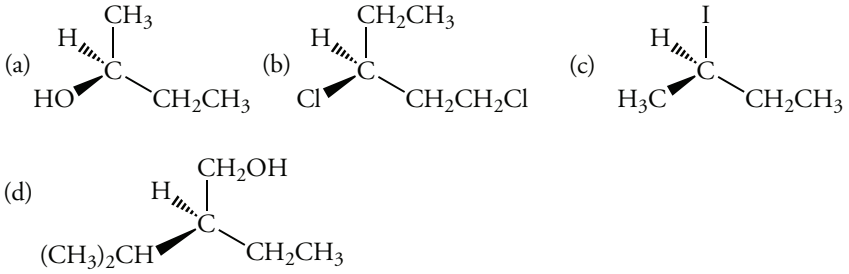
8.27 Draw the structure of each of the following compounds.

(a) (*R*)-2-chloropentane (b) (*R*)-3-chloro-1-pentene (c) (*S*)-3-chloro-2-methylpentane

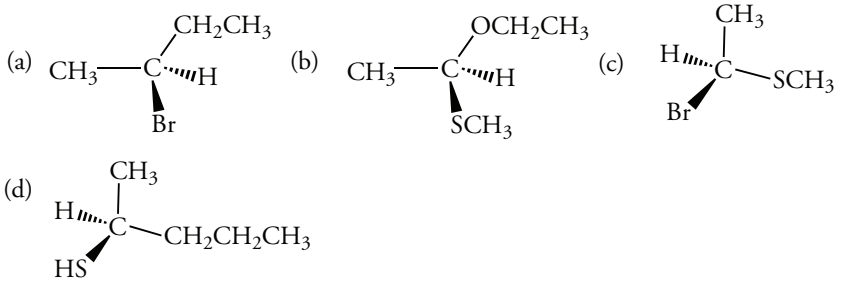
8.28 Draw the structure of each of the following compounds.

(a) (*S*)-2-bromo-2-phenylbutane (b) (*S*)-3-bromo-1-hexyne (c) (*R*)-2-bromo-2-chlorobutane

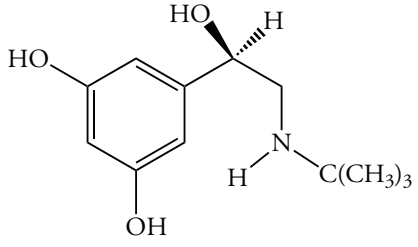
8.29 Assign the configuration of each of the following compounds.



8.30 Assign the configuration of each of the following compounds.

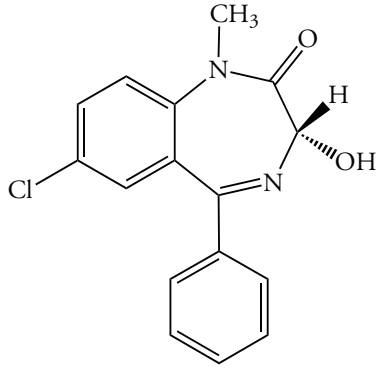


8.31 Assign the configuration of terbutaline, a drug used to treat bronchial asthma.



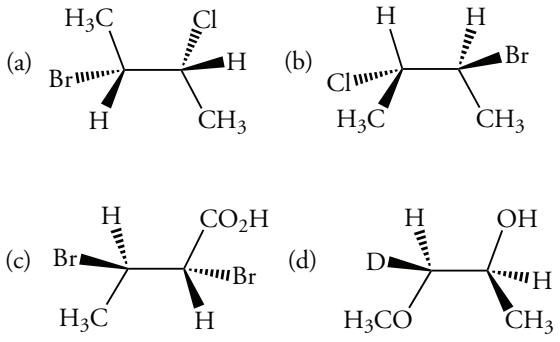
terbutaline

8.32 Assign the configuration of the following hydroxylated metabolite of diazepam, a sedative.

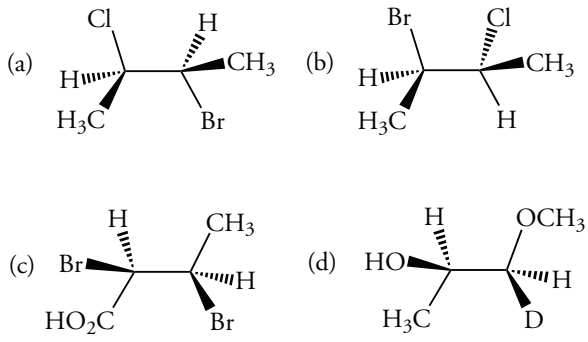


Diastereomers

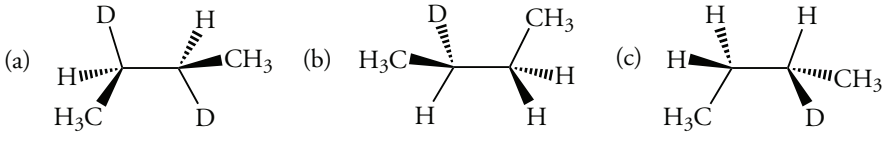
8.33 Assign the configuration of each of the following compounds.



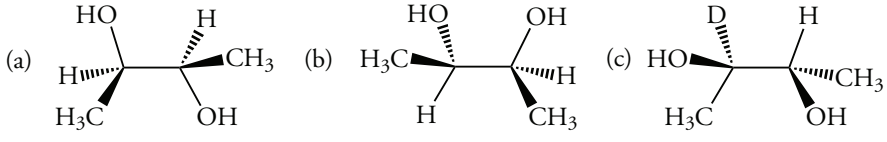
8.34 Assign the configuration of each of the following compounds.



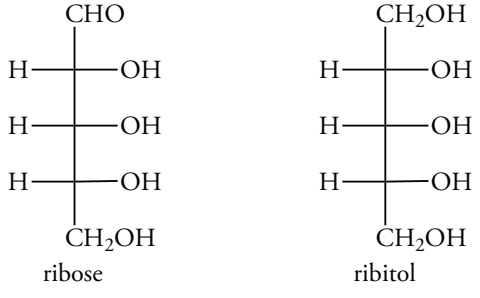
8.35 Assign the configuration of each of the following compounds.



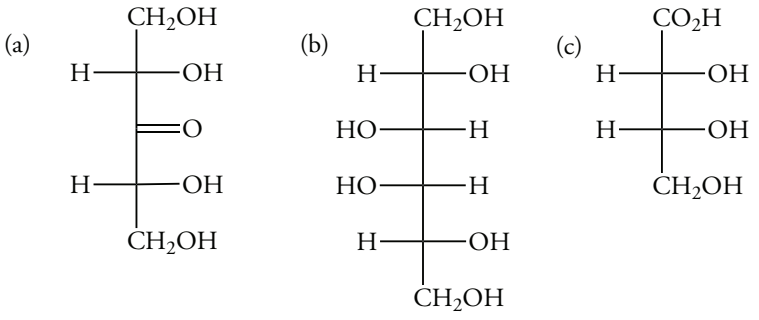
8.36 Assign the configuration of each stereogenic center in the following structures. Based on the assignment, determine if the structure is *meso*.



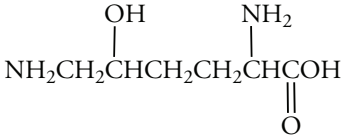
8.37 Ribose is optically active, but ribitol, its reduction product, is optically inactive. Why?



8.38 Which of the following carbohydrate derivatives are *meso* compounds?

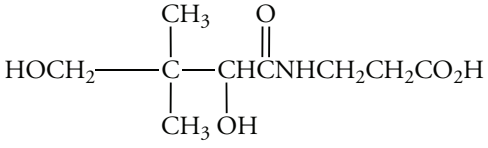


8.39 5-Hydroxylysine is an amino acid isolated from collagen. Determine the number of possible stereoisomers.



5-hydroxylysine

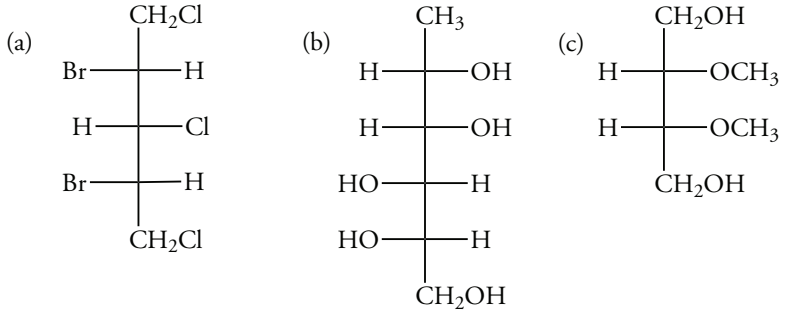
8.40 Consider the structure of pantothenic acid (vitamin B_3) and determine the number of possible stereoisomers.



pantothenic acid

8.41 There are four isomeric 2,3-dichloropentanes, but only three isomeric 2,4-dichloropentanes. Explain why.

8.42 Which of the following structures are *meso* compounds?



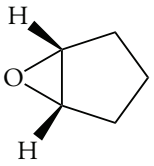
Cyclic Compounds

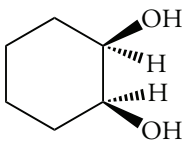
8.43 Which of the following compounds has a plane of symmetry?

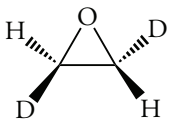
(a) *cis*-l,2-dibromocyclobutane (b) *trans*-l,2-dibromocyclobutane

(c) *cis*-l,3-dibromocyclobutane (d) *trans*-l,3-dibromocyclobutane

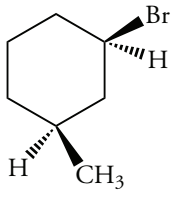
8.44 Which of the following structures has a plane of symmetry?

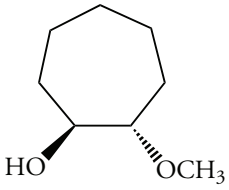
(a) 

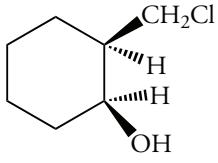
(b) 

(c) 

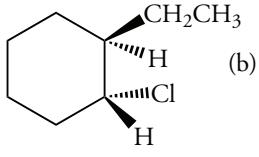
8.45 Assign the configuration of each stereogenic center in the following structures.

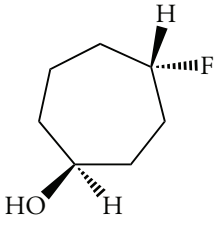
(a) 

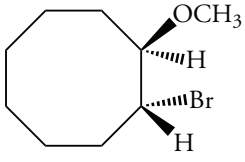
(b) 

(c) 

8.46 Assign the configuration of each stereogenic center in the following structures.

(a) 

(b) 

(c) 

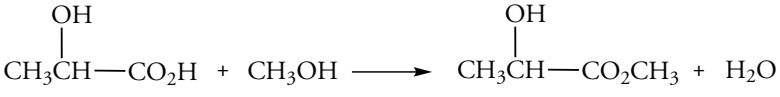
Resolution of Enantiomers

8.47 Reaction of a racemic mixture of A_R,A_S with a resolving agent X_R yields diastereomers. The A_R–X_R isomer is less soluble than A_R–A_S. Consequently, the A_S isomer is obtained optically pure. Describe the experimental results if X_S were available as a resolving agent.

8.48 Resolution of a racemic mixture yields one enantiomer with $[\alpha]_D = +44°$ and another enantiomer with $[\alpha]_D = -33°$. One enantiomer is optically pure. Which one? What is the optical purity of the other enantiomer?

Reactions of Chiral Compounds

8.49 (*R*)-(–)-Lactic acid is converted into a methyl ester when it reacts with methanol. What is the configuration of the ester? Can you predict its sign of rotation?



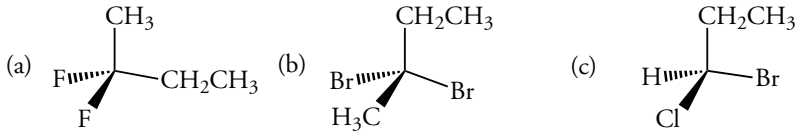
8.50 Free radical chlorination of (*S*)-2-bromobutane gives a mixture of compounds resulting from attack at any of the four nonequivalent carbon–hydrogen bonds. The products of reaction at C-l and C-4 are both optically active. Explain why.

8.51 Free radical chlorination of (*S*)-2-fluorobutane gives a 31% yield of 2-chloro-2-fluorobutane. What is the expected stereochemistry of the product?

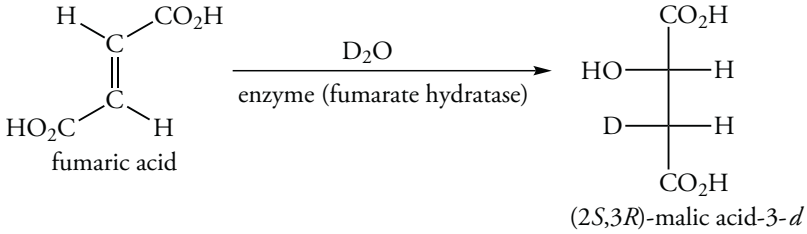
8.52 Free radical chlorination of (*S*)-2-bromobutane at the C-2 atom gives an optically inactive product, but reaction at C-3 gives an optically active product. Explain why.

Prochiral Centers

8.53 Consider the atoms in each of the following structures and indicate which are prochiral. Which have enantiotopic groups? Which have diastereotopic groups?

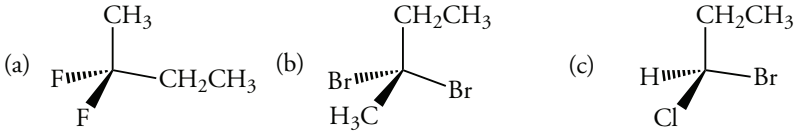


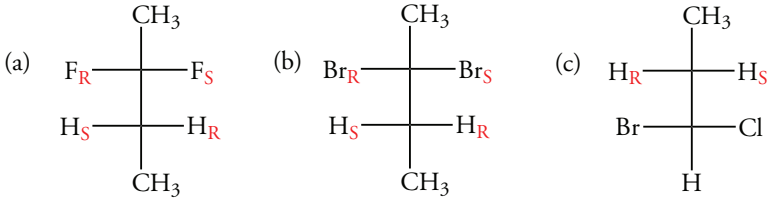
8.54 Addition of water to fumaric acid yields (*S*)-malic acid as part of the citric acid cycle. When D_2O is used, the product is (2*S*,3*R*)-malic acid-3-d. Is the addition reaction *syn* or *anti*? Are the two carbon atoms of the double bond equivalent or not?



8.53 Consider the atoms in each of the following structures and indicate which are prochiral. Which have enantiotopic groups? Which have diastereotopic groups?

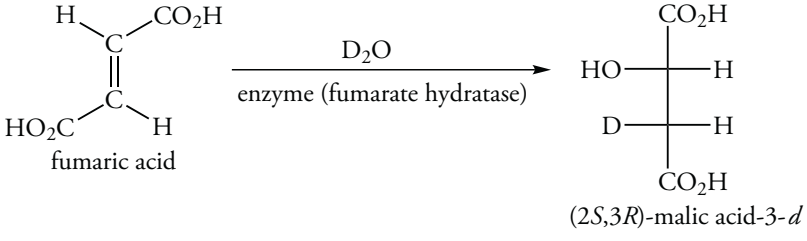
Answer: (a) The two fluorine atoms are prochiral, as are the hydrogen atoms of the methylene group. Each of these atoms is enantiotopic.
(b) The two bromine atoms are prochiral, as are the hydrogen atoms of the methylene group. Each of these atoms is enantiotopic.
(c) The two hydrogen atoms of the methylene group are prochiral. They are diastereotopic because the C-1 atom is chiral.

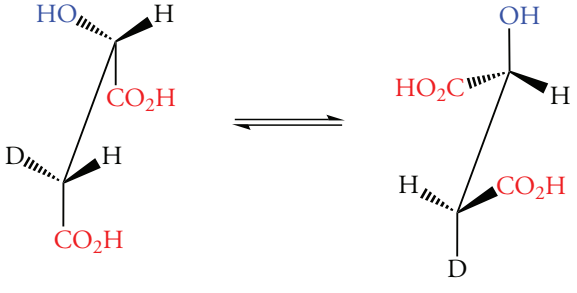




8.54 Addition of water to fumaric acid yields (*S*)-malic acid as part of the citric acid cycle. When D_2O is used, the product is (2*S*,3*R*)-malic acid-3-d. Is the addition reaction *syn* or *anti*? Are the two carbon atoms of the double bond equivalent or not?

Answer: Draw a three-dimensional representation of the Fischer projection and rotate about the C-2 to C-3 bond to obtain a staggered conformation placing the deuterium and the hydroxyl group in an *anti* arrangement assuming that an *anti* addition reaction occurred. In this conformation, the two —CO_2H groups are arranged as if the addition reaction occurred by an *anti* periplanar transition state. Thus, the addition is indeed *anti*.





9 Haloalkanes and Alcohols
Introduction to Nucleophilic Substitution and Elimination Reactions



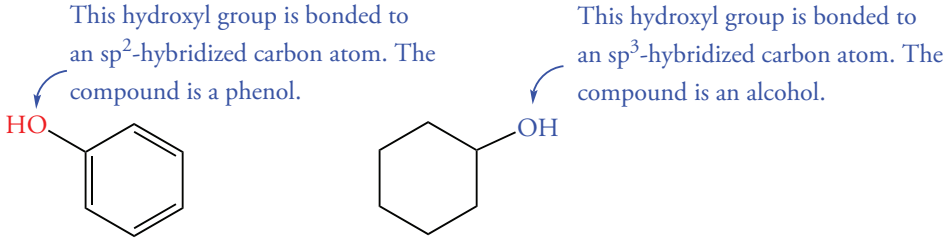
Cholesterol

9.1 Functionalized Hydrocarbons

We introduced the concept of functional groups and their role in the organization of the study of organic chemistry in Chapter 2. But so far, we have discussed only the chemistry of two functional groups—the multiple bond of alkenes and alkynes—which are part of the hydrocarbon skeleton. Now we will start to examine the first of many functional groups containing electronegative atoms. In this chapter, we consider haloalkanes (alkyl halides) and alcohols, including some reactions that interconvert haloalkanes and alcohols. We will discuss alcohols in much greater depth in Chapter 15.

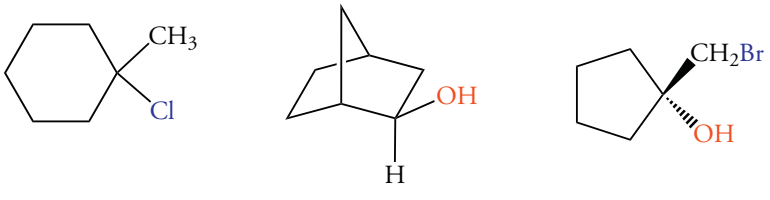
Compounds with a halogen atom bonded to an sp^3-hybridized carbon atom are called **haloalkanes.** Halogens can also bond to an sp^2-hybridized carbon atom of an aromatic compound or an alkene. However, since the chemistry of these compounds is very different, we will not consider them in this chapter. Compounds with the halogen atom bonded to an sp-hybridized carbon atom, which are very unstable, are seldom encountered. We will primarily focus on the chemistry of chloro and bromo compounds. Iodo compounds are less stable. The chemistry of fluoro compounds is somewhat different from the other halogen compounds, and we will not discuss fluoro compounds in this text.

Alcohols contain a hydroxyl group bonded to an sp^3-hybridized carbon atom. Compounds in which a hydroxyl group is bonded to the sp^2-hybridized carbon atom of a benzene ring are called **phenols.** The distinction between an alcohol and a phenol is illustrated by the two isomeric structures shown below. We will discuss the chemistry of phenols, which differs from that of alcohols, in Chapter 23.



Classification of Haloalkanes and Alcohols

Haloalkanes and alcohols are classified as primary (1°), secondary (2°), or tertiary (3°) according to the number of alkyl groups bonded to the carbon atom bearing the halogen or hydroxyl group.

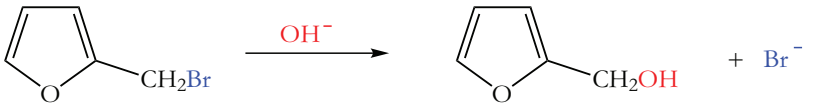


Tertiary chloride | Secondary alcohol | Primary bromide, tertiary alcohol

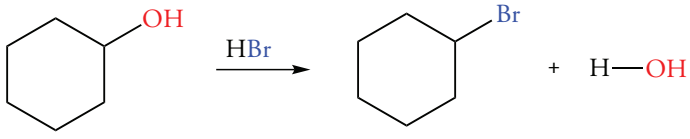
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00009-7
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Interconversion of Haloalkanes and Alcohols

Haloalkanes and alcohols are important starting materials in the synthesis of compounds with other functional groups. Primary haloalkanes react with hydroxide ion to give alcohols, although we will see that elimination reactions compete with substitution for secondary and tertiary halides.

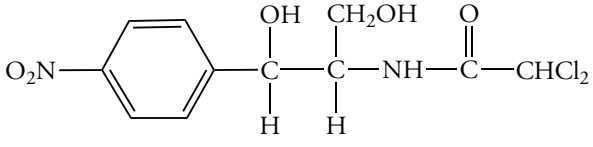


Alcohols react with hydrogen halides to form haloalkanes. The rate of the reaction differs for primary, secondary, and tertiary alcohols.



Problem 9.1

Classify the halide and alcohol functional groups in the broad-spectrum antibiotic chloramphenicol.

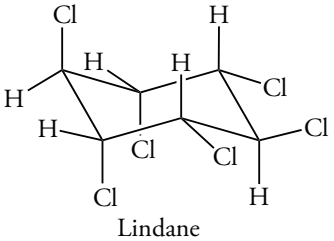


Sample Solution

Only one carbon atom is bonded to a chlorine atom, and it is a primary carbon, so chloramphenicol is a primary haloalkane. The hydroxyl group nearest the benzene ring is on a secondary carbon, so it is a secondary alcohol, the CH_2OH group is a primary alcohol.

Problem 9.2

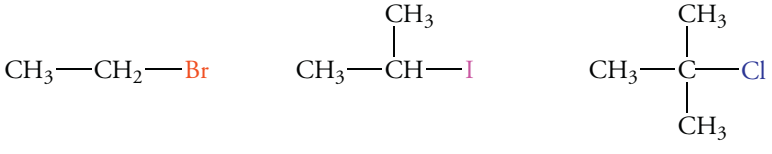
Classify the carbon centers containing chlorine in the insecticide lindane.



Lindane

9.2 NOMENCLATURE OF HALOALKANES

Haloalkanes with simple structures are often given a common name consisting of the name of the alkyl group followed by the name of the halide; that is, they are named as alkyl halides. A few common examples are shown below.

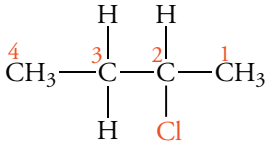


Ethyl bromide | Isopropyl iodide | *tert*-Butyl chloride

IUPAC Names of Haloalkanes

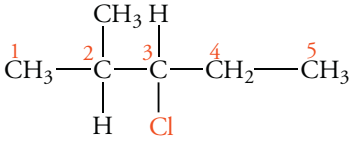
Haloalkanes are named in the IUPAC system by an extension of the rules we outlined earlier for alkanes.

1. Identify the longest continuous chain of carbon atoms that includes the hydroxyl group; this is, the parent chain.

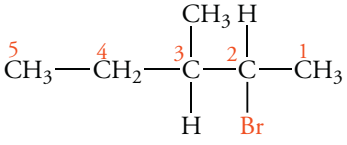


2-Chlorobutane

2. If the parent chain has branching alkyl groups, number the chain from the end nearer the first substituent whether it is an alkyl group or a halogen atom.

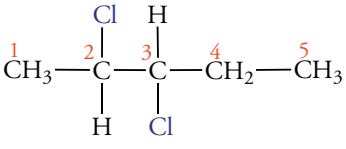


3-Chloro-2-methylpentane

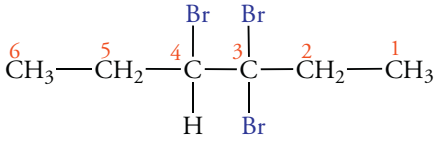


2-Bromo-3-methylpentane

3. If the compound contains two or more halogen atoms of the same type, indicate them with the prefixes di-, tri-, etc. Give each halogen atom a number that corresponds to its position in the parent chain.

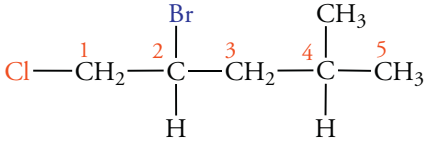


2,3-Dichloropentane



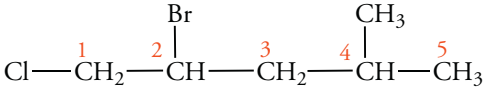
3,3,4-Tribromohexane

4. If a compound contains different halogen atoms, number them according to their positions on the chain and list them in alphabetical order.



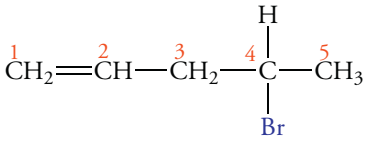
2-Bromo-1-chloro-4-methylpentane

5. If the chain can be numbered from either end based on the location of the substituents, begin at the end nearer the substituent that has alphabetical precedence, whether it is an alkyl group or a halogen atom.

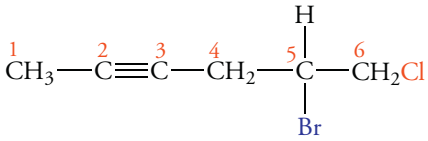


2-Bromo-1-chloro-4-methylpentane

6. In a halogen-containing compound with a double or triple bond, the unsaturated unit takes precedence in numbering the carbon chain. Place the number indicating the position of the multiple bond in front of the name of the alkene (or alkyne). Use the number that indicates the position of the halogen group as a prefix to the name of the alkene (or alkyne).

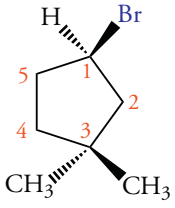


4-Bromo-1-pentene

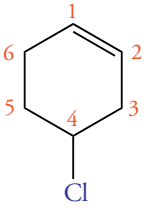


5-Bromo-6-chloro-2-hexyne

7. Number the halocycloalkanes from the carbon atom bearing the halogen atom unless another functional group, such as a double bond, takes precedence. Number carbon atoms in the ring to give the lower number to the substituent.



1-Bromo-3,3-dimethylcyclopentane



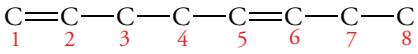
4-Chlorocyclohexene

Problem 9.3

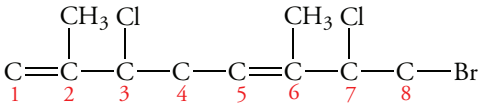
(*E*)-8-Bromo-3,7-dichloro-2,6-dimethyl-l,5-octadiene is produced by a species of red algae. Draw its structure.

Sample Solution

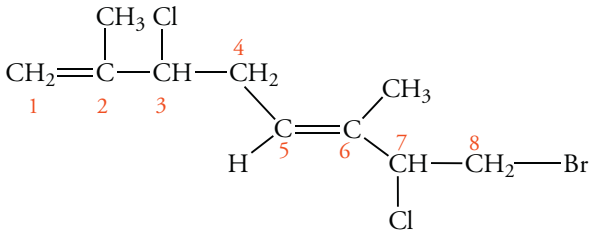
Draw the eight-carbon-atom parent chain and select a direction for numbering it. Place double bonds between the C-l and C-2 and between the C-5 and C-6.



Next, place a bromine atom at C-8, chlorine atoms at C-3 and C-7, and methyl groups at the C-2 and C-6.



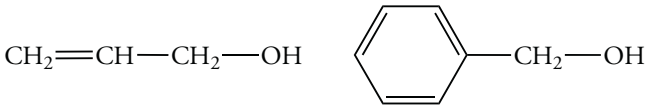
C-l must have two attached hydrogen atoms; no geometric isomers are possible about this double bond. Arrange the configuration about the double bond between the C-5 and C-6. The higher priority groups at both the C-5 and C-6 are the alkyl groups that are part of the parent carbon chain. Place the atoms of the carbon chain on the opposite sides of the double bond to obtain the (*E*) configuration. Finally, fill in the requisite hydrogen atoms.



(*E*)-8-Bromo-3,7-dichloro-2,6-dimethyl-l,5-octadiene

9.3 NOMENCLATURE OF ALCOHOLS

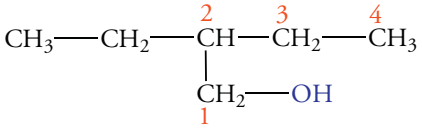
Alcohols that contain one to four carbon atoms have common names consisting of the name of the alkyl group followed by the term "alcohol." For example, CH_3CH_2OH is ethyl alcohol and $CH_3CH(OH)CH_3$ is isopropyl alcohol. Other common names are allyl alcohol and benzyl alcohol, whose structures are shown below.



Allyl alcohol Benzyl alcohol

The IUPAC system of naming alcohols is as follows.

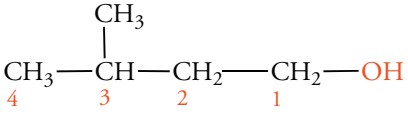
1. Identify the longest continuous chain of carbon atoms that includes the hydroxyl group as the parent chain.



The longest chain that contains the hydroxyl group has four carbon atoms, although the longest chain has five carbon atoms.

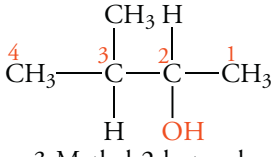
2-Ethyl-1-butanol

2. Name the parent by substituting the suffix *-ol* for the final *-e* of the corresponding alkane.



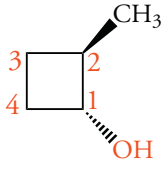
3-Methyl-1-butanol

3. Indicate the position of the hydroxyl group using the number of the carbon atom to which it is attached. Number the chain so that the carbon atom bearing the hydroxyl group has the lower number.

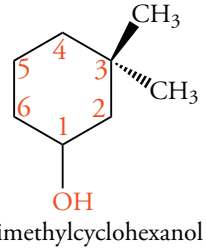


3-Methyl-2-butanol

4. When a hydroxyl group is attached to a ring, number the ring starting with the carbon atom bearing the hydroxyl group. Continue numbering in the direction that gives the lowest numbers to carbon atoms with substituents such as alkyl groups. Do *not* use the number 1 in the name to indicate the position of the hydroxyl group.

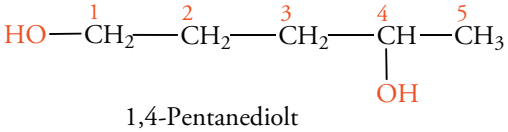


trans-2-Methylcyclobutanol



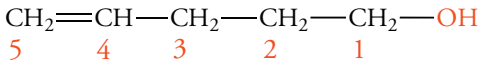
3,3-Dimethylcyclohexanol

5. Alcohols that contain two or more hydroxyl groups are called diols, triols, and so on. Retain the terminal *-e* in the name of the parent alkane and add the suffix -diol or -triol. Indicate the positions of the hydroxyl groups in the parent chain by numbers.

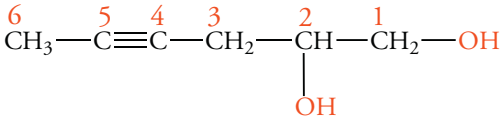


1,4-Pentanediolt

6. When an alcohol contains a double or triple bond, the hydroxyl group takes precedence in numbering the carbon chain. Place the number that indicates the position of the multiple bond in front of the name of the alkene (or alkyne) and drop the final *-e*. Append the number that indicates the position of the hydroxyl group to the name of the alkene (or alkyne) along with the suffix *-ol*.



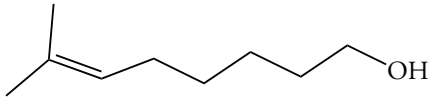
4-Pentene-1-ol



4-Hexyne-1,2-diol

Problem 9.4

What is the IUPAC name for citronellol, a compound found in geranium oil and used in perfumes?



Citronellol

Sample Solution

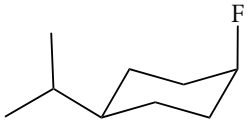
The longest carbon chain that contains the hydroxyl group has eight carbon atoms. The hydroxyl group is on the carbon atom located on the right side of the chain. This carbon atom is C-l. Numbering the chain from right to left, the methyl groups are at C-3 and C-7. The double bond is located at C-6. The name is 3,7-dimethyl-6-octen-l-ol.

Problem 9.5

Menthol is the most stable stereoisomer of 2-isopropyl-5-methylcyclohexanol. Draw the chair conformation of this compound.

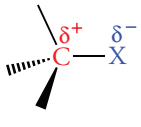
Problem 9.6

What is the IUPAC name of the following containing compound?



9.4 STRUCTURE AND PROPERTIES OF HALOALKANES

We recall that the halogens are more electronegative than carbon. As a result, the carbon atom of a carbon–halogen bond bears a partial positive charge. The halogen atom has an equal and opposite partial negative charge.



where X = F, Cl, Br, I

Because the carbon atom in a C–X bond has a partial positive charge, it is *electrophilic*. It reacts with anions or neutral molecules such as water that have an unshared electron pair which have a full or partial negative charge. We shall have much to say about these reactions later in this chapter and in Chapter 10.

The atomic radii of the halogens increase going from top to bottom in the periodic table. This trend is reflected in the bond lengths of the carbon–halogen bond.

	$CH_3—F$	$CH_3—Cl$	$CH_3—Br$	$CH_3—I$
bond length (pm)	139	178	193	214

The polarizability of an atom (Section 2.8) is a measure of the ease with which its electrons can be distorted in an electric field. The polarizability of the halogen atoms increases as we move down the periodic table: F < CI < Br < I. Highly polarizable atoms interact more strongly by van der Waals forces than less polarizable atoms. Therefore, intermolecular forces for haloalkanes increase in the order RF < RCI < RBr < RI. The effect of intermolecular forces is reflected in the boiling points of haloalkanes, which increase in the same order as the polarizability of their halogen components.

	$CH_3—CH_2—F$	$CH_3—CH_2—Cl$	$CH_3—CH_2—Br$	$CH_3—CH_2—I$
boiling point (°C)	–37.7	12.7	38.4	72

Fluoroalkanes and chloroalkanes that contain a single halogen atom are less dense than water. Compounds with two or more chlorine atoms are more dense than water. All bromoalkanes and iodoalkanes have greater densities than water (Table 9.l).

Table 9.1
Boiling Points and Densities of Haloalkanes

Compound	*Boiling Point (°C)*	*Density (g/mL)*
CH_3F	–78	1.44
CH_3Cl	27	2.22
CH_3Br	40.2	1.47
CH_3I	42	2.28
CH_2Cl_2	40	1.34
$CHCl_3$	61	1.50
CCl_4	77	1.60
CH_3CH_2F	–38	1.70
CH_3CH_2Cl	12	0.92
CH_3CH_2Br	38	0.716
$CH_3CH_2CH_2F$	3	0.782
$CH_3CH_2CH_2Cl$	47	0.89
$CH_3CH_2CH_2Br$	71	1.35
$CH_3CH_2CH_2I$	102	1.75

Table 9.2
Boiling Points and Solubilities of Alcohols

Compound	*Boiling Point (°C)*	*Solubility (g/100 mL water)*
Methanol	65	Miscible
Ethanol	78	Miscible
1-Propanol	97	Miscible
1-Butanol	117	7.9
1-Pentanol	137	2.7
1-Hexanol	158	0.59
1-Heptanol	176	0.09
1-Octanol	194	Insoluble
1-Nonanol	213	Insoluble
1-Decanol	229	Insoluble

9.5 STRUCTURE AND PROPERTIES OF ALCOHOLS

The C—O—H bond angle in methyl alcohol is 108.9°, approximately the tetrahedral bond angle (Figure 9.1). According to VSEPR theory, the lone pair electrons in the remaining two sp^3 hybrid orbitals of the oxygen atom are directed to the remaining comers of a tetrahedron. The radius of the oxygen atom is smaller than the radius of a carbon atom. As a result, the O—H bond length (96 pm) is shorter than the C—H bond length (110 pm), and the C—O bond length (140 pm) is shorter than a C—C bond length (154 pm).

The dipole moments of ethanol and propane are 1.69 and 0.08 D, respectively. Alcohols are much more polar than alkanes because they have both a polar C—O bond and a polar O—H bond. Alcohols form strong intermolecular hydrogen bonds, and these bonds have an enormous influence on their physical properties.

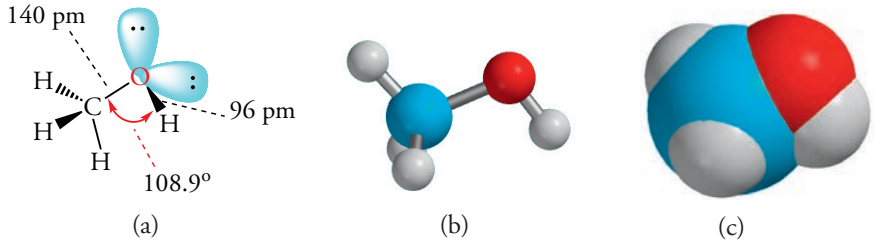


Figure 9.1
Structure of Methanol
(a) The oxygen atom of methanol is sp^3-hybridized. The C—O—H bond angle is close to the tetrahedral bond angle. The two sets of lone pair electrons are in sp^3 hybrid orbitals that are directed to two of the corners of a tetrahedron. (b) Ball-and-stick model of methanol. (c) Space-filling model of methanol.

Boiling Points of Alcohols

The hydroxyl group of an alcohol can serve as both a hydrogen bond donor and a hydrogen bond acceptor. As a consequence, much more energy is needed to separate hydrogen-bonded alcohol molecules than is required to disrupt the relatively weak London forces in alkanes.

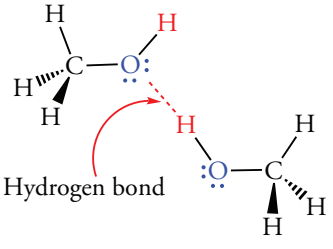


Figure 9.2 shows the relationship between the boiling points of the alcohols and alkanes that have approximately the same molecular weight. As the molecular weights of alkanes and alcohols increase, the two curves approach each other. In alcohols having high molecular weights, hydrogen bonding is still possible, but interactions due to London forces increase because the carbon chain is longer. Hence, the difference in boiling points between an alcohol and an alkane of comparable molecular weight decreases.

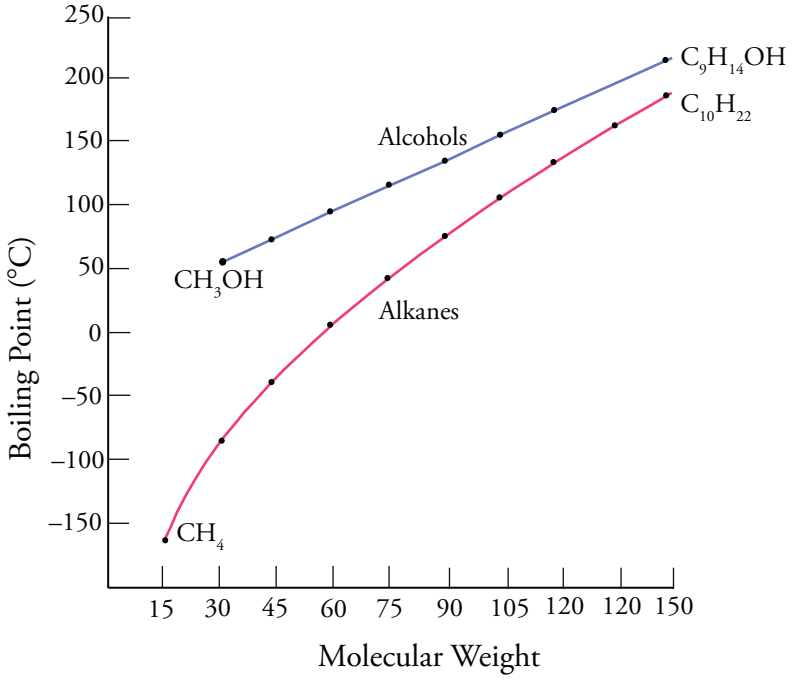


Figure 9.2
Comparison of the Boiling Points of Alcohols and Alkanes
The boiling points of alkanes and alcohols increase with increasing chain length. Alcohols have higher boiling points than alkanes of comparable molecular weight. This difference decreases as the length of the carbon chain increases.

Solubility of Alcohols in Water

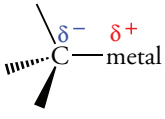
The ability of alcohols to form hydrogen bonds has an important effect on their solubilities in water. Table 9.2 lists the solubilities of some alcohols that contain unbranched alkyl groups. The lower molecular weight alcohols are soluble in water in all proportions. These molecules, like water, are highly polar, and we know that "like dissolves like." Water and alcohols can hydrogen bond to one another. However, as the size of the alkyl group increases, alcohols more closely resemble alkanes, and the hydroxyl group has less effect on their physical properties. Water can still form hydrogen bonds to the hydroxyl group. However, the long chain interferes with other water molecules and prevents them from hydrogen bonding to each other. The formation of a hydrogen bond between an alcohol and water releases energy. However, the energy released is not sufficient to compensate for disrupting the extensive hydrogen-bonding network of water. As a result, the solubility of alcohols decreases with increasing size of the alkyl group.

Alcohols as Solvents

Ethanol is an excellent solvent for many organic compounds, especially those with lone pair electrons that are hydrogen bond acceptors. Polar compounds dissolve readily in the "like" polar solvent. Nonpolar compounds dissolve in alcohols to some extent, but the solubility is often limited because the extensive hydrogen-bonding network of the alcohol must be broken to accommodate the solute.

9.6 ORGANOMETALLIC COMPOUNDS

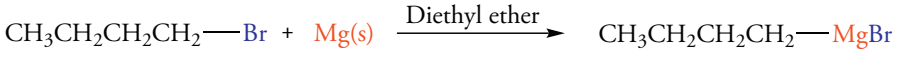
Organic halogen compounds are widely used to prepare reactive compounds containing a carbon–metal bond. They are collectively known as **organometallic compound**s. Metals that form organic derivatives include lithium, magnesium, zinc, mercury, and copper. Although each type of organometallic compound has unique properties, there are also some common features. Many have such a high negative charge density on carbon that they act as carbanions.



In this chapter, we discuss the preparation of organometallic compounds containing magnesium and copper. We will describe a few reactions. We will discuss the chemistry of these important synthetic compounds in Chapter 17 and in several later chapters.

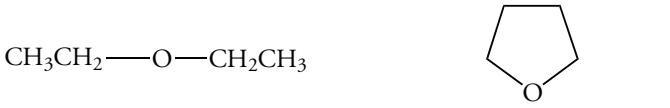
Grignard Reagents

Haloalkanes and other compounds with the halogen atom bonded to either sp^3-hybridized or sp^2-hybridized carbon atoms (aryl and vinyl halides) react with magnesium metal to yield organomagnesium halides called **Grignard reagents**. Grignard reagents are usually prepared in diethyl ether ($CH_3CH_2O–CH_2CH_3$). *An ether solvent is essential for the reaction.* The French chemist Victor Grignard discovered this reaction in 1900, and it has been studied and used extensively ever since.



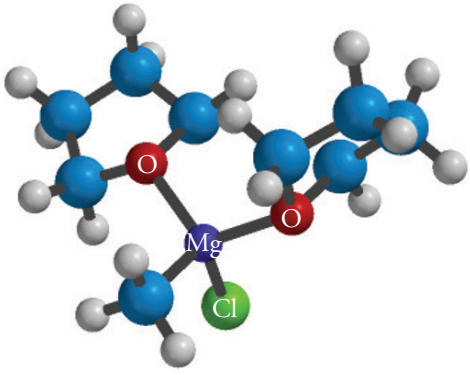
1-Bromobutane — 1-Butylmagnesium bromide

Grignard reagents form easily from 1°, 2°, and 3° alkyl halides, although their reactivities differ. Aryl and vinyl halides react somewhat more slowly, and the cyclic ether tetrahydrofuran (THF) is required to prepare Grignard reagents of these compounds. The higher boiling point of the cyclic ether provides more vigorous reaction conditions, but the rate of the reaction also increases because THF solvates the Grignard reagent better than diethyl ether.



Diethyl ether
bp 35 °C

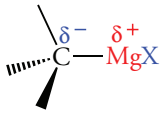
Tetrahydrofuran
bp 65 °C



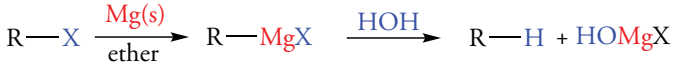
Molecular model of a complex of methyl-magnesium chloride, a Grignard reagent, in which two molecules of tetrahydrofuran, THF, are bound to magnesium. The model is based on the crystal structure.

The order of reactivity of the halogens in haloalkanes is I > Br > CI >> F. Organofluorides are so unreactive that they are never used to prepare Grignard reagents. Organohalogen compounds containing bromine and chlorine are readily available, and are commonly used to prepare Grignard reagents. Grignard reagents are used synthetically to form new carbon–carbon bonds. A Grignard reagent has a very polar carbon–magnesium bond in which the carbon atom has a partial negative charge and the metal a partial positive charge.

The polarity of the carbon–magnesium bond is opposite that of the carbon–halogen bond of haloalkanes. Because the carbon atom in a Grignard reagent has a partial negative charge, it resembles a carbanion, and it reacts with electrophilic centers such as the carbonyl carbon atom of aldehydes, ketones, and esters. We will discuss this chemistry extensively in later chapters.



Grignard reagents react rapidly with acidic hydrogen atoms in molecules such as alcohols and water. When a Grignard reagent reacts with water, a proton replaces the halogen, and the product is an alkane. The Grignard reagent therefore provides a pathway for converting a haloalkane to an alkane in two steps.

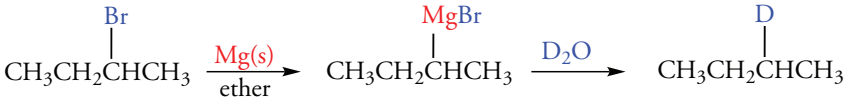


Problem 9.7

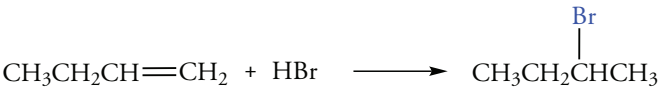
Devise a synthesis of $CH_3CH_2CHDCH_3$ starting from 1-butene and heavy water (D_2O).

Sample Solution

Reaction of a Grignard reagent, RMgBr, with D_2O will yield R—D. The necessary Grignard reagent is obtained from the corresponding bromoalkane, RBr.

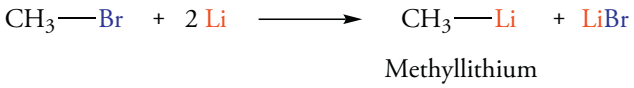


The required 2-bromobutane can be prepared from 1-butene by adding HBr. This reaction occurs according to Markovnikov's rule, and a hydrogen atom adds to the less substituted carbon atom of the double bond.



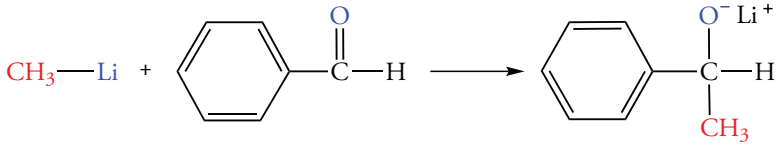
Organolithium Reagents

Lithium reacts with haloalkanes to give organolithium reagents. For example, bromomethane reacts with lithium to give methyllithium. The organic portion of the organolithium reagent behaves as a carbanion.

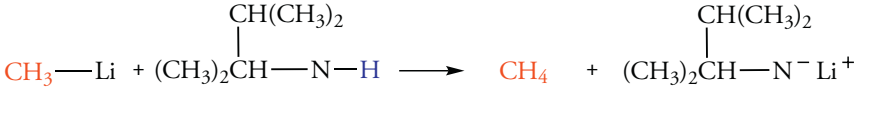


Methyllithium

Methyllithium reacts with carbonyl compounds to place the equivalent of a "methyl carbanion" (CH_3^-) at the carbon atom of a carbonyl group, as in benzaldehyde.



Organolithium compounds are used as bases to remove protons from very weak acids. The pK_a of methane is about 50, and the methyl carbanion is one of the strongest bases encountered in organic chemistry. Organolithium compounds, such as methyllithium, are used to prepare conjugate bases of a variety of organic compounds. For example, amines react with methyllithium in an acid–base reaction to form amide salts. The equilibrium constant for the reaction of methyllithium with diisopropylamine is approximately 10^{14}.



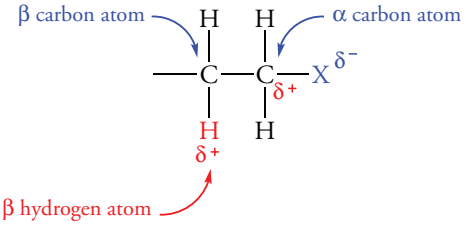
Diisopropylamine
$K_a = 10^{-36}$

$K_a = 10^{-50}$

Lithium diisopropylamide

9.7 REACTIONS OF HALOALKANES

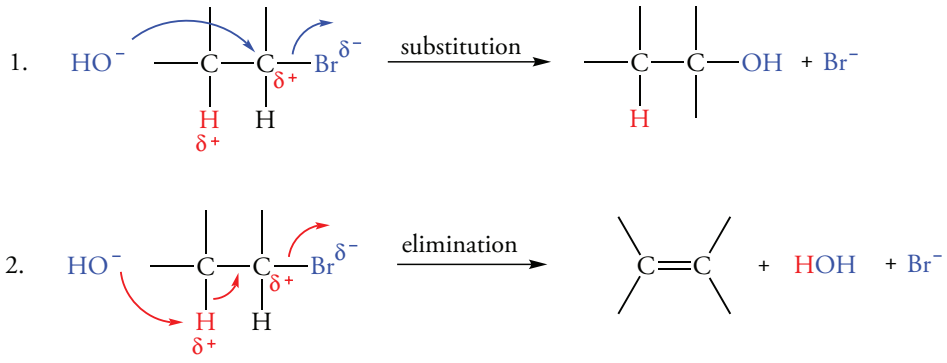
Haloalkanes have two potential reactive sites. One is the carbon atom bonded to the halogen atom—called the α carbon atom. The α carbon atom is electropositive because the halogen is more electronegative than carbon. Thus, it attracts reactants having a negative or partial negative charge. Therefore, the electropositive carbon reacts with **nucleophiles**. The second site of reactivity in a haloalkane is the hydrogen atom bonded to the adjacent carbon atom, called the β carbon atom. The hydrogen on the β carbon atom is more acidic than the hydrogen atoms in alkanes because the halogen atom on the α carbon atom withdraws electron density by an inductive effect.



The reaction of the nucleophile hydroxide ion with a haloalkane can occur in either of two ways:

1. Hydroxide ion can displace the halide ion in a substitution reaction.

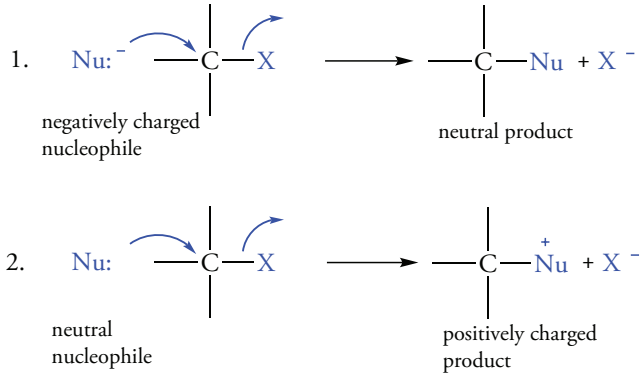
2. However, the hydroxide ion is not only a nucleophile but also a strong base that can remove a proton from the β carbon atom. When the proton is extracted, the halide ion can depart, and a double bond forms in an elimination reaction.



The substitution and elimination reactions usually occur concurrently, and mixtures of products result. In this chapter, we first consider the substitution reaction and then the elimination reaction. In the next chapter (Chapter 10), we will evaluate the conditions that cause one reaction to be favored over the other.

9.8 NUCLEOPHILIC SUBSTITUTION REACTIONS OF HALOALKANES

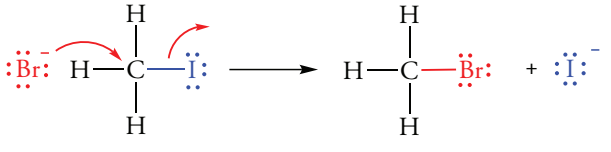
In a nucleophilic substitution reaction, the nucleophile donates an electron pair to the electrophilic carbon atom to form a new bond between the carbon and the nucleophile. The nucleophile may be either negatively charged, as in the case of OH^-, or neutral, as in the case of NH_3. These two types of nucleophiles are commonly represented as Nu:$^-$ and Nu:. If the nucleophile is negatively charged, the product has no net charge. If the nucleophile is neutral, the product is positively charged. The haloalkane is called the substrate because it is the compound upon which the reaction occurs.



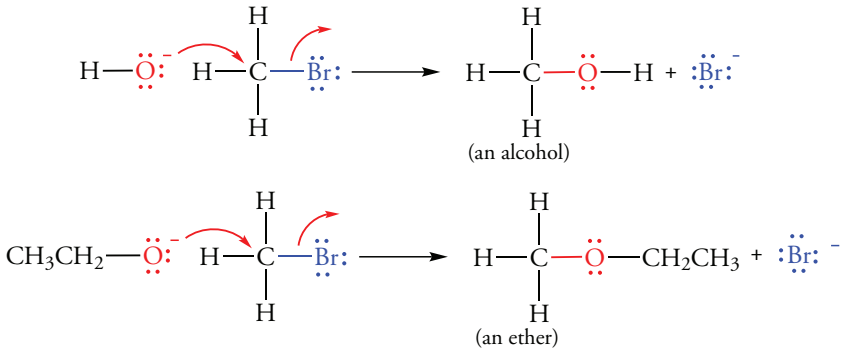
The nucleophile displaces an atom or group of atoms in the reaction, and this group—called the **leaving group**—has an electron pair that was originally part of the C—X bond. The leaving group can be negatively charged, as in the case of halide ions. The leaving group can also be neutral if it had a positive charge in the substrate. The hydroxyl group of alcohols can be protonated, thus water is a neutral leaving group.

Haloalkanes are substrates in an extremely broad range of nucleophilic substitution reactions. They react with nucleophilic anions derived from the halogens, oxygen, sulfur, and even carbon. They also react with neutral nucleophiles that contain nitrogen, such as NH_3 and amines.

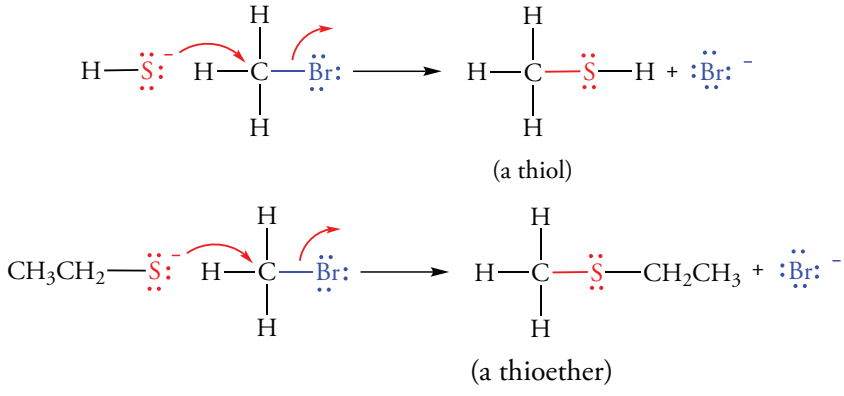
A typical example of a nucleophilic substitution reaction is the substitution of bromide ion for iodide ion in a haloalkane such as iodomethane.



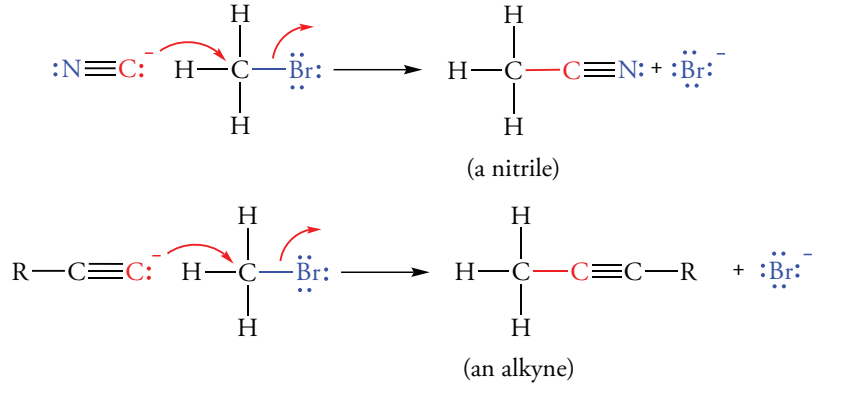
A similar reaction occurs when the hydroxide ion replaces the halide ion to produce an alcohol. When the oxygen-containing nucleophile is an alkoxide ion (RO^-), the product is an ether.



Haloalkanes also undergo nucleophilic substitution reactions with sulfur-containing nucleophiles such as hydrogen sulfide ion (HS^-) and thiolate ions (RS^-). These reactions yield sulfur analogs of alcohols and ethers; namely, thiols and thioethers.



Haloalkanes also react with carbon nucleophiles. These reactions increase the length of the carbon chain. One example of a carbon-containing nucleophile is cyanide ion (CN^-), which reacts with haloalkanes to give nitriles with the formula R—CN. We will see later that nitriles can be transformed into carboxylic acids and amines. Carbon-containing nucleophiles derived from alkynes are called **alkynide ions**. These nucleophiles, the conjugate bases of alkynes, react to form alkynes containing the carbon atoms of both the haloalkane and the alkynide.

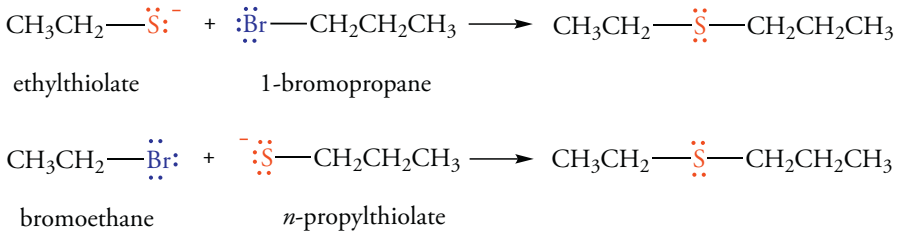


Problem 9.8

Using compounds containing no more than three carbon atoms, propose two ways to prepare CH_3CH_2—S—$CH_2CH_2CH_3$

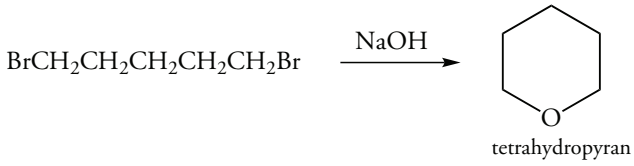
Sample Solution

This compound is a thioether. It can be prepared by the reaction of a thiolate with a primary haloalkane. It has two different alkyl groups bonded to sulfur. One alkyl group can be bonded to the sulfur atom in the thiolate, and the other can be in the haloalkane. Thus, two possible combinations of reactants can yield the product.



Problem 9.9

Write a sequence of steps that accounts for the following reaction of 1,5-dibromopentane to give tetrahydropyran.



9.9 MECHANISMS OF NUCLEOPHILIC SUBSTITUTION REACTIONS OF HALOALKANES

The S_N2 Mechanism

The S_N2 mechanism is a one-step process in which a nucleophile attacks the substrate, and a leaving group, L, departs simultaneously. Because the reaction occurs in one step, it is **concerted**. The substrate and the nucleophile are both present in the transition state for this step. Because two molecules are present in the transition state, the reaction is **bimolecular**, as indicated by the number 2 in the S_N2 symbol. The rate of an S_N2 reaction is first order in the substrate and first order in the nucleophile. If the substrate concentration is doubled, the reaction rate doubles. Similarly, if the concentration of the nucleophile is doubled, the rate again doubles. This relationship between the rate and the concentration of the reactants exists because the reactants must collide for reaction to occur. The probability that the nucleophile will collide with the substrate increases if the concentration of either species is increased or if the concentrations of both are increased.

Figure 9.3 shows the reaction coordinate diagram in the S_N2 reaction of hydroxide ion with chloromethane to give methanol and chloride ion. We see that the transition state contains both hydroxide ion and the substrate. As the reaction proceeds through the transition state, a bond forms between carbon and hydroxide ion, and the bond between carbon and chlorine breaks. In the transition state, neither the nucleophile or the leaving group is fully bonded to carbon. As we will establish shortly, the partial bonds to the nucleophile and leaving group must be collinear. The rate of reaction for haloalkanes by the S_N2 mechanism is methyl > primary > secondary >> tertiary. We attribute this order of reactivity to steric hindrance. Adding alkyl groups to the carbon atom of the carbon–halogen bond shields the carbon atom from attack by nucleophiles in the direction required for the transition state (Figure 9.4). Furthermore, the carbon atom bearing the nucleophile and the leaving group is pentacoordinate in the transition state. As a consequence, there is more crowding in the transition state. The energy barrier for the formation of the transition state increases with the size of the groups bonded to the reactive center, so steric effects are very important.

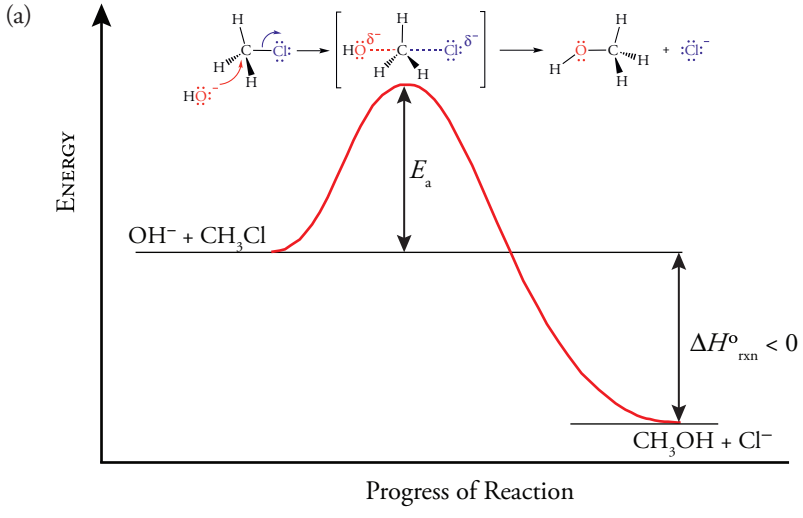


Figure 9.3
Reaction Coordinate Diagram of an S_N2 Reaction
(a) The reaction of hydroxide ion with chloromethane occurs in a single step. The activation energy, E_a, reflects the stability of the transition state, which depends upon the structure of the substrate, the nucleophile, and the leaving group.

Figure 9.3
Reaction Coordinate Diagram of an S_N2 Reaction
(b) The point of maximum energy in the reaction profile in part (a) is the transition state. It is the point of maximum energy on the pathway of minimum energy on the landscape from reactants to products.

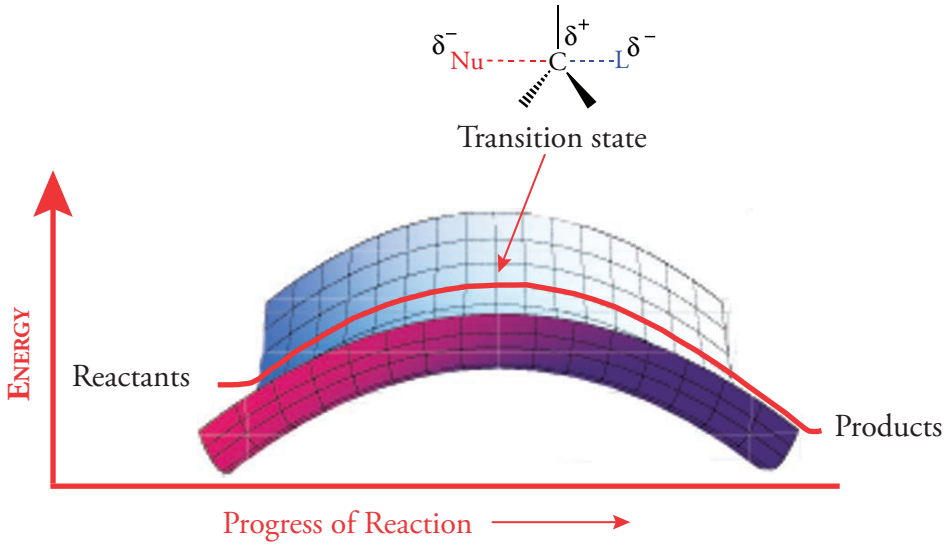
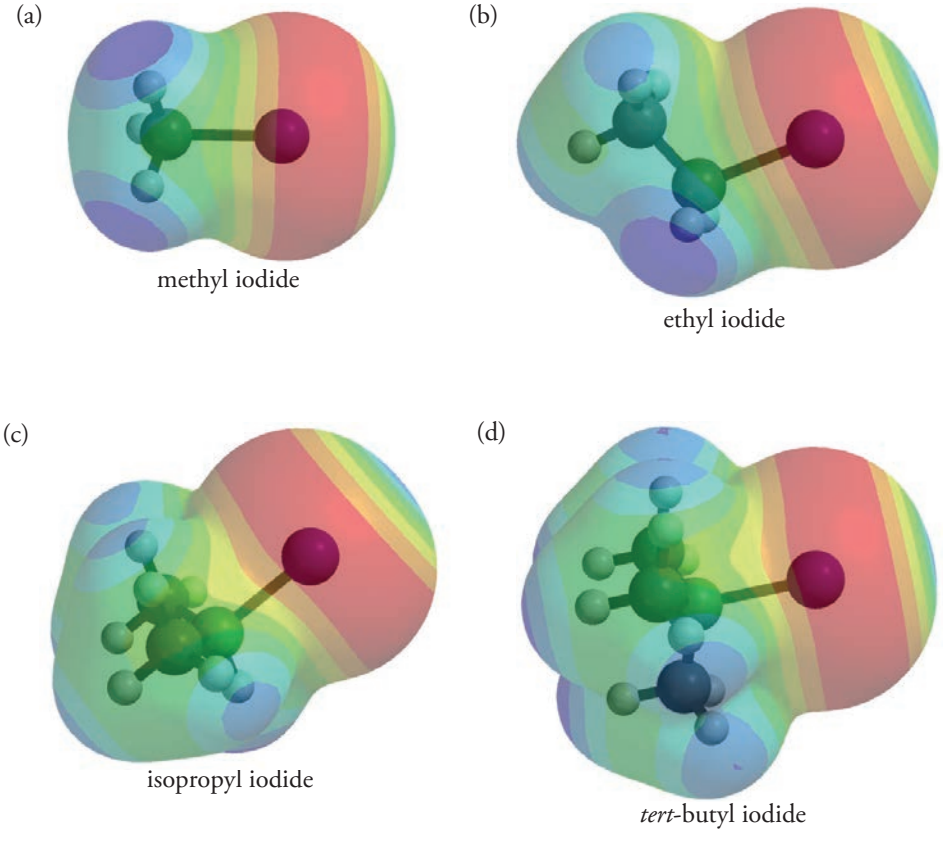
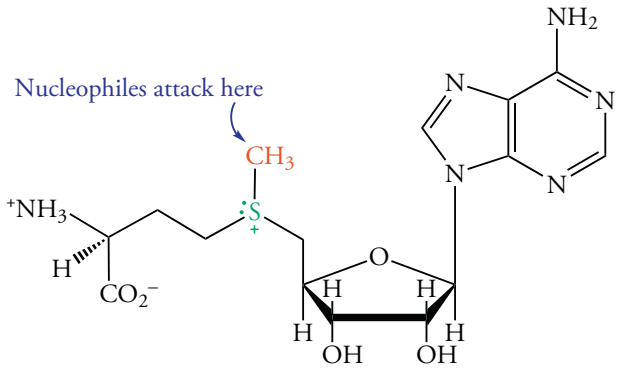


Figure 9.4
Effect of Steric Hindrance on an S_N2 Reaction
As hydrogen atoms are replaced one by one going from a methyl group to a tertiary halide, the reaction becomes slower because the nucleophile cannot easily reach the electrophilic carbon of the substrate. The electron density maps for these alkyl halides show this effect. The rate of an S_N2 reaction decreases in the order methyl > primary > secondary >> tertiary.
In fact, for a tertiary center, the S_N2 mechanism is not observed. Instead, the mechanism changes from S_N2 to S_N1, as we will shortly discover. Regions colored in red have high electron density.



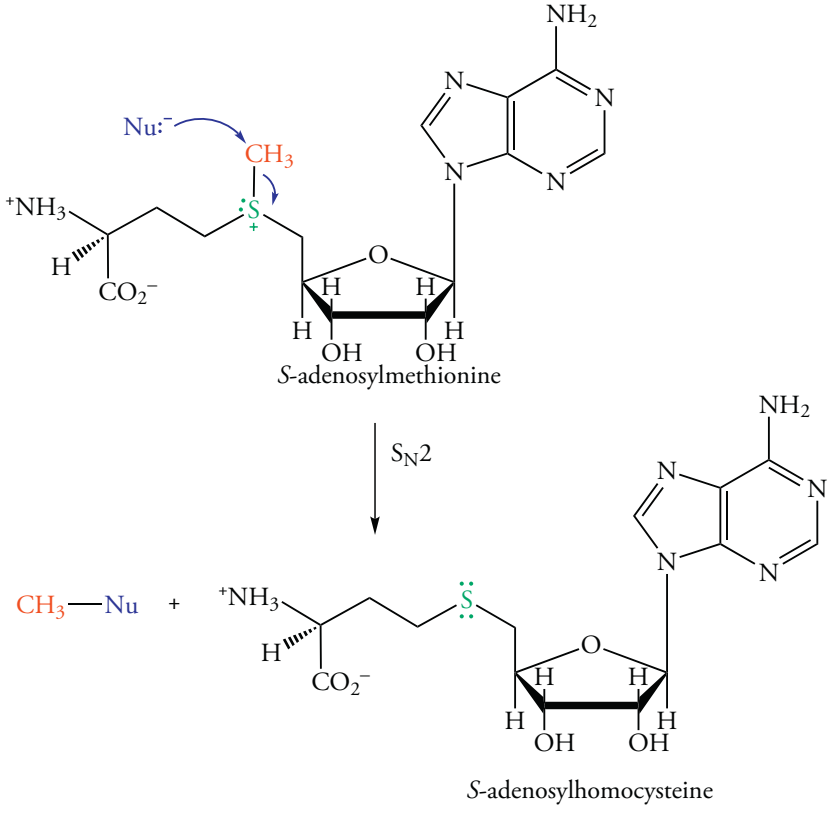
Biological Methylation by an S_N2 Mechanism

An S_N2 reaction occurs in living cells in which a methyl group is transferred from a methylating agent called *S*-adenosylmethionine (SAM) to various biological substrates, including nucleic acids, proteins, and many metabolic intermediates.



S-adenosylmethionine

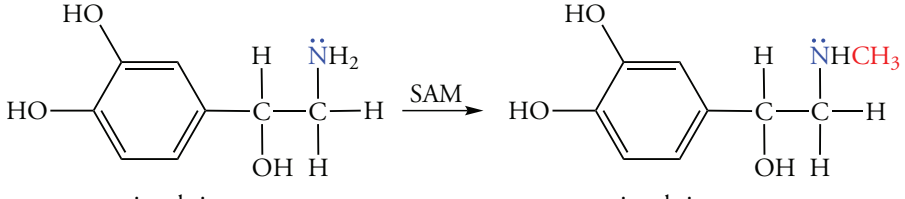
Three carbon atoms are bonded to the positively charged sulfur atom, which is known as a sulfonium ion. It is part of a leaving group called *S*-adenosylhomocysteine. The methyl group in SAM reacts with nucleophiles, which displace *S*-adenosylhomocysteine so that the methyl group is transferred from SAM to the nucleophile. This nucleophilic substitution reaction is shown below with a generic nucleophile (Nu:$^-$) and an abbreviated representation of SAM.



S-adenosylmethionine

S-adenosylhomocysteine

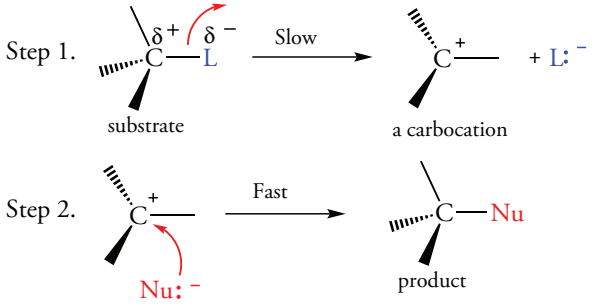
An important example of methyl group transfer from SAM to a nucleophile occurs in the biosynthesis of the neurotransmitter epinephrine. In this reaction, an amino group of norepinephrine attacks the methyl group of *S*-adenosylmethionine in an S_N2 reaction to produce epinephrine. The leaving group is *S*-adenosylhomocysteine, the compound that results from the loss of a methyl group from *S*-adenosylmethionine.



norepinephrine epinephrine

The S_N1 Mechanism

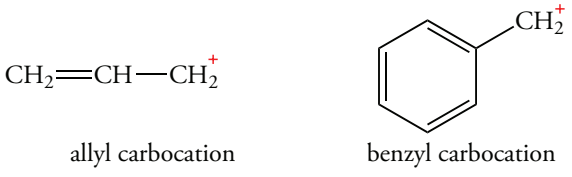
Another pathway for nucleophilic substitution reactions also exists. This process, which proceeds in two steps, is the S_N1 mechanism. It is experimentally distinguished from the S_N2 mechanism in part by a different rate law. In the slow, rate-determining step of the reaction, the bond between the carbon atom and the leaving group breaks to produce a carbocation and a leaving group. In the second, fast step, the carbocation reacts with the nucleophile to form the product. The two-step process is shown below.



The formation of a carbocation is the slow, or *rate-determining*, step. The subsequent step, formation of a bond between the nucleophile and the carbocation, occurs very rapidly. Because the slow step of the reaction involves only the substrate, the reaction is **unimolecular.** Because only the substrate is present in the transition state, the rate of the reaction depends only on its concentration and not on the concentration of the nucleophile.

Figure 9.5 shows a reaction coordinate diagram for the S_N1 mechanism. The rate of the reaction depends on the energy barrier to the formation of the carbocation intermediate. The energy barrier in the second step, the reaction of the nucleophile with the carbocation, is much smaller, so step 2 is very fast. The rate of the second step has no effect on the net rate of the reaction.

The rates of S_N1 reactions decrease in the order tertiary > secondary > primary >> methyl. This trend is exactly the reverse of the trend observed in S_N2 reactions. The relative reactivity of haloalkanes in S_N2 reactions corresponds to the relative stability of carbocation intermediates that form during the reaction. We recall from Chapter 3 that the order of stability of carbocations is tertiary > secondary > primary >> methyl. A relatively stable tertiary carbocation forms faster than a less stable secondary carbocation, which in turn forms very much faster than a highly unstable primary carbocation. However, S_N1 mechanisms are possible at primary centers that are resonance stabilized, such as allyl and benzyl.



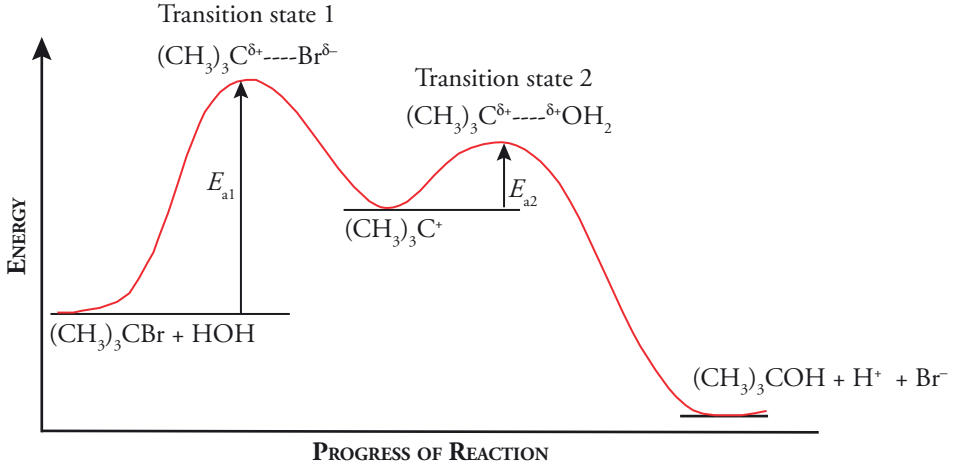
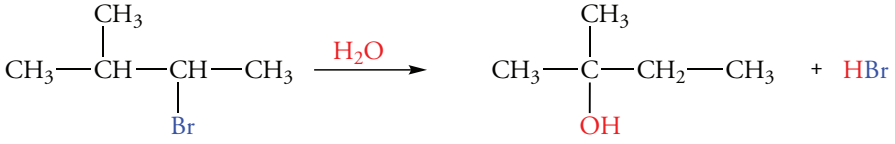


Figure 9.5
Energy Profile of an S_N1 Reaction
The reaction of 2-bromo-2-methylpropane occurs in two steps with the formation of an intermediate carbocation. It forms in the rate-determining step, which does not involve the nucleophile. In the second, fast step, the carbocation reacts with a nucleophile such as water to form the product.

Carbocation Rearrangements in S_N1 Reactions

Although the products of most nucleophilic substitution reactions result from the displacement of a leaving group by a nucleophile, there are examples of rearranged products. We first encountered this phenomenon in Chapter 6, where we saw that the carbocation intermediate produced by adding a proton to an alkene may rearrange to form a more stable carbocation. Because substitution reactions that occur by an S_N1 mechanism produce carbocation intermediates, we are not surprised to find that rearranged substitution products occur.

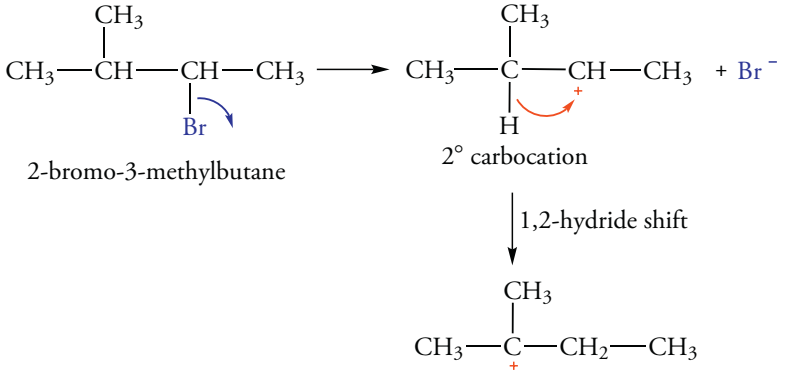
For example, the reaction of 2-bromo-3-methylbutane with water is an S_N1 reaction that gives a rearranged product, 2-methyl-2-butanol, *not* the direct substitution product, 3-methyl-2-butanol.



2-bromo-3-methylbutane

2-methyl-2-butanol
(only observed product)

The product forms by the reaction of the nucleophile, water, with a tertiary carbocation. We recall that such a tertiary carbocation results from the movement of a hydrogen atom, with its bonding pair of electrons, from the tertiary center to the adjacent secondary carbocation. The rearrangement is a 1,2-hydride shift because a hydride ion (H^-) moves between adjacent carbon atoms.

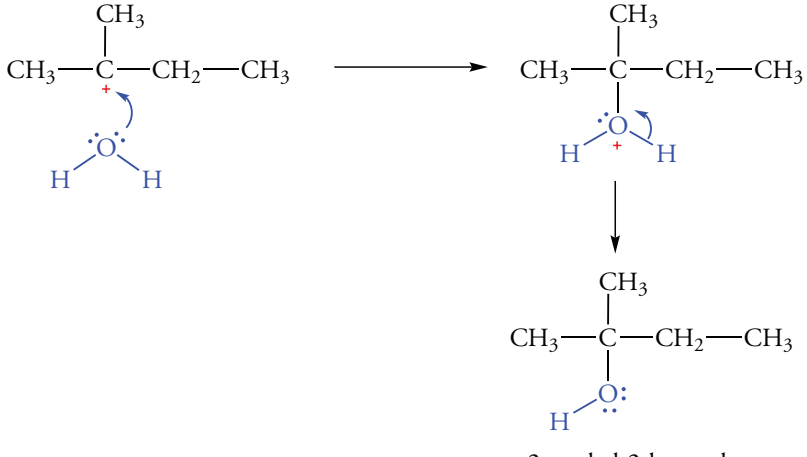


2-bromo-3-methylbutane

2° carbocation

3° carbocation

This hydride shift converts a secondary carbocation into a more stable tertiary carbocation, which reacts with water to produce the rearranged tertiary alcohol.



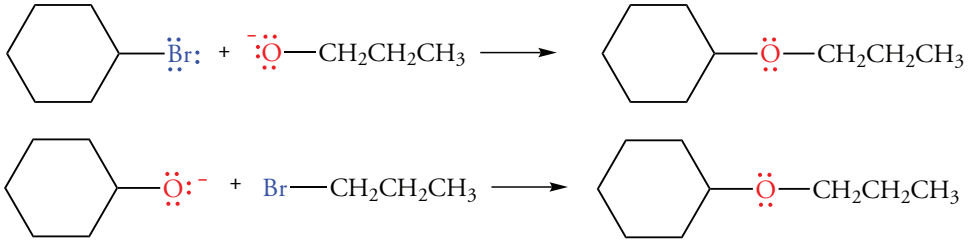
2-methyl-2-butanol

Problem 9.10

The rates of S_N2 reactions of primary haloalkanes can differ substantially. The rate of reaction of 1-bromopentane with a nucleophile is approximately 4×10^6 times faster than the reaction of 2,2-dimethyl-l-bromopropane. Explain why.

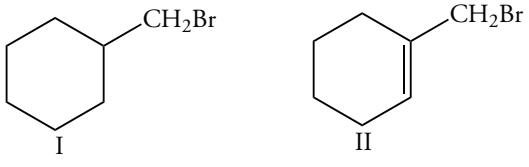
Problem 9.11

Which of the following two possible reactions will produce an ether, propoxycyclohexane, at a faster rate?



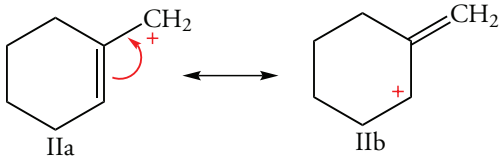
Problem 9.12

Explain why compound I reacts with methanol via an S_N2 mechanism, whereas compound II reacts at a much faster rate by an S_N1 mechanism.



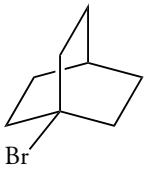
Sample Solution

Both substrates are primary bromides. The reaction of methanol, a neutral nucleophile, with I will tend to occur by an S_N2 allylic carbocation. Resonance stabilization enhances the rate of its formation in an S_N1 process. No such stabilization can occur in the reaction of I.



Problem 9.13

Although 1-bromobicyclo[2.2.2]octane is a tertiary bromide, it cannot react via an S_N1 mechanism. Suggest a reason for its lack of reactivity.

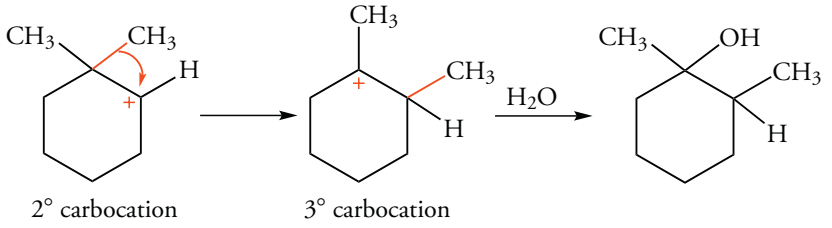


Problem 9.14

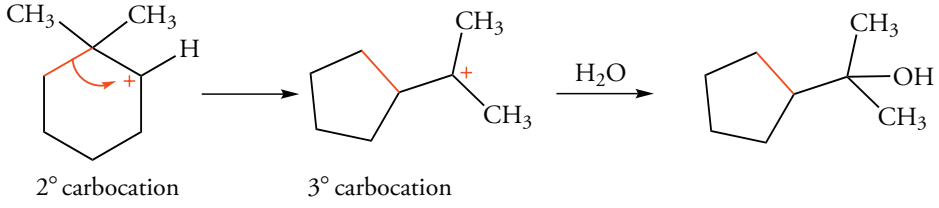
One of the rearranged products in the hydration reaction of 1-bromo-2,2-dimethylcyclohexane with water is 1,2-dimethylcyclohexanol. Explain how this product is formed. What other rearranged alcohol can form?

Sample Solution

This reaction occurs by an S_N1 mechanism via a secondary carbocation that rearranges to give two possible tertiary carbocations. Migration of a methyl group followed by capture of the carbocation gives 1,2-dimethylcyclohexanol.



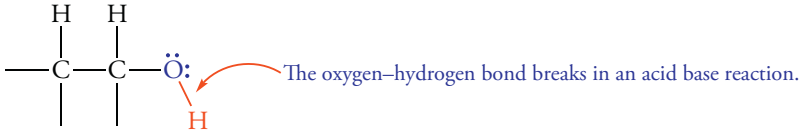
A 1,2-shift of a methylene group of the ring can also occur to give a tertiary carbocation. Water reacts with the rearranged carbocation to give a product that contains a cyclopentane ring.



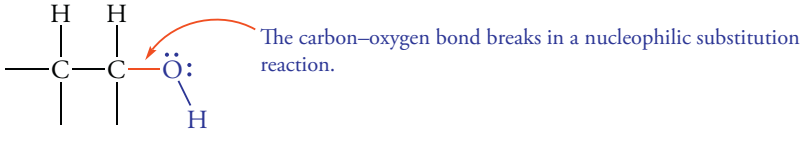
9. 10 REACTIONS OF ALCOHOLS

Alcohols undergo reactions in which several different bonds can break, depending on experimental conditions. In some reactions, the O—H bond breaks; in others, the C—O bond breaks. The C—H bond on the carbon atom bearing the hydroxyl group or the C—H bond on the carbon atom adjacent to that carbon atom bearing the OH group also react under some conditions. We will divide our discussion of the reactions of alcohols into four classes based on the bonds that break. We will discuss the first three classes of reactions in this chapter. We will discuss the fourth in Chapter 15 when we expand our treatment of alcohol reactions and synthesis.

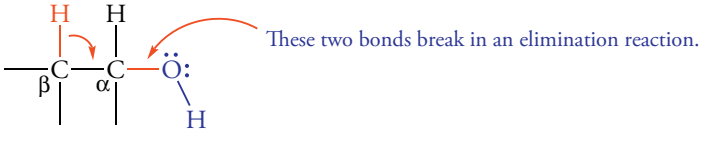
1. The oxygen–hydrogen bond breaks in an acid–base reaction.



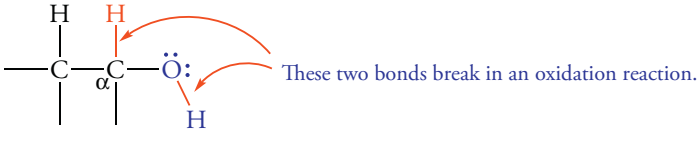
2. The carbon–oxygen bond breaks in a nucleophilic substitution reaction.



3. The carbon–hydrogen bond at the β carbon and the carbon–oxygen bond at the α carbon both break in an elimination reaction.



4. The carbon–hydrogen bond and the oxygen–hydrogen bond at the α carbon break in an oxidation reaction.



9.11 ACID–BASE REACTIONS OF ALCOHOLS

We know that water can act as a proton donor (an acid) in some reactions and as a proton acceptor (a base) in other reactions depending on conditions. Molecules that can act in this way are *amphoteric.* Alcohols can also act as acids or bases. Thus, alcohols are also amphoteric.

Alcohols are slightly weaker acids than water; the K_a of ethanol is 1.3×10^{-16} ($pK_a = 16$) and the K_a of water is 1.8×10^{-16} ($pK_a = 15.7$). The pK_a values of some common alcohols are listed in Table 9.3. We recall that a strong acid has a large K_a and a small pK_a.

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+ \quad K_a = 1.3 \times 10^{-16}$$

$$H_2O + H_2O \rightleftharpoons HO^- + H_3O^+ \quad K_a = 1.8 \times 10^{-16}$$

Table 9.3
Effect of Structure on Acidity of Alcohols

Alcohol	*Formula*	K_a	pK_a
Methanol	CH_3OH	3.2×10^{-16}	15.5
Ethanol	CH_3CH_2OH	1.3×10^{-16}	15.9
Isopropyl alcohol	$(CH_3)_2CHOH$	1×10^{-18}	18.0
tert-Butyl alcohol	$(CH_3)_3COH$	1×10^{-19}	19.0
2-Chloropropanol	$ClCH_2CH_2OH$	5×10^{-15}	14.3
2,2,2-Trifluoroethanol	CF_3CH_2OH	4×10^{-13}	12.4
3,3,3-Trifluoropropanol	$CF_3CH_2CH_2OH$	2.5×10^{-15}	14.6
4,4,4-Trifluorobutanol	$CF_3CH_2CH_2CH_2OH$	4×10^{-16}	15.4

The acidity of alcohols increases when electronegative substituents are added to a carbon atom near the hydroxyl group. Such substituents withdraw electron density from the oxygen atom by an inductive effect that weakens the O—H bond, which destabilizes the alcohol. The substituents also stabilize the negative charge of the conjugate base. Replacing a hydrogen atom at C-2 of ethanol with a chlorine atom decreases the pK_a from 15.9 to 14.3, which means that K_a increases by a factor of 50. Replacing all three hydrogen atoms at C-2 of ethanol with the more electronegative fluorine atoms decreases the pK_a to 12.4, which corresponds to an increase in acidity of more than 1000-fold. The effect of the electron-withdrawing CF_3 group decreases with distance from the oxygen atom. The pK_a of 4,4,4-trifluorobutanol, for example, is similar to the pK_a of a primary alcohol such as ethanol. When an alcohol loses a proton, an alkoxide ion forms. Because alcohols are weaker acids than water, alkoxides are stronger bases than hydroxide ion. Alkoxides are used as bases in organic solvents because they are more soluble than hydroxide salts. Alkoxide ions can be easily prepared by adding an alkali metal to an alcohol.

$$CH_3OH + Na \rightleftharpoons \underset{\text{methoxide ion}}{CH_3O^-} + 1/2\ H_2 + Na^+$$

$$(CH_3)_3COH + K \rightleftharpoons \underset{\textit{tert}\text{-butoxide ion}}{(CH_3)_3CO^-} + 1/2\ H_2 + K^+$$

These oxidation–reduction reactions resemble the reaction of alkali metals with water. Alcohols react somewhat less vigorously with alkali metals than water.

Alcohols can act as bases because they have two lone pairs of electrons on the oxygen atom. Since alcohols are very weak bases, they can only be protonated to form the conjugate acid, an alkyloxonium ion, by a strong acid. The formation of an alkyloxonium ion is analogous to the reaction of water with a strong acid to give the hydronium ion. Alkyloxonium ions are intermediates in many reactions of alcohols catalyzed by strong acids.

$$CH_3CH_2OH + HA \rightleftharpoons \underset{\text{(an alkoxonium ion)}}{CH_3CH_2OH_2^+} + A^-$$

$$H_2O + HA \rightleftharpoons \underset{\text{(hydronium ion)}}{H_3O^+} + A^-$$

9. 12 SUBSTITUTION REACTIONS OF ALCOHOLS

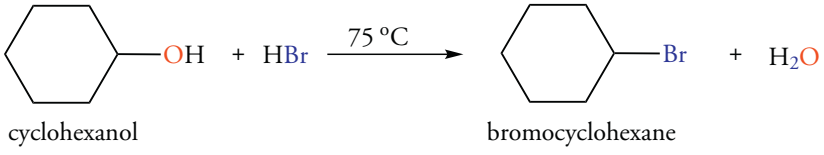
The hydroxyl group of an alcohol can be replaced by a halogen using a hydrogen halide. For example, treating a primary alcohol with hydrogen bromide (HBr) produces a bromoalkane. Similarly, treating a primary alcohol with HCl in the presence of $ZnCl_2$, which is required as a catalyst, produces an alkyl chloride.

$$CH_3CH_2CH_2OH + HBr \longrightarrow CH_3CH_2CH_2Br + H_2O$$

$$CH_3CH_2CH_2CH_2OH + HCl \xrightarrow{ZnCl_2} CH_3CH_2CH_2CH_2Cl + H_2O$$

These reactions also occur when secondary and tertiary alcohols are the substrates. Their relative rates depend on the type of alcohol. The rate of reaction decreases in the order tertiary > secondary > primary alcohols. For example, a typical reaction temperature for a primary alcohol such as 1-hexanol is about 125 °C. In contrast, a secondary alcohol such as cyclohexanol reacts at about 75 °C.

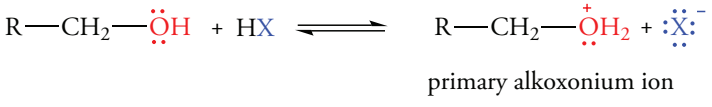
$$\underset{\text{1-hexanol}}{CH_3(CH_2)_4CH_2OH} + HBr \xrightarrow{125\ ^\circ C} \underset{\text{1-bromohexane}}{CH_3(CH_2)_4CH_2Br} + H_2O$$



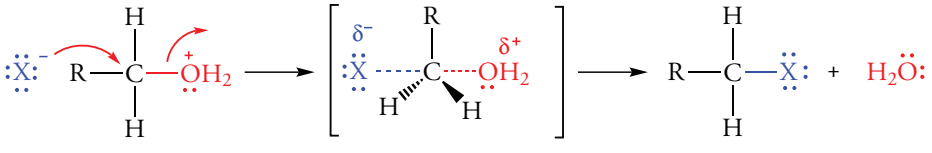
Reaction Mechanisms

Like the reaction of alkyl halides with nucleophiles such as hydroxide ion, alcohols react with nucleophiles by two reaction mechanisms. The mechanism depends on the structure of the alkyl group. Primary alcohols react with nucleophiles by an S_N2 mechanism. Tertiary alcohols react with nucleophiles by an S_N1 mechanism. The mechanism for the reaction of nucleophiles with secondary alcohols is often, but not always, S_N1. In every class of alcohol, the leaving group is a water molecule, not hydroxide ion. An acid catalyst is required to form the conjugate acid of the alcohol, an alkyloxonium ion.

The alkyloxonium ions of primary alcohols react with hydrogen halides via an S_N2 mechanism in which a water molecule is displaced by the halide ion, X^-.



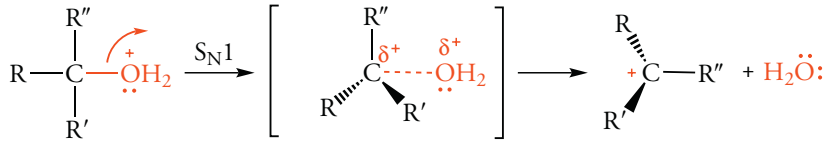
primary alkoxonium ion



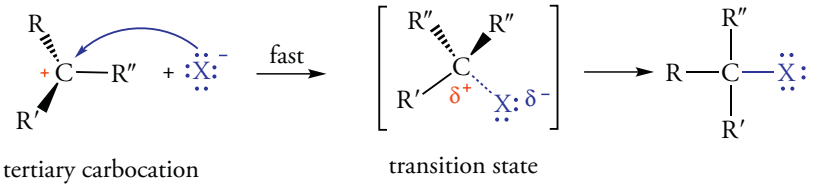
The above reaction occurs in the presence of an acid catalyst. In the absence of a catalyst, hydroxide ion would have to be displaced from the alcohol by a halide ion. Because both the leaving group and nucleophile are negatively charged, the carbon atom has a larger positive charge in the transition state in the uncatalyzed reaction than in the acid-catalyzed reaction. Protonation of the alcohol gives a neutral leaving group. The departure of a neutral leaving group from a developing carbocation center requires less energy than the departure of a negatively charged leaving group such as the hydroxide ion. Therefore, the reaction is much faster in the presence of the acid catalyst.

The activation energy for the displacement of water as a leaving group is smaller than for the displacement of hydroxide ion. Thus, water is a better leaving group than hydroxide ion. There is a general correlation between basicity and leaving-group ability. *A weak base is a better leaving group than a stronger base in both S_N2 and S_N1 reactions.*

Alkyloxonium ions of tertiary alcohols react with hydrogen halides by an S_N1 mechanism in which a water molecule leaves in the rate-determining step. The positive charge is dispersed in the transition state between the carbon and oxygen atoms, and eventually shifts to the carbon atom.



The carbocation formed in the rate-determining step then combines with the halide ion to give the observed product in a fast second step.



Structural Effects in S_N2 and S_N1 Mechanisms

Primary alcohols react by an S_N2 mechanism in which water is displaced by the nucleophilic halide ion because the primary carbon atom is sterically accessible to the nucleophile. The alternate S_N1 mechanism would have a high activation energy because the transition state would resemble a highly unstable primary carbocation. We used a similar argument to explain the direction of electrophilic addition to double bonds. According to the Hammond postulate, the structure of a transition state resembles the species that is most similar to it in energy. In the case of the S_N1 mechanism for the reaction of an alkyloxonium ion, a positive charge is developed at the carbon atom in the transition state. Because the intermediate carbocation forms in an endothermic process, the structure of the transition state resembles that intermediate (Figure 9.6). Thus, the activation energy for the S_N1 reaction for alcohols increases in the order 3° < 2° < 1° << methyl. Only 3° and 2° alcohols react by an S_N1 mechanism.

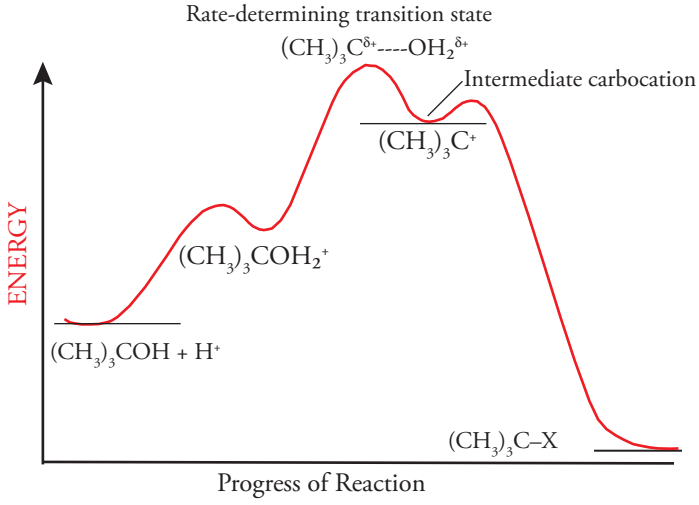
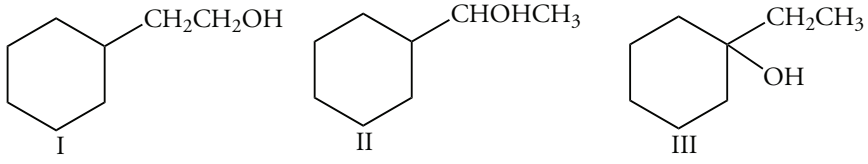


Figure 9.6
Reaction Coordinate Diagram for Substitution Reaction of an Alcohol
The acid-catalyzed substitution reaction of 2-methyl-2-propanol occurs in two steps from the alkyloxonium ion with the formation of an intermediate carbocation. The carbocation forms in the rate-determining step, which does not involve the nucleophile. In the second, fast step, the carbocation reacts with a nucleophile such as a halide ion to form the product.

Problem 9.15

What is the most likely mechanism for the reaction of each of the following isomeric alcohols with HBr?



Problem 9.16

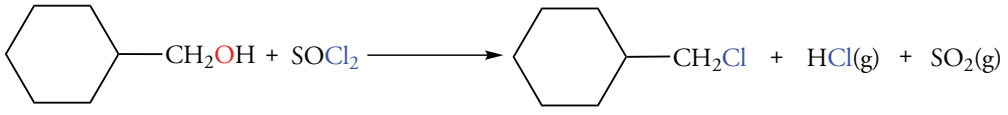
The reaction of *cis*-l-methylcyclohexanol with HBr yields 1-bromo-l-methylcyclohexane. Write a mechanism to explain the origin of this product.

9. 13 ALTERNATE METHODS FOR THE SYNTHESIS OF ALKYL HALIDES

Alkyl halides are starting materials for the synthesis of many functional groups. One method of preparing alkyl halides is a substitution reaction of an alcohol with a hydrogen halide. However, strong acids, such as hydrogen halides, catalyze elimination reactions that often compete with substitution reactions. For example, we will discuss the acid-catalyzed dehydration reaction in Section 9.16. To avoid this competing reaction, alternate synthetic methods have been developed that do not use strongly acidic reagents.

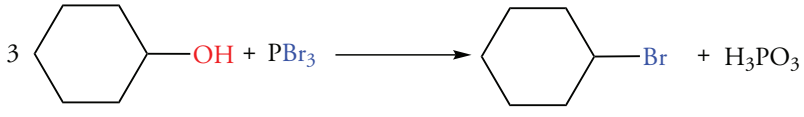
Primary and secondary alcohols, which react only slowly with HBr and HCl, react readily with thionyl chloride and phosphorus trihalides, such as phosphorus tribromide, to give the corresponding alkyl halides. The products of these reactions are easily separated from the inorganic by-products. Thionyl chloride produces hydrogen chloride and sulfur dioxide, which are released from the reaction as gases. The chloroalkane remains in solution.

$$CH_3(CH_2)_4CH_2OH + SOCl_2 \longrightarrow CH_3(CH_2)_4CH_2Cl + HCl(g) + SO_2(g)$$



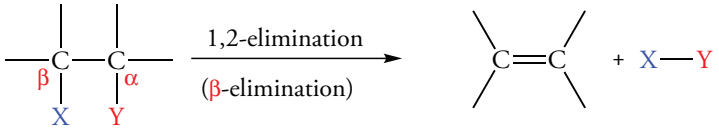
The reaction of an alcohol with phosphorus tribromide produces phosphorous acid, which has a high boiling point, and is water soluble. Therefore, the bromoalkane can be separated from the reaction mixture by distillation or by adding water to dissolve the phosphorous acid and then extracting the halide with ether.

$$3\ R{-}OH + PBr_3 \longrightarrow 3\ R{-}Br + \underset{\text{phosphorous acid}}{H_3PO_3}$$



9. 14 ELIMINATION REACTIONS

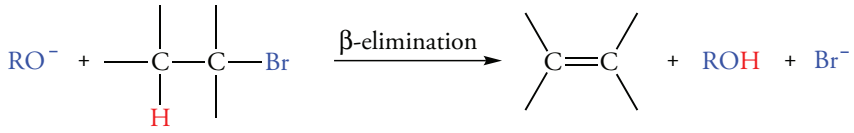
A single reactant molecule splits into two products in an elimination reaction. One product molecule contains most of the atoms in the reactant, and the remaining atoms are found in a second, smaller molecule. The atoms eliminated to form the smaller molecule are usually initially located on adjacent carbon atoms in the reactant. For this reason, the most common elimination reactions are called **1,2-elimination reactions**. They are also called **β-eliminations**.



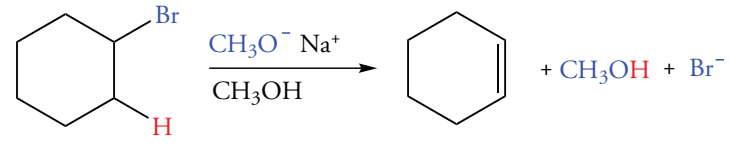
Elimination reactions are described by the name of the molecule undergoing elimination. The names are the same as those used for addition reactions, but the prefix *de-* is added. For example, the elimination of halogen atoms on two adjacent carbon atoms is **dehalogenation**; the elimination of water is **dehydration**; the elimination of a hydrogen halide is **dehydrohalogenation**, and in the case of a specific halogen halide such as hydrogen bromide, **dehydrobromination.**

Dehydrohalogenation

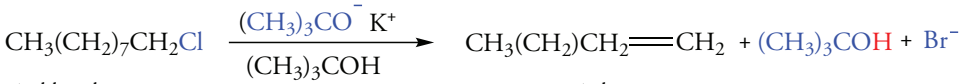
The dehydrohalogenation of an alkyl halide is a good laboratory method for the synthesis of alkenes because alkyl halides are readily available from reactions of several other starting materials. Considered by itself, this reaction has a very unfavorable equilibrium constant. However, if we use a strong base such as alkoxide anion to extract a proton on the carbon adjacent to the bromine, the reaction becomes highly favorable.



The dehydrohalogenation of alkyl halides is usually carried out with sodium methoxide in methanol, sodium ethoxide in ethanol, or potassium *tert*-butoxide in either *tert*-butyl alcohol or dimethyl sulfoxide, $(CH_3)_2SO$.



bromocyclohexane cyclohexene

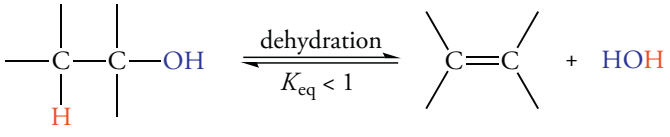


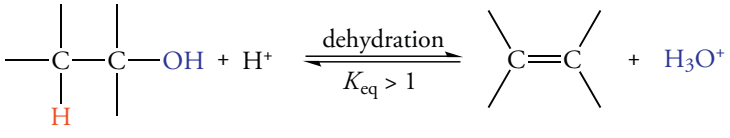
1-chlorodecane 1-decene

For the two reactions shown above, only a single alkene can result from the dehydrohalogenation of the alkyl halide. In alkyl halides having two or three adjacent carbon atoms with hydrogen atoms that could lead to different elimination products, a regioselectivity is observed. We will discuss this feature of dehydrohalogenation reactions in Section 9.17.

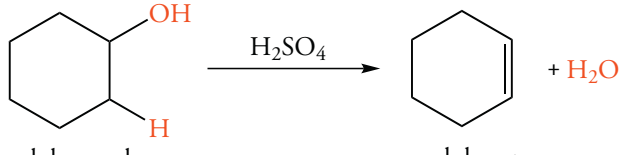
Dehydration

Dehydration is an unfavorable process because the alkene is less stable than the alcohol. The dehydration reaction is favored by using a concentrated acid such as sulfuric acid. The reaction produces the hydronium ion (H_3O^+) rather than water, and since the formation of the hydronium ion is strongly favored, the reaction as a whole proceeds readily.





The reaction is pulled to completion by distilling the alkene from the reaction mixture, which is an application of Le Châtelier's principle. Since a given alkene has a much higher boiling point than the alcohol from which it was formed, distillation is an efficient method for isolating the product.



cyclohexanol bp 161 °C cyclohexene bp 83 °C

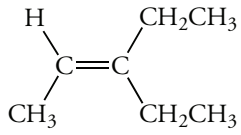
As is the case for the dehydrohalogenation of alkyl halides, the reaction is regioselective. We will discuss this feature of dehydration reactions in Section 9.18.

Problem 9.17

The dehydrobromination of 3-bromo-3-ethylpentane gives a single product, but the dehydrobromination of 2-bromo-2-methylbutane gives two products. What are the structures of the products for both reactions?

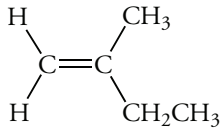
Sample Solution

In 3-bromo-3-ethylpentane there are three equivalent methylene groups adjacent to the carbon atom bearing the bromine atom. Elimination of HBr can only give a single product, 3-ethyl-2-pentene.

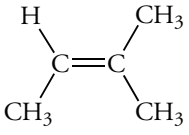


3-ethyl-2-pentene

In 2-bromo-2-methylbutane the carbon atoms adjacent to the carbon atom bearing the bromine atom are two methyl groups and a methylene group. The products are 2-methyl-1-butene and 2-methyl-2-butene.



2-methyl-1-butene



2-methyl-2-butene

Problem 9.18

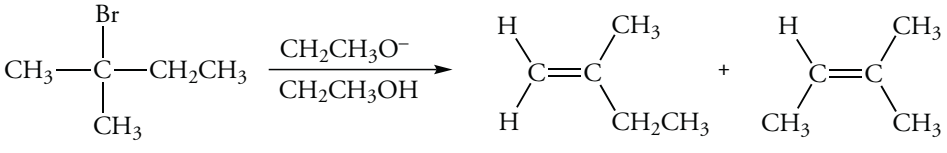
The C-2 and C-4 methylene units of 3-bromopentane are equivalent. However, the dehydrobromination of 3-bromopentane gives two products. Write their structures.

Problem 9.19

Two alkenes are produced in the dehydration of 2-methyl-2-butanol, but three are produced in the dehydration of 2-pentanol. Write the structures of the products of both reactions.

9.15 REGIOSELECTIVITY IN DEHYDROHALOGENATION

When two or more products can form in the dehydrohalogenation of an alkyl halide, it turns out that they are not formed in equal amounts. The more highly substituted alkene, which is more stable, is the major product. This is shown by the dehydrobromination of 2-bromo-2-methylbutane.



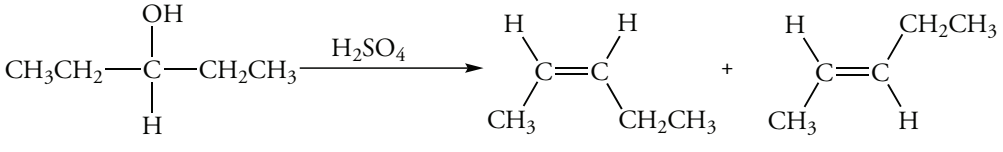
2-methyl-1-butene (30%)

2-methyl-2-butene (70%)

At first glance the reaction may not appear to be very regioselective. However, when we consider the number of hydrogen atoms that could be eliminated to lead to each product, it is actually quite regioselective. The more substituted alkene is the major product even though the less substituted alkene would be expected to be favored on statistical grounds. That is, the reactant has six equivalent hydrogen atoms that could be lost to give 2-methyl-l-butene, but only two can be lost to give 2-methyl-2-butene. The mechanism for the reaction has to explain this discrepancy.

The regioselectivity observed for 1,2-elimination reactions was summarized by Alexander Zaitsev in 1875. **Zaitsev's rule** states that the more substituted alkene is favored in 1,2-elimination reactions. We know that alkenes are stabilized by alkyl groups bonded to sp^2-hybridized carbon atoms, so Zaitsev simply observed that the major product of an elimination reaction is the more stable isomer.

As a corollary of Zaitsev's rule concerning the formation of the more stable isomer, we can account for the composition of mixtures of geometric isomers. For example, dehydrobromination of 3-bromopentane yields a mixture of *cis*- and *trans*-2-pentenes. The *trans* isomer is the major product.



cis-2-pentene (25%)

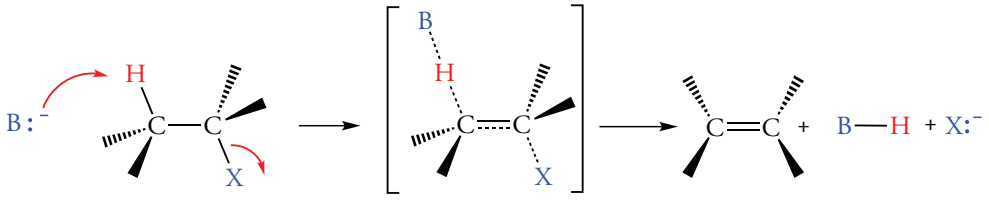
trans-2-pentene (75%)

9. 16 MECHANISMS OF DEHYDROHALOGENATION REACTIONS

Elimination reactions can occur by two mechanisms. They are designated **E2** and **E1**, where E refers to elimination and the integers designate the molecularity—that is, the number of species in the transition state—of the rate-determining step of the reaction. The molecularity is reflected in the kinetics of the reaction. Reactions that are first order in the alkyl halide and first order in base are second order overall, and occur by an E2 mechanism. This behavior is observed for primary and secondary alkyl halides. Reactions that are first order in alkyl halide, and are independent of the base concentration, occur by an El mechanism. This behavior is observed for tertiary alkyl halides. The reaction rate increases in the order RF < RCl < RBr < RI regardless of the class of alkyl halide. Although alkyl chlorides and alkyl bromides are most commonly used in synthesis, the iodide ion formed from the alkyl iodides is the best leaving group. Alkyl fluorides are not used for the synthesis of alkenes.

The E2 Mechanism

Like the S_N2 reaction mechanism, the E2 mechanism is a one step, concerted process. In an E2 dehydrohalogenation reaction, the base removes a proton on a β-carbon atom adjacent to the carbon atom that contains the leaving group (the α-carbon). As the proton is removed, the leaving group departs, and a double bond forms. The transition state is shown for the general base, which is represented by $B:^-$ (X represents the halide). The base in an E2 reaction is also a nucleophile, and we will see in Chapter 10 that S_N2 reactions compete with E2 reactions.



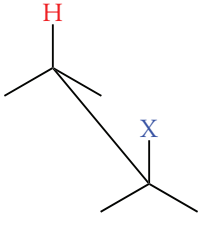
Transition state for E_2 reaction.

The carbon–hydrogen and carbon–halogen bonds are partially broken in the transition state, so the strength of the carbon–halogen bond affects the rate of the reaction. Alkyl iodides have the weakest carbon–halogen bond. Therefore, they react at the fastest rate.

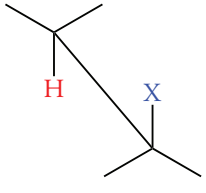
A partial double bond develops in the transition state for the E2 elimination. The partially formed double bond in the transition state is stabilized by alkyl groups just as the double bond of alkenes is stabilized by alkyl groups. Therefore, the transition state for the formation of the more substituted alkene has the lower energy barrier.

Stereoelectronic Effects in the E2 Reaction

When a special arrangement of orbitals in forming or breaking bonds controls the direction of a reaction, the outcome is called a **stereoelectronic effect**. An E2 reaction is **periplanar** when all reacting atoms—the two carbon atoms and the two atoms to be eliminated— lie in the same plane. An E2 reaction is **anti periplanar** if the hydrogen and halide atoms are on the opposite sides of the molecule, separated by a 180° dihedral angle, and **syn periplanar** when they are on the same side of the molecule, separated by a 0° dihedral angle. In the latter case, the groups are eclipsed.



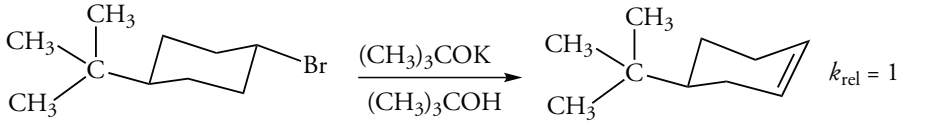
Syn periplanar, dihedral angle between H and X is 0°.



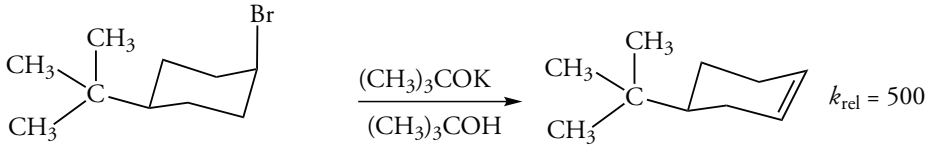
Anti periplanar, dihedral angle between H and X is 180°.

Both arrangements allow π overlap of incipient parallel 2p orbitals as the σ bonds are broken. The more common anti periplanar geometry corresponds to the staggered anticonformation, which is easily achieved in conformationally flexible molecules. The syn periplanar geometry corresponds to an eclipsed conformation, which is important only in some rigid, cyclic compounds.

The effect of conformation on E2 reactions is demonstrated by the difference in the rates of the dehydrobromination of *cis*- and *trans*-1-bromo-4-*tert*-butylcyclohexane. The axial bromine atom of the *cis* isomer is eliminated about 500 times faster than the equatorial bromine atom of the *trans* isomer. Both isomers yield 4-*tert*-butyl-cyclohexene.

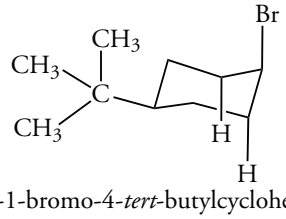


trans-1-bromo-4-*tert*-butylcyclohexane 4-*tert*-butylcyclohexene

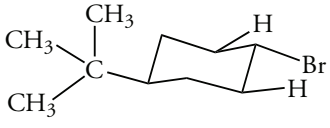


cis-1-bromo-4-*tert*-butylcyclohexane 4-*tert*-butylcyclohexene

Figure 9.7 shows that the axial bromine atom of the *cis* isomer is anti periplanar with respect to the axial hydrogen atoms at C-2 and C-6. Therefore, the most favorable geometry for elimination is "built into" the molecule, and no conformational equilibria are required to achieve it. In the *trans* isomer, however, no hydrogen atoms are anti periplanar to the equatorial bromine atom. To eliminate HBr in the *trans* isomer, a hydrogen atom that lies at a 60° dihedral angle with respect to the bromine atom must be removed. This process or any other reaction of a distorted ring that moves the two atoms into a better geometry for elimination requires more energy. Hence, the reaction rate is slower.



cis-1-bromo-4-*tert*-butylcyclohexane



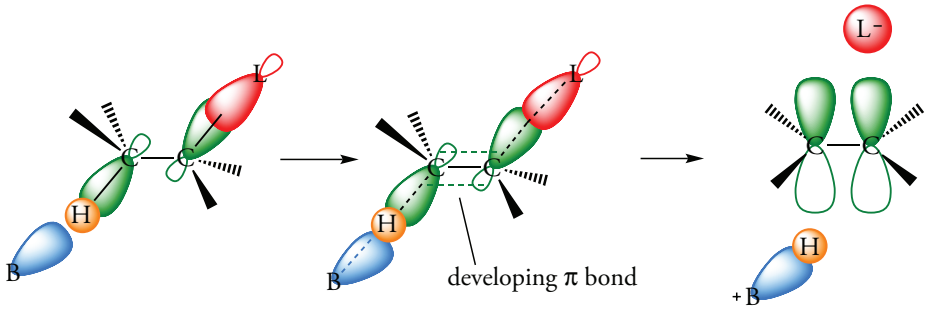
trans-1-bromo-4-*tert*-butylcyclohexane

Figure 9.7
Stereochemistry of E2 Elimination Reactions
The preferred relationship between a proton and a leaving group, in this case a bromine atom, is anti periplanar. This situation exists in *cis*-1-bromo-4-*tert*-butylcyclohexane, in which the halogen and flanking hydrogens have a dihedral angle of 180°. However, in *trans*-1-bromo-4-*tert*-butylcyclohexane the dihedral angle between the halogen and the flanking hydrogen atoms is 60°, so the *trans* isomer cannot easily undergo an E2 reaction.

The stereoelectronic effect reflects the geometry of the developing π bond in the transition state for the reaction. The anti periplanar arrangement is favored because it aligns the σ orbitals of the sp^3-hybridized C—H and C—X bonds; so, they can partially overlap as they become the 2p π orbitals in the product (Figure 9.8). A similar argument holds for the syn periplanar transition state.

Figure 9.8
Orbital Geometry in E2 Reactions

Partial overlap of the developing π orbitals in the transition state for an E2 reaction in which the leaving group and the proton are in an anti periplanar relationship.

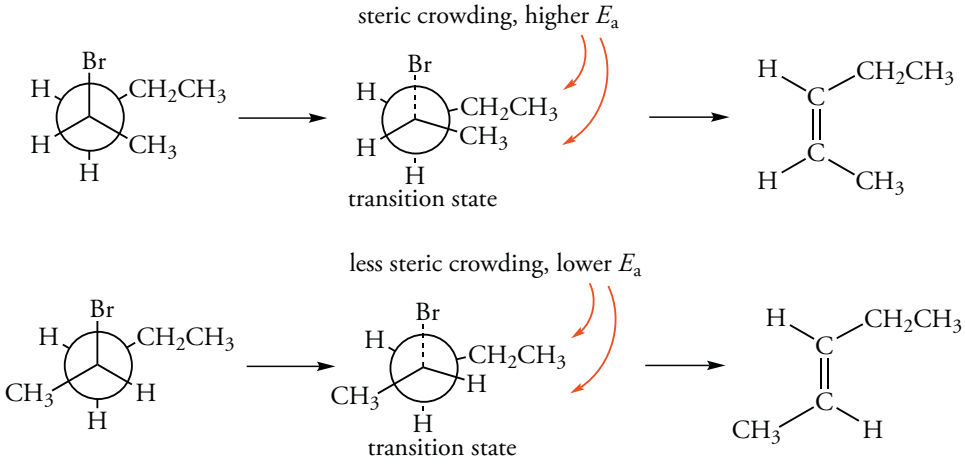


Stereoselectivity in E2 Reactions

We have seen that elimination reactions of alkyl halides are stereoselective, and yield the more stable *trans*-alkene as the major product. The geometry for the anti periplanar transition state of the E2 mechanism accounts for this observation. As the hydrogen and halogen atoms are eliminated, the groups bonded to the developing sp^2-hybridized carbon atoms must move closer together in the transition state. In the final product, they must all be in the same plane. Figure 9.9 shows the two conformations required to form *cis*- and *trans*-2-pentenes from 2-bromopentane. The transition state leading to the *cis* isomer has more steric strain because the two alkyl groups are moved closer together. As a consequence, the energy of this transition state is higher than that for formation of the *trans* isomer. The rate of the formation of the *cis* isomer is therefore slower than that of the *trans* isomer.

Figure 9.9
Steric Effects in E2 Reactions

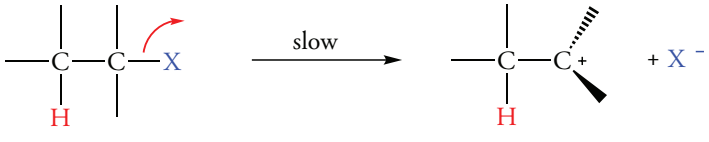
The stability of the *cis*- and *trans*-alkenes produced in the E2 reaction reflects the stabilities of the transition states leading to them. Steric crowing in the transition state leading to the *cis* isomer raises the activation energy relative to the transition state for forming the *trans* isomer. Therefore, the *trans* isomer forms faster and is the major product.



The E1 Mechanism

The E1 mechanism, which occurs in the dehydrohalogenation of tertiary alkyl halides, is a two-step process. The first step is formation of a carbocation by a heterolytic cleavage of the C—X bond. This step is rate determining.

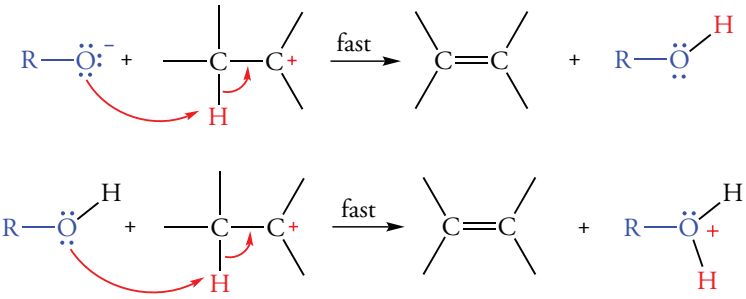
Step 1. Ionization



As in the E2 reaction, the strength of the carbon–halogen bond affects the rate of the reaction. In fact, the differences in reactivity are larger in El reactions because only the carbon–halogen bond breaks in the rate-determining step. Alkyl iodides have the weakest carbon–halogen bond, and hence react at the fastest rate. We recall that the formation of a carbocation is also the first step for the S_N1 reaction. We will see in Chapter 10 that the El mechanism competes with an S_N1 mechanism.

Because the rate-determining step of an El reaction involves only the substrate, the formation of the carbocation is a unimolecular reaction. In the second, more rapid deprotonation step, a base such as an alkoxide ion or a solvent such as an alcohol removes a proton from a β-carbon atom adjacent to the cationic center. The overall result is loss of HX and formation of a π bond. These possibilities are outlined below.

Step 2. Deprotonation



Problem 9.20

How many products can result from the dehydrobromination of 3-bromo-2,3-dimethylpentane? Predict the major alkene product formed. Predict the alkene formed in the smallest amount.

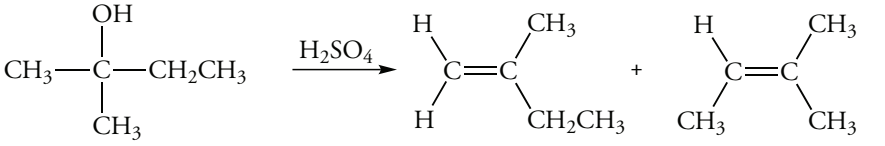
Problem 9.21

The product of the dehydrobromination of *trans*-1-bromo-2-methylcycIohexane is not 1-methylcyclohexene, the Zaitsev product, but rather 3-methylcyclohexene. Explain why. (Hint: Remember that the ring-flipping process gives a mixture of two conformations.)

9. 17 REGIOSELECTIVITY IN DEHYDRATION REACTIONS

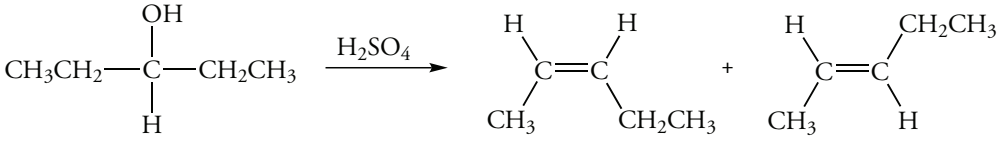
Regioselectivity in the Dehydration of Alcohols

The dehydration of an alcohol is an elimination reaction that requires breaking the carbon–oxygen bond and a carbon–hydrogen bond on an adjacent, β-carbon atom. Thus, dehydration of alcohols having two nonequivalent β-carbon atoms adjacent to the OH-bearing carbon atom can form a mixture of products. In such cases, the more substituted alkene is the major product. For example, the dehydration of 2-methyl-2-butanol yields 2-methyl-2-butene as the major product. The isomeric 2-methyl-1-butene forms in a substantially smaller quantity.



2-methyl-2-butanol → 2-methyl-1-butene (10%) + 2-methyl-2-butene (90%)

This product distribution is another example of Zaitsev's rule. Zaitsev's rule can be extended to mixtures of geometric isomers. That is, the major product is the more stable *trans*-alkene. For example, 3-pentanol yields a mixture of *cis*- and *trans*-2-pentenes. The *trans* isomer is the major product. Thus, the dehydration of an alcohol is both regioselective and stereoselective.



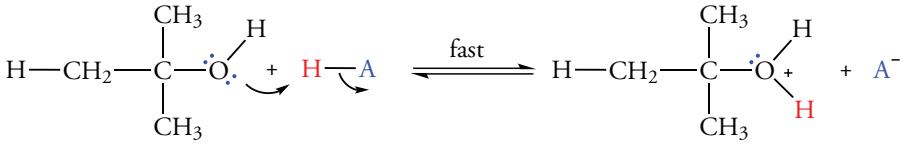
cis-2-pentene (25%) + *trans*-2-pentene (75%)

Mechanism of Alcohol Dehydration Reactions

The mechanism for the dehydration of an alcohol must account for two experimental observations. First, the dehydration reaction requires an acid catalyst. Second, the order of reactivity of alcohols decreases in the order 3° > 2° > 1°. These facts remind us of the substitution reaction of tertiary and secondary alcohols using hydrogen halides, which occurs by an S_N1 process. Only primary alcohols react by an S_N2 mechanism.

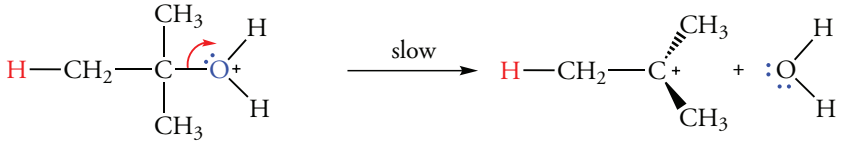
Tertiary and secondary alcohols undergo acid-catalyzed dehydration by an El mechanism; primary alcohols are dehydrated by an E2 mechanism. In either mechanism, the first step is the rapid protonation of the lone pair electrons of the oxygen atom to produce an alkyloxonium ion. The acid is represented as HA in the reaction mechanism for the dehydration of *tert*-butyl alcohol shown below.

Rapid, reversible protonation of the alcohol by the acid catalyst

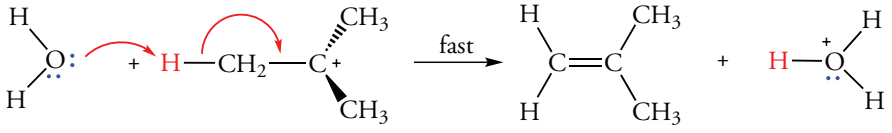


After the alcohol has been protonated, an El mechanism occurs in two steps. First, a tertiary alcohol loses water in a first order process to produce a tertiary carbocation. Second, a proton is then rapidly transferred to a Lewis base from a β-carbon atom to the tertiary carbocation.

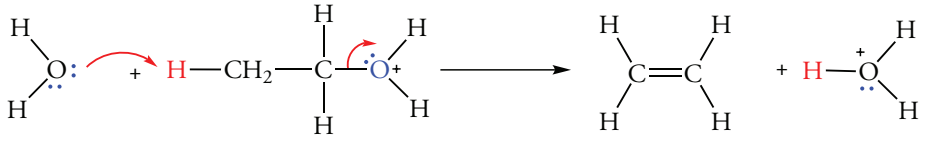
Step 1. Loss of water to give a 3° carbocation



Step 2. Loss of a proton to give a an alkene

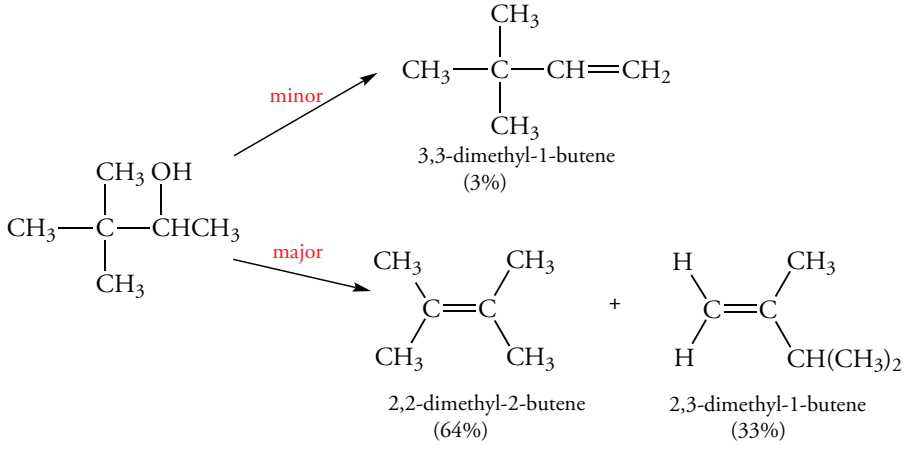


Elimination reactions of primary alcohols occurs by an E2 mechanism in an acid-catalyzed reaction. First, the acid protonates the oxygen of a primary alcohol to give a primary alkyl oxonium ion. Then, water is lost by an E2 mechanism because a primary carbocation is too unstable to form in an El process. This concerted step resembles the reaction of primary alkyl halides with a base. The proton of the alkyl oxonium ion is deprotonated by a Lewis base, which is water in the dehydration of alcohols. The electron pair in the C—H bond "moves" to form a carbon–carbon double bond, and the electron pair of the C—O bond is retained by the oxygen atom. The reaction with ethanol illustrates the process. In both the E1 process and the E2 dehydration reaction, the acid serves only as a catalyst. It is regenerated in the last step of the reaction.



Rearrangements in Dehydration Reactions

Because dehydration of secondary and tertiary alcohols occurs via carbocation intermediates, rearrangement reactions are common. For example, in the dehydration of 3,3-dimethyl-2-butanol, only 3% of the dehydration product maintains the original carbon skeleton. The remaining 97% is a mixture of two isomeric alkenes with a rearranged carbon skeleton.

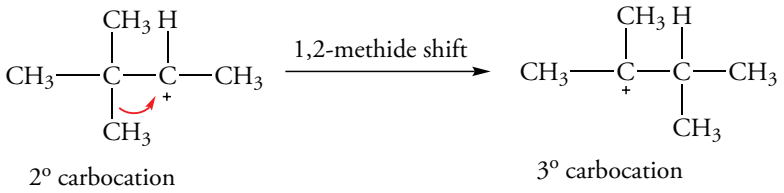


3,3-dimethyl-1-butene (3%)

2,2-dimethyl-2-butene (64%)

2,3-dimethyl-1-butene (33%)

Since the first step in the reaction is the formation of a carbocation, migration of a methyl group in a 1,2-methide shift gives a rearranged tertiary carbocation. This rearranged carbocation accounts for most of the product.



2° carbocation 3° carbocation

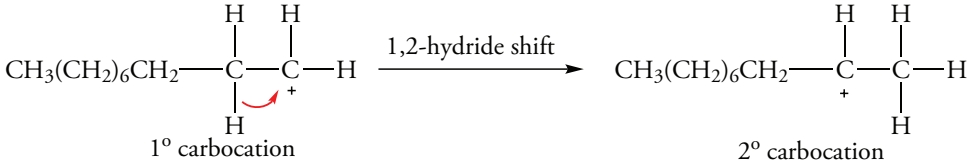
The rearrangement reaction is favored because tertiary carbocations are more stable than secondary carbocations. We recall that the same rearrangement occurs in the addition reaction of HCl with 3,3-dimethyl-l-butene, which gives not only the expected product, 2-chloro-3,3-dimethylbutane, but 2-chloro-2,3-methylbutane as well (Section 6.4).

The more substituted 2,3-dimethyl-2-butene forms from loss of a proton from C-3 of the tertiary carbocation. The less substituted 2,3-dimethyl-l-butene forms from the loss of any of the six hydrogen atoms located at the two methyl groups bonded to the carbocation center. Although the reaction of the rearranged carbocation may not appear to be very regioselective, it actually is. The more substituted alkene is favored even though the least substituted alkene would be expected on statistical grounds. That is, any of six equivalent hydrogen atoms could be lost to give 2,3-dimethyl-1-butene, but only one hydrogen atom scan be lost to give 2,3-dimethyl-2-butene. Thus, the regioselectivity of the reaction reflects the relative stability of the two possible alkenes.

Alkyl groups other than the methyl group can also migrate from one carbon atom to an adjacent carbon atom if the resulting carbocation is more stable. Therefore, mixtures of alkenes result, and the dehydration of alcohols is somewhat limited as a synthetic method to form specific alkenes.

We recall that the dehydrohalogenation of primary and secondary alkyl halides occurs via an E2 mechanism, and that rearranged products are not obtained. Thus, dehydrohalogenation of an alkyl halide using a strong base is a better synthetic method to form alkenes than the dehydration of an alcohol.

In Section 6.4, we saw that 1,2-hydride shifts occur in the carbocations formed in addition reactions. We have also seen that 1,2-hydride shifts can also occur in carbocations that are generated in dehydration reactions if a more stable carbocation results. Such 1,2-hydride shifts occur even in the dehydration of primary alcohols. For example, the dehydration of 1-decanol gives 1-decene as a minor product, which may result from an E2 mechanism. However, the major product is largely a mixture of *cis*- and *trans*-2-decenes. This product could result from loss of a proton by an E1 mechanism from a secondary carbocation formed by a hydride shift of a primary carbocation.

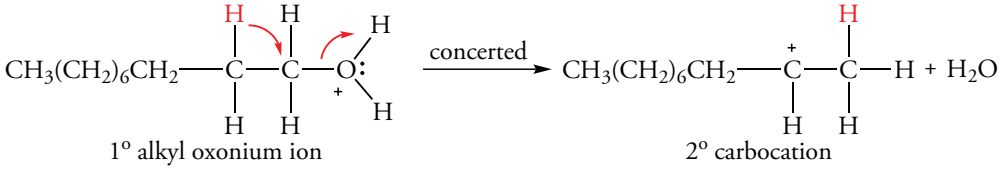


1° carbocation 2° carbocation

$CH_3(CH_2)_6CH{=}CHCH_3$

mixture of *cis*- and *trans*-isomers

However, unstable primary carbocations do not form directly. Thus, it is likely that a shift of the hydride ion from C-2 to C-l to form the secondary carbocation occurs in a concerted process as water leaves C-l.



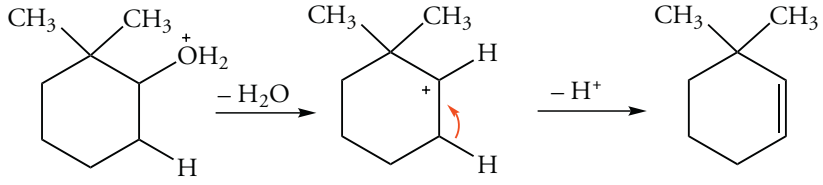
1° alkyl oxonium ion 2° carbocation

Problem 9.22 Predict the major product formed in the dehydration of each of the following alcohols.
(a) l-methylcyclohexanol (b) 3-ethyl-2-pentanol (c) l-isopropylcyclohexanol

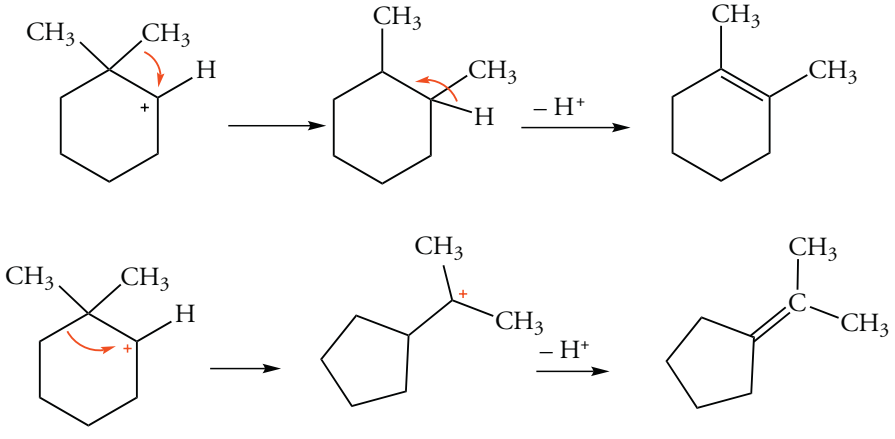
Problem 9.23 Draw the structures of the three isomeric cycloalkenes resulting from the dehydration of 2,2-dimethylcyclohexanol.

Sample Solution

Protonation of the alcohol, followed by loss of a proton from the methylene group of the secondary carbocation gives 3,3-dimethylcyclohexene.



However, the secondary carbocation can rearrange to two possible tertiary carbocations, either of which can lose a proton, to give isomeric cycloalkenes.



Problem 9.24

Write the structures of the products of the dehydration of 3-methyl-2-butanol.

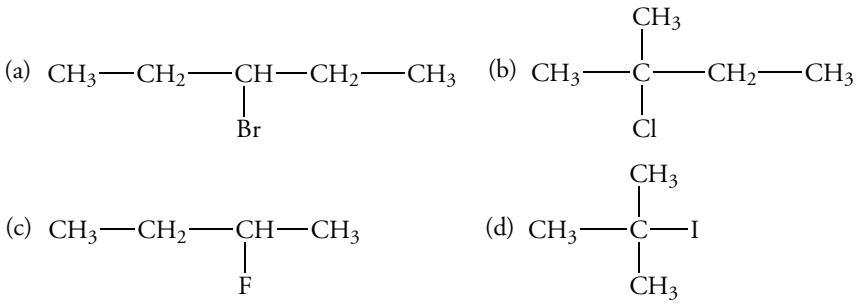
Problem 9.25

Write the structures of two alkenes that form when 2,2-dimethyl-1-propanol is heated in sulfuric acid, and predict which is the major isomer.

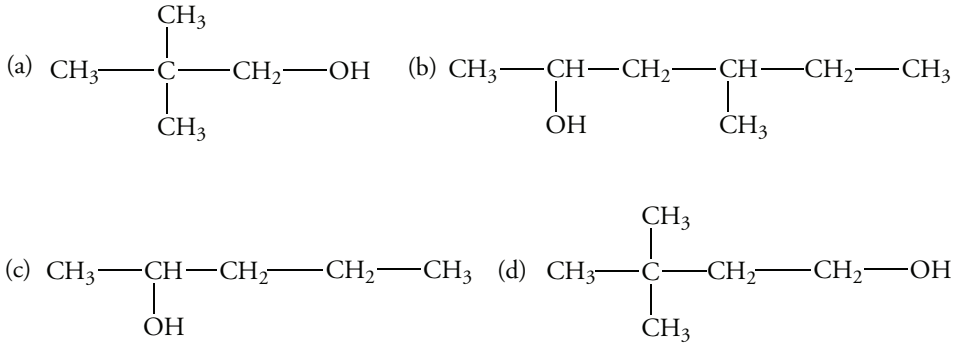
EXERCISES

Classification of Haloalkanes and Alcohols

9.1 Classify each of the following haloalkanes.

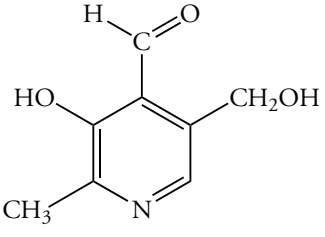


9.2 Classify each of the following alcohols.

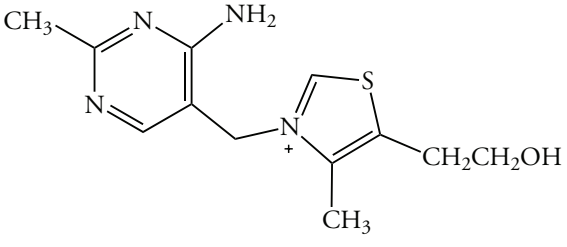


9.3 Classify each of the hydroxyl groups in the following vitamins.

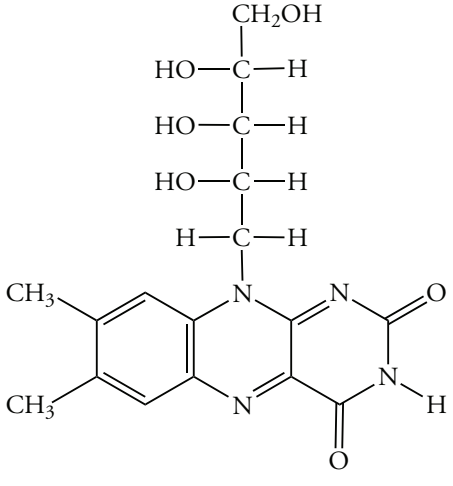
(a) pyridoxal (vitamin B_6)



(b) thiamine (vitamin B_1)

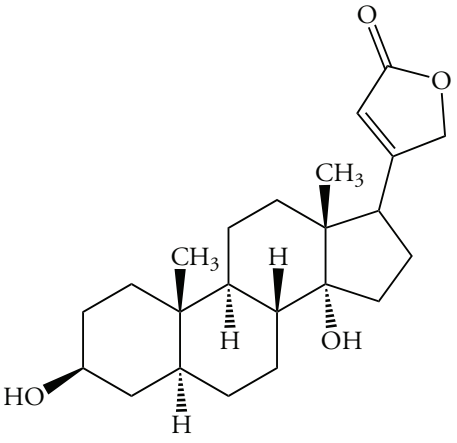


(c) riboflavin (vitamin B_2)

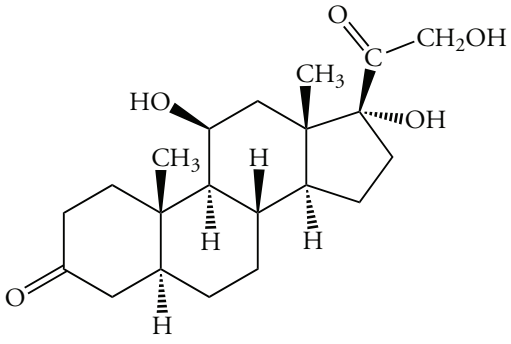


9.4 Classify each of the hydroxyl groups in the following steroids.

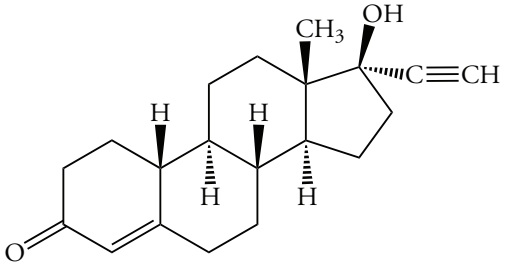
(a) digitoxigenin, a cardiac glycoside



(b) hydrocortisone, an antiinflammatory drug



(c) norethindrone, an oral contraceptive



Nomenclature of Haloalkanes

9.5 What is the IUPAC name for each of the following compounds?

(a) vinyl fluoride (b) allyl chloride (c) benzyl bromide

9.6 What is the IUPAC name for each of the following compounds?

(a) $(CH_3)_3CCH_2Cl$ (neopentyl chloride) (b) $(CH_3)_2CHCH_2CH_2Br$ (isoamyl bromide)

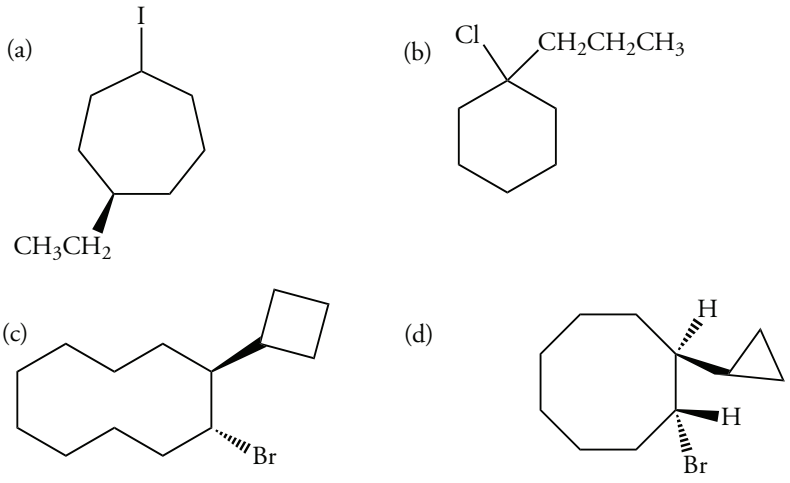
(c) $C_6H_5CH_2CH_2F$ (phenethyl fluoride)

9.7 Draw the structure of each of the following compounds.

(a) *cis*-l-bromo-2-methylcyclopentane (b) 3-chlorocyclobutene

(c) (*E*)-1-fluoro-2-butene (d) (*Z*)-l-bromo-1-propene

9.8 What is the IUPAC name for each of the following compounds?



Nomenclature of Alcohols

9.9 Write the structural formula of each of the following compounds

(a) 2-methyl-2-pentanol (b) 2-methyl-1-butanol (c) 2,3-dimethyl-1-butanol (d) cyclopentanol (e) *trans*-2-methylcyclohexanol

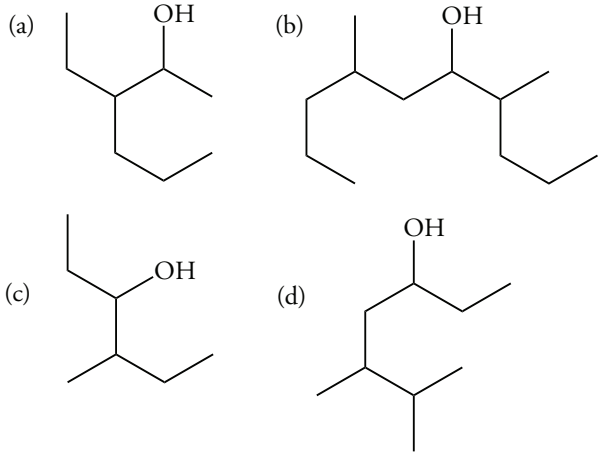
(f) 1,3-propandiol (g) 1,2,4-butanetriol

9.10 What is the IUPAC name for each of the following compounds?

(a) 2-methyl-3-pentanol (b) 3-ethyl-3-pentanol (c) 4-methyl-2-pentanol (d) l-ethylcyclohexanol (e) *cis*-3-ethylcyclopentanol

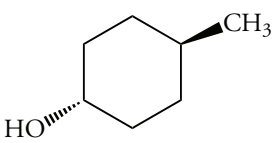
(f) 1,2-hexanediol (g) 1,2,3,4,5,6-hexanehexol

9.11 What is the IUPAC name for each of the following compounds?

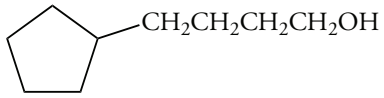


9.12 What is the IUPAC name for each of the following compounds?

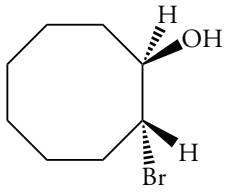
(a)



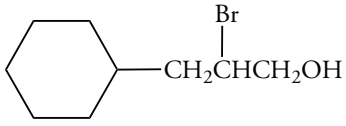
(b)



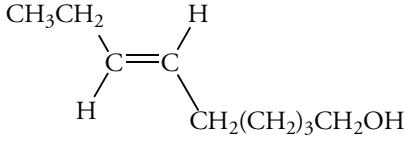
(c)



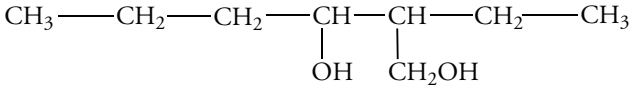
(d)



9.13 Name the sex attractant of the Mediterranean fruit fly.



9.14 Name the following compound, which is a mosquito repellent.



Properties of Haloalkanes

9.15 Which compound is more polar, methylene chloride (CH_2Cl_2) or carbon tetrachloride (CCl_4)?

9.16 Tribromomethane is more polar than tetrabromomethane, but their boiling points are 150 and 189 °C, respectively. Explain why the more polar compound has the lower boiling point.

9.17 The dipole moment of (*Z*)-1,2-dichloroethene is 1.90 D. Predict the dipole moment of the *E* isomer.

9.18 The dipole moment of 1,2-dichloroethane is 1.19 D. What does this value indicate about the conformational equilibrium of this compound?

Physical Properties of Alcohols

9.19 1,2-Hexanediol is very soluble in water but 1-heptanol is not. Explain why these two compounds with similar molecular weights have different solubilities.

9.20 Ethylene glycol and 1-propanol boil at 198 and 97 °C, respectively. Explain why these two compounds with similar molecular weights have different boiling points.

9.21 Explain why 1-butanol is less soluble than 1-propanol in water.

9.22 Suggest a reason why 2-methyl-1-propanol is much more soluble than 1-butanol in water.

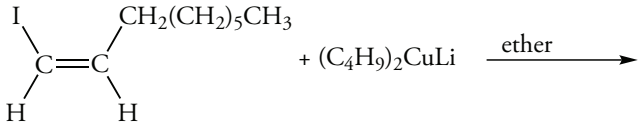
Organometallic Reagents

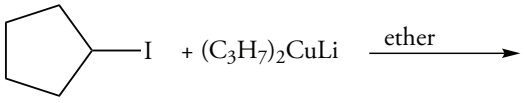
9.23 Devise a synthesis of 1-deutero-1-methylcyclohexane starting from 1-methylcyclohexene.

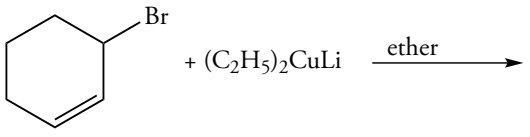
9.24 Devise a synthesis of 1,4-dideuterobutane starting from any organic compound that does not contain deuterium.

9.25 Devise two syntheses to prepare 2-methyloctane using reagents containing alkyl groups with five or fewer carbon atoms.

9.26 Write the products of the following reactions for Gilman reagents that contain primary alkyl groups.

(a) 

(b) 

(c) 

Nomenclature of Alcohols

9.27 Write the structure of the product obtained for each of the following combinations of reactants.

(a) 1-chloropentane and sodium iodide (b) 1,3-dibromopropane and excess sodium cyanide (c) benzyl chloride and sodium acetylide

(d) 2-bromobutane and sodium hydrosulfide (NaSH)

9.28 What haloalkane and nucleophile are required to produce each of the following compounds?

(a) $CH_3CH_2CH_2C{\equiv}CH$ (b) $(CH_3)_2CHCH_2CN$ (c) $CH_3CH_2SCH_2CH_3$ (d) $C_6H_5CH_2OH$

Mechanism of Nucleophilic Substitution Reactions

9.29 Which compound in each of the following pairs reacts at the faster rate with sodium iodide in an S_N2 process to yield an alkyl iodide?

(a) 1-chlorohexane or 2-chlorohexane (b) bromocyclohexane or 1-bromo-1-methylcyclohexane

(c) 2-bromo-4-methylpentane or 2-bromo-2-methylpentane

9.30 Rank the following compounds in order of increasing S_N2 reactivity with a common nucleophile.

I: 1-bromohexane II: 1-bromo-2-methylpentane III: l-bromo-3-methylpentane

9.31 Which compound in each of the following pairs reacts at the faster rate in an S_N1 process under the same reaction conditions?

(a) bromocyclohexane or 1-bromo-1-methylcyclohexane (b) 2-bromobutane or l-bromo-2-methylpropane

(c) 2-bromobutane or 2-methyl-2-bromobutane

9.32 Which compound in each of the following pairs reacts at the faster rate in an S_N1 process under the same reaction conditions?

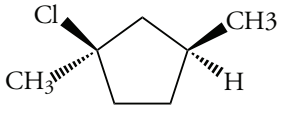
I: 2-bromohexane II: 2-bromo-2-methylpentane III: 1-bromo-2-methylpentane

9.33 Predict the product of the reaction of one molar equivalent of sodium iodide with 1,3-dichlorohexane.

9.34 Treatment of the following compound with sodium sulfide yields C_4H_8S. What is the structure of the product? How is it formed?

$Br{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}Br + NaS \rightarrow C_4H_8S$

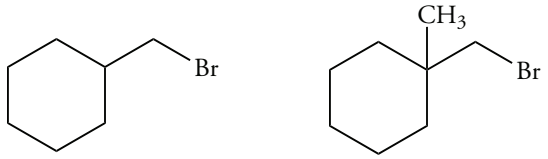
9.35 Reaction of the following compound with water under S_N1 conditions yields a mixture of two alcohols. Explain why.



9.36 Reaction of either 3-bromo-1-butene or (*Z*)-1-bromo-2-butene with water under S_N1 conditions yields the same product. Explain why.

9.37 The rate of reaction of *cis*-1-bromo-4-*tert*-butylcyclohexane with methylthiolate (CH_3S^-) is faster than for the *trans* isomer. Suggest a reason for this difference.

9.38 Which of the following two compounds reacts at the faster rate with sodium cyanide?



I II

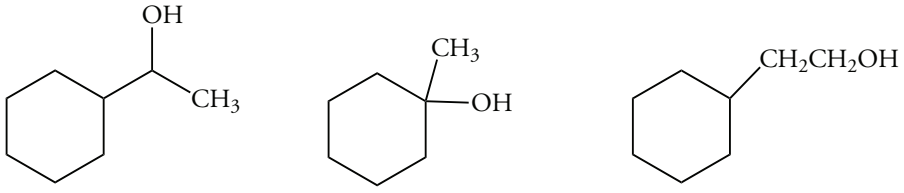
Acid–Base Properties of Alcohols

9.39 1,1,1-Trichloro-2-methyl-2-propanol is used as a bacteriostatic agent. Compare its pK_a to that of 2-methylpropanol.

9.40 Which base is the stronger, methoxide ion or *tert*-butoxide ion? Explain your reasoning.

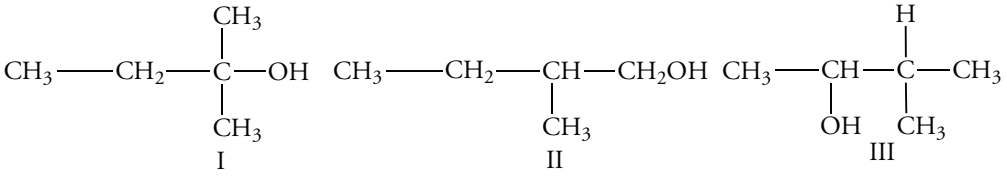
Formation of Alkyl Halides from Alcohols

9.41 Rank the following compounds according to their rates of reaction with HBr.

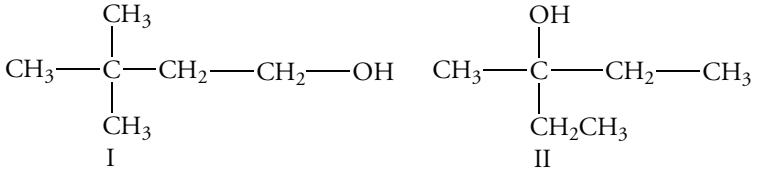


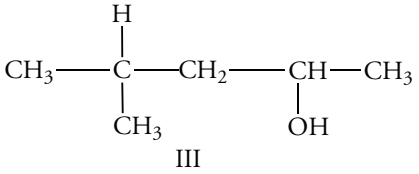
I II III

9.42 Rank the following compounds according to their rates of reaction with HCl and $ZnCl_2$.

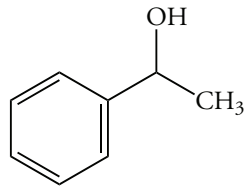


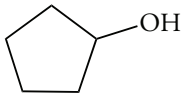
9.43 Write the structure of the product of reaction for each of the following compounds with PBr_3.

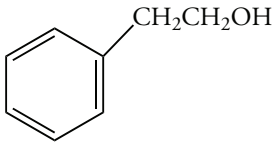




9.44 Write the structure of the product of reaction for each of the following compounds with $SOCl_2$.

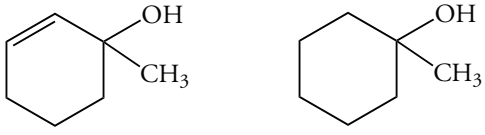
(a) 

(b) 

(c) 

9.45 Reaction of 3-buten-1-ol with HBr yields a mixture of two products: 3-bromo-l-butene and 1-bromo-2-butene. Explain why. (Hint: The reaction of this allyl alcohol occurs via an S_N1 process.)

9.46 The rate of reaction of the following unsaturated alcohol with HBr is faster than the rate of reaction of the saturated alcohol. Explain why.



9.47 Which of the compounds in Exercises 9.41 and 9.42 may yield rearranged products?

9.48 The reaction of 2-octanol with HBr gives 2-bromooctane and 3-bromooctane in a 13:1 ratio. Explain how 3-bromooctane forms in this reaction.

Regioselectivity in Dehydrohalogenation

9.49 Consider each of the following isomeric compounds with the molecular formula $C_6H_{13}Br$. Which ones will give only a terminal monosubstituted alkene when they undergo dehydrobromination by an E2 process?

I: $CH_3CH_2CH_2CH_2CH_2CH_2Br$ II: $CH_3CHBrCH_2CH_2CH_2CH_3$

III: $CH_3CH_2CHBrCH_2CH_2CH_3$ IV: $(CH_3)_2CHCH_2CH_2CH_2Br$

V: $(CH_3)_2CHCH_2CHBrCH_3$ VI: $(CH_3)_2CHCHBrCH_2CH_3$

VII: $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2Br$ VIII: $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCHBrCH_3$

IX: $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}BrCH_2CH_3$ X: $BrCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}CH_2CH_3$ (CH_3 also on the lower carbon)

XI: $(CH_3)_3CCH_2CH_2Br$ XII: $(CH_3)_3CCHBrCH_3$

XIII: $(CH_3)_2CH\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2Br$ XIV: $(CH_3)_2CH\underset{\displaystyle CH_3}{\underset{|}{C}}BrCH_3$

9.50 Consider each of the compounds in Exercise 9.49. Which ones can undergo dehydrobromination by an E2 process to give only a terminal disubstituted alkene?

9.51 Consider each of the compounds in Exercise 9.49. Which ones can undergo dehydrobromination by an El process?

9.52 Consider each of the compounds in Exercise 9.49. Which ones cannot undergo dehydrobromination?

9.53 Consider each of the compounds in Exercise 9.49. Which ones can undergo dehydrobromination to give at least one set of *E*,*Z* stereoisomers among the products.

9.54 Consider each of the compounds in Exercise 9.49. Which ones can undergo dehydrobromination to give a trisubstituted alkene among the products? Which ones can undergo dehydrobromination to give a tetrasubstituted alkene among the products?

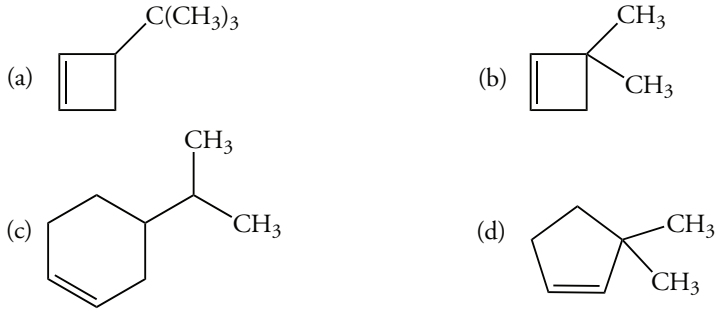
9.55 How many alkenes can form from each of the following compounds via an E2 process? Write the structure of each alkene.

(a) l-bromopentane (b) 2-chlorohexane (c) 3-iodoheptane (d) (*S*)-2-bromononane

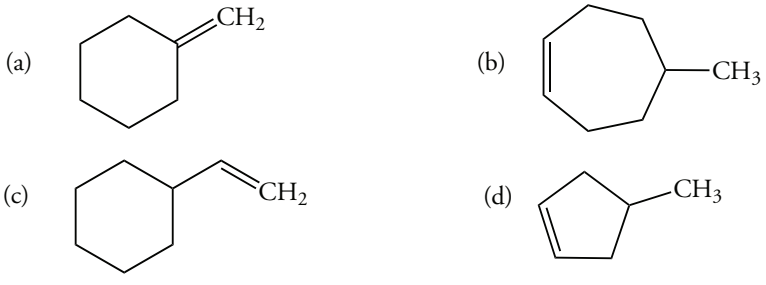
9.56 How many alkenes can form from each of the following compounds via an E2 process? Write the structure of each alkene.

(a) 3-bromo-2-methylhexane (b) 2-chloro-3-methylhexane (c) 3-iodo-4-ethylhexane (d) 4-bromo-4-methylheptane

9.57 What bromo compound can give each of the following unsaturated compounds in the best yield by an E2 process?

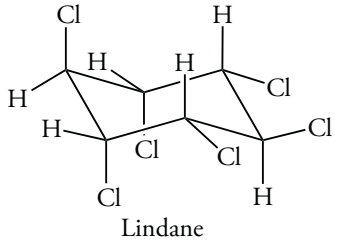


9.58 Which of the following unsaturated compounds can be obtained in good yield by an E2 process from a bromo compound?



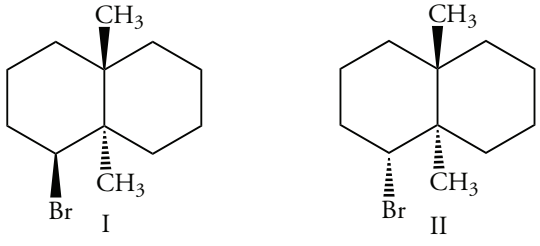
Stereoelectronic Effects in Dehydrohalogenation

9.59 Explain why the following isomer undergoes an E2 reaction about 1000 times slower than any of the other stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane.

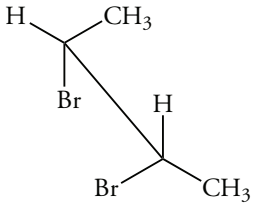


Lindane

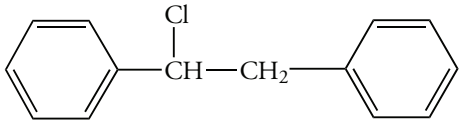
9.60 One of the following two isomeric bicyclic compounds undergoes an E2 elimination much faster than the other. Identify the compound that reacts at the faster rate and explain why.



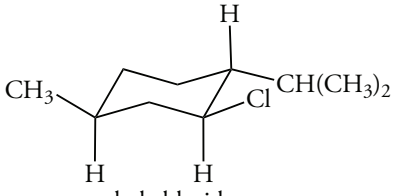
9.61 What is the configuration of the alkene formed by the elimination of one molar equivalent of HBr from the following compound?



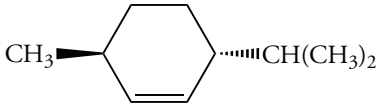
9.62 An E2 elimination of 1-chloro-1,2-diphenylethane can yield a mixture of (*E*)- and (*Z*)-1,2-diphenylethene. How would the *E*/*Z* ratio of isomers for this reaction compare to the *E*/*Z* ratio for the E2 elimination of 2-bromopentane?



9.63 When menthyl chloride reacts with sodium ethoxide in ethanol, the only alkene product is 2-menthene. Explain why.

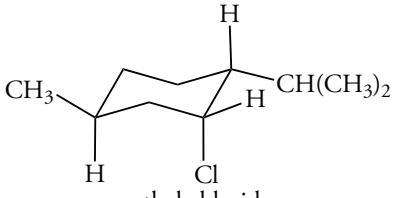


menthyl chloride

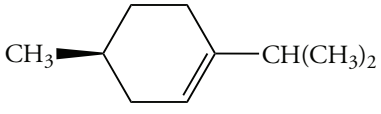


2-menthene

9.64 When neomenthyl chloride reacts with sodium ethoxide in ethanol, the only alkene product is 3-menthene. Explain why.

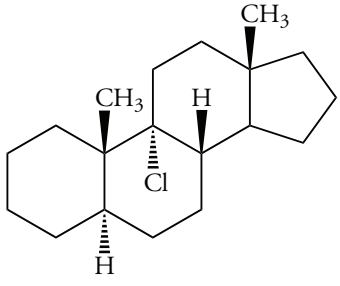


neomenthyl chloride

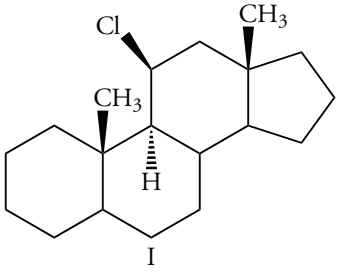


3-menthene

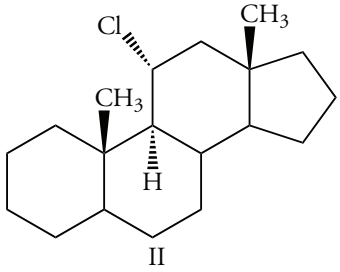
9.65 Draw the structure of the alkene formed in an E2 elimination of the following compound.



9.66 Which of the following compounds reacts at the faster rate in an E2 elimination reaction?

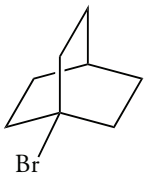


I



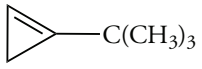
II

9.67 The following compound cannot undergo dehydrobromination under either El or E2 conditions. Explain why.



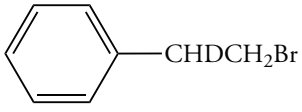
1-bromobicyclo[2.2.2]octane

9.68 Explain why 1-*tert*-butylcyclopropene is difficult to synthesize by a dehydrohalogenation reaction.

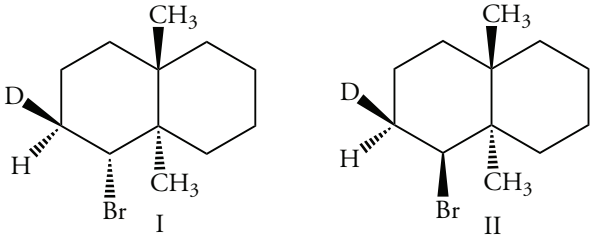


1-*tert*-butylcyclopropene

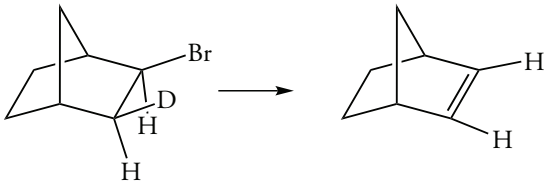
9.69 Reaction of 1-bromo-2-deutero-2-phenylethane with *tert*-butoxide in *tert*-butyl alcohol gives a 7:1 ratio of deuterated and nondeuterated phenylethenes. Write the structures of the products. What does the data suggest about the ease of abstraction of deuterium versus hydrogen?



9.70 Dehydrobromination of each of the following compounds gives a single product. One compound yields a cycloalkene containing deuterium, the other yields a cycloalkene that does not contain deuterium. Which compound is which?



9.71 Although the following reaction of the deuterated bicyclic compound with a strong base occurs at a somewhat slow rate, it gives the indicated product by an E2 mechanism. Explain why the product forms.

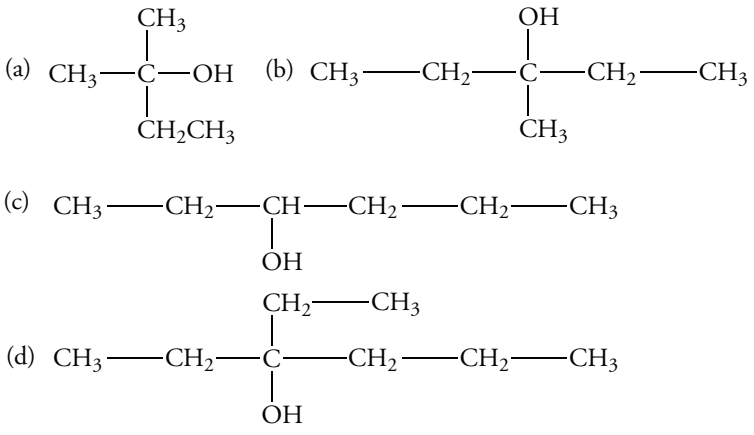


9.72 One of the following 2,3-dichlorobicyclo[2.2.1]heptanes undergoes an E2 elimination using potassium *tert*-butoxide in *tert*-butyl alcohol about 100 times as fast as the other. Which compound reacts at the faster rate? The same product, 2-chlorobicyclo[2.2.1] hept-l-ene, forms in both reactions.

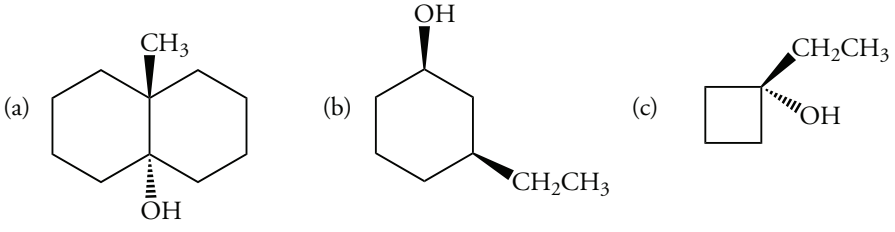


Dehydration of Alcohols

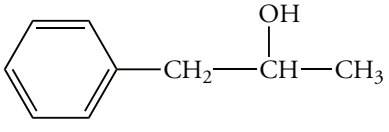
9.73 Draw the structure of the dehydration product(s) when each of the following compounds reacts with sulfuric acid. If more than one product forms, predict the major isomer assuming that no rearrangement reactions occur.



9.74 Draw the structure of the dehydration product(s) when each of the following compounds reacts with sulfuric acid. If more than one product forms, predict the major isomer assuming that no rearrangement reactions occur.

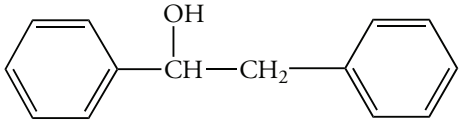


9.75 Write the expected product of the acid-catalyzed dehydration of l-phenyl-2-propanol. The reaction is more rapid than the dehydration of 2-propanol. Explain why.



1-phenyl-2-propanol

9.76 Explain why 1,2-diphenylethanol dehydrates extremely easily.



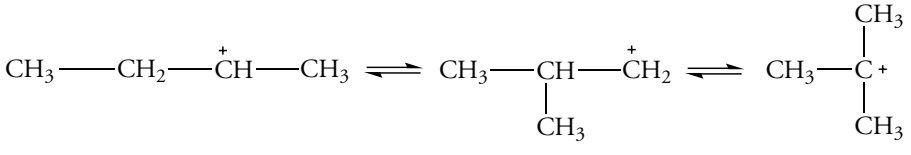
1,2-Diphenylethanol

9.77 Dehydration of *cis*-2-methylcyclohexanol yields two products in a 5:1 ratio. What are the structures of the two products?

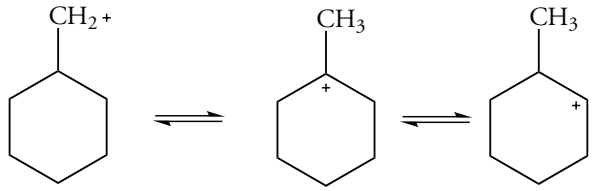
9.78 Dehydration of cyclododecanol yields two isomeric products in approximately equal amounts. Catalytic hydrogenation of either compound yields cyclododecane. What are the structures of the two products?

Carbocation Rearrangement in S_N1 and E1 Reactions

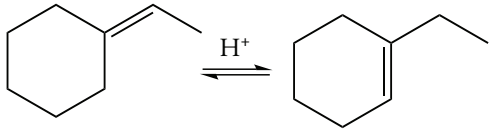
9.79 The following isomerization reactions occur in some industrial processes. Write a mechanism that accounts for each step. Indicate whether each reaction is energetically favorable or unfavorable.



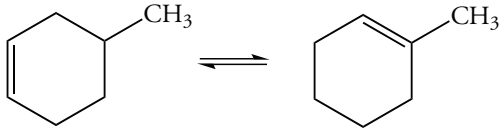
9.80 Write a mechanism that accounts for each step of the rearrangement of the carbocation shown below. Indicate whether each reaction is energetically favorable or unfavorable.



9.81 Ethylidenecyclohexane and l-ethylcyclohexene can be equilibrated using an acid catalyst. Write a mechanism that accounts for this conversion.



9.82 4-Methylcyclohexene isomerizes to 1-methylcyclohexene over alumina (an acidic substance). Write a mechanism that accounts for this conversion.

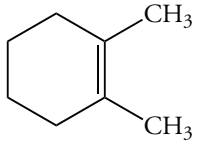


Rearrangement in Dehydration Reactions

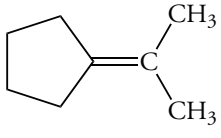
9.83 Dehydration of 2,2,4-trimethyl-3-pentanol with acid gives a complex mixture of the alkenes in the indicated percentages. Write a mechanism that accounts for each product.

I: 2,3,4-trimethyl-1-pentene	29%	II: 2,4,4-trimethyl-1-pentene	24%
III: 3,3,4-trimethyl-1-pentene	2%	IV: 2,4,4-trimethyl-2-pentene	24%
V: 3,3,4-trimethyl-2-pentene	18%	VI: 2-isopropyl-3-methyl-1-butene	3%

9.84 Dehydration of 2,2-dimethylcyclohexanol with acid gives both of the following isomeric alkenes. Write a mechanism that accounts for each product.



1,2-dimethylcyclohexene



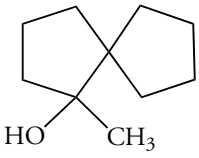
isopropylidinecyclopentane

9.85 1-Methylcyclopentene is one of the dehydration products obtained from l-cyclobutyl-l-ethanol. Write a mechanism that accounts for this reaction.

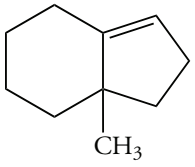
9.86 3,3-Dimethylcyclopentene is one of the dehydration products obtained from 2-cyclobutyl-2-propanol. Write a mechanism that accounts for this reaction.

9.87 1-*tert*-Butylcyclohexene is one of several dehydration products obtained from 1,2,2-trimethylcycloheptanol. Two rearrangements are required for this transformation. Write a mechanism accounting for these reactions.

9.88 Dehydration of 2-methyl-2-spiro[4.4]nonanol gives a mixture containing 1-methyl-6-bicyclo[4.3.0]nonene. Write a mechanism that accounts for the formation of this product.



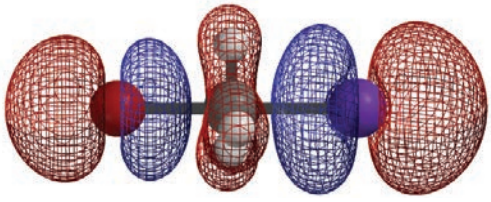
2-methyl-2-spiro[4.4]nonanol



1-methyl-6-bicyclo[4.3.0]nonene

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10 Nucleophilic Substitution and Elimination Reactions



Transition state for an S_N2 reaction

In Chapter 9, we introduced the basic principles of nucleophilic substitution and elimination reactions. We focused almost entirely upon the reactions of haloalkanes and alcohols. In this chapter, we will expand upon these reactions and consider a much wider range of nucleophiles, leaving groups, substrates, solvents, and their effects on nucleophilic substitution and elimination reactions. We will ask:

1. What properties determine the nucleophilicity of a given species, and how does its reactivity compare to other nucleophiles?

2. How does the leaving group influence the reaction?

3. How does the structure of the substrate influence the reaction?

4. How does the solvent influence the reaction? The answers to these questions will greatly increase our understanding of these important reactions.

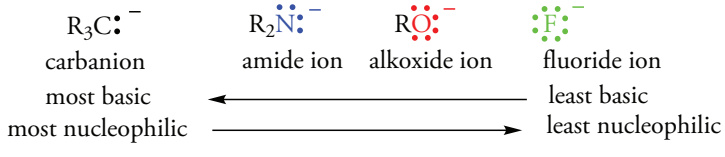
In S_N2 reactions, the rate of the reaction depends upon how readily the nucleophile displaces the leaving group from a carbon atom. The reactivity of the nucleophile is called **nucleophilicity**. Since the nucleophile is an electron pair donor, a nucleophile is also a base. Therefore, strongly basic nucleophiles can also cause a competitive elimination reaction because they can extract a proton from a β-carbon atom; the leaving groups depart in an E2 mechanism. The E2 reaction depends upon the basicity of the nucleophile. The terms nucleophilicity and basicity describe different phenomena. The nucleophilicity of a species affects the *rate* of a substitution reaction. Therefore, when we compare nucleophilicities, we are comparing the energies of transition states. In contrast, the basicity of a nucleophile reflects the equilibrium constant for an acid–base reaction in which the nucleophile extracts a proton from a substrate. When we compare basicities, we are comparing the relative energies of reactants and products.

The nucleophilicities and basicities of a series of structurally and chemically related nucleophiles—such as halide ions, oxygen-containing anions, and sulfur-containing anions—are not always related in a simple way. However, we can often find trends based on periodic properties of the elements, as we shall see below. Table 10.1 lists the *relative rates* of reaction of various nucleophiles with iodomethane. The reference nucleophile for the substitution reaction is methanol, a poor nucleophile, which is assigned a relative rate, $k_{rel} = 1$. Since iodomethane is a primary haloalkane, we know that these reactions all occur by an S_N2 mechanism.

10.1 PROPERTIES OF NUCLEOPHILES

Trends in Nucleophilicity Within a Period

When nucleophilic ions having the same charge are in the same period of the periodic table, nucleophilicity and basicity parallel each other and decrease from left to right in the period. For example, we know that hydroxide ion is more basic than fluoride ion. Hydroxide ion is also more nucleophilic. It displaces an iodide ion from methyl iodide about 4000 times faster than fluoride ion.



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Table 10.1

Relative Rates of Reaction of Nucleophiles with Iodomethane

Nucleophile	*Relative Rate*
CH_3OH	1
NO_3^-	30
F^-	5×10^2
SO_4^{-2}	3×10^3
$CH_3CO_2^-$	2×10^4
Cl^-	2.5×10^4
NH_3	3.2×10^5
N_3^-	6×10^5
Br^-	6×10^5
CH_3O^-	2×10^6
I^-	2.5×10^7
CH_3S^-	1×10^9

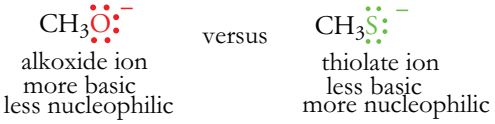
When we compare the acidities of methanol, pK_a 15.5, and hydrogen fluoride, pK_a 3.7, we see that the conjugate base of methanol, methoxide anion, is a far stronger base than fluoride. Therefore, as we noted earlier, we expect methoxide to be a better nucleophile than fluoride. Table 10.1 shows that methoxide reacts 4000 times faster with iodomethane than fluoride.

Effects of Solvent on Nucleophilicity

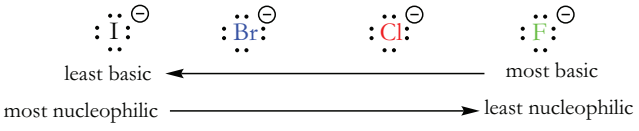
We must also consider the effect of the solvent. The solvation of anions by protic solvents such as ethanol decreases their nucleophilicity. The hydrogen atom of a protic solvent forms a hydrogen bond to a strongly electronegative element such as oxygen. The small fluoride ion, with its more concentrated charge, is strongly solvated by hydrogen bonds between its lone pair electrons and the hydrogen atom of the hydroxyl group (Figure 10.1). To react, a solvated nucleophile must lose some solvent molecules, so the nucleophile can approach the carbon center and start to form a bond to it. As a consequence, nucleophilicity is greatly decreased in a protic solvent.

Trends in Nucleophilicity Within a Group

The order of nucleophilicity is opposite to the order of basicity for nucleophiles derived from atoms in the same group of the periodic table. First, consider the nucleophilicities of methane thiolate (CH_3S^-) and methoxide (CH_3O^-). Methane thiol is a stronger acid (pK_a = 10.6) than methanol (pK_a = 15.5), and methoxide is therefore a stronger base than methane thiolate. However, methane thiolate is much more nucleophilic than methoxide (Table 10.1). The ratio of the relative rates for methylthiolate and methoxide in the displacement of iodide from methyl iodide is about 500 to 1. To react, a solvated nucleophile must lose some solvent molecules, so the nucleophile can approach the carbon center and start to form a bond to it. Therefore, its nucleophilicity is greatly decreased.



A similar inverse relationship between basicity and nucleophilicity occurs for the halides. Hydrogen iodide is a strong acid, and hydrogen fluoride is a weak acid. Thus, iodide ion is a weaker base than fluoride ion. However, for the series of halide ions, iodide ion is an excellent nucleophile and fluoride ion is a very poor nucleophile. The ratio of relative rates for iodide ion and fluoride ion in the displacement of iodide ion from iodomethane is about 50,000 to 1.



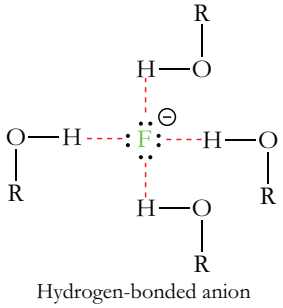
We can explain this order of nucleophilicities within a group of the periodic table by analyzing the **polarizability** of the nucleophile. The polarizability of a nucleophile is a measure of the degree to which its electron cloud is distorted in an electric field. The atomic radii of elements increase going down a family in the periodic table. As the size of an ion increases, its polarizability increases. The polarizability of a nucleophile is important in a nucleophilic substitution reaction because an electron pair in the nucleophile forms a bond to the electrophilic carbon atom during the reaction (Figure 10.2). The orbital containing an electron pair in the iodide ion can be distorted to overlap with the back lobe of the sp^3 hybrid orbital of the electrophilic carbon atom. However, fluorine is strongly electronegative, and a fluoride ion tends to hold onto the electrons in its outer 2p orbitals. Therefore, overlap of an orbital of fluoride with the back lobe of the sp^3 hybrid orbital of the carbon atom is less favorable.

The trend of anion nucleophilicity within a period of the periodic table is also affected by solvation. The larger, more polarizable anions are less strongly hydrogen bonded to protic solvents than smaller, less polarizable anions. As a result, less energy is required to shed solvent molecules from the larger ion to enable it react as a nucleophile. Thus, large anions are better nucleophiles than smaller anions because they are *both* more polarizable and less strongly solvated.

Another way to describe nucleophilicity is to say that a highly polarizable nucleophile, which is likely to be a weak base, is a *soft nucleophile*. Similarly, a base that is not very polarizable, which is likely to be a strong base, is a *hard nucleophile*.

Figure 10.1 Solvation of Ions by Proteolytic Solvent

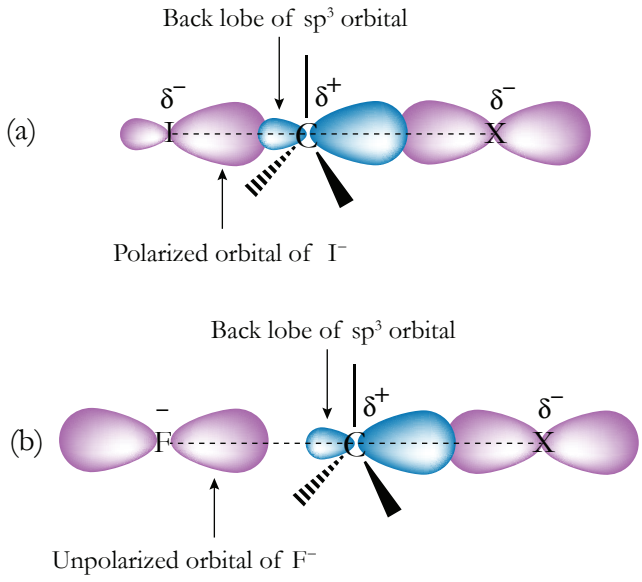
The nucleophilicity of anions in a protic solvent such as an alcohol is diminished because of hydrogen bonding between the anion and the solvent.



Hydrogen-bonded anion

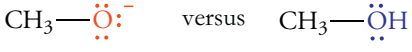
Figure 10.2 Polarizability and Nucleophilicity

(a) The nonbonded electrons of iodide are highly polarizable. One of the nonbonding electron pairs can overlap effectively with the back lobe of the sp^3-hybridized carbon atom in a nucleophilic substitution reaction. Therefore, iodide is an excellent nucleophile, even though it is not very basic.
(b) The valence electrons of fluoride, in contrast, are not very polarizable and do not effectively overlap the back lobe of the sp^3-hybridized carbon atom in a nucleophilic substitution reaction. Therefore, fluoride is a poor nucleophile, even though it is much more basic than iodide.



Effect of Charge on Nucleophilicity

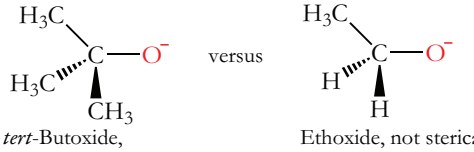
When a nucleophile can exist as either an anion or its uncharged conjugate acid, the anion is more nucleophilic than the conjugate acid. A negatively charged nucleophile is more strongly attracted to the electrophilic carbon atom than an uncharged nucleophile. For example, alkoxide ions (RO^-) are better nucleophiles than alcohols (ROH). Thus, methoxide ion displaces an iodide ion from methyl iodide about 2×10^6 times faster than methanol (Table 10.1). Similarly, hydroxide ion is a better nucleophile than water.



alkoxide ion		alcohol
more basic		less basic
more nucleophilic		less nucleophilic

Steric Effects on Nucleophilicity

The rate of an S_N2 reaction is strongly affected by bulky groups near the reaction center, which hinder the approach of the nucleophile (Section 9.9). Therefore, the size of the nucleophile is also important. Steric crowding in the transition state increases with the size of the nucleophile. We find, for example, that the larger *tert*-butoxide ion is a poorer nucleophile in S_N2 reactions than the smaller ethoxide ion.



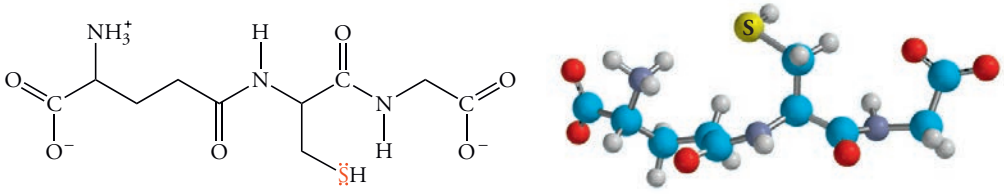
tert-Butoxide, sterically hindered, poor nucleophile.

Ethoxide, not sterically hindered, better nucleophile.

The order of basicities of alkoxides is opposite to the order of nucleophilicity. Thus, *tert*-butoxide ion is a stronger base than ethoxide ion. Steric hindrance has little effect on the ease of abstraction of a proton in acid–base reactions. Steric repulsions are less severe when the base approaches a small hydrogen atom than when it approaches the more crowded environment at a tetravalent carbon atom.

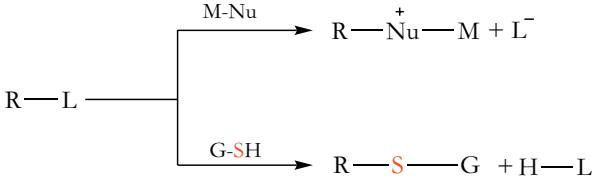
10.2 BIOLOGICAL S_N2 REACTIONS BYSULFUR-CONTAINING NUCLEOPHILES

Many cellular molecules possess a nucleophilic *sulfhydryl* group (—SH). One of the most important is glutathione. Glutathione is present at a concentration of about 1–5 mM in most animal cells. It participates in several enzyme-catalyzed reactions. In some reactions, glutathione acts as a reducing agent. In others, its nucleophilic sulfhydryl group reacts with certain toxic intermediates that are produced when drugs are metabolized in liver cells. The type of reaction that occurs depends on the cell type, and the nature of the enzyme that catalyzes the reaction.



glutathione

The sulfhydryl group of glutathione, often abbreviated GSH, is a nucleophile that displaces substituents bonded to carbon. The various leaving groups of reactive metabolites are represented with an L. They are all strongly electron-withdrawing groups, and they make the carbon atom to which they are bonded partially positively charged, and therefore susceptible to nucleophilic attack. The molecule that attacks the reactive metabolite can be an essential macromolecule with a nucleophilic center (M—Nu:) or glutathione (GSH). Thus, glutathione protects cells by reacting with toxic metabolites, represented below by R—L, before they react with other cellular macromolecules (M—Nu:).



Glutathione also provides some degree of protection against toxic industrial chemicals. Among these are benzyl, allyl, and methyl halides. However, long-term exposure to these chemicals eventually overwhelms the protection provided by glutathione and damages the organism.

Problem 10.1

Trimethylamine, $(CH_3)_3N$, is a good nucleophile, but trimethylborane, $(CH_3)_3B$, is not. Explain the difference in the nucleophilicities of these two compounds.

Problem 10.2

Which is expected to be the stronger base, an amide ion or an amine? Which is expected to be the better nucleophile?



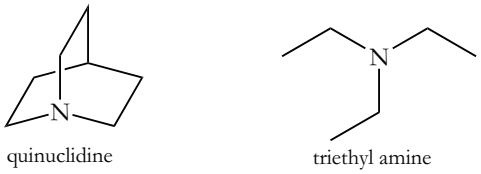
an amide ion an amine

Problem 10.3

Which is expected to be the better nucleophile, diethyl sulfide, $(CH_3CH_2)_2S$, or diethyl selenide, $(CH_3CH_2)_2Se$?

Problem 10.4

Quinuclidine reacts about 50 times faster than triethylamine to displace iodide ion from iodomethane. Suggest a reason for the different nucleophilicities of these two compounds, which contain the same number of alkyl groups bonded to the nitrogen atom.



quinuclidine triethyl amine

10.3 STEREOCHEMISTRY OF NUCLEOPHILIC SUBSTITUTION REACTIONS

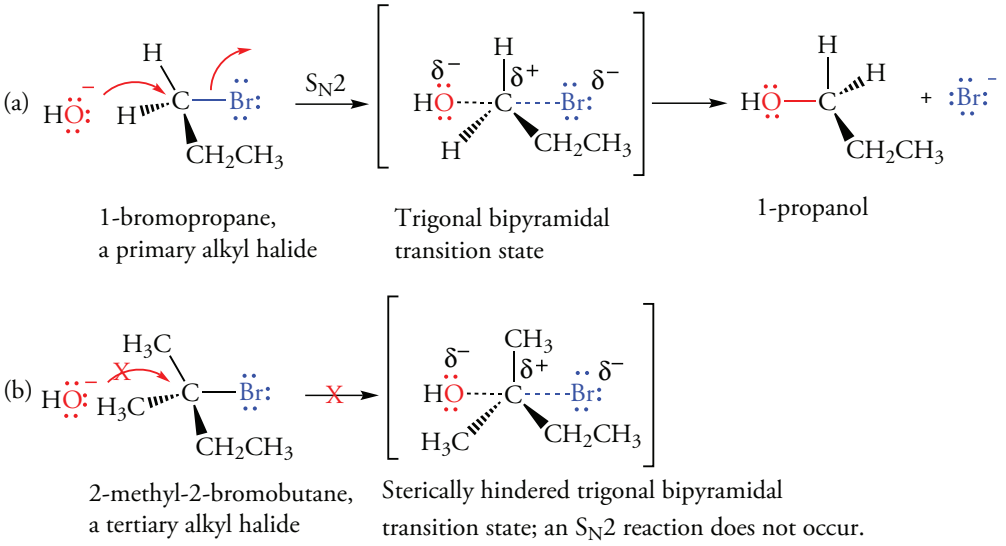
Part of the evidence for the existence of two possible mechanisms for nucleophilic substitution reactions is the kinetic order of the reaction (Section 9.9). We know an S_N2 mechanism is a one-step process in which the nucleophile attacks the substrate and the leaving group departs simultaneously. In this concerted, bimolecular process, the substrate and the nucleophile are both present in the transition state. The rate of the reaction depends on the concentrations of both the nucleophile and the substrate.

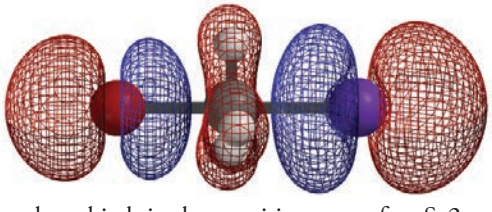
In other nucleophilic substitution reactions, the rate of the reaction depends only on the concentration of the substrate, not on that of the nucleophile. These unimolecular reactions, designated S_N1, occur in two steps. In the first step, the bond between the carbon atom and the leaving group breaks to produce a carbocation and a leaving group. In the second step, the carbocation reacts with the nucleophile to form the product. The first step in an S_N1 reaction, formation of a carbocation, is the slow, or rate-determining step. The second step, formation of a bond between the nucleophile and the carbocation, occurs very rapidly. Since the slow step of the reaction involves only the substrate, the reaction is a first-order process.

Now we will consider important information about the chirality of the reactant and the product that also distinguishes between the S_N2 and S_N1 mechanisms. The stereochemical consequences of the two mechanisms differ because the transition states in the two mechanisms differ. In the S_N2 mechanism, the nucleophile and the substrate form a pentacovalent transition state in the shape of a trigonal bipyramid. In the S_N1 mechanism, when the leaving group departs, the resulting carbocation is a planar, sp^2-hybridized carbocation.

Stereochemistry of the S_N2 Mechanism

In the transition state for the S_N2 mechanism, neither the nucleophile nor the leaving group is fully bonded to carbon. As the reaction proceeds through the transition state, a bond between carbon and the nucleophile forms and the bond between carbon and the leaving group breaks. Part of the evidence for this transition state is provided by the relative rates of reaction for haloalkanes, which decrease in the order methyl > primary > secondary > tertiary. This trend parallels the size of the alkyl groups bonded to the carbon atom that bears the halogen atom. These alkyl groups shield the back of the carbon atom from attack by nucleophiles along a line collinear with the carbon–halogen bond (Figure 10.3). This **steric hindrance** blocks the approach of the nucleophile and slows the rate of the reaction.





(c) Molecular orbitals in the transition state of an S_N2 reaction.

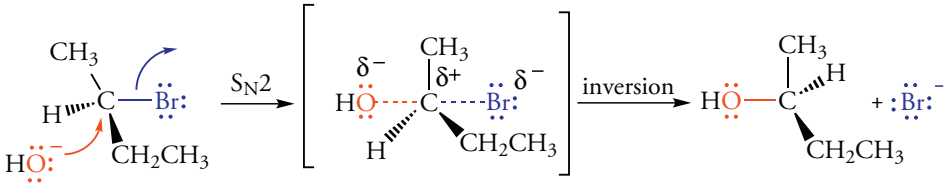
Figure 10.3 Steric Effects in S_N2 Reactions

(a) Primary alkyl halides react with nucleophiles by an S_N2 mechanism that proceeds through a trigonal bipyramidal transition state.

(b) Tertiary alkyl halides do not react by an S_N2 mechanism because the substrate blocks the approach of the nucleophile. The trigonal bipyramidal transition state cannot form because it is too sterically crowded.

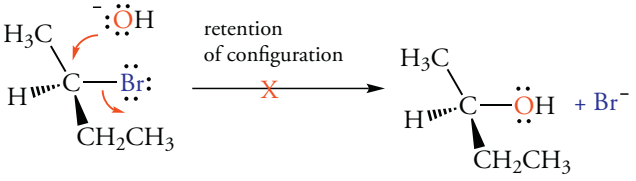
(c) The linear arrangement of the nucleophile and the leaving group in the transition state for an S_N2 reaction requires a primary or secondary center on carbon because a tertiary center blocks the approach of the nucleophile.

This model for the transition state is based on experimental evidence. When (*R*)-2-bromobutane reacts with sodium hydroxide, the substitution product is (*S*)-2-butanol. The reaction therefore occurs with **inversion of configuration**. This result indicates that the nucleophile approaches the electrophilic carbon atom from the back side—that is, from the side directly opposite the leaving group. The leaving group departs simultaneously from the opposite side of the substrate.



(*R*)-2-bromobutane Trigonal bipyramidal transition state (*S*)-2-butanol

If the hydroxide ion had bonded to the carbon atom on the side that was originally occupied by the leaving group, the product would have the same configuration as the reactant. This stereochemical process, termed **retention of configuration**, does not occur.

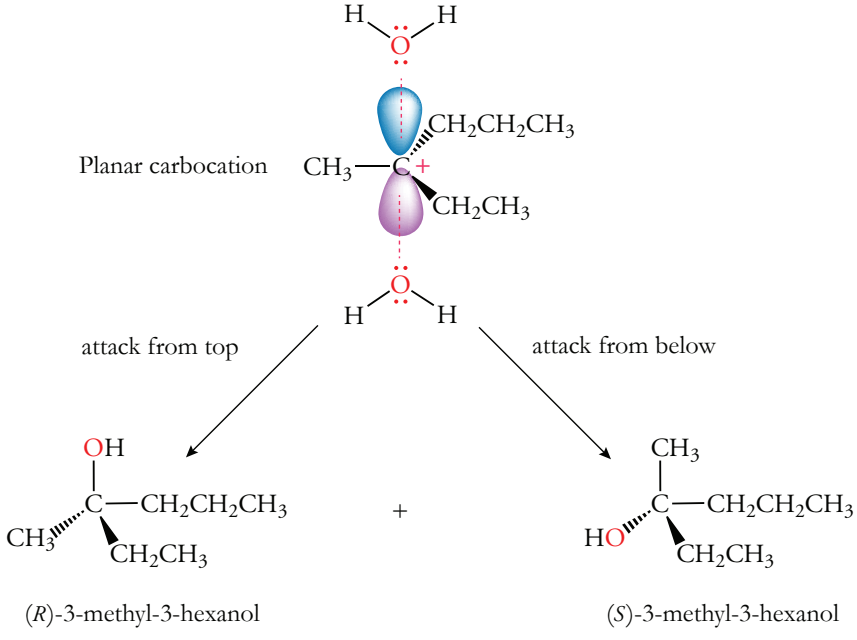


(*R*)-2-bromobutane (*R*)-2-butanol (not observed)

Stereochemistry of the S_N1 Mechanism

The rate of S_N1 reactions decreases in the order 3° > 2° > 1° >> methyl. This relative reactivity parallels the order of stability of the carbocation formed in the rate-determining ionization step (Section 9.9). A relatively stable tertiary carbocation forms faster than a less stable secondary carbocation, which in turn forms very much faster than a highly unstable primary carbocation. Stereochemical studies also support the existence of a carbocation in an S_N1 mechanism.

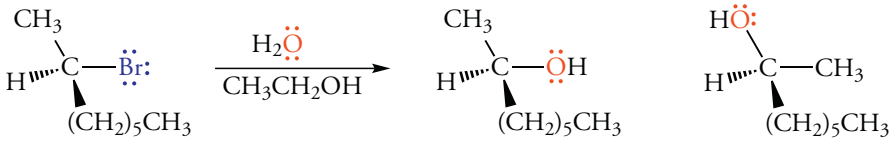
In the preceding section, we saw that S_N2 reactions at chiral centers occur with inversion of configuration. In contrast, an S_N1 reaction at a chiral center reaction usually gives a mixture of enantiomers. For example, (*S*)-3-bromo-3-methylhexane reacts with water, a poor nucleophile, to give a racemic mixture of 3-methyl-3-hexanol. The reaction occurs by way of an achiral carbocation intermediate with a plane of symmetry (Figure 10.4). Because the carbocation intermediate has a plane of symmetry, the nucleophile can attack equally well from either side of the plane to give a racemic mixture.



(*R*)-3-methyl-3-hexanol (*S*)-3-methyl-3-hexanol

Figure 10.4 Stereochemical Effects in S_N1 Reactions
A chiral starting material, (*S*)-3-methyl-3-bromohexane, reacts with water to give a tertiary carbocation. This intermediate is planar and can be attacked by water from either the top or the bottom side to give a racemic mixture of products. The reaction proceeds by an S_N1 mechanism.

(*S*)-3-bromo-3-methylhexane, which gives a racemic mixture with no optical rotation, is a tertiary alkyl halide. However, for some reactants, the product is partially racemic. That is, the product consists of two enantiomers with a slight excess of the enantiomer with an inverted configuration. The reaction of (*R*)-(–)-2-bromooctane, a secondary alkyl halide, with water in a mixed solvent of water–ethanol provides an example of this phenomenon.



(*R*)-(–)-2-bromooctane

(*R*)-(–)-2-octanol (17%)

(*S*)-(+)-2-octanol (83%)

The optical rotation of the product is not zero, so only partial loss of optical activity is observed. The enantiomeric excess (see Section 8.3) of the product formed by net inversion is calculated as 66% based on the observed optical activity. The mixture contains 83% *S* and 17% *R* products.

The partial net inversion in S_N1 reaction occurs because the carbocation is not entirely free of the leaving group prior to attack by the nucleophile. Note that in Figure 10.4, the tertiary carbocation was shown as a symmetrical species solvated on both sides. However, in less stable carbocations, such as the secondary carbocation derived from 2-bromooctane, the anion of the leaving group hovers near the side from which it just departed. Hence, that face of the carbocation is shielded by the anion, so the carbocation is captured preferentially by a nucleophile that attacks from the opposite face. The experimental result is formation of a net excess of the product with inversion of configuration.

Although products of S_N1 processes may be only partially racemic, there is a clear stereochemical distinction between the two nucleophilic substitution mechanisms. The pentacoordinate transition state of the S_N2 mechanism results in complete inversion of configuration.

Problem 10.5

The reaction of (*S*)-2-bromobutane in ethanol and water proceeds via an S_N1 mechanism. Write the structures of the products.

Problem 10.6

The optical rotation of (*S*)-(+)-2-bromobutane after its recovery from a solution of bromide ion in acetone as solvent is smaller than that of the original sample. Explain why. Based on this explanation, what will be the optical rotation after a prolonged period of time?

Sample Solution

The only way that the original reactant could lose its optical activity would be if a bromide ion displaced in a substitution reaction returned and reacted with the original S-enantiomer in another S_N2 reaction, which would also occur with inversion of configuration. The R-isomer forms each time a displacement occurs. Eventually, the process will produce a racemic mixture.

10.4 S_N1 VERSUS S_N2 REACTIONS

The Effect of Substrate Structure on S_N1 and S_N2 Reaction

The most important factor in determining whether an S_N1 or an S_N2 mechanism will prevail for a given reaction is the degree of branching of the carbon atom bearing the leaving group. That atom is called the α carbon. We can make the following generalizations.

1. Primary haloalkanes react in nucleophilic substitution reactions by an S_N2 mechanism.

2. Tertiary haloalkanes react by an S_N1 mechanism.

3. Secondary haloalkanes may react by either mechanism, depending on the nature of the nucleophile and the solvent.

Relative rate, S_N2: methyl > primary > secondary > tertiary (not observed)

Relative rate, S_N1: tertiary > secondary > primary (not observed)

For substitution of bromide ion by iodide ion, the relative rates of reaction of bromomethane, bromoethane, and 2-bromopropane differ by a factor of more than 200,000. These are S_N2 reactions.

Haloalkane:	CH_3Br	CH_3CH_2Br	$CH_3CHBrCH_3$
Relative rate, S_N2:	2.2×10^5	1.4×10^3	1

The degree of branching of at the β-carbon also has a huge effect on the rate of an S_N2 reaction. The reactivities of primary alkyl halides decrease by several orders of magnitude when branching at the β-carbon atom increases (Table 10.2). This decrease in the rate of reaction with increased branching results from steric hindrance. Branching hinders the approach of the nucleophile from the back side, as shown by the conformations in Figure 10.5. Certain conformations of 1-bromopropane and 1-bromo-2-methylpropane allow ready approach of the nucleophile. The methyl groups bonded to the β-carbon are not near the path of the approaching nucleophile. However, every conformation of 1-bromo-2,2-dimethylpropane has a methyl group that interferes with the nucleophile.

Table 10.2
Relative Rates of S_N2 Reactions of Branched Bromoalkanes

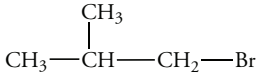
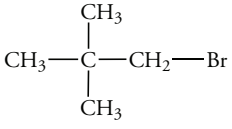
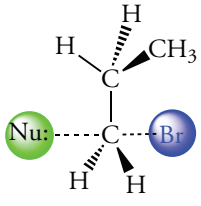
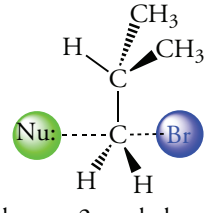
Bromoalkane	*Relative Rate (I^-)*	*Relative Rate ($CH_3CH_2O^-$)*
$CH_3—CH_2—Br$	1	1
$CH_3—CH_2—CH_2—Br$	0.8	0.3
	3.0×10^{-3}	3.0×10^{-2}
	1×10^{-5}	4×10^{-6}

Figure 10.5 Steric Effects of β-Substituents in S_N2 Reactions

β-Substituents decrease the rates of S_N2 reactions by interfering with the approach of the nucleophile. Both 1-bromopropane and 1-bromo-2-methylpropane have conformations in which the methyl groups do not completely hinder the approach of the nucleophile. However, in 1-bromo-2,2-dimethylpropane, no conformation exists that allows the nucleophile to reach the β-carbon, so the rate is very slow.

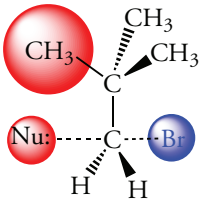


1-bromopropane



1-bromo-2-methylpropane

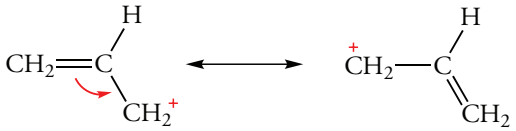
Steric hindrance by methyl group.



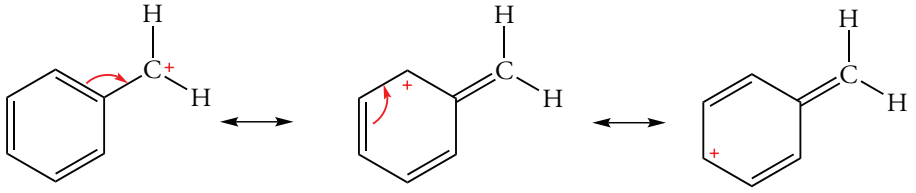
1-bromo-2,2-dimethylpropane

Structural features that stabilize carbocations favor the S_N1 mechanism over the S_N2 mechanism. Stabilizing the carbocation lowers the energy of the transition state, so the rate of the reaction increases (Figure 10.6).

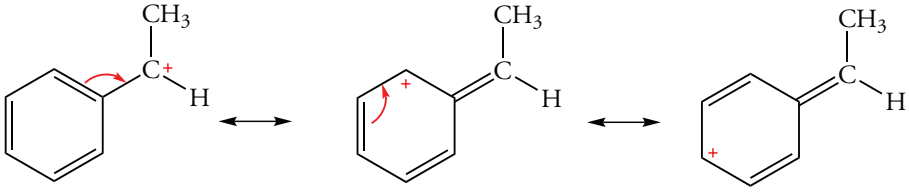
Figure 10.6 Resonance Structures of Allylic and Benzylic Carbocations



Allyl carbocation (1°)



primary benzylic carbocation



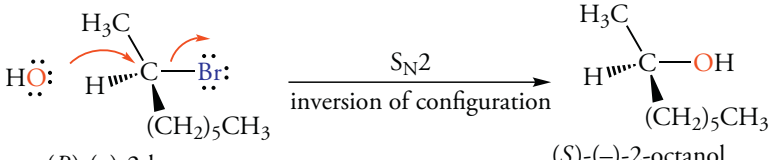
secondary benzylic carbocation

Allylic and benzylic carbocations are primary, but allyl and benzyl halides tend to react by an S_N1 mechanism. Since they are resonance stabilized, these primary carbocations are approximately as stable as secondary alkyl carbocations. Furthermore, secondary resonance-stabilized allylic and benzylic carbocations are as stable as tertiary alkyl carbocations. Any substrate that can form these secondary carbocations reacts by the S_N1 mechanism.

The Effect of the Nucleophile on S_N1 and S_N2 Reactions

The nature of the nucleophile can favor one mechanism over the other. This is particularly true for substrates such as secondary alkyl halides, which, as we have seen, can react by either an S_N1 or an S_N2 mechanism. If the nucleophile is highly polarizable, such as thiolate ion (RS^-), it tends to react with an alkyl halide by an S_N2 reaction. On the other hand, if the nucleophile is an uncharged species, such as H_2O or CH_3OH, an S_N1 mechanism is more likely with the same alkyl halide.

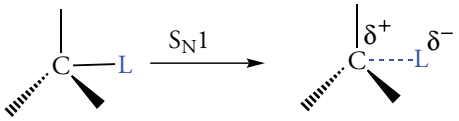
In Section 10.3, we described the reaction of the secondary alkyl halide (*R*)-(–)-2-bromooctane with water in a mixed solvent of water–ethanol, which occurs by an S_N1 process with some net inversion of configuration. In the presence of a better nucleophile, such as hydroxide ion, the configuration of the substitution product is completely inverted. This reaction occurs by an S_N2 mechanism.



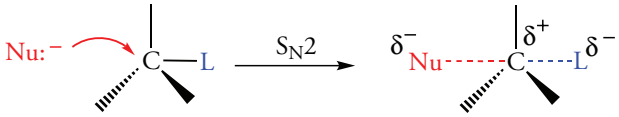
(*R*)-(–)-2-bromooctane (*S*)-(–)-2-octanol

The Effect of the Leaving Group on Nucleophilic Substitution Reactions

The leaving group affects the rate of both S_N2 and S_N1 reactions. Most leaving groups are either displaced as anions in S_N2 processes or generated as anions by ionization in S_N1 processes. In the transition states for both the S_N2 and the S_N1 processes, some negative charge is transferred to the leaving group. Thus, stabilizing the charge of the anion in the leaving group increases the rate of either reaction.



Charge development in the transition state for an S_N1 reaction.



Charge development in the transition state for an S_N2 reaction.

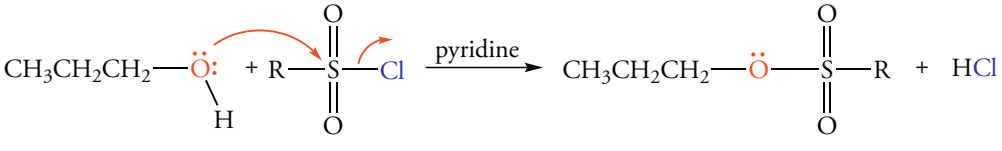
The stability of anions is inversely related to their basicity. As a result, the best leaving groups are the weakest bases. Halide ions are good examples. Hydrogen iodide is the strongest acid of the hydrogen halides, and iodide ion is the weakest base. Iodide and bromide are excellent leaving groups, chloride ion is a fair leaving group, and fluoride ion is a very poor leaving group. The relative rates of reaction for S_N2 reactions involving these leaving groups in a reaction with a common nucleophile are $I^- > Br^- > Cl^- >> F^-$.

Leaving group:	I^-	Br^-	Cl^-	F^-
Relative rate, S_N2:	2	1	0.02	1×10^{-5}

The same general relationship is also found for S_N1 reactions, but the rate differences tend to be somewhat greater. In an S_N1 reaction, the carbon–halogen bond must be completely broken, compared to only partial bond breaking, aided by the simultaneous "push" of the nucleophile, in an S_N2 reaction.

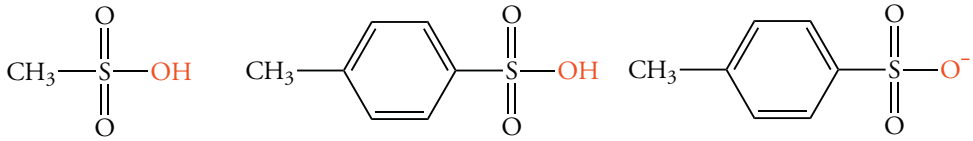
Because the hydroxide ion is a very strong base, it is an exceedingly poor leaving group regardless of the reaction mechanism. To displace oxygen from alcohols, the reaction must be carried out under acidic conditions where the hydroxyl group is protonated. Under these conditions, water is the leaving group. Loss of water as a leaving group occurs at a rate comparable to that of chloride ion.

The ease with which an oxygen atom of an alcohol leaves can be increased by transforming the hydroxyl group into a sulfonate ester, which is prepared by treating an alcohol with an alkyl or aryl sulfonyl chloride, RSO_2Cl or $ArSO_2Cl$. The oxygen atom of the alcohol displaces a chloride ion from the sulfur atom. Pyridine acts as a base to neutralize the HCl formed during the reaction.

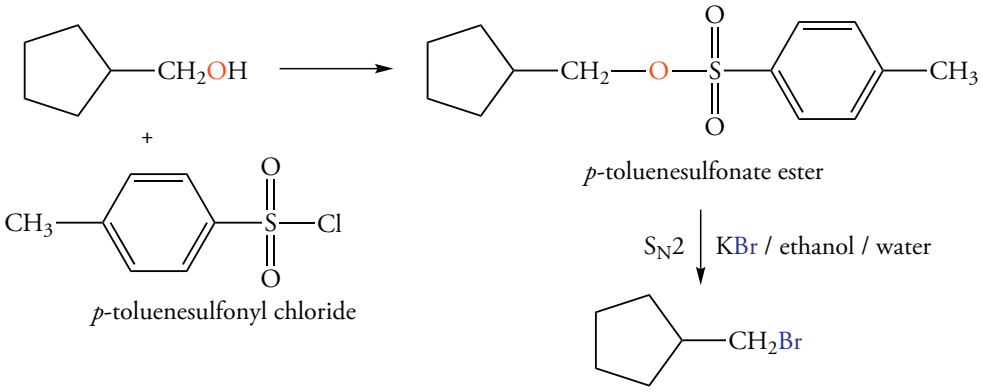


1-propanol (a sulfonyl chloride) (an alkyl sulfonate ester)

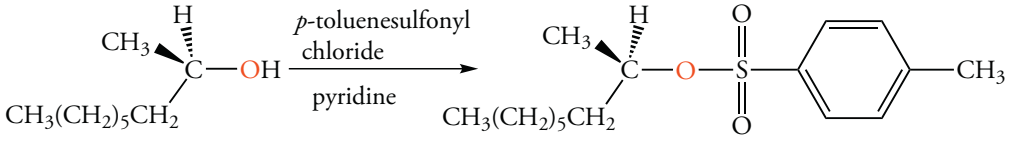
Sulfonic acid is very strong acid, so the related conjugate base, a substituted sulfonate ion, is a very weak base. When a nucleophile reacts with a sulfonate ester, a sulfonate ion is the leaving group. For example, halide anions readily react with alkyl methanesulfonates or alkyl *p*-toluenesulfonates (commonly called tosylates and abbreviated —OTs in equations) to give haloalkanes. Primary alkyl tosylates react about 10^3 times faster than primary alkyl iodides. For example, the following reaction sequence of reaction occurs readily. Since no acids are present in the reaction sequence, no competing rearrangement reactions occur.



methanesulfonic acid *p*-toluenesulfonic acid *p*-toluenesulfonate (a weak base)

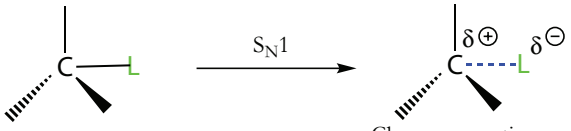


In the conversion of an alcohol into a tosylate, the configuration at a chiral center bonded to oxygen is not affected because the carbon–oxygen bond does not change. The configuration of the tosylate and the alcohol will thus be the same.

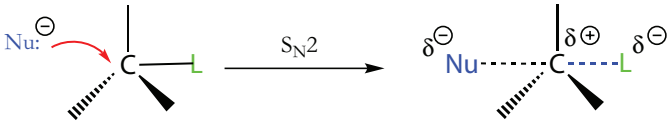


The Effect of the Solvent on Nucleophilic Substitution Reactions

Until now, we have not paid much attention on the role of the solvent in nucleophilic substitution reactions, but the choice of solvent can tip the balance in favor of one substitution mechanism or another. We noted that secondary haloalkanes can react by either an S_N1 or an S_N2 mechanism. In these cases, the polarity of the solvent plays an important role. The S_N1 process forms a carbocation intermediate. Because a polar solvent stabilizes charged species better than a non polar solvent, a polar solvent increases the rate of S_N1 reactions. Reactions that occur via an S_N2 mechanism are also affected by solvent polarity, but the effect is smaller and depends on the charge type. The nucleophilic reactant in an S_N2 reaction is usually negatively charged, and so is the transition state structure, where the negative charge is distributed over several atoms.



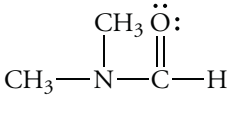
Charge separation occurs in the transition state for an S_N1 reaction.



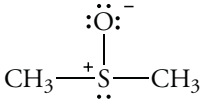
Net negative charge is dispersed in the transition state for an S_N2 reaction.

We recall that the dielectric constant of a solvent is related to its ability to stabilize charge (Section 2.9). Thus, a solvent with a high dielectric charge stabilizes ions in solution. Therefore, the rates of the S_N1 reactions increase as the dielectric constant of the solvent increases (Table 10.3). We see considerable effects in S_N2 reactions, in which the solvent affects nucleophilicity.

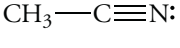
We recall that a protic solvent interacts strongly with nucleophilic anions by forming hydrogen bonds with the unshared pairs of electrons on the nucleophiles (Figure 10.1). When the nucleophile is hydrogen bonded to the solvent, its nucleophilicity decreases. Polar solvents that do not have protons available for hydrogen bonding to nucleophiles are called *polar aprotic* solvents. Examples of polar aprotic solvents include dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and acetonitrile. The electron pairs of the oxygen atoms of these aprotic solvents solvate cations, but not anions (Figure 10.7).



dimethylformamide (DMF)

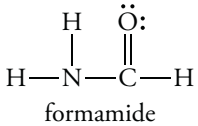


dimethylsulfoxide (DMSO)

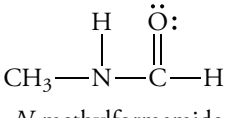


acetonitrile

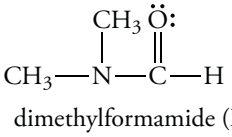
For example, these solvents bind the cation of KCN by orienting their negative ends around it. Because there are no electropositive hydrogen atoms in aprotic solvents, the CN^- ion cannot be effectively solvated; it is called a "naked anion." Thus, the nucleophilicity of CN^- is greater in dimethyl sulfoxide than in ethanol. *An aprotic solvent such as dimethyl sulfoxide favors an S_N2 reaction.*



formamide



N-methylformamide



dimethylformamide (DMF)

The rates of substitution of 1-bromobutane by azide ion (N_3^-) in both protic and aprotic solvents, listed in Table 10.4, illustrate the difference in the nucleophilicity of solvated and unsolvated anions. The rates of reaction of the unsolvated anions in aprotic solvents are substantially larger than for the solvated anions in a protic solvent such as water.

Figure 10.7 Solvation of Cations by Polar Aprotic Solvents

Cations are solvated by polar aprotic solvents. The partner anion (counterion) remains unsolvated and "naked." As a result, its nucleophilicity increases.

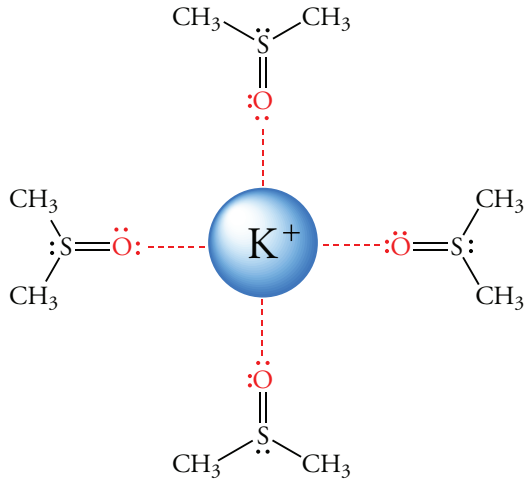


Table 10.3
Relative Rates of S_N1 Reactions and Solvent Polarity

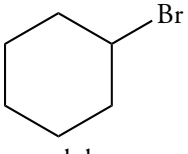
Solvent	*Dielectric Constant*	*Relative Rate*
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5×10^3
Water	78	1.5×10^5

Table 10.4
Relative Rates of S_N2 Reactions and Solvent Polarity
$CH_3(CH_2)_2CH_2Br + N_3^- \rightarrow CH_3(CH_2)_2CH_2N_3 + Br^-$

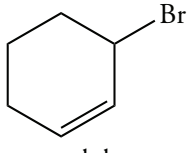
Solvent	*Relative Rate*
Methanol	1
Formamide	12
Methylformamide	45
Dimethylformamide	1.2×10^6

Problem 10.7

Explain why the reaction of 3-bromocyclohexene with methanol (CH_3OH) is faster than the reaction of bromocyclohexane with methanol.



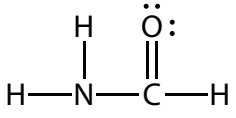
bromocyclohexane



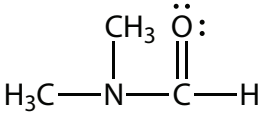
3-bromocyclohexene

Problem 10.8

The relative rates for the conversion of 1-iodobutane into 1-chlorobutane in methanol, formamide, and dimethylformamide are 1, 12, and 1.2×10^6, respectively. Explain the small rate difference between methanol and formamide and the large rate difference between formamide and dimethylformamide.



formamide



dimethylformamide (DMF)

10.5 MECHANISMS OF ELIMINATION REACTIONS

In Chapter 9, we saw that we can prepare alkenes by dehydrohalogenation. The dehydration of alcohols also gives alkenes, but this reaction occurs with rearrangement of the carbocation, and gives mixtures of products having different carbon skeletons. The elimination of a hydrogen halide from an alkyl halide is a complex process. We must consider both regiochemistry and stereoelectronic effects. These effects are related to the mechanism of the reaction, which may be either E2 or E1.

In this section, we use concepts developed in our discussion of S_N2 and S_N1 reactions, and we see how experimental variables affect the product formed in a dehydrohalogenation reaction. The structural features that control S_N2 and S_N1 substitution and E2 and E1 elimination reactions are related.

Like the S_N2 reaction mechanism, the E2 mechanism is a one-step, concerted process. In an E2 dehydrohalogenation reaction, the base—which is also a nucleophile—removes a proton from the β-carbon atom. As the proton is removed, the leaving group departs, and a double bond forms. The rate of an E2 reaction depends on the concentrations of the substrate and the base. If the substrate concentration is doubled, the reaction rate also doubles, as in S_N2 processes. Thus, the rates of E2 and S_N2 mechanisms are affected in the same way, and the two mechanisms compete with each other.

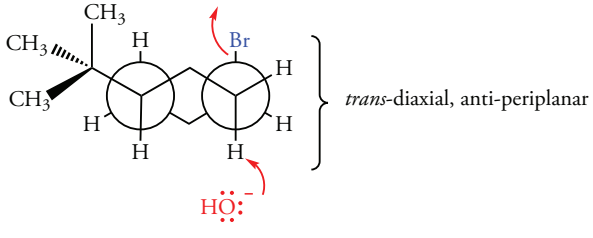
An E1 mechanism occurs in two steps, and the rate-determining step is the formation of a carbocation intermediate. An S_N1 reaction also proceeds in two steps, and the rate-determining step is formation of a carbocation intermediate. Therefore, an E1 mechanism competes with an S_N1 mechanism. Because the rate determining step of an E1 reaction involves only the substrate, the formation of the carbocation is a unimolecular reaction. The carbocation can either react with a nucleophile to form a substitution product or lose a proton to give an elimination product.

Stereoelectronic Effects in Elimination Reactions

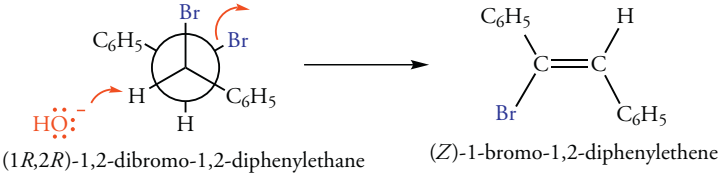
The chirality of the reactant and the product allows us to distinguish the E2 and E1 mechanisms. The stereochemical consequences of the two mechanisms differ because of the different structures of the intermediates and transition states in these mechanisms.

We recall that an E2 reaction requires a precise molecular arrangement, termed a *stereoelectronic* effect, which we illustrated using cyclic compounds such as *cis*- and *trans*-1-bromo-4-*tert*-butylcyclohexanes (Section 9.18). An E2 reaction is favored by the *anti*periplanar arrangement of the hydrogen and halogen atoms because this arrangement aligns the orbitals properly for the formation of the π bond. The *anti*periplanar arrangement is easily seen in a Newman projection formula (Figure 10.8). We can imagine the process as removal of the proton to provide an electron pair that attacks the neighboring carbon atom from the back side to displace the leaving group in a reaction resembling an S_N2 mechanism.

Figure 10.8 Stereoelectronic Effects in E2 Reactions
The E2 reaction is most favorable when the hydrogen on the β-carbon and the halogen are in an *anti*periplanar conformation. This is the case in *cis*-1-bromo-4-*tert*-butylcyclohexane. A Newman projection structure shows this favorable conformation.



The stereoelectronic effect of the E2 reactions can also be established with conformationally flexible, open chain molecules, if they have chiral centers, for example, the dehydrobromination of (l*R*,2*R*)-1,2-dibromo-1,2-diphenylethane. A specific staggered conformation is required to properly align the sp^3 hybrid orbitals of the C—H and C—Br bonds. This alignment can yield only the *Z* isomer in a concerted E2 reaction.



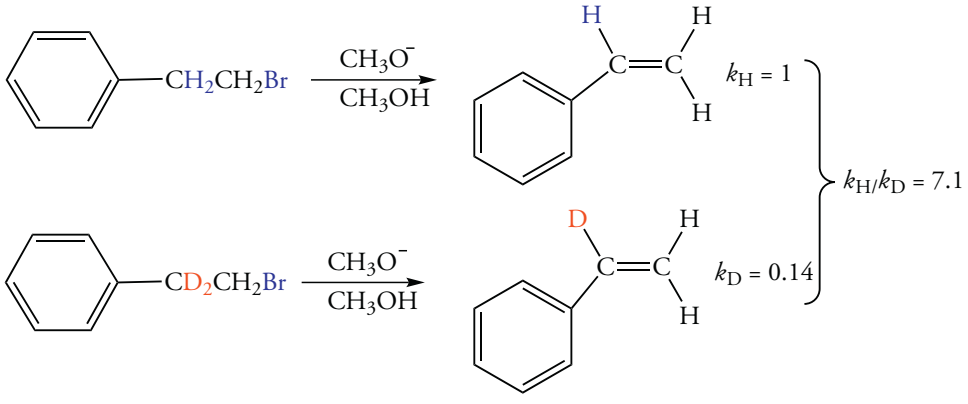
(1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane (*Z*)-1-bromo-1,2-diphenylethene

There is no special geometric requirement for an E1 reaction. Once the carbocation forms, any of the hydrogen atoms on carbon atoms adjacent to the positive center can be lost.

Deuterium Isotope Effects in Elimination Reactions

The E1 and E2 elimination mechanisms can also be distinguished by a primary *deuterium isotope effect*, which measures the degree to which C—H and C—D bonds are broken in the rate-determining step. The carbon–hydrogen bond is slightly weaker than the carbon–deuterium bond. If a C—H bond is broken in a rate-determining step, then the corresponding C—D bond in the isotopically substituted compound would require more energy to reach the transition state. The deuterium-labeled compound therefore would react at a slower rate. If a C—H (or C—D) bond cleavage occurs in a fast step after the rate-determining step, the rates would be the same. This means that we can distinguish between the E2 and El reactions by placing deuterium where it can be abstracted by a base.

For example, the rates of dehydrobromination of 1-bromo-2-phenylethane and l-bromo-2,2-dideuterio-2-phenylethane differ by a factor of seven.



The ratio of the rate constants for the undeuterated and deuterated compounds, expressed as k_H/k_D, is 7.1. This result tells us that the C—H and C—D bonds are broken in the rate-determining step of the reaction. And this in turn tells us that reaction occurs by an E2 mechanism.

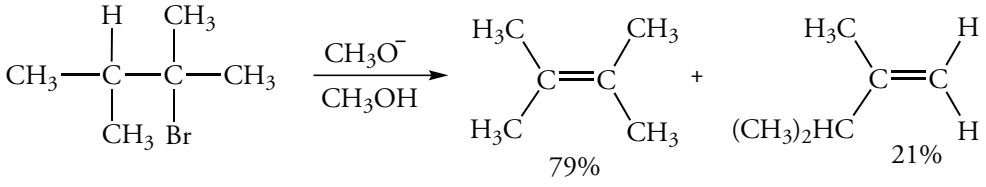
There is no deuterium isotope effect in an El process. There is still a difference in the rates at which the C—H and C—D bonds are broken, but we can't directly measure it because the C—H and C—D bonds break after the rate-determining step.

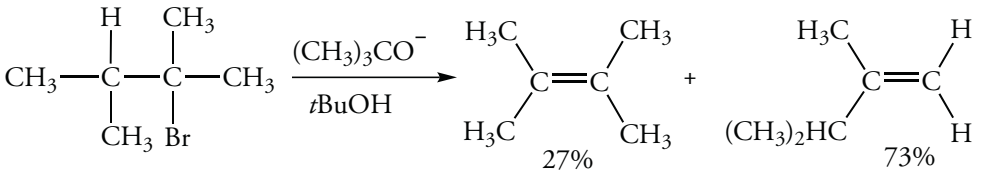
Base Strength and Competing E2 and E1 Mechanisms

Because the base participates in the rate-determining step of an E2 reaction, the rate of the reaction depends on the strength of the base. The steric size of the base affects the regiochemistry of the reaction. Because the base is not involved in the rate-determining step of the El reaction, it might appear reasonable to expect no effect on the composition of the product mixture. Such a conclusion is valid if the base is weak, such as an alcohol solvent. Without a strong base, a proton transfer occurs from the carbocation to the solvent in the El process. However, a strong base causes a competing E2 reaction. As a result, the products arise from two competing processes.

Steric Effect of the Base on the Regiochemistry of E2 Reactions

In Section 10.1, we saw that the difference in the sizes of the methoxide ion and the *tert*-butoxide ion causes marked differences in the rates of S_N2 reactions. We noted that steric factors are much less important in determining the ease of abstraction of a proton. However, such effects do exist, and they are in the direction that we would expect. That is, more highly hindered bases tend to abstract the least sterically hindered protons. This fact is established for the reaction of 2-bromo-2,3-dimethylbutane with various alkoxide ions. The major product with methoxide ion is the more highly substituted alkene—the Zaitsev product. However, with *tert*-butoxide, the major product is the least substituted alkene.





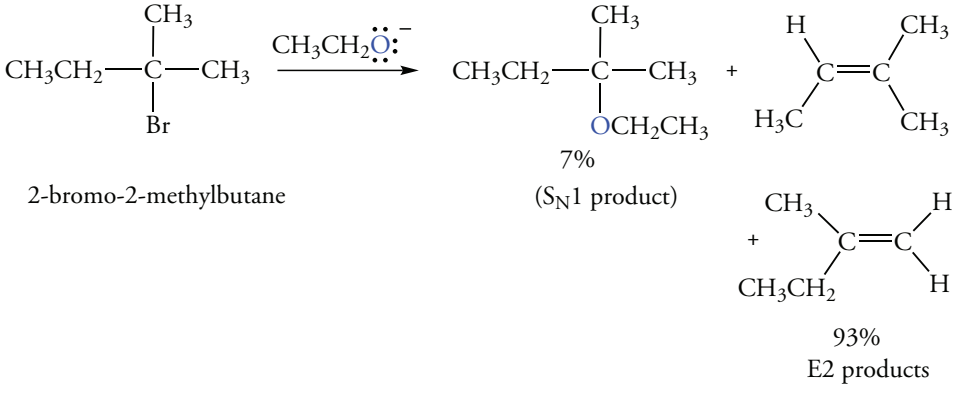
Thus, we have now established that sterically hindered bases tend to not only increase the proportion of E2 to S_N2 products but also increase the amount of the least substituted alkene—the "non-Zaitsev" product.

10.6 EFFECTS OF STRUCTURE ON COMPETING SUBSTITUTION AND ELIMINATION REACTIONS

Substitution and elimination reactions compete with one another, giving rise to a wide variety of product mixtures. The reactions depend to a large extent on the structure of the substrate. We will consider the reactions of haloalkanes and consider them by type: primary, secondary, and tertiary.

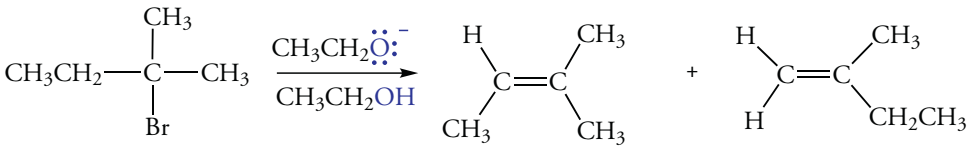
Competing Substitution and Elimination Reactions of Tertiary Haloalkanes

Tertiary haloalkanes undergo substitution reactions only by an S_N1 mechanism because there is too much steric hindrance for an S_N2 reaction to occur. However, a tertiary haloalkane can undergo an elimination reaction by either an E2 or an El process. The mechanism depends on the basicity of the nucleophile and the polarity of the solvent. If the nucleophile is a weak base, S_N1 and El processes compete, and the amounts of the two types of products depend only on the stability of the carbocation that forms as an intermediate. For example, 2-bromo-2-methylbutane reacts in ethanol to give about 64% of an ether product from an S_N1 process. The ratio of S_N1 to El products is about 2:1.



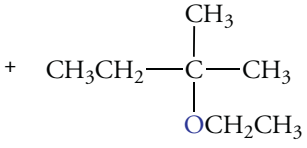
2-bromo-2-methylbutane

However, if sodium ethoxide, a strongly basic nucleophile, is added to the ethanol, an E2 reaction competes with the substitution reaction. The amount of elimination product is increased to a total of about 93% of the product mixture. Only 7% of the ether product is formed. Most of the elimination product is derived from the E2 reaction.



2-bromo-2-methylbutane

92%
(mostly E2 products)



7 %
(S_N1 product)

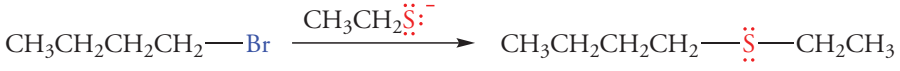
We can summarize the behavior of tertiary haloalkanes as follows:

1. If the nucleophile is a weak base, tertiary haloalkanes react by either an S_N1 or E1 mechanism, and the S_N1 reaction is favored.

2. If the nucleophile is a strong base, tertiary haloalkanes react by either an S_N1 or E2 mechanism, and the E2 reaction is favored.

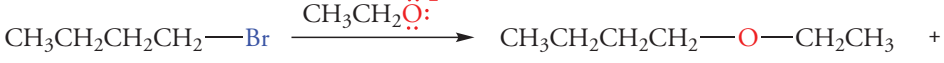
Competing Substitution and Elimination Reactions of Primary Haloalkanes

Primary haloalkanes can undergo either S_N2 or E2 reactions. They do not undergo S_N1 or El reactions because a primary carbocation is very unstable. Primary haloalkanes react with strongly nucleophilic, weakly basic reactants, such as ethyl thiolate ($CH_3CH_2S^-$), exclusively by an S_N2 process. However, a primary haloalkane reacts with ethoxide ion, a weaker nucleophile, but a stronger base than ethyl thiolate, to give some elimination product.



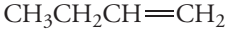
1-bromobutane

S_N2 product
(100%)



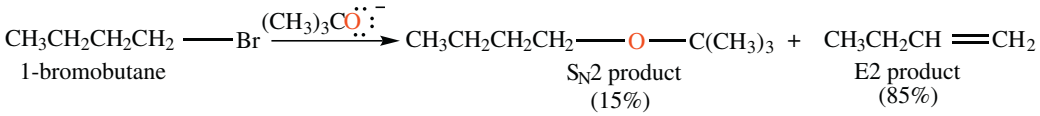
1-bromobutane

S_N2 product
(90%)



E2 product
(10%)

If a primary haloalkane is treated with *tert*-butoxide ion instead of ethoxide, the amount of elimination product increases significantly. The *tert*-butoxide ion is not only more basic than the ethoxide ion also much more sterically hindered. The combination of these two factors favors elimination by an E2 process over substitution by an S_N2 process.



We can summarize the behavior of primary haloalkanes as follows:

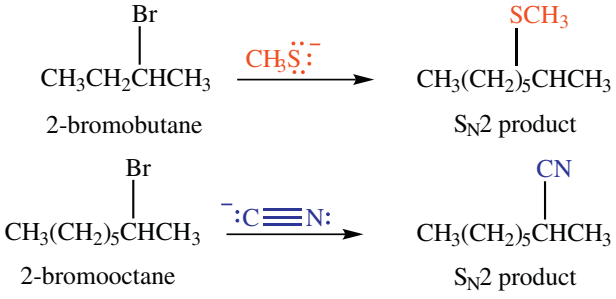
1. If the nucleophile is a weak base, primary haloalkanes react exclusively by an S_N2 mechanism.

2. If the nucleophile is a strong base *that is <u>not</u> sterically hindered*, primary haloalkanes react by either an S_N2 or an E2 mechanism, with the S_N2 reaction predominating by a wide margin.

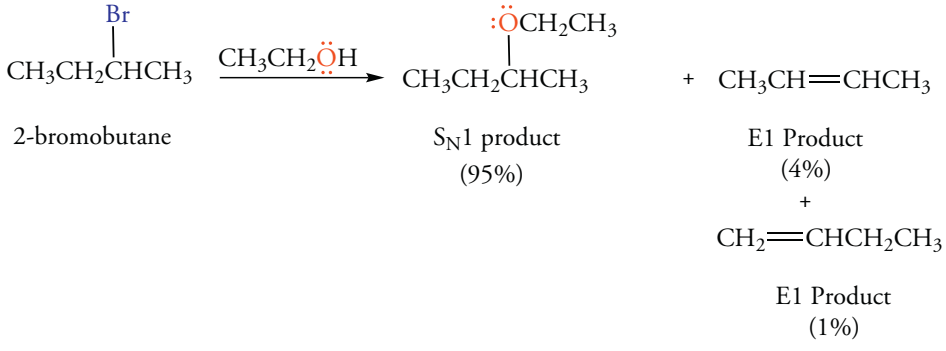
3. If the nucleophile is a strong base *that <u>is</u> sterically hindered*, primary haloalkanes react by either an S_N2 or E2 mechanism, with the E2 reaction predominating by a wide margin.

Competing Substitution and Elimination Reactions of Secondary Haloalkanes

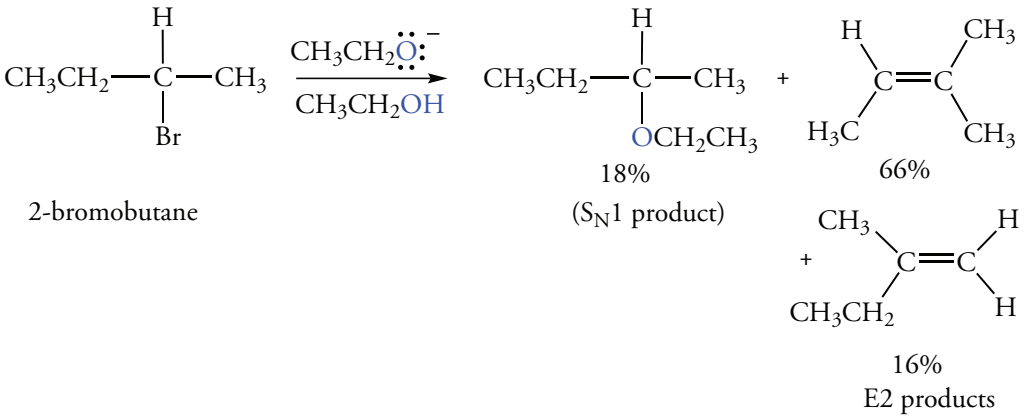
Secondary haloalkanes can react by S_N2, E2, S_N1, and E1 mechanisms, and it is sometimes difficult to predict which of these processes will occur in a given reaction. However, secondary haloalkanes tend to react with strong nucleophiles that are weak bases, such as thiolates or cyanide ion, by an S_N2 process.



On the other hand, a secondary haloalkane tends to react with weak nucleophiles that are also weak bases, like ethanol, by an S_N1 mechanism with some accompanying E1 product.



We can tip the scales in the other direction by adding sodium ethoxide to ethanol. By adding this strong base, we find that the product of the S_N1 reaction drops to 18% of the total, and E2 products account for the rest.



The reactions of secondary haloalkanes can proceed by S_N2, E2, S_N1, and E1 mechanisms, depending on the reaction conditions.

1. If the nucleophile is *strong*, secondary haloalkanes react by an S_N2 mechanism.

2. If the nucleophile is *weak*, secondary haloalkanes react by either an S_N1 or E1 mechanism, and the S_N1 reaction is favored by a wide margin.

3. If the nucleophile is a strong base, secondary haloalkanes react by either an S_N1 or E2 mechanism, and the E2 reaction is favored by a wide margin.

Problem 10.9

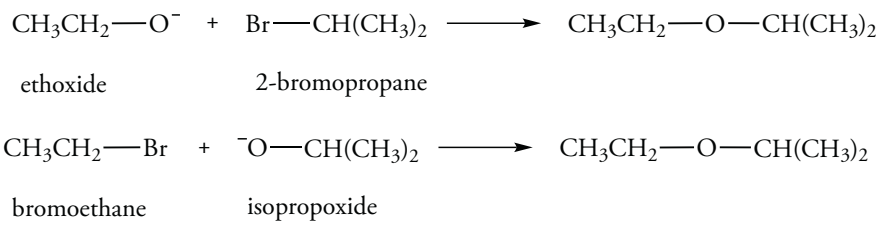
The ratio of elimination to substitution products for the reaction of 2-bromo-2-methylbutane depends on the concentration of the base. For 0.05 and 1.0 M sodium ethoxide, the percentages of elimination product are 56% and 98%, respectively. Explain these data.

Problem 10.10

The amount of elimination product for the reaction of 1-bromooctadecane with an alkoxide in the corresponding alcohol solvent is about 1% for methoxide ion and 85% for *tert*-butoxide ion. Explain these data.

Problem 10.11

Which of the following two methods of preparing the ether $CH_3CH_2OCH(CH_3)_2$ will give the better yield?



Sample Solution

The reactants in both reactions are a haloalkane and the conjugate base of an alcohol, an alkoxide. The ether has two different alkyl groups bonded to oxygen, one from the alkoxide and the other from the haloalkane.

The first reaction is a nucleophilic substitution at a secondary center by a nucleophile that is also a strong base. A competing elimination reaction to yield propene will also occur, thus decreasing the yield of the ether product. The second reaction occurs by an S_N2 reaction at a primary center, which tends to occur with little competition from an elimination reaction. Therefore, the second reaction is the better way to make the desired product.

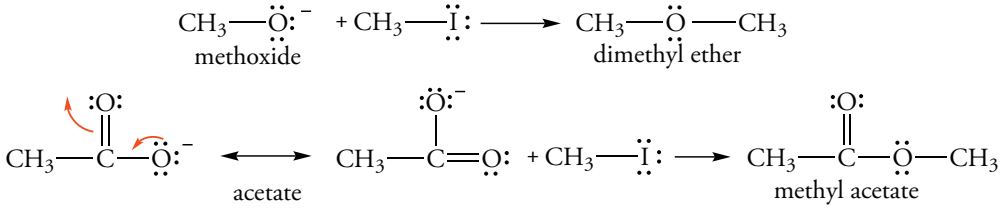
Exercises

Nucleophilicity

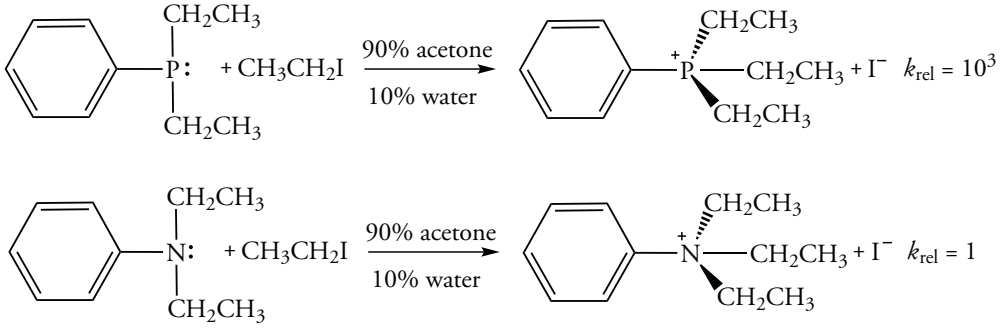
10.1 Hydroxylamine (NH_2OH) is a nucleophile. Write its Lewis structure. Which atom supplies the electrons in nucleophilic substitution reactions?

10.2 Thiocyanate ion (SCN^-) reacts with alkyl halides to give thiocyanate products (R—SCN). The cyanate ion (OCN^-) reacts to form isocyanate products (R—NCO). Write the Lewis structures of the ions. Explain the difference in the sites of reactivity for the two ions.

10.3 Reaction of methoxide ion with an alkyl halide to give dimethyl ether is about 100 times faster than the reaction of acetate ion with an alkyl halide to give an ester, methyl acetate. Explain why.



10.4 Diethylphenylphosphine reacts with iodoethane about 10^3 times faster than the nitrogen analog, diethylaniline. Explain why.



10.5 Dimethyl sulfide, $(CH_3)_2S$, reacts with iodomethane to displace iodide ion two times faster than diethyl sulfide, $(CH_3CH_2)_2S$. Explain why.

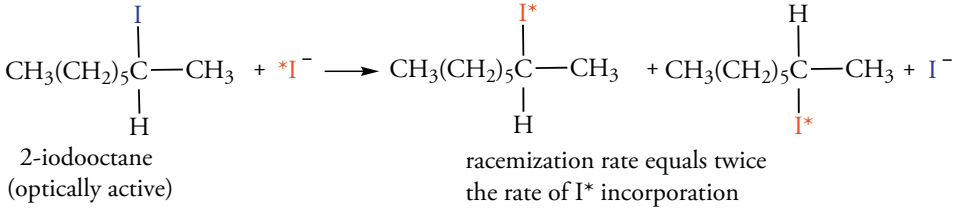
10.6 Triethylarsine, $(CH_3CH_2)_3As$, reacts with iodomethane only four times faster than dimethyl selenide, $(CH_3)_2Se$. However, ammonia reacts with iodomethane 3×10^5 times faster than water. Compare the difference in rate.

Stereochemistry of Substitution Reactions

10.7 Reaction of (*R*)-(–)-2-butanol with HBr yields a mixture of 87% (*S*)-(+)-2-bromobutane and 13% (*R*)-(–)-2-bromobutane. What is the optical purity of the product? What is the mechanism for this substitution reaction?

10.8 Reaction of (*R*)-2-methyl-l-butanol with HBr yields 1-bromo-2-methylbutane. Predict the configuration of the product. What is the mechanism for this substitution reaction?

10.9 The rate of incorporation of radioactive iodide into optically active 2-iodooctane in acetone as solvent leads to racemization at twice the rate of incorporation of radioactive iodine. Explain how these data support an S_N2 mechanism.

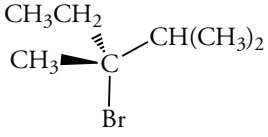


10.10 The reaction of (*S*)-2-bromooctane with cyanide ion gives a cyano compound with an *R* configuration. However, reaction of (*S*)-2-bromooctane with iodide ion followed by reaction of the alkyl iodide with cyanide ion gives a cyano compound with the *S* configuration. Explain these data.

10.11 *trans*-l-Chloro-3-methylcyclopentane reacts with sodium iodide in acetone to give *cis*-1-iodo-3-methylcyclopentane. What is the mechanism of this reaction?

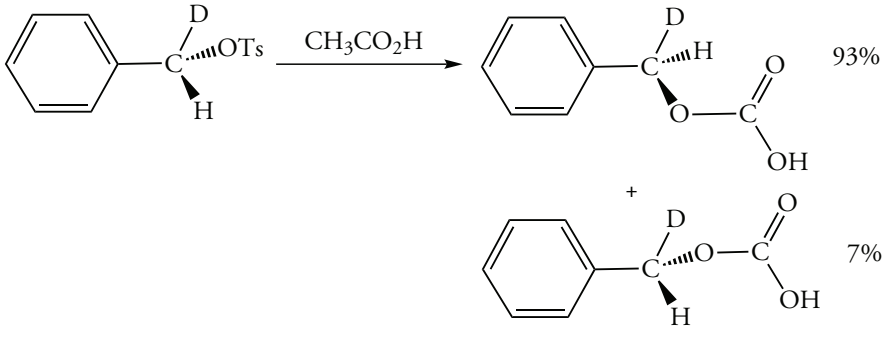
10.12 Write the product expected from the reaction of *cis*-1-bromo-2-methylcyc1opentane with cyanide ion.

10.13 The following compound has the *R* configuration. Draw the product expected from the reaction of this compound in ethanol, indicating the stereochemistry.

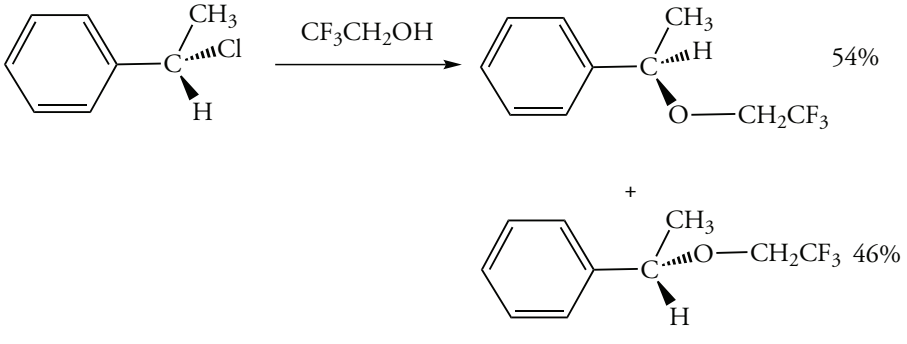


10.14 (*S*)-l-Chloro-l-phenylethane reacts in a 20% water–80% acetone solution to give a 51:49 ratio of (*R*)- and (*S*)-1-phenyl-1-ethanol. Explain why the product is highly racemic even though the reactant is a secondary alkyl halide.

10.15 The reactant in the following reaction has the *S* configuration. Based on the composition of the product mixture, what is the mechanism of the reaction?

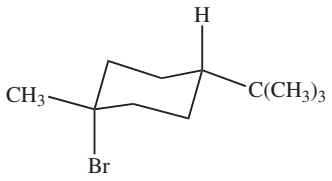


10.16 The reactant in the following reaction has the *S* configuration. Based on the composition of the product mixture, what is the mechanism of the reaction?

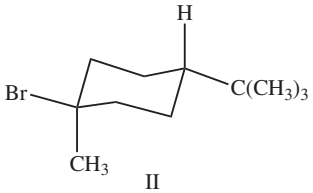


10.17 What is the configuration of the tosylate prepared from (*R*)-2-butanol? What is the configuration of the iodide obtained by reacting that tosylate with iodide ion in acetone?

10.18 Write the product expected from the reaction of each of the following compounds in aqueous acetone.



I



II

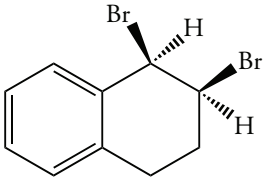
Reactivity in Substitution Reactions

10.19 1-Bromo-1,1-diphenylethane reacts very rapidly in ethanol. Explain this observation.

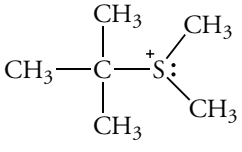
10.20 4-Chloro-2,2,4,6,6-pentamethylheptane reacts in aqueous acetone about 500 times faster than *tert*-butyl chloride does. Explain why.

10.21 3-Bromo-1-butene and (*E*)-1-bromo-2-butene react at the same rate in aqueous acetone. Explain why. An identical mixture of two substitution products is obtained from either compound. What are the structures of the products?

10.22 The following compound reacts in methanol to rapidly replace one of the two bromine atoms by a methoxy group. Which bromine atom is replaced?



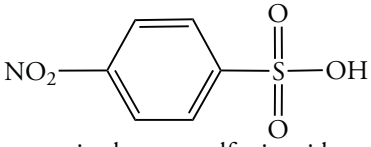
10.23 The following sulfonium ion reacts in 80% ethanol–20% water to give 36% 2-methyl-1-propene. The remaining 64% of the product is a mixture of two substitution products. What are the substitution products? *tert*-Butyl chloride reacts under the same conditions to give the identical mixture of products. Explain this observation.



10.24 The relative rates of substitution of bromide by ethoxide in ethanol for methyl, ethyl, propyl, and butyl bromides are 1, 0.057, 0.018, and 0.013, respectively. Explain these data.

10.25 Trifluoromethanesulfonyl chloride reacts with alcohols to form sulfonate esters. Would you expect the "trifylates" to be more or less reactive than the methanesulfonate esters?

10.26 A nitro group is electron withdrawing. Would you expect the sulfonate esters of *p*-nitrobenzenesulfonic acid to be more or less reactive than the tosylates?



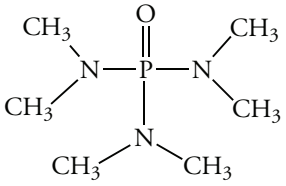
p-nitrobenzenesulfonic acid

10.27 Explain why ethanol (CH_3CH_2OH) can solvate both cations and anions. Explain why dimethyl ether, $(CH_3)_2O$, is a poorer solvent for ionic compounds. Discuss the solvation characteristics of both solvents for both cations and anions.

10.28 *trans*-1-Iodo-3-methylcyclopentane reacts with KF in DMF to give a fluoro compound. What is its configuration? The iodo compound reacts with KF in ethanol to give products that do not contain fluorine. Explain these data.

Solvent Effect in Substitution Reactions

10.29 The structure of hexamethylphosphoramide (HMPA) is shown below. Its dielectric constant is 30. How do you expect HMPA to affect the rates of S_N1 and S_N2 reactions?



hexamethylphosphoramide
(HMPA)

10.30 The rate constant for the displacement of iodide from iodomethane by fluoride ion is 10^6 times faster in dimethyl formamide than in methanol. Explain why.

10.31 Methyl tosylate reacts with halide ions in water. The rate constants for the reaction in water decrease in the order $k_{I^-} > k_{Br^-} > k_{Cl^-}$. The rate constants for the reactions in acetone stand in the order $k_{I^-} < k_{Br^-} < k_{Cl^-}$ Explain these data.

10.32 The equilibrium constant for the reaction of bromomethane with iodide ion is 15 in water and 0.6 in acetone. Explain these data.

$$CH_3Br + I^- \rightleftharpoons CH_3I + Br^-$$

Elimination Reactions

10.33 Attempted displacement of iodide ion by fluoride in acetone usually fails because elimination products result. Explain why elimination is favored over substitution.

10.34 The product mixture obtained in the reaction of isobutyl bromide with sodium ethoxide in ethanol contains 62% 2-methyl-1-propene. The reaction using potassium *tert*-butoxide in *tert*-butyl alcohol contains 92% 2-methyl-1-propene. Explain why.

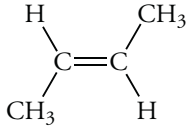
10.35 The product mixture obtained in the reaction of *sec*-butyl bromide with 1 M sodium ethoxide in ethanol contains 78% unsaturated material. What are the products and which of them should predominate? Using 4 M sodium ethoxide in ethanol, the product mixture is 91% unsaturated material. Why?

10.36 The unsaturated compounds obtained in the reaction of 2-bromo-2,3-dimethylbutane with the alkoxide of 3-ethyl-3-pentanol are 92% 2,3-dimethyl-l-butene and 8% 2,3-dimethyl-2-butene. Compare these data with the data for reaction of *tert*-butoxide with the same compound (Section 10.5).

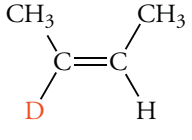
10.37 E2 reactions of tosylates occur using alkoxide ions as bases in the related alcohol solvent. Determine the stereochemistry of the 2-phenyl-2-butene formed from reaction of the tosylate of (2*R*,3*R*)-3-phenyl-2-butanol.

10.38 The tosylate of *cis*-2-phenylcyclohexanol undergoes an elimination reaction much more rapidly with *tert*-butoxide in *tert*-butyl alcohol than does the *trans* isomer. The product is exclusively 1-phenylcyclohexene. Explain these data.

10.39 The following products are obtained from the E2 reaction of (2*S*,3*R*)-2-bromo-3-deuterio-butane using sodium ethoxide in ethanol. Explain why. Predict the products from the E2 reaction of (2*S*,3*S*)-2-bromo-3-deuterobutane.

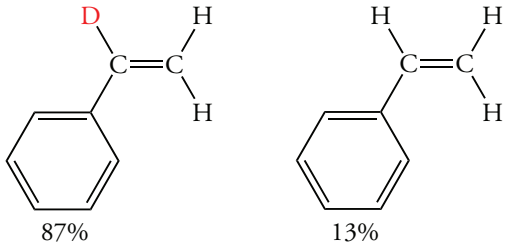


trans-2-butene

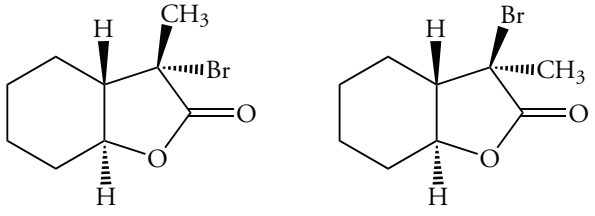


(*Z*)-2-deutero-2-butene

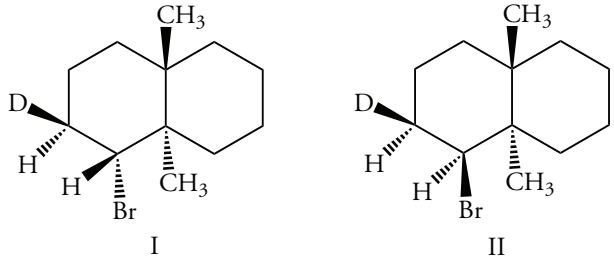
10.40 The E2 reaction of l-bromo-2-deutero-2-phenylethane gives the following compounds. Explain why the deutero product is the major product.



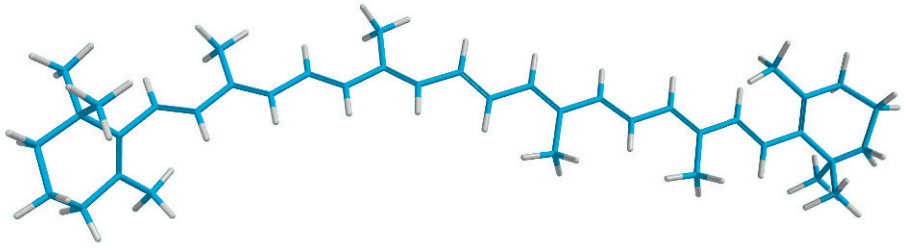
10.41 The E2 reaction of each of the following compounds with sodium methoxide in methanol proceeds regiospecifically to give different compounds. What is the structure of the compounds derived from each stereoisomer?



10.42 Predict the E2 product formed in the reaction of each of the following compounds. Which compound reacts at the faster rate?



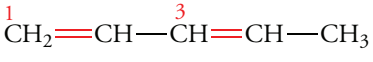
11 Conjugated Alkenes and Allylic Systems



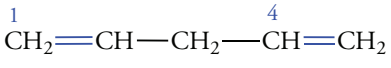
11.1 CLASSES OF DIENES

Compounds that contain two or more double bonds are ubiquitous in nature. In this chapter, we will focus upon a subset of those compounds called **conjugated alkenes.** A conjugated alkene contains a sequence of alternating double and single bonds: π–σ–π. The simplest conjugated alkenes contain two conjugated double bonds and are called **dienes.** If more than one sigma bond separates two double bonds, they are **isolated**, or **nonconjugated**, and their properties resemble those of simple alkenes. On the other hand, the properties of conjugated dienes differ considerably from simple alkenes. Conjugated dienes are the major subject of this chapter. Dienes can also have two double bonds that share a common atom. They are known as **cumulated dienes**. They are relatively rare, and we will discuss them only briefly.

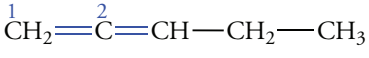
We name polyenes by changing the parent name from *-ane* to *-adiene*, *-atriene*, *-atetraene*, and so forth to indicate the number of double bonds in the compound. The positions of the double bonds are given by a number for each one, as shown in the examples below.



1,3-pentadiene, conjugated diene



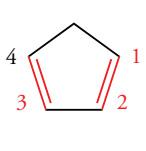
1,4-pentadiene, nonconjugated diene



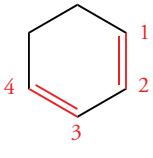
1,2-pentadiene, cumulated diene

We name cyclic dienes as follows:

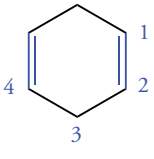
1. Name the ring size; cyclobuta-, cyclopenta-, and so forth.
2. After the ring has been named, determine the number of double bonds: diene, triene, and so forth.
3. Select one carbon atom of one double bond in the ring as C-1, then indicate the position of the second double bond with the smallest number. A few examples are shown below. Note that in these structures, the double bonds in cyclopentadiene and 1,3-cyclohexadiene are conjugated; the double bonds in 1,4-cyclohexadiene are isolated or nonconjugated.



cyclopentadiene



1,3-cyclohexadiene



1,4-cyclohexadiene

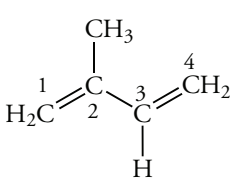
conjugated dienes

nonconjugated diene

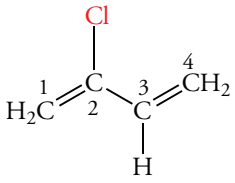
Isoprene and Neoprene

Natural rubber is a polymer of isoprene, a conjugated diene. Synthetic rubbers called neoprenes are produced by the polymerization of chloroprene, a synthetic conjugated diene. Neoprene is used in many commercial products, from industrial hoses to wet suits for scuba diving and surfing.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00011-5
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isoprene: conjugated diene



chloroprene: conjugated diene

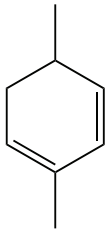
Terpenes have two or more isoprene units as their common structural feature. They can have different degrees of unsaturation and a variety of functional groups. Terpenes are classified according to the number of isoprene units they contain.

1. Monoterpenes contain two isoprene units.
2. Sesquiterpenes contain three isoprene units. (The prefix *sesqui* means "one and a half.")
3. Diterpenes contain four isoprene units.
4. Triterpenes contain six isoprene units.

Figure 11.1 shows the structures of some terpenes.

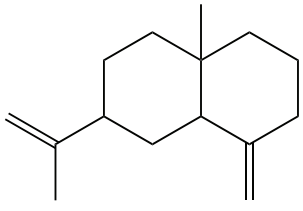
Figure 11.1
Structures of a few terpenes.

Monoterpene



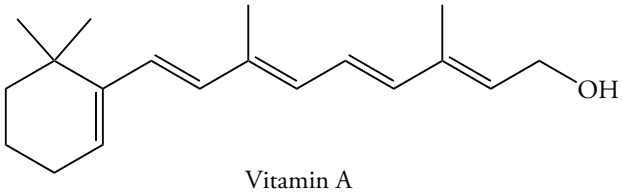
α-phellandrene
(eucalyptus)

Sesquiterpene

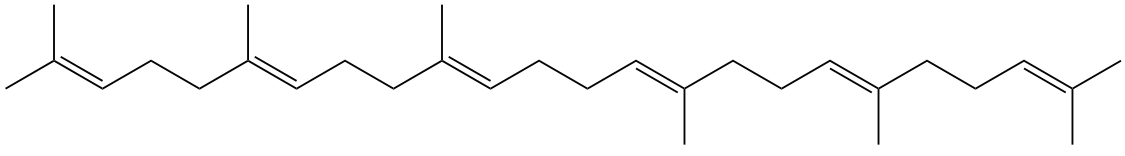


α-selinene
(celery)

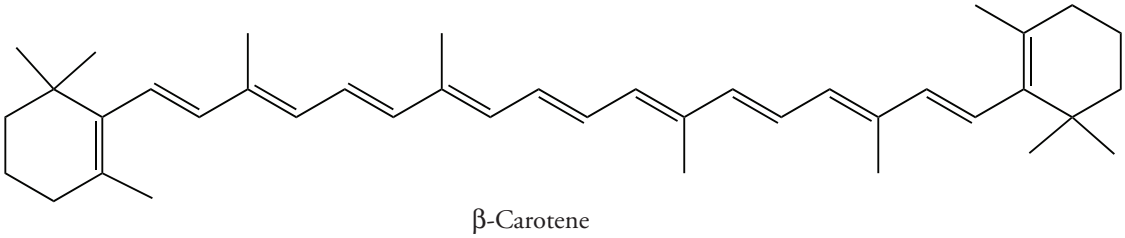
diterpene



Vitamin A
(present in mammalian tissue and fish oil)

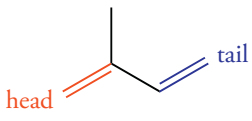


Squalene
(triterpene)



β-Carotene
(teraterpene)

The two or more isoprene units of terpenes usually bond head to tail. Although terpenes contain a variety of functional groups, it is usually easy to identify the isoprene units.

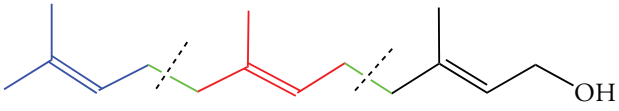


isoprene
2-methyl-1,3-butadiene



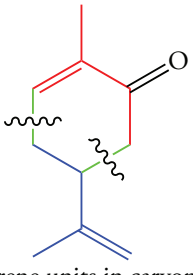
two isoprene units linked head to tail

Farnesol contains three isoprene units joined head to tail. Dashed lines indicate where the three units are joined.



isoprene units in farnesol

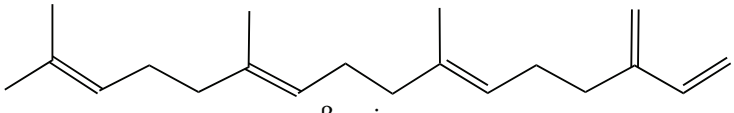
Many terpenes contain one or more rings—carvone, for example— and we can also divide them into isoprene units.



isoprene units in carvone

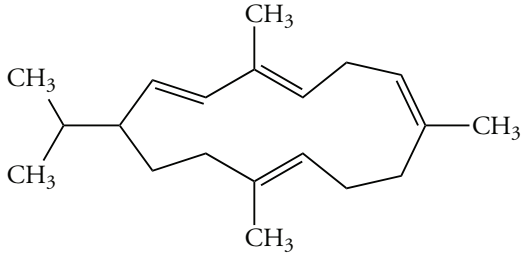
Terpenes are abundant in the oils of plants and flowers, and they have distinctive odors, flavors, and colors. They are responsible for the odor of pine trees and for the colors of carrots and tomatoes. β-Carotene, found in carrots, and vitamin A are both terpenes. A biochemical reaction in mammals splits and oxidizes β-carotene into two molecules of vitamin A.

Problem 11.1 Classify the double bonds (conjugated vs. isolated) found in β-springene, a sex attractant secreted by the dorsal gland of the springbok, a South African gazelle.



β-springene

Problem 11.2 Classify the following terpene (monoterpene, diterpene, etc.) and indicate its division into isoprene units. Then, identify the conjugated double bonds.



11.2 STABILITY OF CONJUGATED DIENES

We saw earlier (Section 5.11) that we can determine the relative stabilities of isomeric alkenes by comparing their heats of hydrogenation ($\Delta H^\circ_{\text{hydrogenation}}$) when the hydrogenation reactions yield the same product.

Figure 11.2 shows the calculated heats of hydrogenation for the terminal double bonds of 1,4-pentadiene and (E)-1, 3-pentadiene. This figure also includes the heat of hydrogenation of the second double bond of each compound to form pentane. The average heat of hydrogenation of a terminal monosubstituted double bond is about 126 kJ mole^{-1}. Thus, the heats of hydrogenation of the double bonds of 1,4-pentadiene are typical for a monosubstituted double bond. The heat of hydrogenation of the double bond of (E)-2-pentene also lies within the range for trans-disubstituted alkenes. However, the heat of hydrogenation of the monosubstituted (terminal) double bond of (E)-1,3-pentadiene is about 15 kJ mole^{-1} less than expected for an isolated double bond. The terminal double bond is therefore more stable than an isolated double bond in 1,4-pentadiene. The increased stability of the conjugated double bond results from an interaction of the two double bonds. This effect is **resonance stabilization**.

We can show this resonance stabilization for conjugated double bonds of butadiene in terms of Lewis structures, as shown below. The dipolar form is the minor contributor to the resonance hybrid because it takes energy to separate charges.

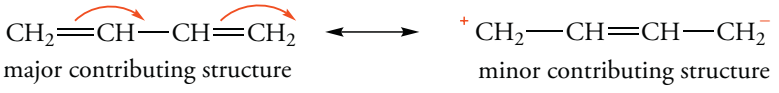
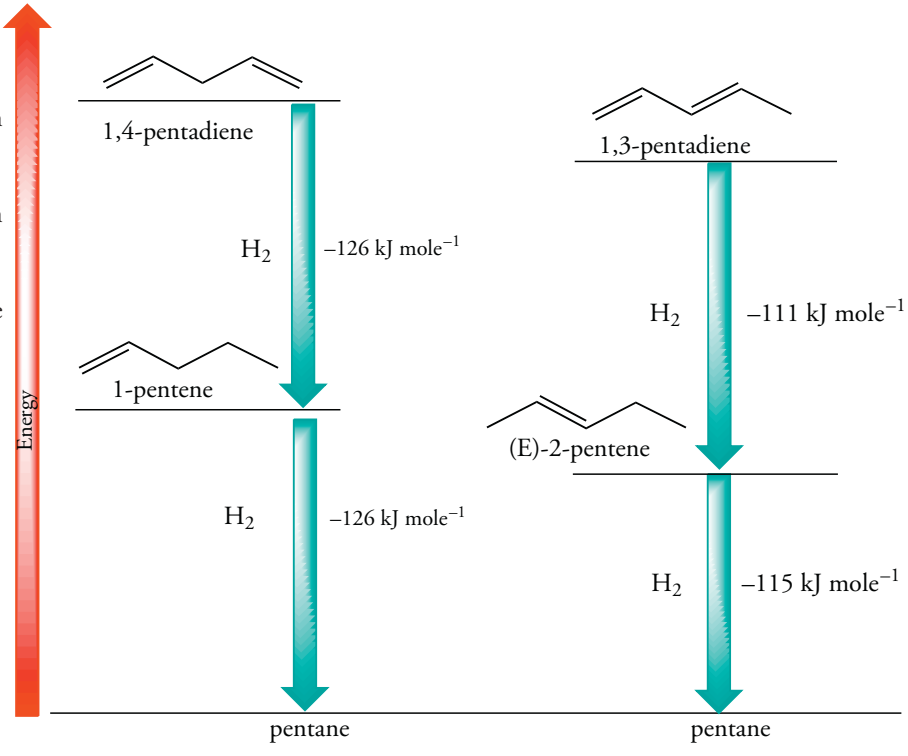


Figure 11.2
Heats of Hydrogenation and Resonance Energy
(E)-1,3-pentadiene is more stable than 1,2-pentadiene for two reasons:

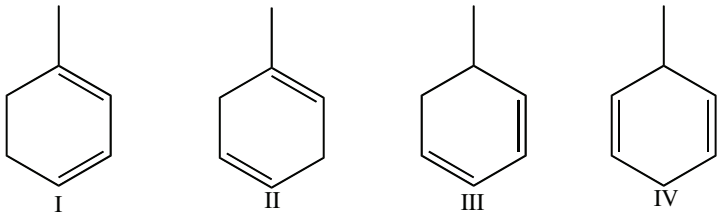
1. (E)-1,3-pentadiene is more substituted than 1,4-pentadiene.

2. The double bonds in (E)-1,3-pentadience are conjugated, but the double bonds in 1,4 pentadiene are not.



Problem 11.3 Estimate the total heats of hydrogenation of 2E, 4E-heptadiene, and of 2E,5E-heptadiene.

Problem 11.4 Arrange the following methylcyclohexadienes in order of decreasing heats of hydrogenation to form methylcyclohexane.



Sample Solution

Conjugation of double bonds and the degree of substitution of double bonds are two structural features that result in lower heats of hydrogenation. Compounds I and III are conjugated dienes and are resonance stabilized. Their heats of hydrogenation are smaller than for the two nonconjugated dienes. Compound I has the lowest heat of hydrogenation because it has a higher degree of substitution at the double bond than compound III. For the same reason, the heat of hydrogenation of compound II is less than for compound IV. The order is IV > II > III > I.

Problem 11.5

Arrange the following compounds in order of increasing heats of hydrogenation.

I 1,6-Dimethyl-1,3-cycloheptadiene
II 3,6-Dimethyl-l,4-cycloheptatdiene
III 2,7-Dimethyl-1,4-cycloheptadiene
IV l,3-Dimethyl-l,3-cycloheptadiene
V 2,4-Dimethyl-1,4-cycloheptadiene

11.3 MOLECULAR ORBITALS OF ETHENE AND 1,3-BUTADIENE

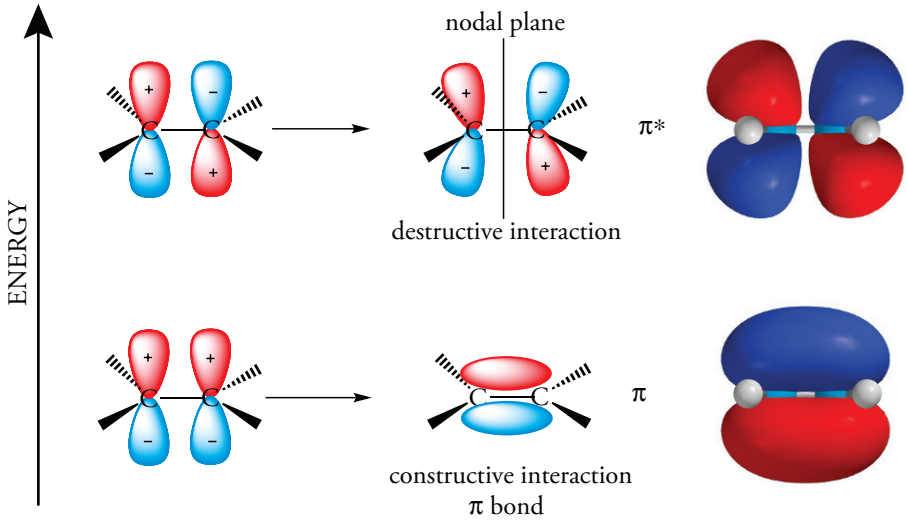
Molecular Orbitals of Ethene

Many decades ago, the German Chemist Erich Hückel developed a mathematical method that describes the interactions of 2p orbitals in π bonds. This method generates molecular orbitals by making a linear combination of 2p atomic orbitals. *The number of molecular orbitals always equals the number of atomic orbitals from which they are made.* If we start with two 2p atomic orbitals, we must obtain two π molecular orbitals. Let's consider ethene, the simplest compound with a π bond. The most stable, bonding molecular orbital results from adding the wave equations for the two 2p orbitals. This is equivalent to adding two waves in phase, which results in constructive interference. We obtain the second molecular orbital of ethene by subtracting the equations for the two 2p orbitals. The result is the higher energy, antibonding molecular orbital. Subtracting the two equations is equivalent to destructive interference between two waves, and there is a **nodal plane** between the two sp^2-hybridized carbon atoms linked by the σ bond.

We can visualize the bonding and antibonding p orbitals using the 2p orbitals of the two carbon atoms and then "overlapping" them (Figure 11.3). We can do this in two ways, which correspond to adding or subtracting the equations for the wave functions of the atomic orbitals. Adding the equations is in-phase combination; subtracting the equations is out-of-phase combination. The plus and minus signs placed within each lobe of a 2p orbital indicate the phase of the wave function in that volume of space, *not* electrical charges. Overlap of the "+" with "+," or "–" with "–," reinforces the wave function to give constructive overlap. This arrangement of orbitals forms a bonding molecular orbital (MO), designated π_1. The second possibility corresponds to subtracting wave functions. In this case, the wave functions of the atomic orbitals cancel, which as we noted above is equivalent to destructive interference. This arrangement of orbitals forms an antibonding MO, π_2.

A MO can contain 0, 1, or 2 electrons. The bonding MO, π_1, in ethene has two paired electrons; the antibonding orbital of ethene, π_2, is empty.

Figure 11.3
Orbital Overlap in Pi Bond
The side-by-side overlap of two 2p orbitals in ethene leads to two molecular orbitals. Constructive overlap gives the bonding π, molecular orbital. The destructive overlap of the two orbitals gives a higher energy, antibonding molecular orbital, π*.

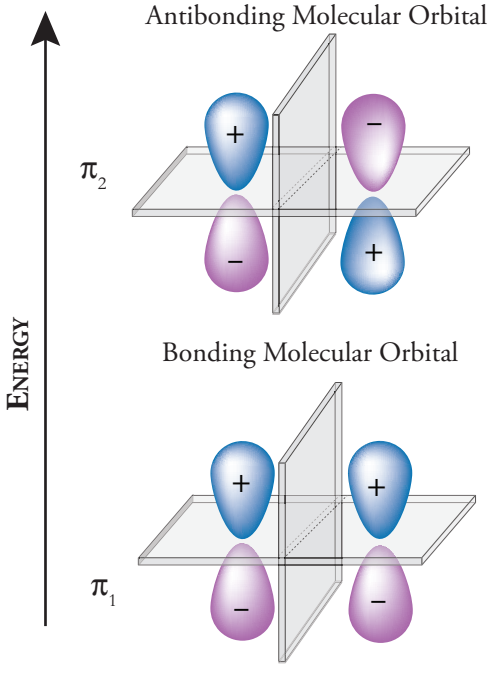


Symmetry of Molecular Orbitals

How are electrons distributed in a molecular orbital? In quantum mechanics, the square of the equation for the orbital gives the probability of finding an electron within a given region of space. For symmetric molecules such as ethene, the value of the square of the wave function must be the same at symmetrical points. So, for the bonding molecular orbital shown at the right of Figure 11.3, the mathematical value of the square of the equation at the point marked with a (+) sign is the same as the value at the point marked by the (–) sign.

Look at the relationship between the signs of the lobes of the atomic orbitals with respect to the horizontal nodal plane located in the plane of the molecule. The wave function has a value of zero in a nodal plane. In the atomic orbitals $2p_1$ and $2p_2$ the magnitude of the wave function on opposite sides of the plane is the same, but the *sign* of the wave function is different. The wave function is *antisymmetric* with respect to this nodal plane. Now look at the symmetry of the two wave functions with respect to a vertical plane that is perpendicular to the plane of the molecule (Figure 11.4). In the case of π_1 there is no change in sign, and the wave function is symmetric with respect to the vertical plane. For π_2 the sign changes, and the wave function is antisymmetric with respect to the vertical plane. For π_2 the vertical plane is a nodal plane, and π_2 is an antibonding orbital.

Figure 11.4 Symmetry of π Molecular Orbitals of Ethene
The π molecular orbitals of ethene have opposite symmetries with respect to the vertical plane that bisects the π bond. The bonding orbital is symmetric with respect to the vertical plane. However, the antibonding orbital is antisymmetric with respect to this plane. Thus, for the antibonding orbital, the vertical plane is also a nodal plane.



Guidelines for generating the molecular orbitals of conjugated π systems are listed below.

1. The number of π molecular orbitals is the same as the number of 2p orbitals used to form them. So, if we begin with *n* 2p orbitals we obtain *n* π molecular orbitals.

2. The energies of the π molecular orbitals are symmetrically distributed above and below the energy of the isolated, atomic 2p orbitals.

3. The energies of bonding molecular orbitals are lower than the energies of antibonding molecular orbitals.

4. Each molecular orbital has a horizontal nodal plane that contains the carbon nuclei.

5. The molecular orbitals for polyenes containing *n* atoms can have from zero to $(n - 1)$ vertical nodal planes.

6. The energies of the orbitals increase with the number of vertical nodal planes.

7. Each molecular orbital must be symmetric or antisymmetric with respect to a vertical plane between the atoms at the center of the π system.

8. Each bonding π molecular can contain a maximum of two electrons.

Molecular Orbitals of 1,3-Butadiene

We can use the above guidelines to construct the molecular orbitals resulting from a linear combination of the four 2p orbitals of 1,3-butadiene (Figure 11.5).

The linear combination of the four 2p orbitals of 1,3-butadiene gives four molecular orbitals: two are bonding and two are antibonding. In the lowest energy molecular orbital, π_1, all lobes of the 2p atomic orbitals overlap constructively. Therefore, π_1 does not have any vertical nodal planes. However, the relative contributions of the 2p orbitals to the wave function are not equal. The contributions of the four 2p orbitals to the molecular orbitals of the π system are shown in Figure 11.5. As the energy of the MO's increases, the number of vertical nodal planes increases apace.

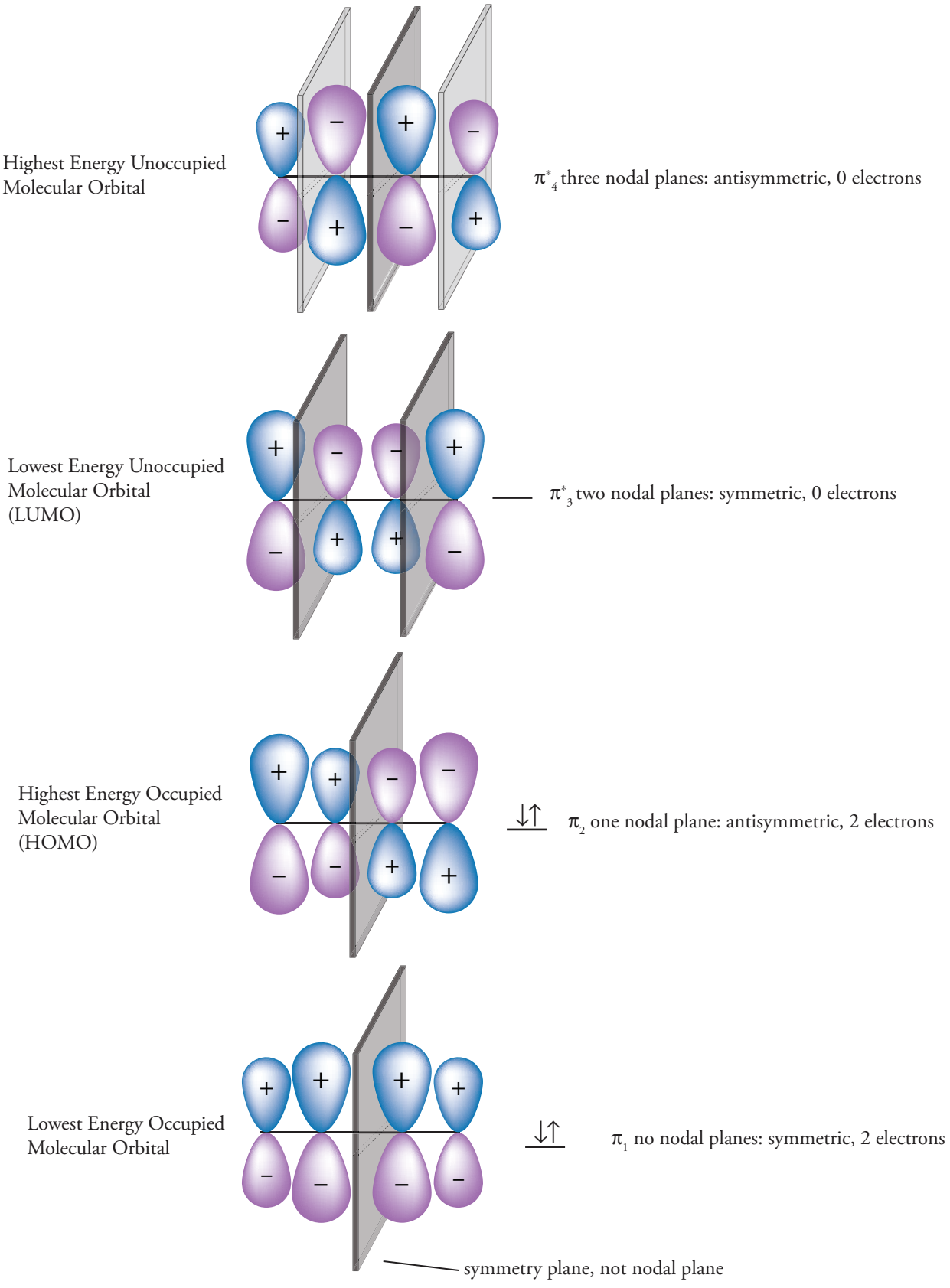


Figure 11.5 (a) Molecular Orbitals of 1,3-Butadiene

The unequal sizes of the 2p atomic orbitals from which the π MOs are made to show the degree to which they contribute to the molecular orbital. A bonding interaction results from constructive overlap of 2p orbitals of the same sign. Nodal planes are shown between carbon atoms as vertical lines; this is where destructive overlap occurs. The energy of the orbitals increases as the number of nodal planes increases. The sign of the orbital inverts going from one side of a nodal plane to the other. Note that π_2 is the highest occupied MO (HOMO) and that π_3 is the lowest unoccupied MO (LUMO).

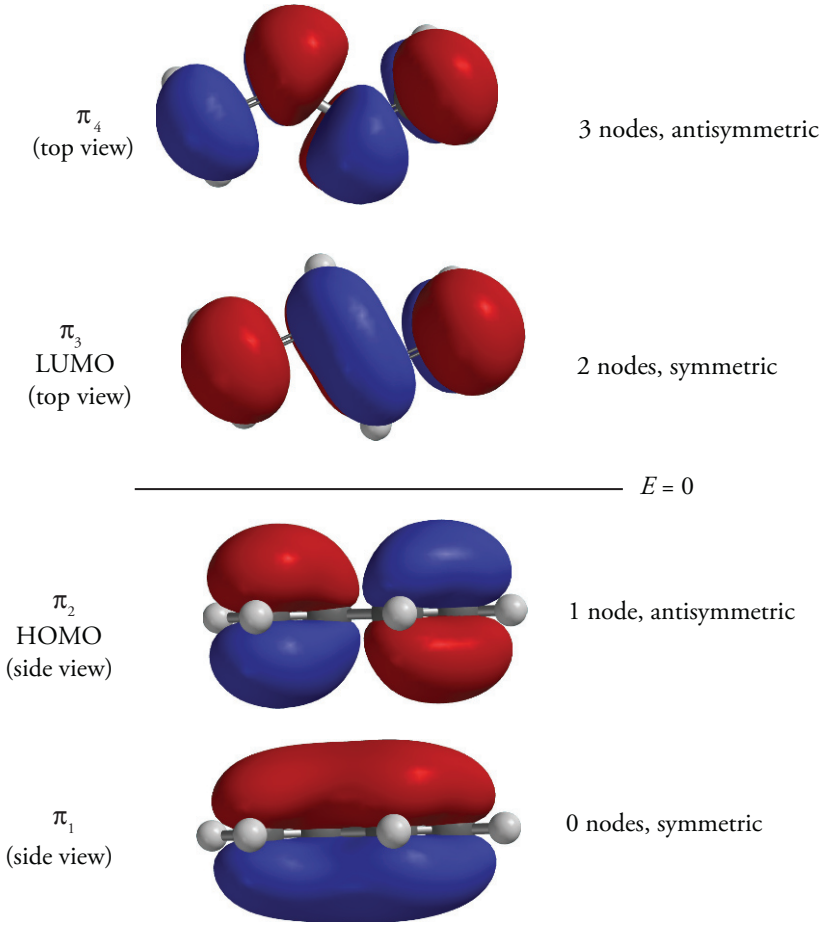


Figure 11.5
(b) Electron Densities of the Molecular Orbitals of 1,3-Butadiene

The π_1 molecular orbital contains two electrons. It has the lowest energy because it has no vertical nodal planes. Substantial double bond character exists between C-2 and C-3 atoms, a feature not represented by the Lewis structure of the major resonance contributor of butadiene. The π_2 molecular orbital, which has higher energy, also contains two electrons. π_2 is the highest energy occupied molecular orbital, HOMO. It is antisymmetric with respect to a nodal vertical plane between C-2 and C-3. Bonding interactions occur both between C-1and C-2 and between C-3 and C-4. The antibonding π_3 and π_4 molecular orbitals have more vertical nodal planes and have higher energy than the bonding molecular orbitals. The π_3 molecular orbital contains two antibonding interactions and one bonding interaction. π_3 is the lowest energy unoccupied molecular orbital, LUMO. The π_4 molecular orbital has three nodal planes and no bonding interactions.

Problem 11.6

How many molecular orbitals of 1,3,5-hexatriene contain bonding π electrons? Sketch each one, showing vertical nodal planes, and determine the symmetry of each wave function.

Problem 11.7

What is the symmetry of the highest energy molecular orbital containing electrons in 1,3,5,7-octatetraene?

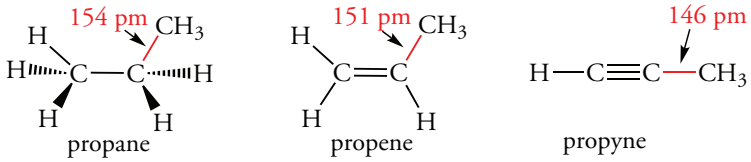
Sample Solution

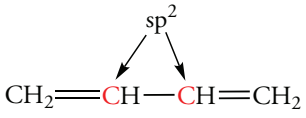
The eight 2p electrons in 1,3,5,7-octatetraene are located in four molecular orbitals, the highest energy one being π_4. We know that π_1 of linear, conjugated polyenes is symmetric and that the symmetry of consecutive orbitals alternates with increasing energy. Thus, π_2 is antisymmetric, π_3 is symmetric, and π_4 is antisymmetric. The symmetry of conjugated orbitals always alternates in the following order, beginning with the most stable bonding orbital: symmetric, antisymmetric until we have accounted for all of the orbitals.

11.4 STRUCTURAL EFFECTS OF CONJUGATION IN 1,3-BUTADIENE

Effects on Bond Length

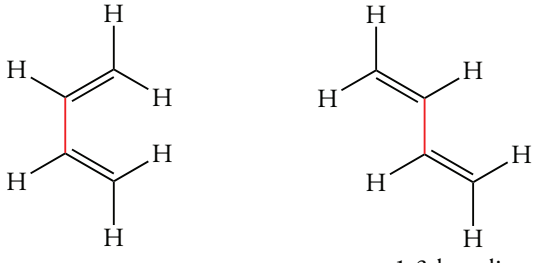
We recall that the length of carbon-carbon σ bonds depends on the hybridization of both carbon atoms. The bond length between the sp^3-hybridized methyl carbon atom and the sp^3-, sp^2-, and sp-hybridized central carbon atoms of propane, propene, and propyne, show this effect. The bond length for sp^2-sp^3 bonded atoms, 151 pm, is 3 pm shorter than that of sp^3-sp^3 bonded atoms. If there were no double bond character between C-2 and C-3 in butadiene, we might expect a bond length of 148 pm. However, the bond length of 1,3-butadiene is 146 pm. The molecular orbital model predicts a shorter bond length than would be expected from a Lewis structure because of the continuous overlap in π_1.





Effect of Conjugation On the Barrier to Rotation of 1,3-Butadiene

1,3-Butadiene can exist in either of two conformations around the C-2 and C-3 bond. If the two vinyl groups are *cis* to the σ bond, the conformation is called s-*cis*; if they are *trans*, the conformation is called s-*trans*.



The s-*cis* and s-*trans* conformations of 1,3-butadiene can interconvert by rotation around the C-2 to C-3 bond. We recall that the barrier to rotation in alkanes is small, about 12-16 kJ $mole^{-1}$. Although the anticonformations of alkanes are more stable than the eclipsed conformations, rotation around alkane σ bonds is very fast.

In contrast, the rotational barrier for the interconversion of the s-*cis* and s-*trans* conformations of 1,3-butadiene is much higher, 28 kJ $mole^{-1}$, than in alkanes. When the C-2 to C-3 bond rotates around its axis, it passes through a transition state in which the planes of the two vinyl groups are perpendicular (Figure 11.6). In the transition state, the double bonds are localized because the two π bonds are perpendicular to each other. Therefore, the resonance stabilization of 1,3-butadiene is lost because there is no longer a bonding interaction between C-2 and C3. Therefore, the energy barrier is much higher than for rotation around the C-2 to C-3 σ bond of butane.

Problem 11.8

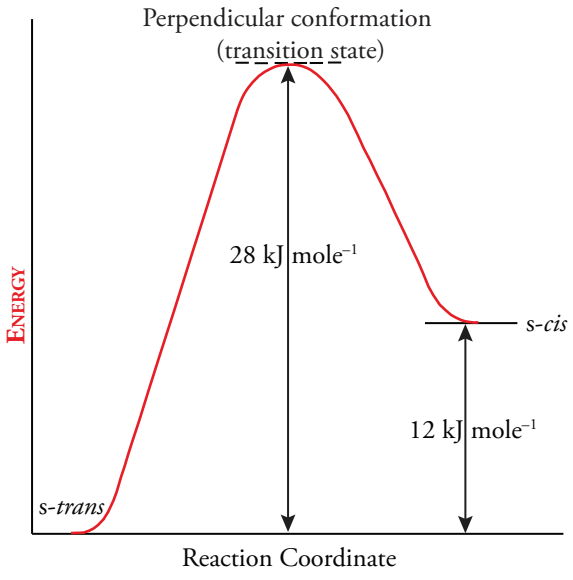
Draw the structure of the planar conformations of (2Z,4Z)-hexadiene and determine whether the equilibrium constant for conversion of the s-*trans* to s-*cis* conformation is larger or smaller than the same equilibrium for 1,3-butadiene.

Problem 11.9

How is the equilibrium constant for the s-*trans* to s-*cis* conversion affected by the size of alkyl groups in 2,3-dialkyl-substituted 1,3-butadienes?

Figure 11.6 Interconversion of s-*trans* and s-*cis* 1,3-Butadiene

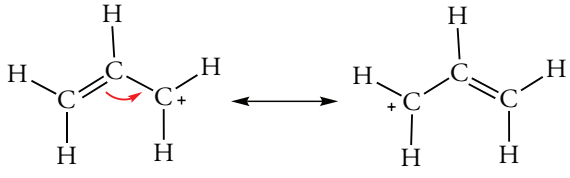
Rotation around the C-2 to C-3 bond interconverts the s-*trans* and s-*cis* conformational isomers. The s-*trans* conformation has all 2p orbitals aligned parallel to one another to form a resonance-stabilized system. In the transition state for rotation, the π bonds are perpendicular to each other. As a result, they cannot interact and their resonance stabilization is lost. The s-*cis* isomer is also planar, but it has a higher energy because of an unfavorable steric interaction between the hydrogens at C- 1 and C-4.



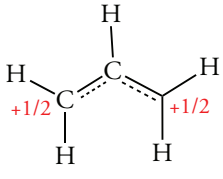
11.5 ALLYLIC SYSTEMS

Allylic Carbocations

In our discussion of S_N1 reactions, we saw that two Lewis structures represent the resonance stabilization of an allylic carbocation (Section 10.3). The positive charge is located on C-1 in one resonance form and on C-3 in the other.

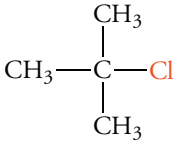


Dashed lines show the delocalization of two charges in the allylic carbocation. The allylic carbocation; C-1 and C-3 each have a partial positive charge of +1/2; C-2 has a charge of zero.

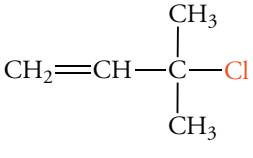


The allyl carbocation is much more stable than a primary alkyl carbocation. We estimate that primary allylic carbocations and secondary carbocations have about the same stability since they form in S_N1 reactions at comparable rates.

For example, 3-chloro-3-methyl-1-butene that reacts with solvents such as water or ethanol is 100 times faster than *tert*-butyl chloride.

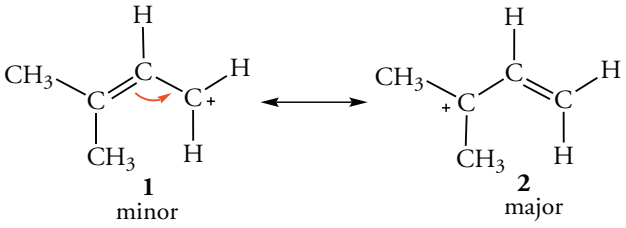


tert-butylchloride
reactive in S_N1 reactions



3-chloro-3-methyl-1-butene
even more reactive in S_N1 reactions

Both compounds have a tertiary carbon—chlorine bond, and they react by an S_N1 mechanism to form tertiary carbocations. However, the carbocation from the unsaturated compound is also allylic, so the charge on the carbocation intermediate is resonance stabilized.



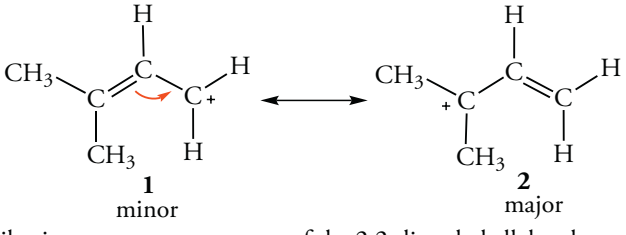
1 minor **2** major

Contributing resonance structures of the 2,2-dimethyl allyl carbocation

Therefore, we expect the transition state leading to the allylic carbocation to be more stable than the transition state leading to the *tert*-butyl carbocation.

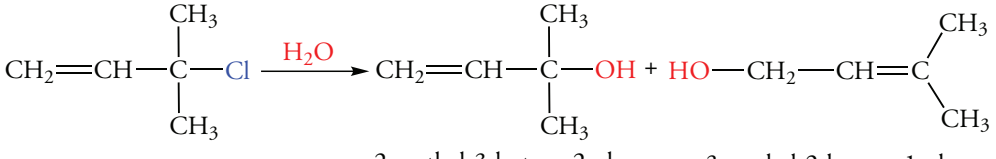
We saw above that the positive charge of an allylic carbocation is distributed equally at C-1 and C-3. However, the charge is not equally distributed in the 1,1-dimethylallylic carbocation. In structure **1**, the positive charge is located at a primary carbon atom, in structure 2 the positive charge is at a tertiary carbon atom. Therefore, resonance form **2** is the major contributing structure.

When 3-chloro-3-methyl-1-butene reacts with water, the intermediate carbocation reacts rapidly in the second step. Since the tertiary center of the allylic carbocation has a greater partial positive charge than the primary center, the tertiary alcohol is the major product.



1 minor **2** major

Contributing resonance structures of the 2,2-dimethyl allyl carbocation

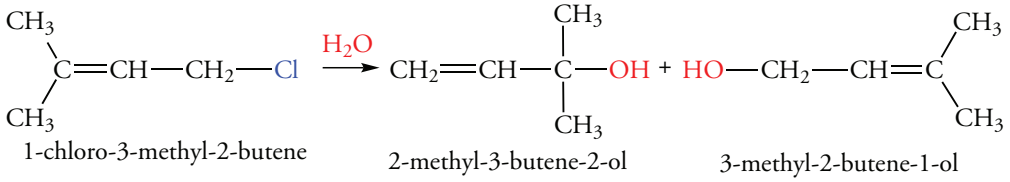


3-chloro-3-methyl-1-butene

2-methyl-3-butene-2-ol
85%

3-methyl-2-butene-1-ol
15%

We observe the same effect in the reaction of 1-chloro-3-methyl-2-butene in water. Once again, the major product arises by reaction of water with the tertiary carbon of the allylic carbocation.



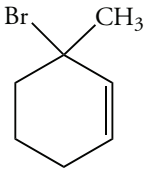
1-chloro-3-methyl-2-butene

2-methyl-3-butene-2-ol
85%

3-methyl-2-butene-1-ol
15%

Problem 11.10

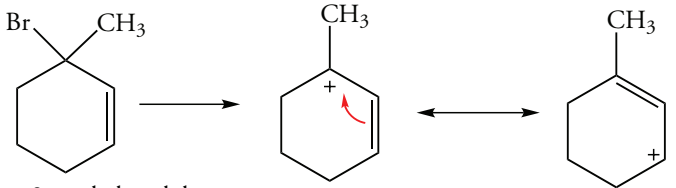
Write the structures of the products that result from an S_N1 reaction of 3-bromo-methyl-cyclohexene with water. What is the major product?



3-bromo-3-methyl-cyclohexene

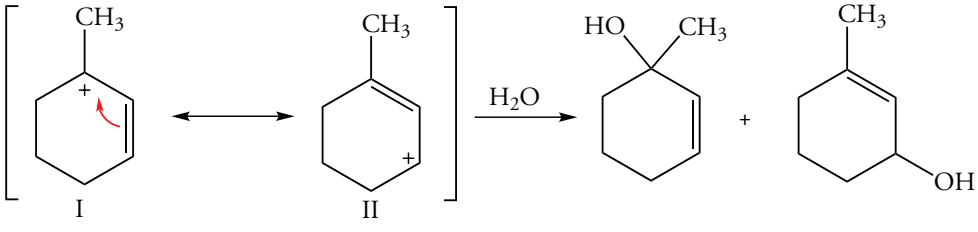
Sample Solution

First, draw the structure of the resonance-stabilized allylic carbocation that forms when the carbon-bromine bond breaks. Second, draw the structures of the resonance-stabilized allylic carbocation. Third, add a bromide ion to the carbocation to obtain the isomeric bromine compound whose ionization would give the same resonance-stabilized carbocation.



3-bromo-3-methyl-cyclohexene

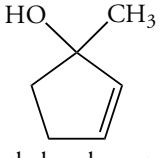
Fourth, write the products that form when this allylic carbocation reacts with water to give two isomeric alcohols.



Since contributing structure I, above, of the resonance hybrid has a positive charge on a tertiary carbon and contributing structure II has a positive charge on a secondary carbon, we expect the major product to be the tertiary alcohol and that is what we observe.

Problem 11.11

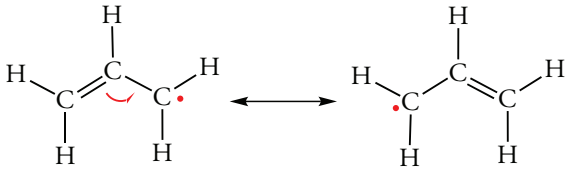
(a) What substitution products form by reaction of the following alcohol with HCl? (b) Which one do you expect to be the major product?



3-methyl-cyclopenten-3-ol

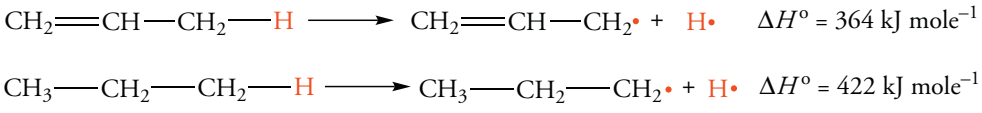
Allylic Free Radicals

Like an allylic carbocation, an allylic radical is resonance stabilized. However, in contrast to an allylic carbocation, which has two electrons in a delocalized π system, an allylic radical has three π electrons, one of which is unpaired. The unpaired electron is delocalized with an equal probability of being at either C-1 or C-3. The central carbon atom has no radical character. Lewis structures for the allylic free radical are shown below.



resonance structures of the allyl free radical

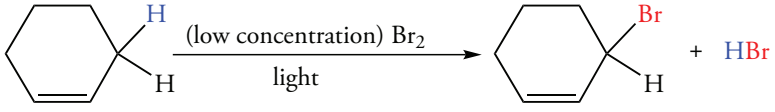
We can compare the stability of the allylic radical versus a primary radical by comparing the bond dissociation energies of the C—H bond of the primary carbon atom of propane to the bond dissociation energy of the allyl C—H bond of propene, as shown below.



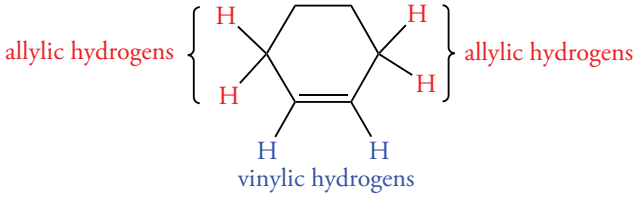
The 58 kJ mole^{-1} difference between these two bond dissociation energies is a direct measure of the resonance energy of the allylic radical.

Free Radical Reactions at Allylic Centers

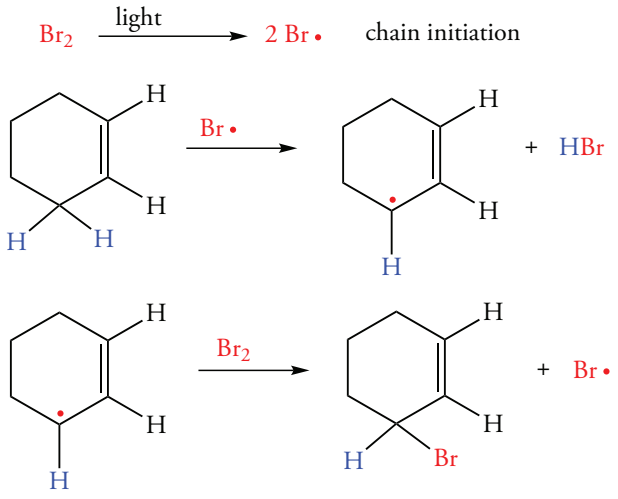
Allyl free radicals form more easily than the corresponding alkyl radical. The enhanced reactivity of an allylic C—H bond is shown in its reaction with low concentrations of bromine. For example, cyclohexene reacts with very low concentrations of bromine when energy is added by a source of light such as a sun lamp. The light causes homolytic cleavage of the Br—Br bond, and the net result of the reaction is replacement of an allylic hydrogen with a bromine atom.



Any of the four equivalent allylic hydrogen atoms of cyclohexene can react under these conditions. The vinyl C—H bonds do not react because the C—H bond energy of sp^2-hybridized carbon atoms is larger than the bond energy of allylic C—H bonds. The four C—H bonds located at non-allylic sites are also less reactive than the allylic C—H bonds. We expect this result based on the difference in the bond dissociation energies cited above for propane versus propene.

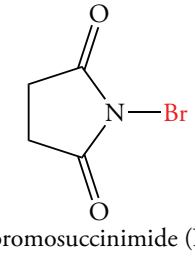


The reaction of cyclohexene with bromine is potentially rather complicated. We know that alkenes react with bromine by an electrophilic addition mechanism. Might not this reaction occur in competition with the allylic bromination reaction at low concentrations of bromine? The answer is "no" because the free-radical chain reaction is much faster than the addition reaction if the concentration of bromine is low. The free-radical chain reaction for reaction of cyclohexene with bromine has the following steps.

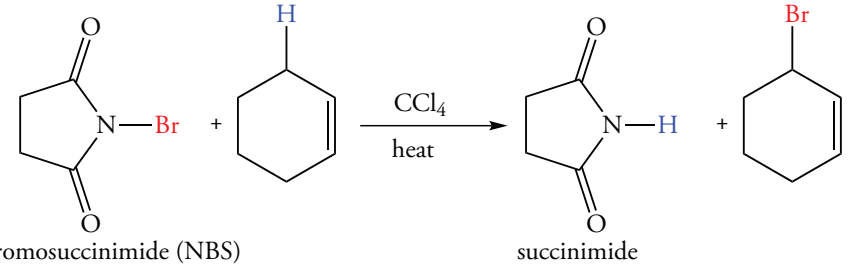


Free Radical Reactions at Allylic Centers Catalyzed by *N*-Bromosuccinimide

Hydrogen bromide continually forms in the reaction. As its concentration increases, might it not add to the double bond in competition with the free-radical allylic bromination? The answer is, it could if it was to accumulate as a reaction product. However, this possibility can be bypassed completely. We can use a reagent called *N-bromosuccinimide* (NBS) to carry out allylic bromination. NBS generates a low concentration of bromine and also prevents the continued production of HBr that would add to the double bond in an electrophilic addition reaction.



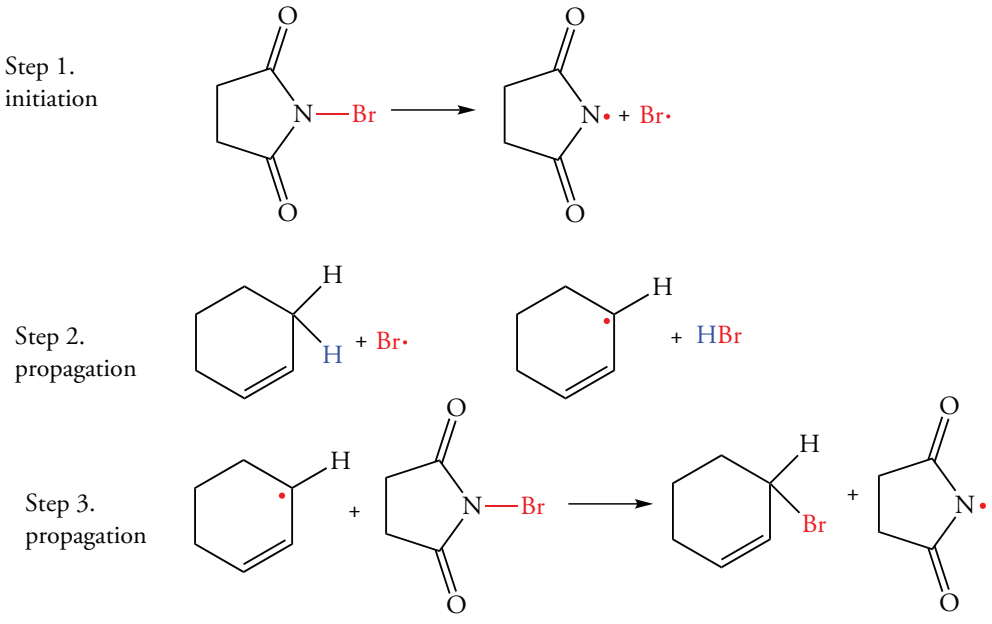
N-bromosuccinimide (NBS)



N-bromosuccinimide (NBS) succinimide

Mechanism of Reaction Catalyzed by NBS

The steps in the reaction mechanism are shown below. The net reaction for allylic bromination with NBS produces neither bromine nor the by-product hydrogen bromide.

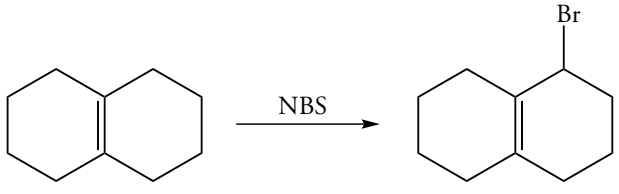


Problem 11.12

Write the structures of all products formed in the allylic bromination of 2-hexene, using 1M equivalent of NBS.

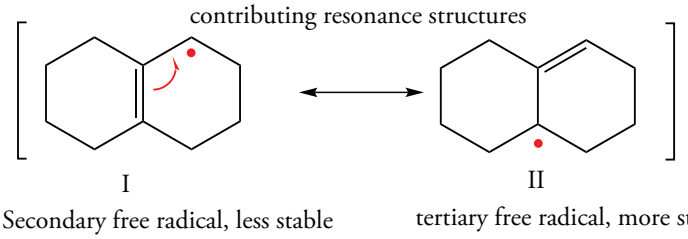
Problem 11.13

Free radical bromination of the following compound using 1M equivalent of NBS gives one allylic bromo compound. (a) Write the structure of a second possible isomeric product. (b) Explain why it is not formed.



Sample Solution

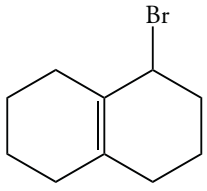
The reaction with NBS generates two resonance structures; one is secondary (I), the other is tertiary (II).



Secondary free radical, less stable

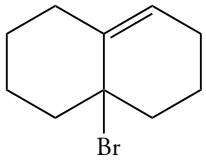
tertiary free radical, more stable

The difference in stabilities of secondary and tertiary free radials is not as large as the difference between second and tertiary carbocations because the carbon atom that has the unpaired electron is less electron deficient. Thus, the stability of the double bond in the product is important. Adding bromine at the tertiary center gives a trisubstituted double bond, but bromination of the secondary allylic center gives a tetrasubstituted double bond, which is more stable. And, that is the major product.



I

More substituted, more stable double bond

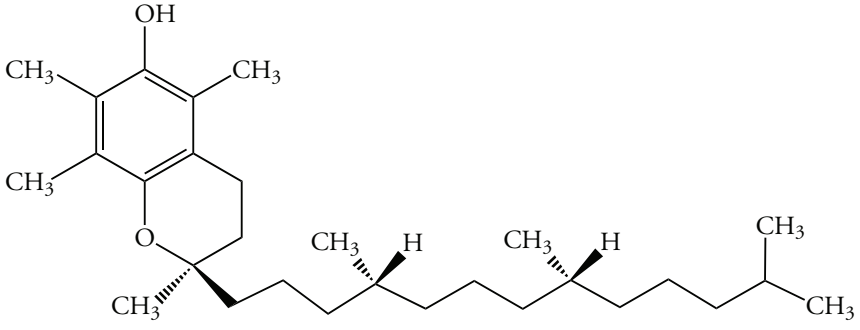


II

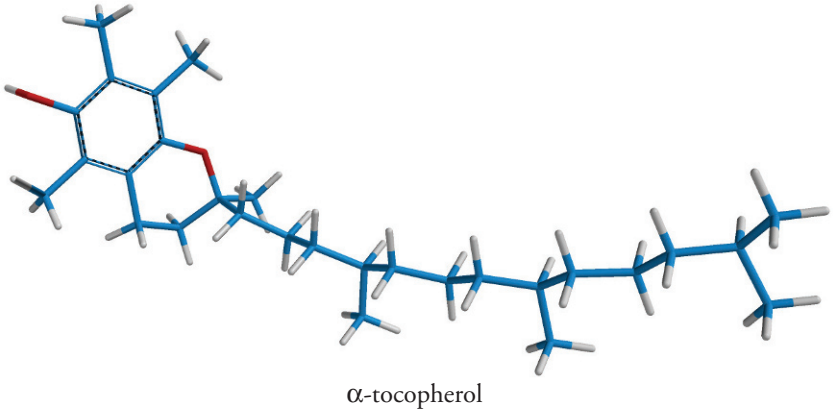
Less substituted, less stable double bond

Allylic Free Radicals and Vitamin E

Free radicals are highly reactive species that wreak havoc on cellular molecules. The antioxidant vitamin E, also called α-tocopherol, reacts with cellular free radicals and converts them to resonance-stabilized free radicals that are much less harmful.

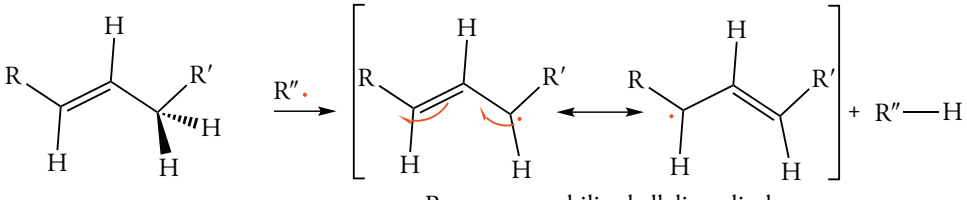


α-tocopherol (Vitamin E)



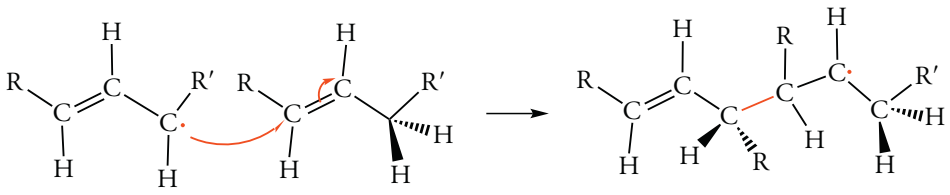
α-tocopherol

For example, a free radical can react with an unsaturated fatty acid in a membrane lipid. First, the radical abstracts an allylic hydrogen atom from the fatty acid to give a resonance-stabilized allylic radical.

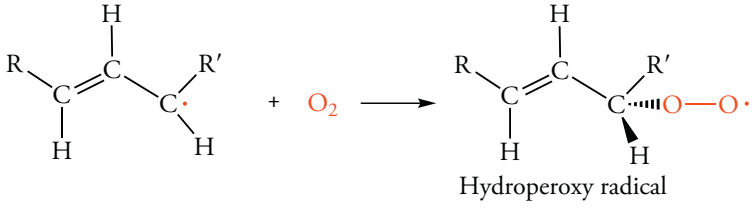


Resonance-stabilized allylic radical

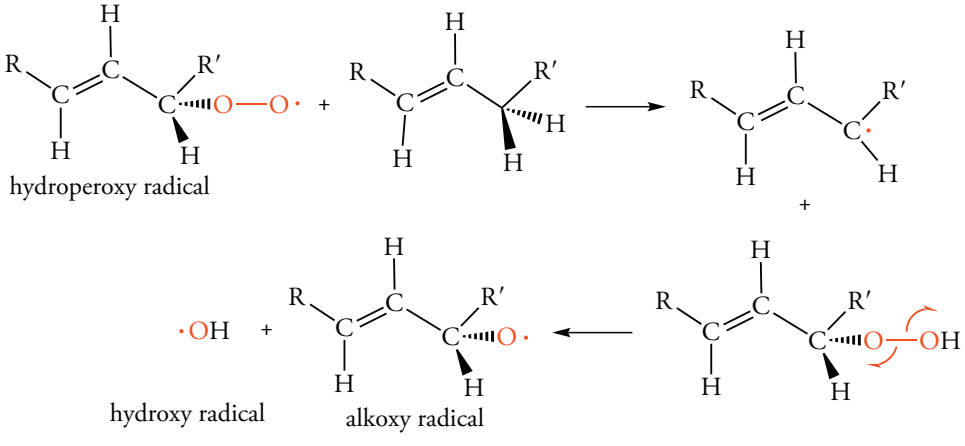
This allylic free radical can then react with another unsaturated fatty acid. This reaction is the first step in a free-radical polymerization process that destroys lipids in biological membranes, killing cells.



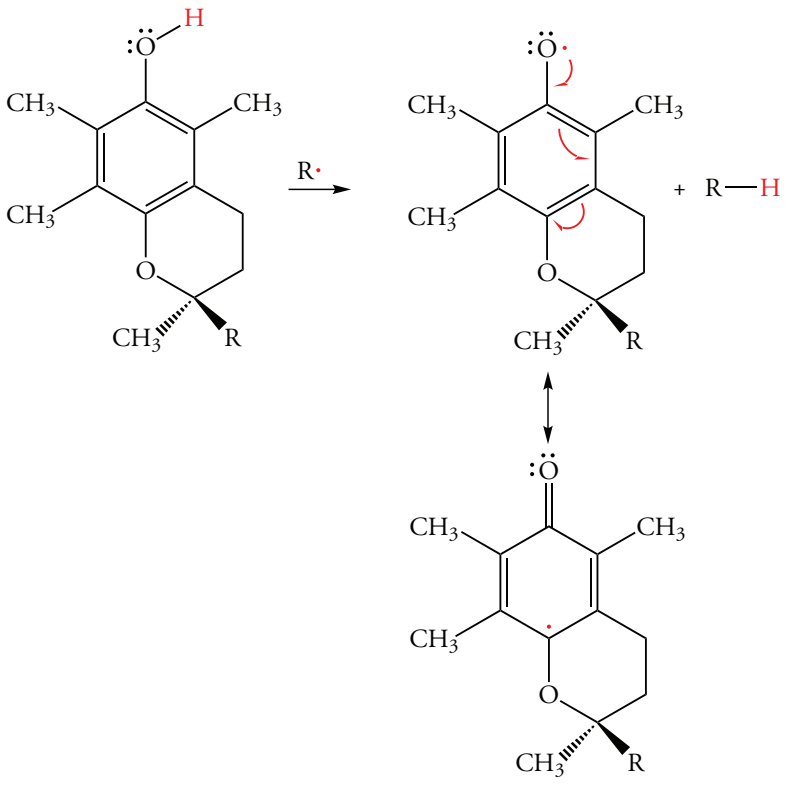
An allylic free radical can also react with oxygen to produce a hydroperoxy radical (HOO·), an even more reactive intermediate. Hydroperoxy radicals can be generated by many pathways. For example, they are sometimes by-products of drug metabolism, and they are formed as intermediates in enzyme-catalyzed reactions.



Disproportionation of the hydroperoxy radical produces an alkoxy radical and a hydroxyl radical, a very dangerous species in biological systems. Free radicals such as these react with many cellular proteins and nucleic acids, causing extensive cellular damage. Free radicals may also play a significant role in the aging process.



Vitamin E interrupts free-radical chain reactions by capturing free radical intermediates. It acts as a scavenger by forming a relatively stable hydroquinone radical. Because the free radical derived from vitamin E is relatively stable, it does not disrupt cellular chemistry.



Many food additives have antioxidant properties similar to those of vitamin E. These additives, much maligned by persons who object to "unnatural food," not only preserve food by preventing free radical oxidation but also preserve the humans who eat them.

11.6 HÜCKEL MOLECULAR ORBITALS OF ALLYL SYSTEMS

We will make the molecular orbitals of allylic systems by the same method we used to make the MOs of 1,3-butadiene. That is, we will make a linear combination of the three 2p orbitals of an allyl system to generate three π molecular orbitals. We label them π_1, π_2, and π_3 in order of increasing energy. Figure 11.7 shows the contributions of the three 2p orbitals to the molecular orbitals of the allyl system. The lowest energy MO, π_1, is symmetric and has no vertical nodal planes. It is bonding. The highest energy MO, π_3, has two vertical nodal planes and has no bonding interactions. It is antibonding. It is also symmetric. Now let's consider π_2. This antisymmetric MO seems highly unusual at first glance. Thus far we have seen nothing like it. This orbital is neither bonding nor antibonding: It is **nonbonding.** Because the allyl system has three carbon atoms, the single vertical nodal plane of π_2 *must* occur at the center carbon atom. There is no π electron density at C-2 in an allylic system. But, you may ask, "Where is the 2p orbital of the C-2 atom?" The answer is that the Hückel method generates new molecular orbitals, and they replace, as it were, the original 2p orbitals.

Any electron in the π_2 MO of an allyl system has the same energy as an electron in a 2p atomic orbital. Therefore, it makes no contribution to the net stability of the molecule, and it does not destabilize the π system either. That is why it is called a nonbonding orbital. Figure 11.8 shows the electron configurations of the π orbitals of the carbocation, radical, and carbanion. Figure 11.7b shows the molecular orbitals of the allyl carbocation. In this case, the nonbonding orbital, π_2, is not occupied.

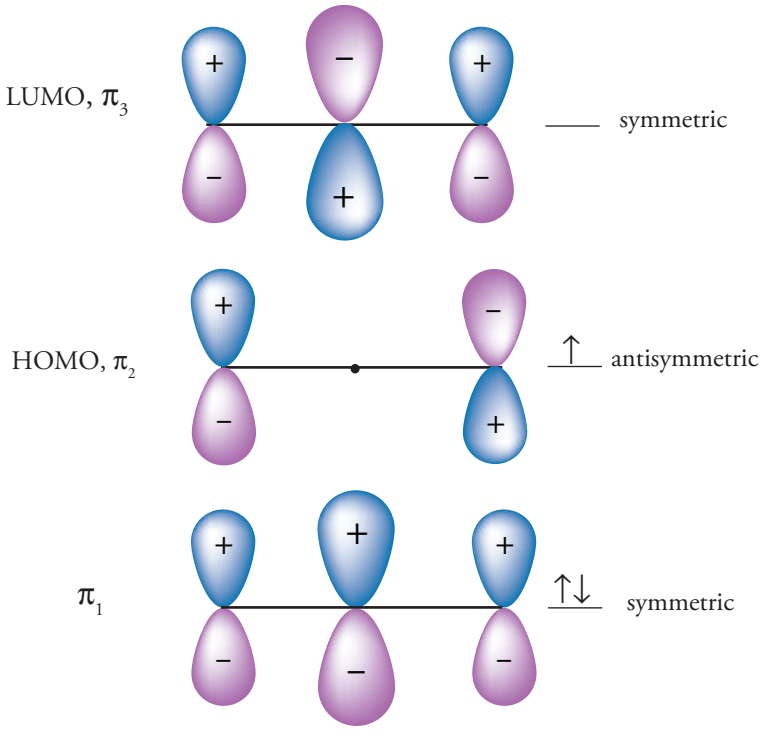


Figure 11.7(a)
Hückel Molecular Orbitals of Allyl Systems
The sizes of the 2p atomic orbitals represent the degree to which the orbitals contribute to the molecular orbitals in the allyl system. The constructive overlap of all three 2p orbitals in the lowest energy molecular orbital is bonding over the whole system. The nonbonding molecular orbital has a nodal plane at the center carbon atom. The electron configuration of the allyl radical is shown.

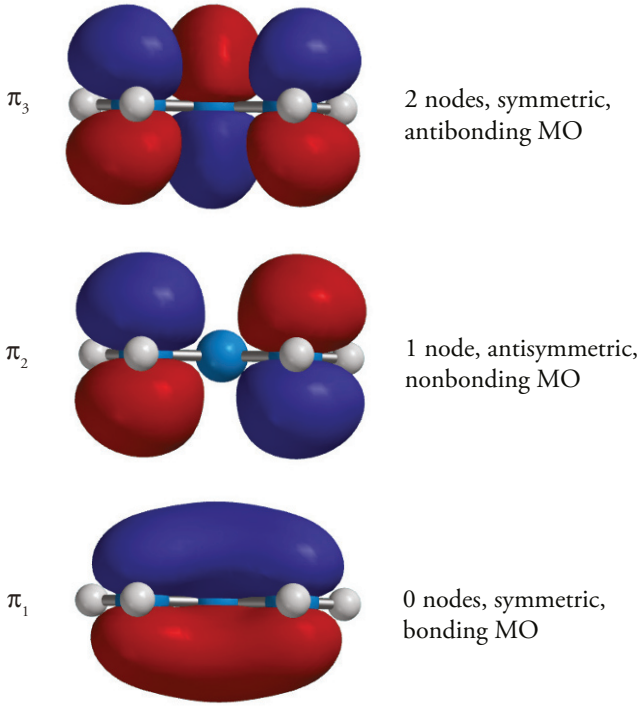
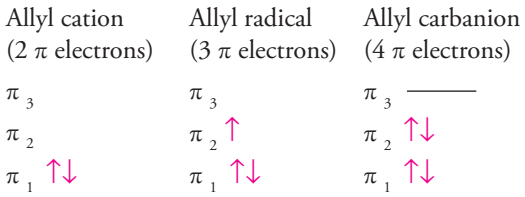


Figure 11.7(b) Molecular Orbitals of Allyl Carbocation
The three molecular orbitals in the allyl carbocation. The bonding orbital, π_1, contains two electrons and the nonbonding orbital, π_2, is empty. The antibonding orbital, π_3, is also empty.

Figure 11.8 Electron Configurations of Allyl Systems
The electrons of the π system occupy the lowest available orbitals.



The allyl radical has the same number of 2p electrons as contributing 2p atomic orbitals, so the radical has no charge. Two 2p electrons are in π_1. The third electron of the radical is located in π_2. When we look at Figure 11.7, we see in that there is a 50% probability of finding an electron at either C-1 or C-3, and *zero* probability of finding an electron at the nodal plane that passes through C-2.

We can determine the electron configuration of the allyl carbanion using the allyl radical as a reference. Adding another electron to the radical gives the anion. The second electron must be paired with the electron already located in the π_2 MO. C-1 and C-3 share the electron pair equally, and each one has a formal charge of –½.

The allyl carbocation has one less electron than the radical. Both electrons of the π system are in π_1, and π_2 is empty. There is a 50% probability of finding a positive charge at either C-1 or C-3, each of which has a formal charge of +½, and zero probability of finding a positive charge at C-2.

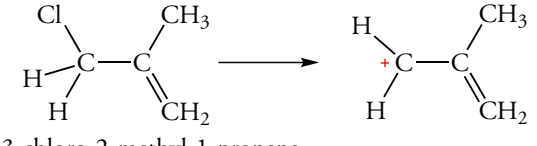
Problem 11.14
Consider the π_3 MO for the pentadienyl radical. How many vertical nodal planes does it have? The unpaired electron must be in π_3. Determine which atoms have radical character.



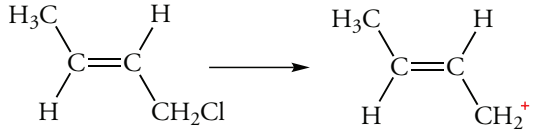
1,3-pentadienyl radical

Problem 11.15
The ionization energies of the carbon-chlorine bond for (E)-1-chloro-2-butene and 3-chloro-2-methyl-1-propene in the gas phase are 672 and 706 kJ $mole^{-1}$, respectively. Using molecular orbital concepts, explain this energy difference based on the stability of the carbocations.

Sample Solution
Both compounds give allyl carbocations. One of the resonance contributors for the carbocation from (E)-1-chloro-2-butene has its positive charge at a secondary carbon atom. In terms of molecular orbital theory, the methyl group is at the "end" of an allyl system, where it affects the stability of the π_2 MO. The two resonance contributors for the carbocation from 3-chloro-2-methyl-1-propene are both primary. In terms of molecular orbital theory, the methyl group is bonded to the "center" carbon of an allyl system. There is a node at the C-2 of the π_2 MO, and the methyl group cannot stabilize the carbocation.



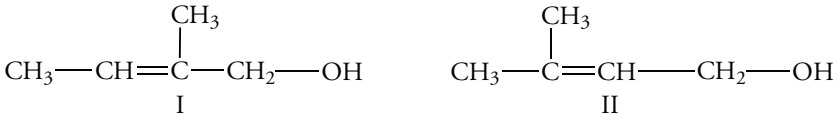
3-chloro-2-methyl-1-propene



(E)-1-chloro-2-butene

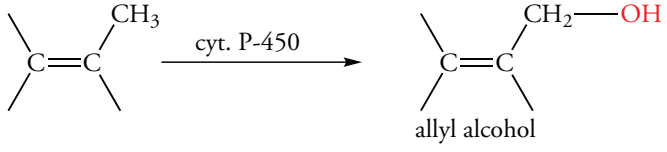
Problem 11.16

Based on molecular orbital theory, which of the following primary alcohols should react faster with HBr in a S_N1 reaction?

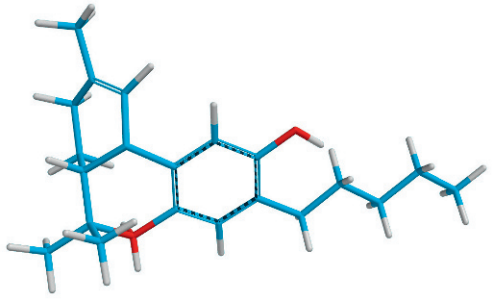


Allylic Oxidation and the Metabolism of Marijuana

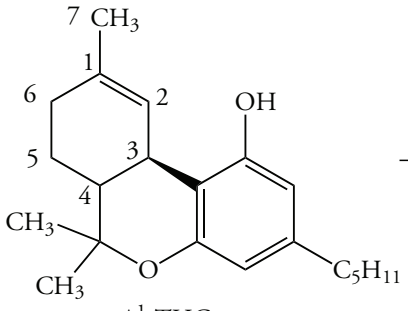
The liver enzyme cytochrome P-450 oxidizes many toxic metabolites and drugs at allylic sites. For example, an allylic oxidation is the first step in the degradation of one of the psychoactive ingredients in marijuana. Although the nature of all steps is not well understood, an allyl radical is a likely intermediate in this process.



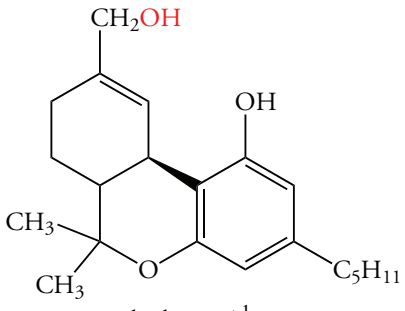
The principle psychoactive component of marijuana contains Δ^1 -tetrahydrocannabinol (Δ^1 - THC), which has three allylic centers. The C-3 and C-6 centers are secondary and the C-7 is primary. Allylic oxidation does not occur at C-3 because of steric hindrance caused by the geminal dimethyl groups. Of the other two possible sites, the C-7 product predominates over the C-6 product even though the C-7 atom is primary. However, the difference in the stabilities of radicals is not as large as the difference in the stabilities of carbocations. Thus, other factors such a steric hindrance could play a role in the regioselectivity of this reaction. The C-7 methyl group is sterically more accessible than the secondary C-6 site. Interestingly, the C-7 product is even more psychoactive than Δ^1-THC.



Δ^1-THC

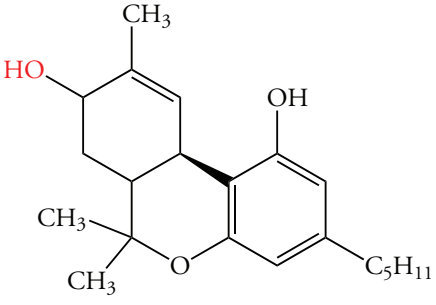


Δ¹-THC



7-hydroxy–Δ¹-THC

+

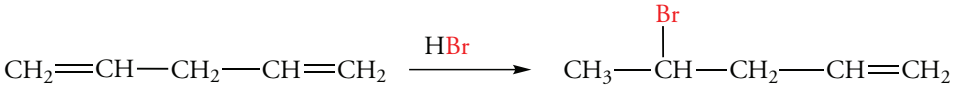


6-hydroxy–Δ¹-THC

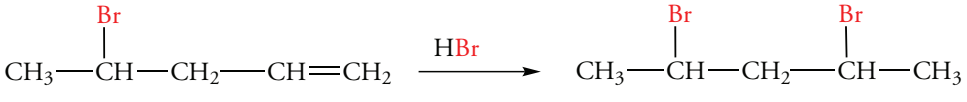
11.7 ELECTROPHILIC ADDITION TO CONJUGATED DIENES

1,2- and 1,4-Electrophilic Addition Reactions

Electrophilic addition reactions to *nonconjugated* alkadienes can occur at one or both double bonds. These reactions occur by **1,2-addition**, and we can use Markovnikov's rule to predict the major products.

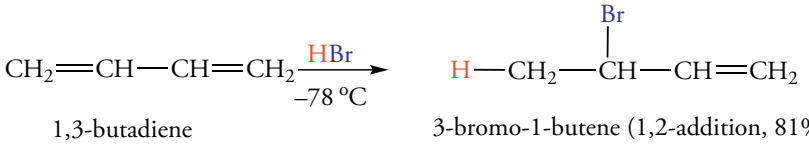


1,4-pentadiene — 4-bromo-1-pentene



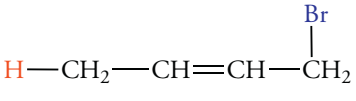
2,4-dibromopentane

The addition of HBr to a conjugated diene is strikingly different. Adding 1M equivalent of HBr at a low temperature yields two products.



1,3-butadiene — 3-bromo-1-butene (1,2-addition, 81%)

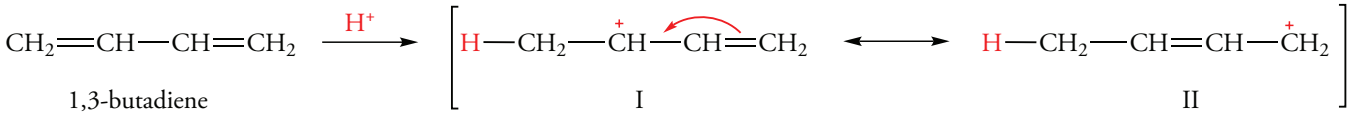
+



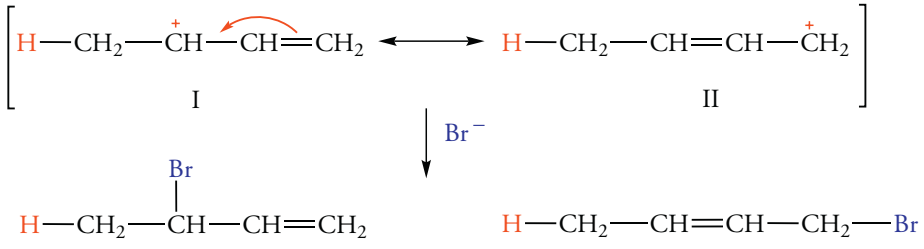
1-bromo-2-butene(1,4-addition, 19%)

The major product, 3-bromo-1-butene, results from electrophilic addition across the C-1 to C-2 double bond. This is a 1,2-addition reaction. The minor product, 1-bromo-2-butene, results from addition of HBr to the C-1 and C-4. This is a **1,4-addition reaction**. Note that the double bond in the product is between C-2 and C-3.

The first step in the reaction is electrophilic addition of a proton to the conjugated diene.



Protonation gives an allylic carbocation, represented by two contributing resonance structures. In the next step, the allylic carbocation reacts with nucleophilic bromide ion at the secondary carbon atom (resonance form I) to give the 1,2-addition product. Bromide ion also reacts at the primary carbon atom (resonance form II) to give the 1,4-addition product.



Kinetic Control of 1,2- and 1,4-Electrophilic Addition Reactions

When HBr adds to 1,3-butadiene at –78 °C, the major reaction product is the one that forms at the faster rate. We say that the process is under **kinetic control**. Kinetically controlled reactions account for the products in most organic reactions. The major product results from the reaction having the lowest energy transition state for the rate-determining step. When HBr reacts with 1,3-butadiene, an allylic carbocation forms in the rate-determining step. This intermediate reacts with bromide anion in a rapid second step (Figure 11.9).

Since the positive charge density at the secondary carbon of the allylic carbocation is greater than at the primary carbon, the nucleophile reacts with C-2 more often than it reacts with C-1. But, the major product is the less substituted and therefore the less stable alkene.

Thermodynamic Control of 1,2- and 1,4-Electrophilic Addition Reactions

Many reactions give an equilibrium mixture of products. In such cases, the product composition reflects the relative stabilities of the products, not their relative rates of formation. Reactions that give equilibrium mixture products are said to be under thermodynamic control.

When the electrophilic addition reaction of HBr to 1,3-butadiene is carried out at 20 °C, the product mixture markedly differs from the product mixture of a reaction carried out at –78 °C. At the higher temperature, the major product results from 1,4-addition.

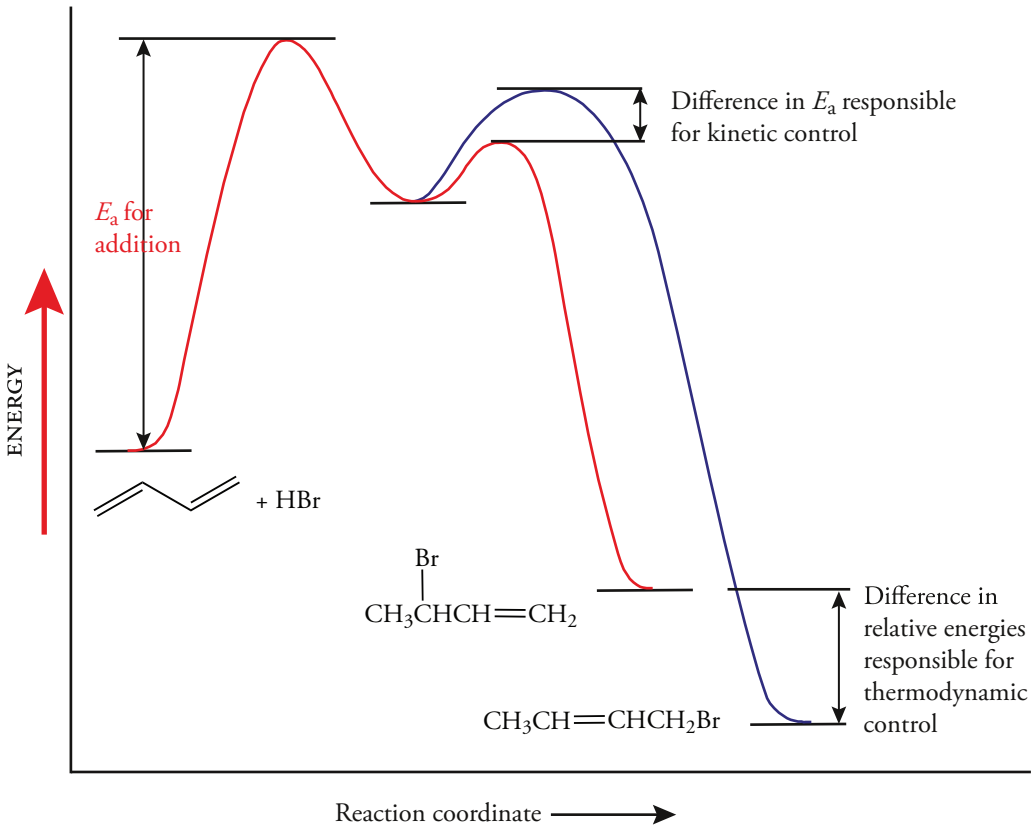


Figure 11.9 Energy Profile for 1,2- and 1,4-Electrophilic Addition Reactions
The energy of the transition state for 1,2-addition of HBr to 1,3-butadiene is lower than the energy of the transition state for 1,4-addition. 1,2-Addition predominates at low temperature because there is not enough energy for the system to reach the transition state for 1,4-addition. This energy difference is responsible for kinetic control of the addition reaction. The 1,4-addition product is more stable than the 1,2-addition product, but it forms more slowly. At higher temperatures, the transition state leading to the more stable product can be attained and leads to 1,4 addition. Thus, at high temperatures, the product composition reflects the relative stabilities of the products, not the relative energies of the transition states leading to them.

$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[20\ ^oC]{HBr} H{-}CH_2{-}\underset{\displaystyle Br}{\underset{|}{CH}}{-}CH{=}CH_2$

1,3-butadiene

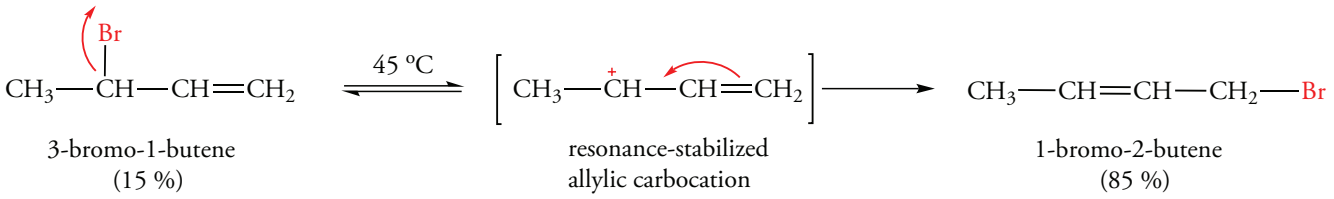
3-bromo-1-butene (1,2-addition, 44%)

+

$H{-}CH_2{-}CH{=}CH{-}CH_2{-}Br$

1-bromo-2-butene(1,4-addition, 56%)

The ratio of products depends on the temperature at which the reaction is carried out. In a separate experiment, when either of the two compounds is heated at 45 °C, an equilibrium mixture with a ratio of 85:15 of 1 -bromo-2-butene to 3 -bromo-1-butene forms.



Even though 3-bromo-1-butene — the product of 1,2-addition— still forms faster, it equilibrates to form the more stable 1-bromo-2-butene. The position of the chemical equilibrium reflects thermodynamic stability, and we know that the disubstituted double bond of 1-bromo-2-butene is more stable than the terminal, monosubstituted double bond in 3-bromo-1-butene. At a higher temperature, the reaction is under thermodynamic control.

Figure 11.9 shows the relative energies of the two transition states leading to 1,2- and 1,4-addition products and the relative energies of these two products. At –78 °C , the energy of the system is too low to ionize the 1,2-addition product, which would form the carbocation intermediate. Thus, the low temperature reaction is irreversible, and the product mixture reflects kinetic control governed by the relative energies of the transition states. At 20 °C, the products ionize to form the allylic carbocation. The less stable 3-bromo-1-butene then reaches equilibrium with the more stable 1-bromo-2-butene.

Problem 11.17

When bromine adds to a conjugated diene, a carbocation forms, not a bromonium ion. (a) Explain why. (b) 1M equivalent of bromine adds to 1,3-butadiene to give a mixture of two products. What are their structures?

Problem 11.18

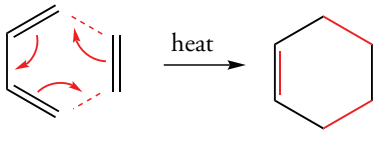
Reaction of 2-methyl-1,3-butadiene with chlorine in water gives a chlorine-containing tertiary alcohol. Draw its structure. Does 1,2- or 1,4-addition occur? What is the electrophile in the reaction?

11.8 THE DIELS–ALDER REACTION

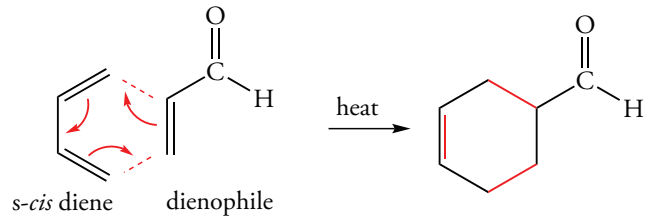
The concepts we have been discussing come into focus in an important reaction in synthetic organic chemistry, the Diels–Alder reaction. In this reaction, a diene with its 4 π electrons reacts with an alkene with its two π electrons to give a cyclohexene ring. Since the product is a ring, it is a **cycloaddition reaction**. Since the 4 π electrons of the diene and the two π electrons of the alkene participate in the reaction. We will discuss the mechanism of this reaction in Chapter 25. In this chapter, we will focus upon its synthetic versatility. The simplest example of a Diels-Alder reaction is the cycloaddition reaction of 1,4-butadiene and ethene to give cyclohexene. In every case, a cyclohexene ring is a product of a Diels–Alder reaction.

The Diels–Alder reaction has three important characteristics.

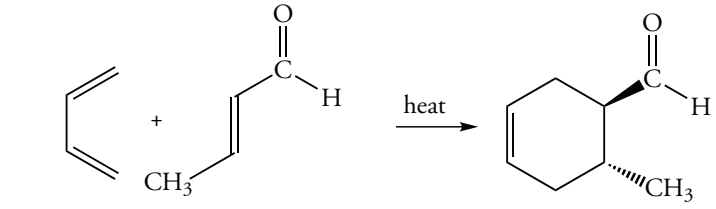
1. It is *concerted*. Thus, there are no intermediates.
2. It is a *thermal reaction*; that is, it is initiated by heat.
3. The transition state for the reaction contains 6 π electrons.

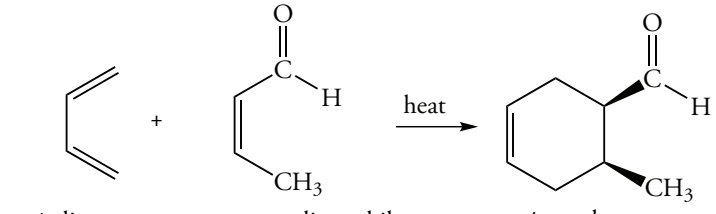


In Section 11.4, we saw that butadiene can exist in either an s-*cis* or an s-*trans* conformation. For open-chain, conjugated dienes, the diene must be in an s-*cis* conformation for the reaction to occur. Reactants that contain conjugated double bonds in a ring, such as cyclopentadiene, react much faster than open-chain conjugated dienes. The alkene that reacts with the diene is called the **dienophile**. Ethene is a poor dienophile, and the reaction is much faster when an electron withdrawing is conjugated to the dienophile.

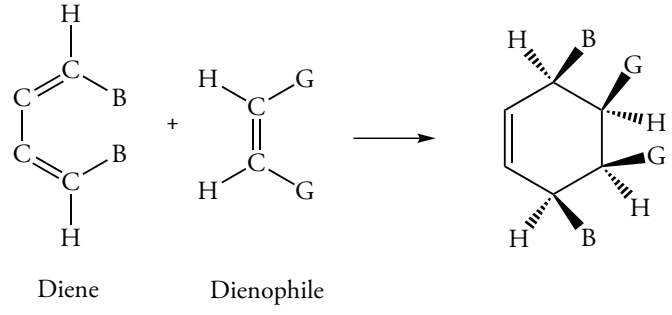


Since the Diels–Alder reaction is concerted, the stereochemistry of the dienophile is retained in the product. The groups that are *trans* in the dienophile are *trans* in the product, and groups that are *cis* in the dienophile are *cis* in the product.

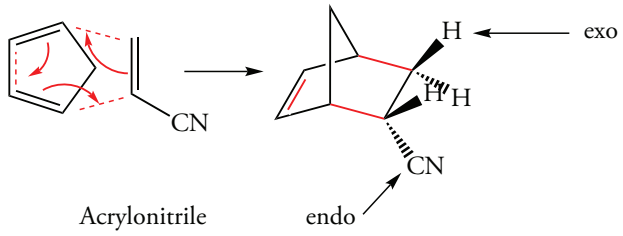




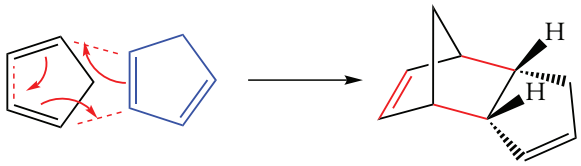
And, since the reaction is concerted, groups that are *trans* in the diene are also *trans* in the product, and groups that are *cis* in the diene are *cis* in the product.



Reactants that contain conjugated double bonds in a ring, such as cyclopentadiene, react much faster than open-chain conjugated dienes. Reactions of a dienophile with a cyclic diene give bicyclic products. The products in bicyclo[2.2.1] ring systems have substituents on the opposite side of one-carbon bridge; that is, they are *endo*.



Cylopentadiene reacts with itself over the course of a few hours in a Diels–Alder reaction. This reaction is reversible, and if the dimer is heated, cyclopentadiene is regenerated.



11.9 THE ELECTROMAGNETIC SPECTRUM

Spectroscopy is a study of the interaction of electromagnetic radiation with molecules. Electromagnetic radiation encompasses X-rays; ultraviolet, visible, and infrared radiation; microwaves, and radio waves. Electromagnetic radiation can be described as a wave that travels at the speed of light (3×10^8 m/sec). Waves are characterized by a wavelength (λ, Greek lambda) and a frequency (ν, Greek nu). The wavelength is the length of one wave cycle, from crest to crest or trough to trough (Figure 11.10). The wavelength is expressed in the metric unit convenient for each type of electromagnetic radiation. The frequency is the number of waves that move past a given point in a unit of time. Frequency is usually expressed in Hertz (Hz). Wavelength and frequency are inversely proportional, and are related by $\lambda = c/\nu$, where c is the speed of light. As the wavelength of electromagnetic radiation increases, its frequency decreases.

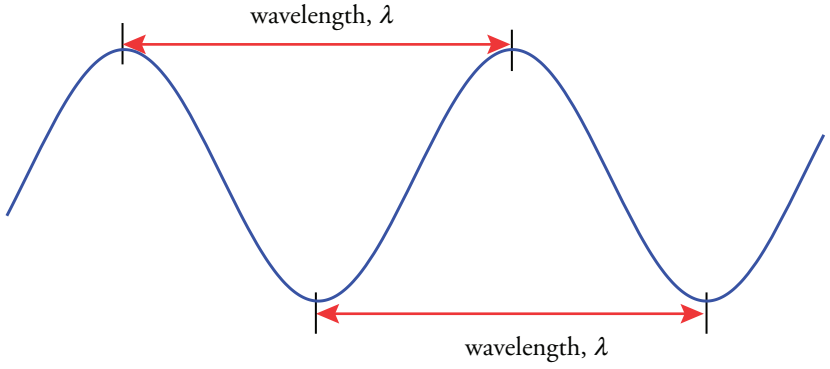


Figure 11.10 Electromagnetic Radiation
The wavelength, λ, of electromagnetic radiation is the distance between any two peaks or troughs of the wave.

The energy, E associated with electromagnetic radiation is quantized. The relationship is given by

$$E = h\nu$$

where h is Planck's constant. The energy of electromagnetic radiation is therefore directly proportional to its frequency. Since wavelength is inversely proportional to frequency, $\lambda = c/\nu$, we can rewrite this as

$$E = \frac{hc}{\lambda}$$

The energy of electromagnetic radiation is also directly proportional to the quantity $1/\lambda$. This quantity is known as the **wavenumber**.

$$E = hc\left(\frac{1}{\lambda}\right)$$

The electromagnetic spectrum spans a range of frequencies and energies extending in frequency from approximately 10^{18} Hz for X-rays to 10^9 Hz for radio waves, and from wavelengths on the order of internuclear separation in molecules (100 pm) for X-rays to centimeters for radio waves. The visible portion of the electromagnetic spectrum spans the range from 400 to 700 nm (Figure 11.11).

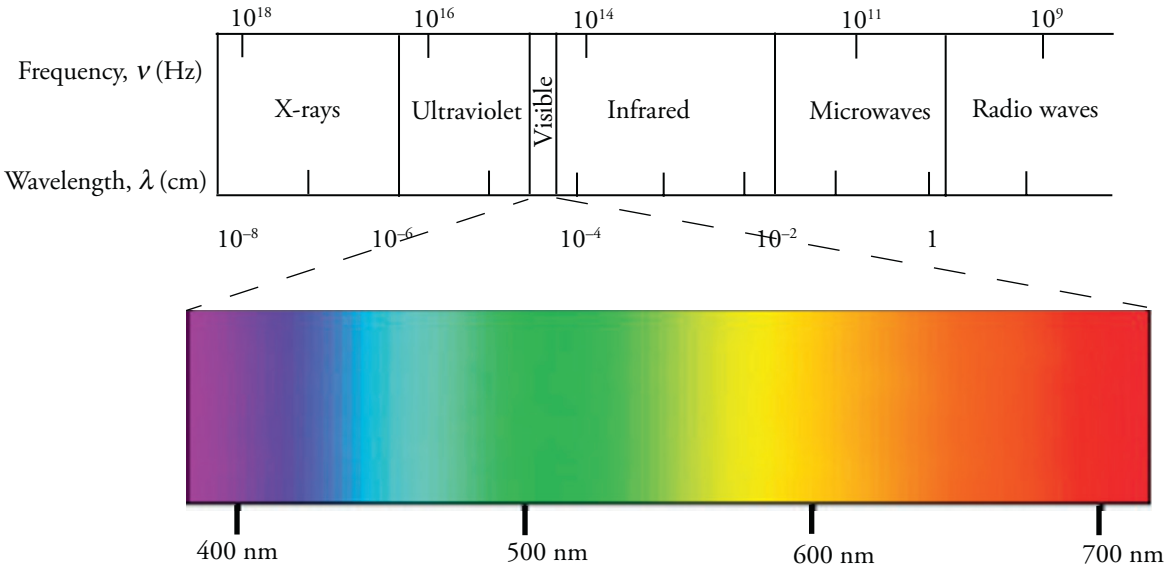


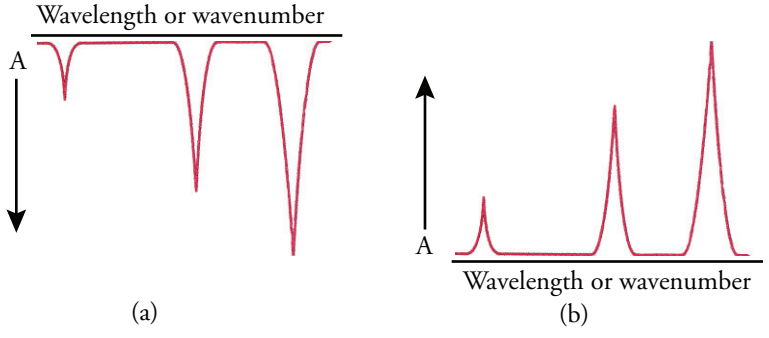
Figure 11.11 Electromagnetic Spectrum

The regions of the spectrum used in organic chemistry. Usually, the wavelength or the reciprocal of the wavelength, the wavenumber, is used to identify absorptions of organic molecules. The visible spectrum is only a tiny sliver of the entire electromagnetic spectrum.

Molecules can absorb only certain discrete amounts of energy. That is, the energy levels of molecules are quantized. To change the energy content of a molecule from E_1 to E_2, the energy difference, $(E_2 - E_1)$, comes from characteristic electromagnetic radiation with a specific frequency (and wavelength). The energy absorbed by the molecule can change its electronic or vibrational energy. For example, ultraviolet radiation causes changes in the electron distribution in π orbitals; infrared radiation causes bonds to stretch and bond angles to bend. We will discuss infrared spectroscopy in Chapter 14.

Figure 11.12 Features of a Spectrum

The portion of the spectrum where no absorption occurs is the base line. This horizontal line may be located at the top or bottom of a graph. Absorption then is recorded as a peak down from the base line. In an infrared spectrum (a), the base line is at top of the spectrum. In an NMR spectrum (b), the base line is at the bottom of the spectrum.



In the various types of spectroscopy, radiation passes from a source through a sample that may or may not absorb certain wavelengths of the radiation. As the wave length is systematically changed, a detector determines which wavelengths of light the sample absorbs. At a wavelength corresponding to the energy $(E_2 - E_1)$ necessary for a molecular change, the molecule absorbs the radiation emitted by the source. The amount of light absorbed by the molecule (absorbance) is plotted as a function of wavelength. At most wavelengths, the amount of radiation detected by the detector equals that emitted by the source because the molecule does not absorb radiation. At such wavelengths, a plot of absorbance on the vertical axis versus wavelength yields a horizontal line (Figure 14.3). When the molecule absorbs radiation of a specific wavelength, the amount of radiation arriving at the detector is less than that emitted by the source. This difference is recorded as an absorbance.

11.10 ULTRAVIOLET–VISIBLE SPECTROSCOPY OF ALKENES AND CONJUGATED SYSTEMS

The ultraviolet region of the electromagnetic spectrum spans wavelengths from 200 to 400 nm. In the ultraviolet region of the electromagnetic spectrum, a molecule with conjugated double bonds absorbs energy. Sigma bonds and isolated carbon-carbon double bonds absorb electromagnetic radiation at shorter wavelengths and higher frequency.

An ultraviolet (UV) spectrum is a plot of the absorbance of light on the vertical axis versus the wavelength of light (in nanometers, nm) on the horizontal axis (Figure 11.13). The wavelength corresponding to the top of the UV "peak" is called the λ_{max}. The absorbance depends on the structure of the compound and the concentration of the sample in the solution. Concentrations in the 10^{-3} to 10^{-5} M range are typically used to obtain a spectrum.

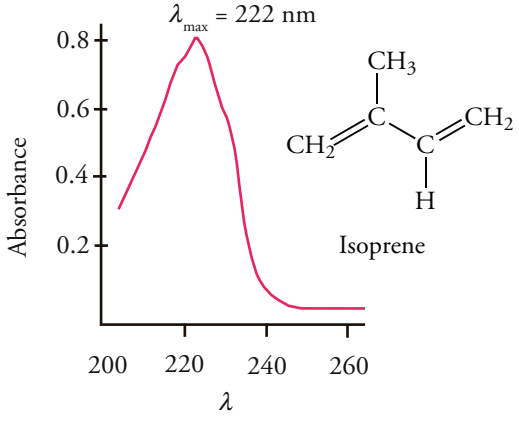


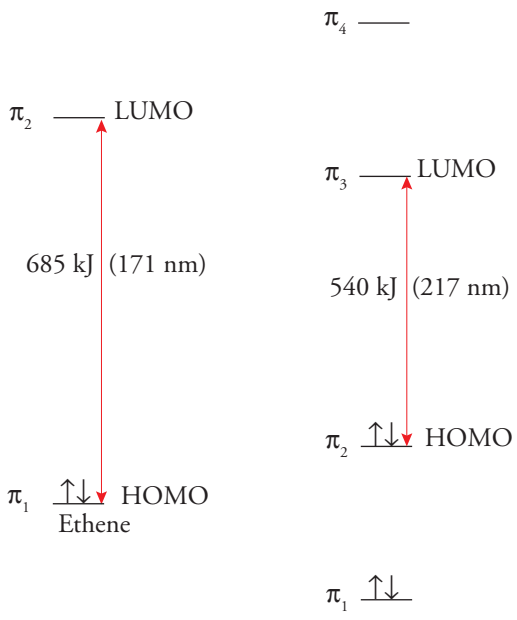
Figure 11.13
UV Spectrum of Isoprene
The ultraviolet spectrum of isoprene dissolved in methanol is representative of the spectra of conjugated dienes. The position of maximum absorption, λ_{max}, occurs at 222 nm.

Molecular Orbitals and Electronic Transitions

The energy absorbed by a double bond in an unsaturated compound moves π electrons in bonding molecular orbitals of the ground state configuration into higher energy, antibonding molecular orbitals of an excited state. The specific wavelength of ultraviolet light required for an electronic transition of π electrons from a ground state to an excited state depends on the difference in energy between the **highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO)**.

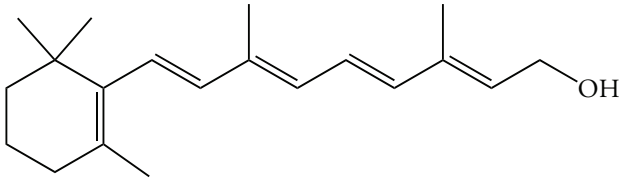
There are two π molecular orbitals in ethene. In the ground state, the bonding electrons are in π_1, the HOMO. An electron is promoted to π_2 the LUMO, when a photon is absorbed whose energy is equal to the difference in energy between these two molecular orbitals. The process is called a $\pi \rightarrow \pi_1^*$ transition (Figure 11.14). As the number of conjugated double bonds increases, the energy gap between the HOMO and the LUMO decreases. Thus, the absorption shifts toward the visible region. Retinol, for example, which has five conjugated double bonds, has a λ_{max} of 325 nm.

Figure 11.14 Molecular Orbitals and Electronic Transitions



Let's consider the effect of conjugation on the energy required for a $\pi \rightarrow \pi_1$ transition. The simplest conjugated diene is 1,3-butadiene. Figure 11.14 compares the energies of the four molecular orbitals of butadiene with the molecular orbitals of ethene. As a result of conjugation, the energy of the lowest energy bonding molecular orbital of 1,3-butadiene, π_1, is more stable than the bonding molecular orbital of ethene. However, the HOMO of butadiene, π_2, is higher in energy than the HOMO of ethene. The LUMO, π_3, of butadiene is also lower in energy than the LUMO of ethene. As a result, the $\pi_2 \rightarrow \pi_3$ transition of butadiene requires less energy than the $\pi \rightarrow \pi_1$ transition for ethene. The $\pi \rightarrow \pi_1$ transition of ethene is beyond the range of conventional ultraviolet spectrometers. The $\pi_2 \rightarrow \pi_3$ transition for butadiene occurs at 217 nm.

As the number of conjugated double bonds increases, the l_{max} shifts more and more toward the visible region of the spectrum. Thus λ_{max} for vitamin A (retinol), which has five conjugated double bonds is 325 nm.



Vitamin A (retinol)

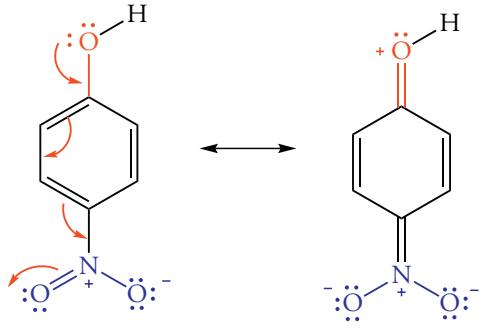
Conjugated Double Bonds and the Colors of Organic Compounds

Compounds that absorb only in the ultraviolet region appear colorless because they do not absorb visible light. A compound appears colored only if absorption occurs in some portion of the visible spectrum. Some naturally occurring compounds with extensively conjugated double bonds absorb at such long wavelengths that the λ_{max} occurs in the visible region (400–800 nm) of the spectrum. β-Carotene, which is present in carrots, absorbs light in the blue-green region of the spectrum at 452 nm. Because it absorbs blue-green light, the light that reaches our eyes is yellow-orange. We see the complement of the absorbed light. The color of a compound therefore provides qualitative information about its λ_{max} (Table 11.1).

Table 11.1
Absorbed Light and Reflected Color

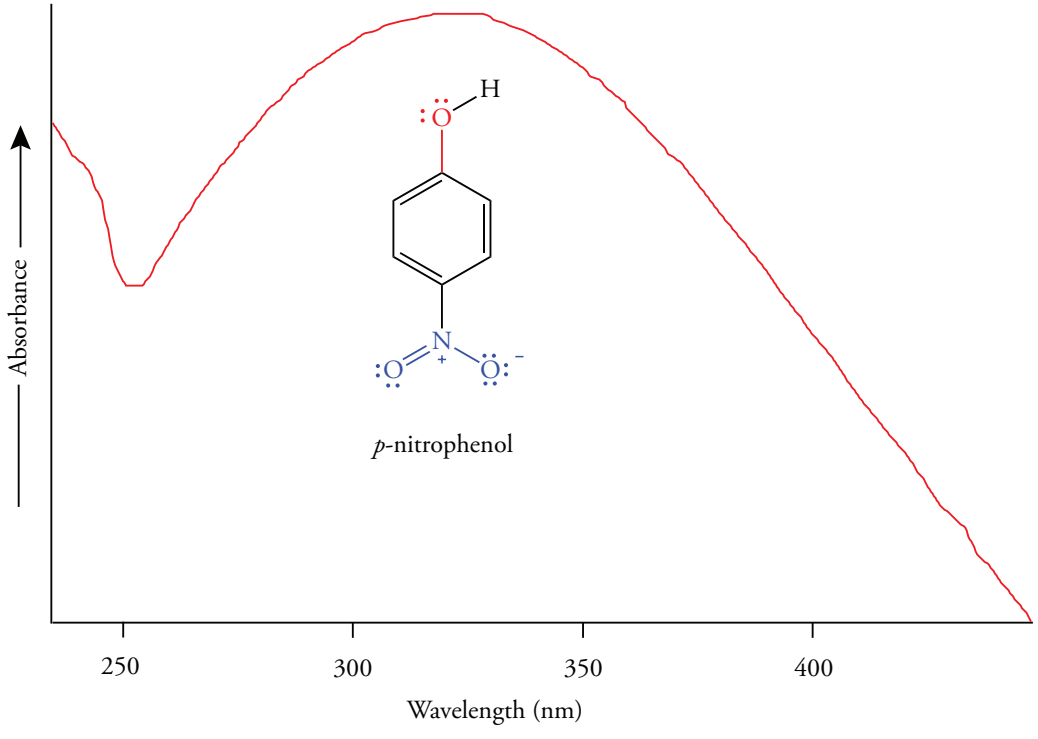
Absorbed Wavelength (nm)	*Reflected Color*
400 (violet)	Yellow-green
450 (blue)	Orange
510 (green)	Purple
590 (orange)	Blue
640 (red)	Blue-green
7300 (purple)	Green

Some kinds of conjugated molecules, such as aromatic compounds, have only ultraviolet absorptions and are colorless. Aromatic compounds may be colored if they have substituents to extend the conjugation. For example, benzene absorbs at 254 nm and is therefore colorless. Phenol and nitrobenzene are also colorless. However, *p*-nitrophenol has a faint yellow color because the two substituents—one electron donating group and an electron withdrawing group—interact to extend the conjugation of the benzene ring (Figure 11.15).



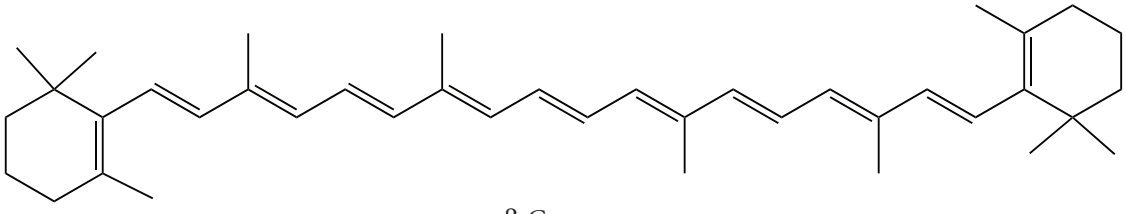
contributing resonance structures of *p*-nitrophenol

Figure 11.15 UV–Visible Spectrum of *p*-Nitrophenol



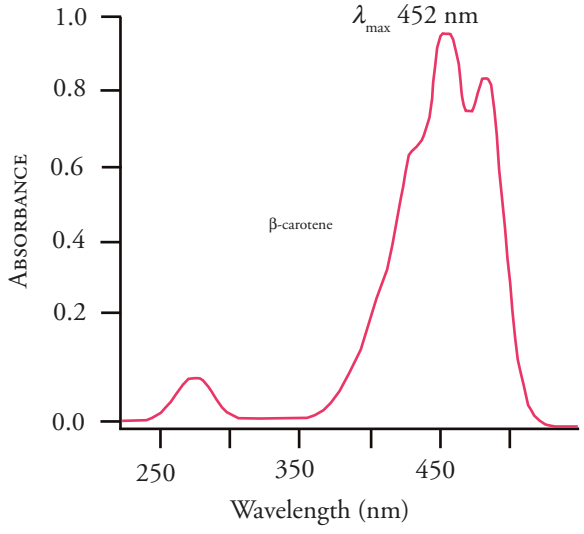
p-nitrophenol

Figure 11.16 shows the spectrum of β-carotene. It has 11 conjugated double bonds, and its λ_{max} has shifted far from the λ_{max} of ethene (171 nm) into the visible region of the spectrum (λ_{max} 252 nm). We are all familiar with its cheerful orange, carrot-color.



β-Carotene

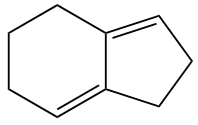
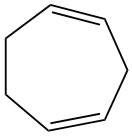
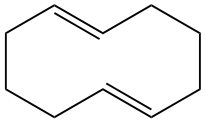
Figure 11.16 Visible Spectrum of β-Carotene

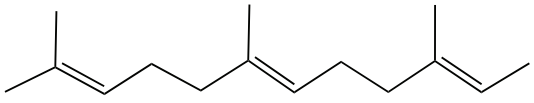


EXERCISES

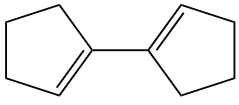
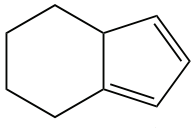
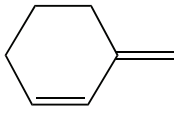
Classes of Polyenes

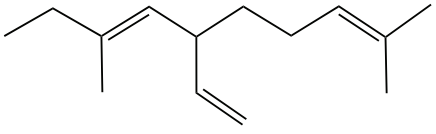
11.1 Which of the following compounds has conjugated double bonds?

(a)  (b)  (c) 

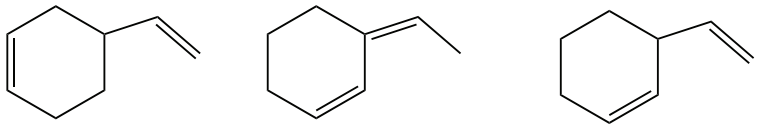
(d) 

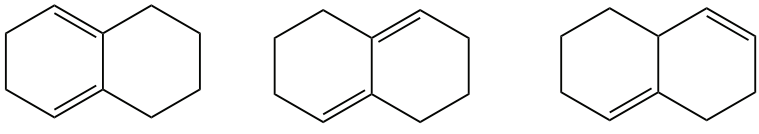
11.2 Which of the following compounds has conjugated double bonds?

(a)  (b)  (c) 

(d) 

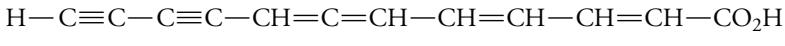
11.3 How many compounds in each of the following sets of isomeric compounds contain conjugated double bonds?

(a) 

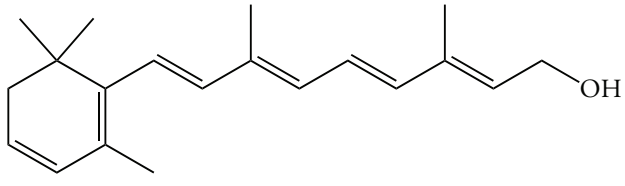
(b) 

11.4 Classify the double bonds in each of the following compounds.

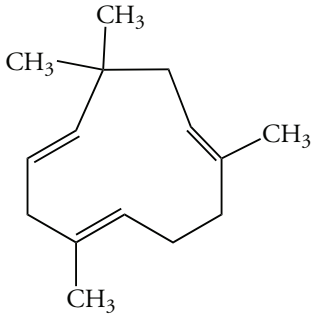
(a) Mycomycin, an antibiotic



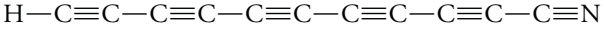
(b) Vitamin A_2, contained in freshwater fish



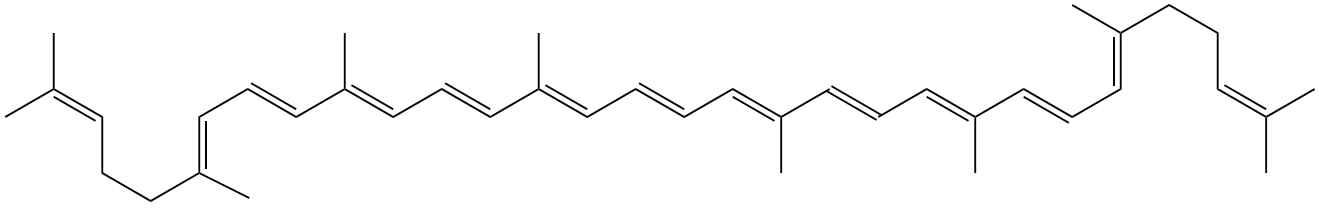
(c) Humulene, a compound found in hops



11.5 Cyanodecapentayne has been identified in intergalactic space by radio astronomers. How many conjugated π bonds are in this compound?



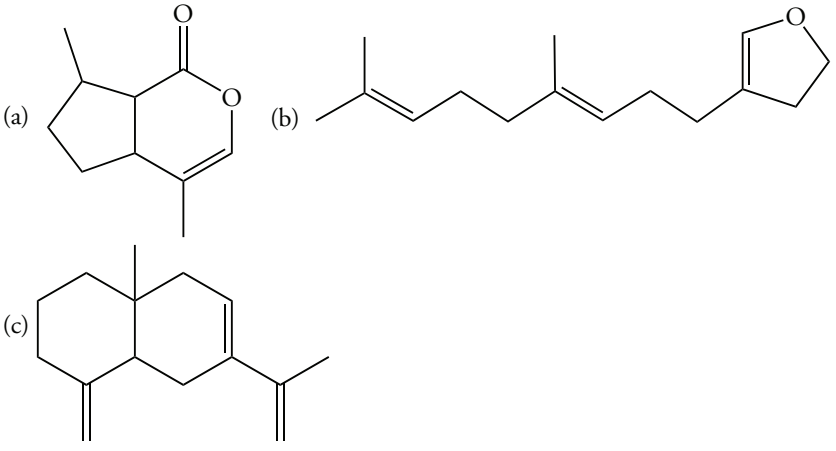
11.6 How many conjugated π bonds are in lycopene, the red pigment in tomatoes?



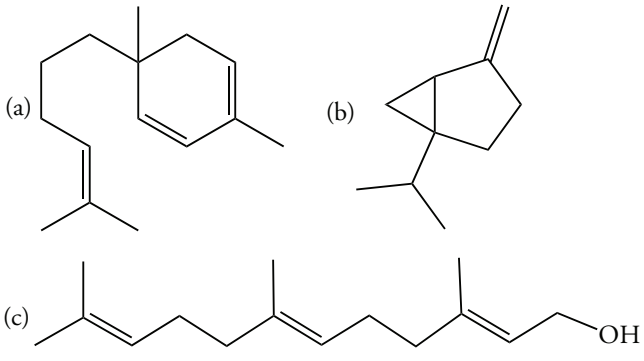
lycopene

Terpenes

11.7 Classify each of the following terpenes and divide it into isoprene units.

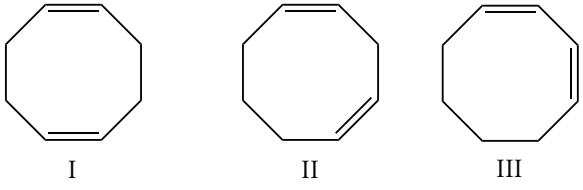


11.8 Classify each of the following terpenes and divide it into isoprene units.



Stability of Polyenes

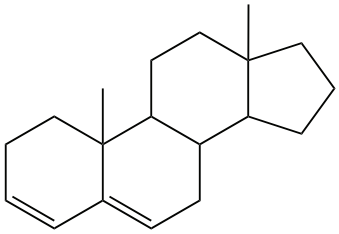
11.9 Which of the following octadienes have the least exothermic heat of hydrogenation?



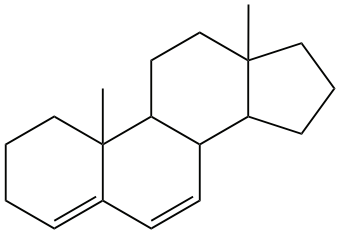
11.10 Estimate the heat of hydrogenation for converting each of the following isomers to hexane.
(a) (E)-1,3-hexadiene (b) (2E,4E)-hexadiene (c) (E)-1,4-hexadiene (d) 1,5-Hexadiene

11.11 In acid solution, 1,4-cyclohexadiene isomerizes to a mixture containing 1,3-cyclohexadiene. (a) Write a mechanism to account for this rearrangement. (b) Which of the two isomers should form the major component of the equilibrium mixture?

11.12 Compare the relative stabilities of the following two dienes. If no competing reactions occur, indicate how the two compounds could be equilibrated using an acid catalyst.



I



II

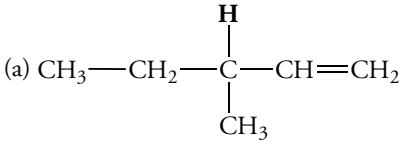
Molecular Orbitals of Polyenes

11.13 Which of the bonding molecular orbitals of 1,3,5,7-octatetraene resembles the Lewis structure for this compound?

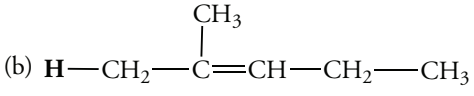
11.14 Determine the symmetry of each molecular orbital of 1,3-butadiene and suggest another guideline that could be added to your list of ways to compare the energies of molecular orbitals.

Allylic Systems

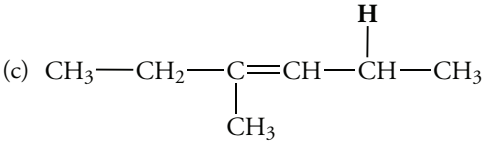
11.15 Write contributing resonance forms for the radical formed by abstraction of the bold hydrogen atom in each structure.



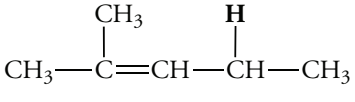
(a)



(b)

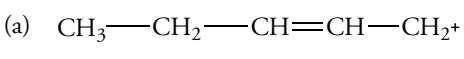


(c)

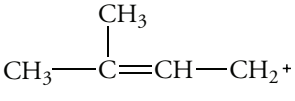


(d)

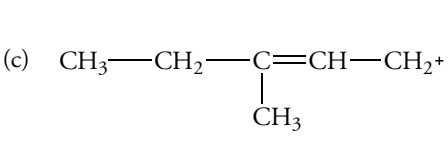
11.16 Write alternate resonance forms for each of the following ions.



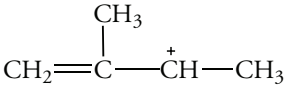
(a)



(b)



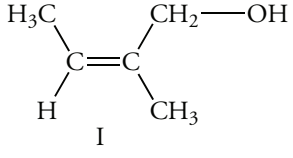
(c)



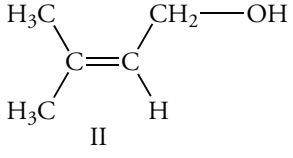
(d)

11.17 The rate of reaction of 1-chloro-3-methyl-2-butene in ethanol to give substitution products is about 6×10^3 times faster than the rate for allyl chloride. Explain why.

11.18 Which of the following two compounds would react faster with HCl to produce an alkyl halide?

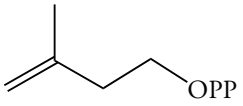


I

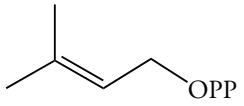


II

11.19 3-Isopentenyl pyrophosphate and 2-isopentenyl pyrophosphate are intermediates in the biosynthesis of terpenes. The pyrophosphate ion is a good leaving group. One of the two compounds reacts more readily to form a carbocation than the other. Which one and why?



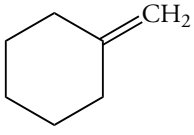
3-isopentenyl pyrophosphate



2-isopentenyl pyrophosphate

11.20 Write the structure of the major substitution product expected from the reaction of 1-methyl-3-cyclohexen-1-ol with HBr.

11.21 Write the structures of the compounds expected for the allylic bromination of methenecyclohexane using 1M equivalent of NBS.



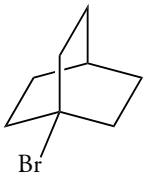
methylenecyclohexane

11.22 The reaction of NBS with 1-octene gives the following products in the indicated yields. Account for each of these products. Explain why the indicated yields are "expected".
(E)-l-bromo-2-octene 44% (Z)-l-bromo-2-octene 39% 3 -bromo-1-octene 17%

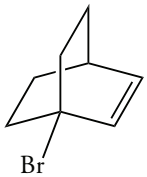
11.23 Alkenes can be chlorinated at the allylic position by *tert*-butyl hypochlorite, $(CH_3)_3C—O—Cl$, which undergoes homolytic cleavage to give the *tert*-butoxy radical and a chlorine atom. Reaction of (E)-4,4-dimethyl-2-pentene with this compound gives two C_3H_9Cl products in the ratio 93:7. What are the structures of these two products?

11.24 Which compound should undergo allylic bromination at the faster rate, 1,3-pentadiene or 1,4-pentadiene? How would the composition of the product mixtures be compared?

11.25 The C—Br bond dissociation energies of the following two compounds are essentially equal. Explain why the allylic compound does not have a lower bond dissociation energy.



I



II

Molecular Orbitals of Allylic Systems

11.26 The highest energy π electrons of the pentadienyl anion are in the π_3 molecular orbital. Draw this orbital, and predict the location of the negative charge for the ion.

$CH_2{=}CH—CH{=}CH—CH_2^-$

pentadienyl anion

11.27 Reaction of the pentadienyl cation with a nucleophile occurs by interaction with an empty molecular orbital. Which orbital? On the basis of this analysis, predict the carbon atoms at which the nucleophile will bond. Is this prediction consistent with the products predicted by writing conventional Lewis resonance forms for the cation?

$CH_2{=}CH—CH{=}CH—CH_2^+$

pentadienyl cation

Conjugate Addition Reactions

11.28 Explain why only one product forms in the addition of 1M equivalent of HBr to 1,3-cyclohexadiene.

11.29 Write the structure of the products formed in the addition of one molar equivalent of DBr to 1,3-cyclohexadiene, indicating the location of the deuterium.

11.30 Explain why the extent of 1,2- versus 1,4-addition cannot be determined for the reaction of 1,3-pentadiene with 1M equivalent of HCl.

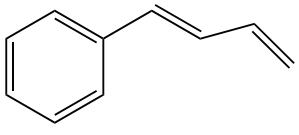
11.31 Write the structures of the products of the addition of one molar equivalent of DCl to 1,3-pentadiene. Can one determine the amounts of 1,2- and 1,4-addition reactions?

11.32 1,3,5-Hexatriene reacts with 1M equivalent of bromine to give only 1,2- and 1,6-addition products. Write the structures of these products. Why there is no 1,4-addition product?

11.33 Reaction of 1,3-butadiene with 1M equivalent of bromine at –15 °C gives a 60:40 mixture of two products. At 60 °C, the product ratio is 10:90. Write the structures of the two products. Explain why different product ratios are observed at the two temperatures.

11.34 Reaction of 2,3-dimethyl-1,3-butadiene with 1M equivalent of HBr gives only one product. Write its structure and explain why this product is favored.

11.35 Reaction of 1-phenyl-1,3-butadiene with 1M equivalent of Cl_2 gives only one product. Write its structure and explain why this product is favored.



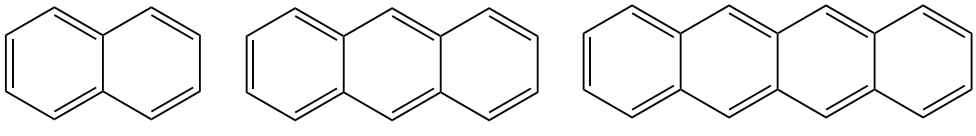
1-phenyl-1,3-butadiene

11.36 Write the structures of the products from the reaction of 1,3-butadiene with an aqueous bromine solution.

11.37 A single chloro alcohol forms in the reaction of 2-methyl-1,3-butadiene with an aqueous chlorine solution. (a) Write its structure (b) Explain why this product is favored.

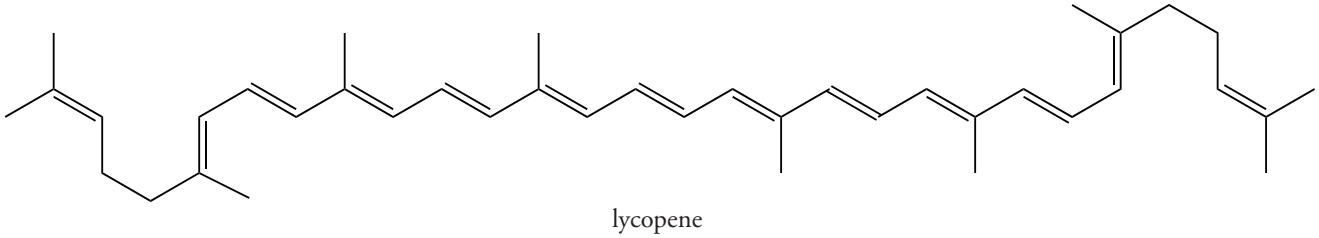
UV Spectroscopy

11.38 The λ_{max} values of naphthalene, anthracene, and tetracene are 314, 380, and 480 nm, respectively. Suggest a reason for this order of the wavelength of maximum absorption. Are any of the compounds colored?

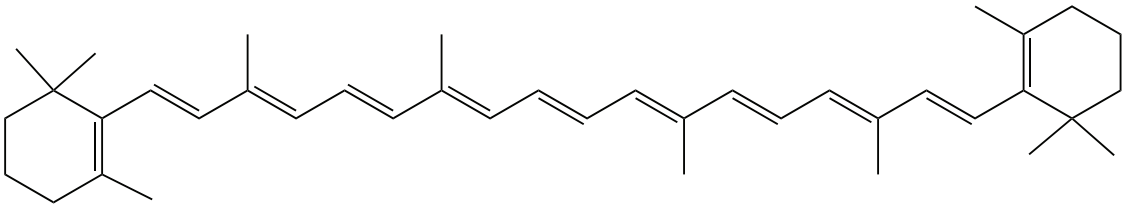


naphthalene anthracene tetracene

11.39 How many conjugated double bonds are contained in lycopene? Compare the conjugation in this compound to that of β-carotene. Using this information, predict the color of lycopene.



lycopene

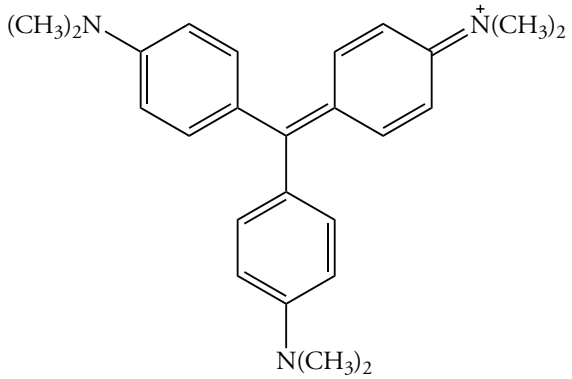


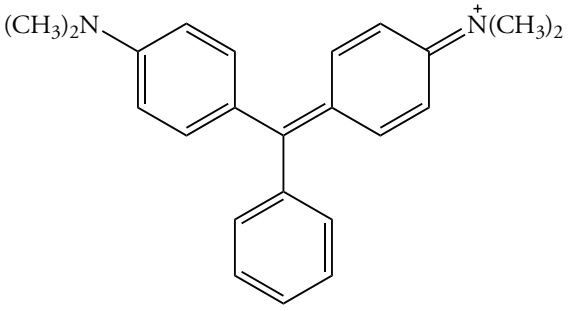
β-carotene

11.40 How might 2,4-hexadiyne be distinguished from 2,5-hexadiyne by ultraviolet spectroscopy?

11.41 The λ_{max} values of 2,4,6-octatriyne and 2,4,6,8-decatetrayne are 207 and 234 nm, respectively. Explain why these values differ.

11.42 Each of the following compounds is an indicator. At pH 7, one appears violet and the other blue-green. Assign each color to the proper indicator.



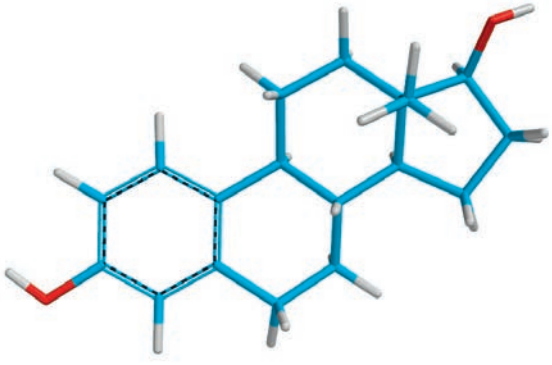


11.43 The λ_{max} of phenol is 210 nm in ethanol. Explain why adding sodium hydroxide to the solution shifts this absorption to 235 nm.

11.44 The λ_{max} values of benzene and *p*-methylaniline (*p*-toluidine) are 204 and 235 nm, respectively. However, when HCl is added, the λ_{max} of benzene is unchanged, whereas the l_{max} of methylaniline changes to 207 nm. Explain the difference in the λ_{max} values for the two compounds and the effect of acid on the spectrum.

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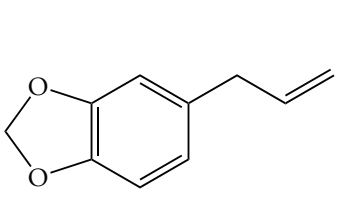
12 Arenes and Aromaticity



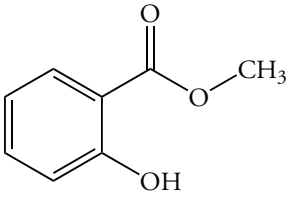
ESTRADIOL

12.1 AROMATIC COMPOUNDS

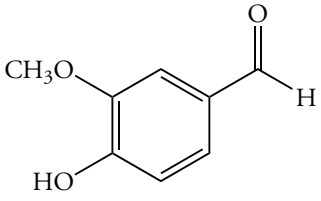
Early chemists used the term "aromatic compounds" to describe substances with a pleasing aroma. It turned out that many of these fragrant compounds contain a benzene ring bonded to one or more substituents. Oil of sassafras, oil of wintergreen, and vanillin are examples.



safrole
(oil of sassafras)

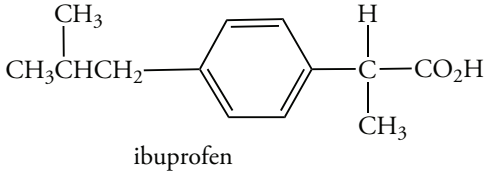


methyl salicylate
(oil of wintergreen)

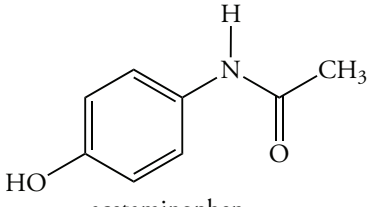


vanillin
(vanilla)

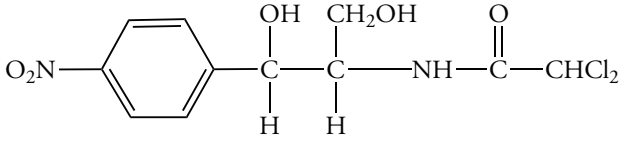
The term aromatic as used by chemists now includes all compounds with at least one benzene ring. Most aromatic compounds do not have pleasing aromas. Some are solids with little or no odor. Solid aromatic compounds include the pain relievers, or analgesics, aspirin, ibuprofen, and acetaminophen, and the antibiotic chloramphenicol.



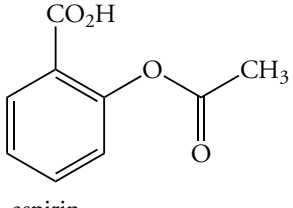
ibuprofen



acetaminophen



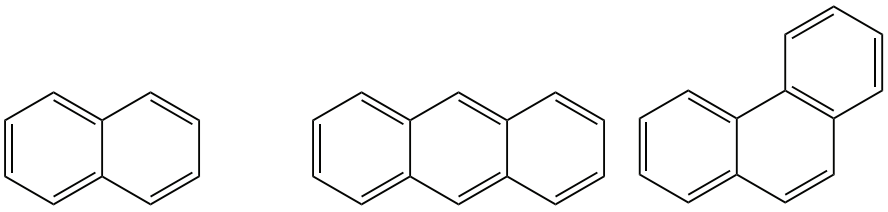
chloramphenicol



aspirin

Substituted benzene compounds belong to a class of conjugated compounds called **arenes**. Examples include benzene, naphthalene, anthracene, and phenanthrene. The common structural feature of arenes is a monocyclic or polycyclic system of π electrons that results in a special stability called **aromaticity**. As a result, aromatic compounds are much less reactive in electrophilic addition reactions than we would expect based on the reactivity of polyenes.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00012-7
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naphthalene anthracene phenanthrene

12.2 THE COVALENT STRUCTURE OF BENZENE

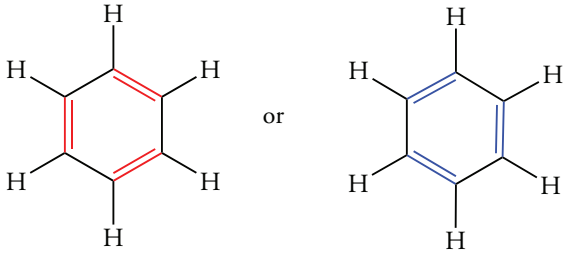
We will often show the structure of benzene as a Lewis structure with a hexagon that contains three "double bonds." However, the double bonds in the Lewis structure are misleading because the chemistry of benzene does not in the least resemble a "triene." For example, benzene does not react with bromine, HBr, or aqueous acid, and does not react with the powerful oxidizing agent potassium permanganate. In short, benzene is remarkably unreactive.

The low reactivity of benzene contradicts what we know about unsaturated compounds. Benzene does not react with most reagents that attack π bonds to form addition products. That is, it does not behave like "1,3,5-cyclohexatriene." Benzene does react with bromine to give a substitution product in which a bromine atom replaces a hydrogen atom, but the reaction requires iron(III) bromide as a catalyst. Only one compound forms, C_6H_5Br.

$$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$$

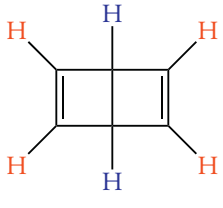
In 1865, a German chemist, F. August Kekulé, suggested that the structure of benzene is a single ring of six carbon atoms linked by alternating single and double bonds. He further proposed that the single bonds rapidly oscillate, so that the single bonds become double bonds and vice versa. Kekulé based his structure on two facts:

1. Converting benzene to bromobenzene gives only one product. Therefore, all six positions of the ring must be equivalent.
2. Converting benzene to dibromobenzene gives three isomers.



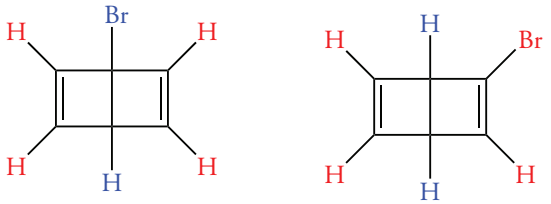
Although it might seem "obvious" to us today that benzene consists of a single ring with six identical carbon atoms and therefore six identical hydrogen atoms, this was by no means obvious to chemists at the time Kekulé made his original proposal.

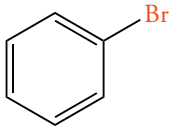
Consider a bicyclic structure for benzene. If a hydrogen atom is replaced by bromine, how many monobromo derivatives are possible?



Hypothetical bicyclic benzene structure with nonequivalent secondary and tertiary hydrogen atoms

There are two sets of equivalent hydrogen atoms: those located at the two equivalent tertiary carbon atoms and those located at the four equivalent vinyl carbon atoms. Thus, two monobromo derivatives would result from replacing a hydrogen atom at either of these two sites. However, only one monobromobenzene exists. Therefore, the bicyclic structure for benzene cannot be correct.

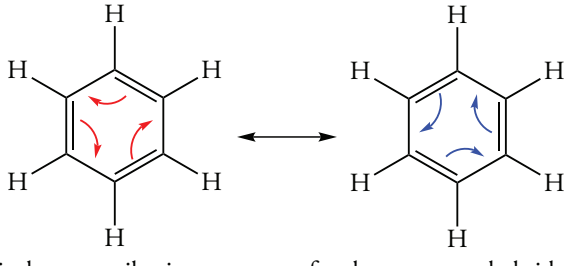




Only one bromobenzene isomer exists. Therefore, all six hydrogen atoms in benzene must be equivalent

Resonance Theory and Benzene

Kekulé reasoned that the rapid oscillation of single and double bonds around the ring makes all six carbon atoms, and therefore all six hydrogen atoms, equivalent. Now we instantly recognize that the two Kekulé structures, which differ only in the positions shown for double bonds, are Lewis resonance structures. Because the two resonance structures are identical, they contribute equally to the resonance hybrid of benzene. Kekule's proposal was nearly correct. Modern measurements show that benzene is a planar molecule in which all carbon-carbon bonds are equivalent. The carbon-carbon bond length, 140 pm, lies between those of a single bond, 154 pm, and a double bond, 133 pm. The carbon-carbon-carbon bond angles of the ring are all 120°. Each carbon atom in benzene is sp^2 hybridized. The carbon atoms link by σ bonds in which the carbon atom shares one electron in each of its σ bonds. Two σ bonds link adjacent carbon atoms. The third links to a hydrogen atom. Each sp^2-hybridized carbon atom has an electron in a 2p orbital perpendicular to the plane of the benzene ring (Figure 12.1). The six 2p orbitals of benzene overlap to share electrons in a six-π-electron system that extends over the entire ring. These electrons are located both above and below the plane of the ring. The delocalization of the electrons over all carbon atoms of benzene accounts for its unique chemical stability.

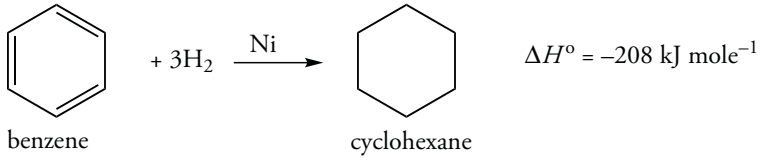


equivalent contributing structures for the resonance hybrid of benzene

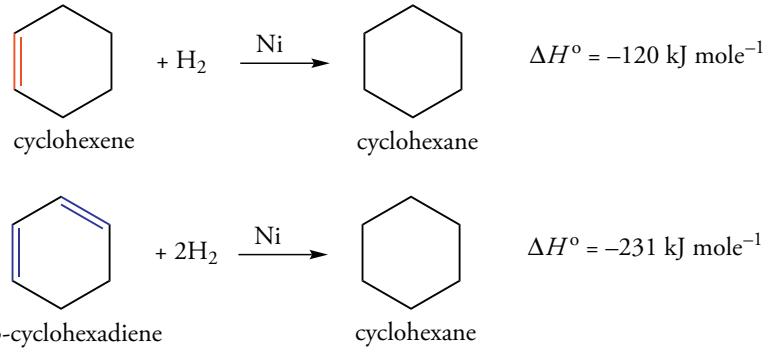
Kekulé reasoned that the rapid oscillation of single and double bonds around the ring makes all six carbon atoms, and therefore all six hydrogen atoms, equivalent. Because the two resonance structures are identical, they contribute equally to the resonance hybrid of benzene. *The bonds do not rapidly oscillate around the ring.*

Resonance Energy

In the preceding chapter, we saw that we can determine the relative stabilities of isomeric alkenes by comparing their heats of hydrogenation ($\Delta H°_{hydrogenation}$) when the hydrogenation reaction yields the same product. We will use the same strategy to estimate the resonance energy of benzene based on its heat of hydrogenation. The stability of benzene compared to the hypothetical 1,3,5-cyclohexatriene is called the **resonance energy** of benzene. Hydrogenating benzene is much more difficult than hydrogenating alkenes or acyclic polyenes. This lack of reactivity is yet another example of the unusual stability of benzene. Conversion of benzene to cyclohexane requires a catalyst such as nickel, 100 atm pressure of hydrogen gas, and a temperature of 200°C. The $\Delta H°_{hydrogenation}$ for the conversion of benzene to cyclohexane is –208 kJ mole^{-1}. First, we estimate the heat of hydrogenation as if there was no resonance stabilization. Without resonance, we would expect the heat of hydrogenation of benzene to be three times that of a double bond in cyclohexene. We can approximate the heat of hydrogenation of a hypothetical "1,3,5-cyclohexatriene" by using the heats of hydrogenation of cyclohexene, 120 kJ mole^{-1}, and 1,3-cyclohexadiene, 231 kJ mole^{-1}, as model compounds.



To calculate the resonance energy of benzene based on its heat of hydrogenation, we first estimate the heat of hydrogenation without resonance. The heats of hydrogenation of alkenes are about 125 kJ mole^{-1}. Without resonance, we would expect the heat of hydrogenation of benzene to be three times that of a double bond. The experimental value for the resonance stabilized molecule is much less. The heat of hydrogenation of a hypothetical "1,3,5-cyclohexatriene" can be approximated using cyclohexene, 120 kJ mole^{-1}, and 1,3-cyclohexadiene, 231 kJ mole^{-1} as model compounds.



We recall that conjugated dienes are resonance stabilized. This stabilization is reflected in the heat of hydrogenation of 1,3-cyclohexadiene, which is slightly less than twice the heat of hydrogenation of cyclohexene. The added stability due to conjugation in 1,3-cyclohexadiene is only 9 kJ mole^{-1}.

1,3 Cyclohexadiene resonance energy = 2(120 kJ mole^{-1}) – (231 kJ mole^{-1}) = 9 kJ mole^{-1}

Similarly, we can calculate the resonance energy of benzene based on the predicted heat of hydrogenation of the hypothetical 1,3,5-cyclohexatriene. Without any interaction between the three double bonds, we would predict a heat of hydrogenation equal to three times the heat of hydrogenation of cyclohexene. Rather than 360 kJ mole^{-1}, only 208 kJ mole^{-1} is released. We conclude that benzene is more stable than 1,3,5-cyclohexatriene by 152 kJ mole^{-1}.

resonance energy = 3(120 kJ mole^{-1}) – (208 mole^{-1}) = 152 kJ mole^{-1}

Figure 12.1 illustrates the resonance stabilization of benzene based on heat of hydrogenation data.

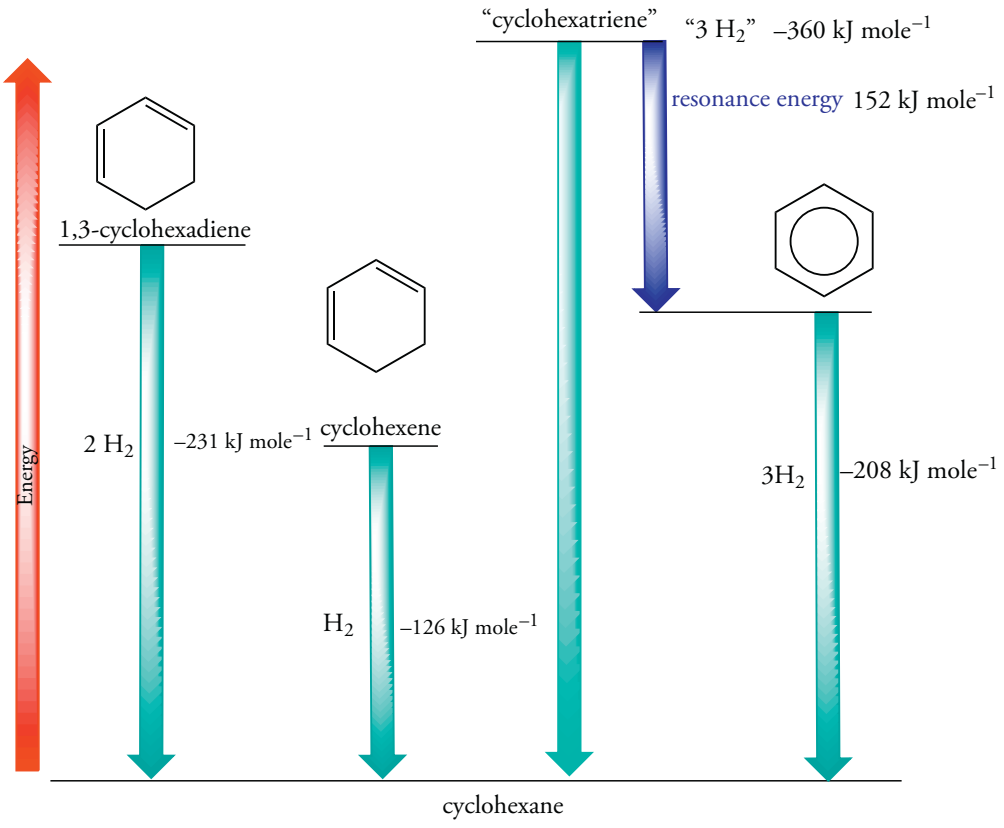


Figure 12.1 Heats of Hydrogenation and the Resonance Stabilization of Benzene
The relative energies of cyclohexene, 1,3-cyclohexadiene, "1,3,5-cyclohexatriene," and benzene and their heats of hydrogenation to form cyclohexane in kJ mole^{-1}.

12.3 THE HÜCKEL RULE

What is responsible for the unusual stability and unique reactivity of benzene?

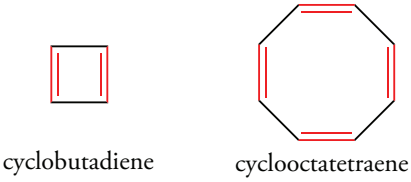
1. To be aromatic, a molecule must be *cyclic*.
2. The molecule must be *planar*.
3. The ring must contain only sp^2-hybridized atoms that can form a delocalized system of π molecular orbitals.
4. *The number of π electrons in the delocalized π system must equal 4n + 2, where n is an integer.*

The "4n + 2 rule" was proposed by Erich Hückel and is known as the **Hückel rule**. The Hückel rule predicts that cyclic π systems having 2 (n = 0), 6 (n = 1), 10 (n = 2), and 14 (n = 3) π electrons will be unusually stable; that is, they will be aromatic.

Benzene meets the criteria for aromaticity, with six π electrons distributed over a six-atom system. We will discuss other examples for various 6, 10, and 14 π electron systems in succeeding sections. We will also see that aromatic compounds with 4n + 2 π electrons need not have 4n + 2 carbon atoms. Furthermore, aromatic compounds can have atoms other than carbon in the ring. They are **heterocyclic** aromatic compounds.

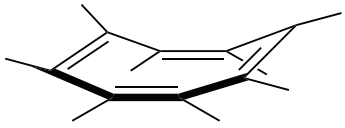
Nonaromatic and Antiaromatic Cyclic Polyenes

Some cyclic conjugated polyenes do not satisfy the Hückel rule and are not aromatic. Two examples are cyclobutadiene and cyclooctatetraene. Both are cyclic polyenes with alternating single and double bonds, but neither is aromatic.



cyclobutadiene cyclooctatetraene

We do not need to look far to find the explanation. The four π electrons of cyclobutadiene do not satisfy the Hückel rule. Cyclobutadiene is extremely unstable and has been isolated only at very low temperature. Its fleeting existence also has been inferred from the products of its reactions. Cyclooctatetraene has eight π electrons. This number that does not satisfy Hückel rule either. Cyclic polyene that have $4n$ π electrons, where n is an integer, are unusually unstable; they are **antiaromatic**.

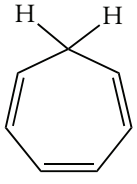


tub conformation of
cyclooctatetraene

Cyclooctatetraene, which has eight π electrons, seems to fit the category of antiaromatic polyenes since it has $4n$ π electrons ($n = 2$). Nevertheless, cyclooctatetraene is a stable molecule, and reacts like an alkene. For example, it undergoes addition reactions with bromine and is easily hydrogenated. Cyclooctatetraene is not planar. It is not antiaromatic because it exists in a "tub" conformation, so its π orbitals cannot overlap to form a continuous π system, which for 8π electrons would be very unstable. Therefore, cyclooctatetraene does not exhibit the general characteristics of either aromatic or antiaromatic compounds. It is **nonaromatic**.

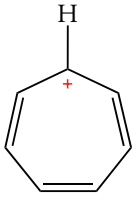
Aromatic Ions

An aromatic ion has $4n + 2$ π electrons in a ring in which every ring atom is sp^2 hybridized and therefore contains a 2p orbital. Let's consider 1,3,5-cycloheptatriene, a conjugated triene.



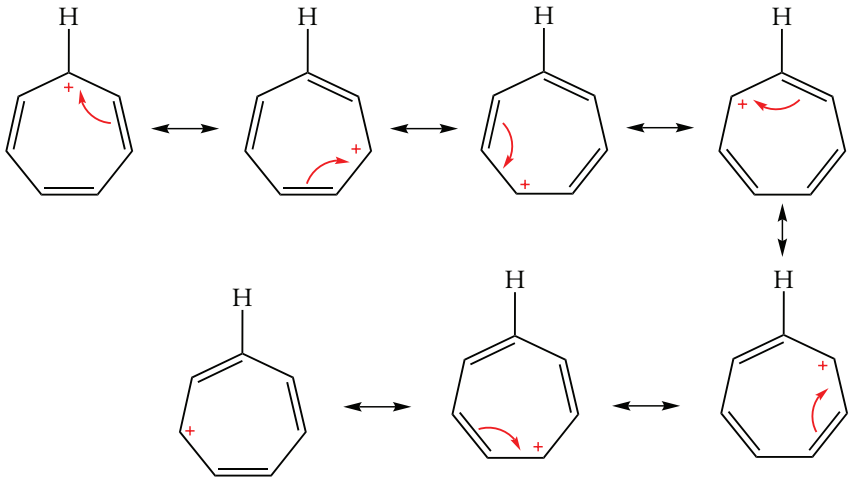
1,3,5-cycloheptatriene

1,3,5-Cycloheptatriene molecule does not have the special stability associated with aromatic compounds because the ring contains an sp^3-hybridized carbon atom. It has a conjugated π system, but the sp^3-hybridized carbon prevents π system from being continuous around the ring. Therefore, delocalization of electrons over all seven carbon atoms is not possible. 1,3,5-Cycloheptatriene is easily hydrogenated. It is also rapidly attacked by electrophilic reagents. So in this respect, it acts like a noncyclic triene such as 1,3,5-heptatriene. However, when 1,3,5-cycloheptatriene is treated with a strong Lewis acid, it loses a hydride ion to form the cycloheptatrienyl cation.



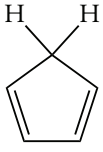
cycloheptatrienyl cation

Every carbon atom in the cycloheptatrienyl cation is sp^2 hybridized, each carbon has a 2p orbital, and the ring contains $4n+2 = 6$ π electrons. Therefore, it is aromatic! Because the cycloheptatrienyl cation, or **tropylium ion**, has six π electrons, it meets the Hückel criteria for aromaticity. Although we won't discuss the chemistry of the tropylium ion, it is more stable than a simple secondary carbocation. Moreover, all its carbon atoms are structurally equivalent, and all its carbon-carbon bonds are of equal length. Lewis structures for cycloheptatrienyl cation are shown below.



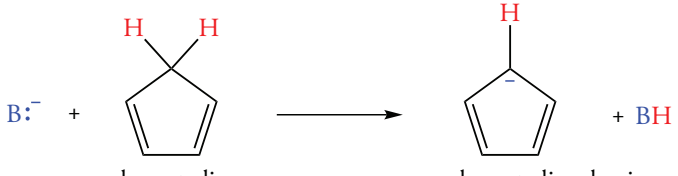
resonance structures of cycloheptatrienyl cation

Next, let's consider 1,3-cyclopentadiene. Four of its carbon atoms are sp^2 hybridized. However, one is sp^3 hybridized, and like cycloheptatriene, it is not aromatic.



cyclopentadiene

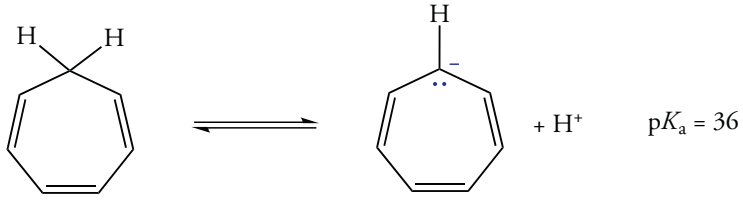
Treating 1,3-cyclopentadiene with a base yields the cyclopentadienyl anion.



cyclopentadiene cyclopentadienyl anion

The cyclopentadienyl anion has a 2p orbital on each carbon atom and six π electrons (Figure 13.3). Thus, it is aromatic. Each carbon atom is sp^2 hybridized, including the one with the negative charge shown in the single Lewis structure. Like the tropylium ion, the cyclic anion is resonance stabilized, so we can write alternative resonance forms that distribute the negative charge over all five ring carbon atoms.

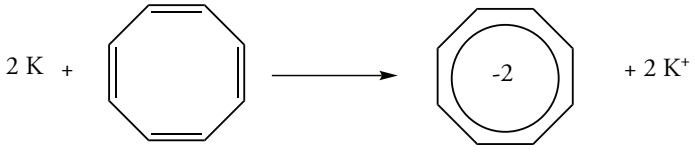
1,3-Cyclopentadiene is surprisingly acidic. It has pK_a value of 16, which is comparable to the pK_a of water. This is a very low pK_a for a hydrocarbon, which reflects the stability of the aromatic cyclopentadienyl anion. Thus, 1,3-cyclopentadiene is far more acidic than other simple alkanes and alkenes. The low pK_a of 1,3-cyclopentadiene is a striking contrast to the high pK_a of 1,3,5-cycloheptatriene.



1,3,5-cycloheptatriene 1,3,5-cycloheptatrienyl anion

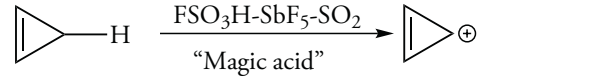
The cycloheptatrienyl anion has several resonance structures, so the negative charge can be delocalized over all seven carbon atoms. Cyclopentatrienyl anion, like cyclbutadiene, has $4n$ π electrons (n = 2), and is unusually unstable. It, too, is antiaromatic. As a result, cycloheptatriene is 10^{20} times less acidic than cyclopentadiene.

We saw earlier that cycloöctatetraene is a stable molecule even though it has eight π electrons, because it is nonplanar. We can imagine that this lack of planarity reflects the destabilization that would result if its eight π electrons were forced into a coplanar arrangement, in which case it would be antiaromatic. However, treating cyclooctatetraene with potassium metal produces cycloöctatetraenyl dianion, Which has 10 π electrons. Therefore, it obeys the Hückel rule ($4n$ + 2 = 10 when n = 2), and is a stable, aromatic species.



cyclooctatetraenyl dianion

Next, let's consider cyclopropene. Two of its carbon atoms are sp^2 hybridized. However, one is sp^3 hybridized and it is not aromatic. However, as in the examples we considered above, it can be converted to an aromatic ion. Cyclopropene can be converted to the cyclopropenium cation by treating it with the very potent acid mixture consisting of flurosulfuric acid, antimony pentafluoride, and sulfur dioxide. This mixture is sometime called "magic acid" because of its ability to produce stable solutions of carbocations.

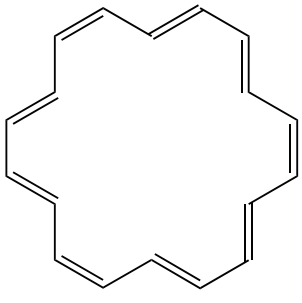


Cyclopropene Cyclopropenium ion

The cyclopropenium ion is aromatic because (1) it is planar, (2) all three carbon atoms are sp^2 hybridized, and (3) it contains $4n$ + 2 π electrons, where n = 0. It is remarkably stable. The heat of formation data show that the cyclopropenium carbocation is more than +30 kcal $mole^{-1}$ more stable than the allyl carbocation.

Problem 12. 1

Annulenes are large monocyclic, conjugated compounds. A prefix within brackets indicates the number of carbon atoms in the ring. Given the structure shown below, and based on the Hückel rule, determine if [18]annulene is aromatic.



[18]annulene

12.4 MOLECULAR ORBITALS OF AROMATIC AND ANTIAROMATIC COMPOUNDS

In our discussion of conjugated polyenes in Chapter 11, we described the Hückel method for making molecular orbitals of π systems. We recall that the Hückel method generates the π system by making a linear combination of molecular orbitals from a starting set of 2p atomic orbitals. For benzene, we start with six 2p atomic orbitals. We must therefore obtain six molecular orbitals because the number of molecular orbitals always equals the number of atomic orbitals from which they are made. Three MOs of benzene are bonding; each holds two electrons. Three are antibonding; they are unoccupied. We can represent the energy levels of benzene graphically. If we inscribe benzene in a circle, then the corners of the hexagon correspond to the relative energies of the MOs (Figure 12.2).

Figure 12.2 shows that π_1 has the lowest energy. It is symmetric and has no vertical nodal planes. The other two bonding orbitals, π_2 and π_3, have the same energy; that is, they are *degenerate*. Each of these orbitals is antisymmetric, and each has a vertical nodal plane. The antibonding orbitals π_4^* and π_5^* are symmetric, degenerate, and have two vertical nodal planes; π_6^* is symmetric and has three vertical nodal planes (Figure 12.3).

Another consequence of the delocalization of the π electrons across the entire ring is that electrons can travel around the ring freely, like electrons in a copper wire. This is reflected in the equal carbon—carbon bond lengths in benzene. Figures 12.3 and 12.3 also show why benzene is unusually stable: if benzene loses an electron and becomes a cation, it loses aromatic stabilization; if it gains an electron, that electron must occupy an antibonding orbitals, which is inherently unstable.

Figure 12.2 Relative Energies of Benzene's MOs and their Occupancy

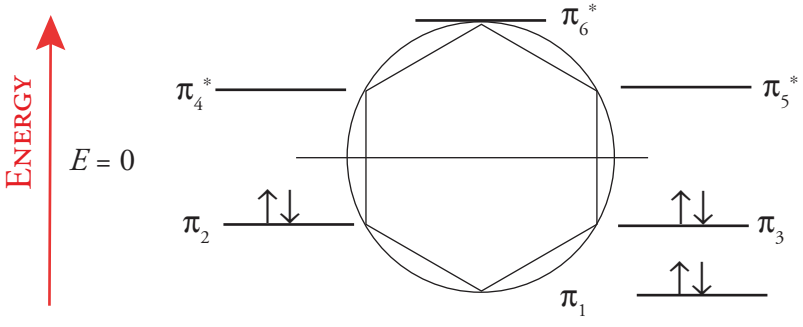


Figure 12.3 Symmetry of Molecular Orbitals in Benzene

Orbitals π_2 and π_3 have the same energy. They are antisymmetric and have one nodal plane. Each of the bonding MOs has two electrons. MOs π_4, π_5, and π_6 have energy greater than zero. They are antibonding and contain no electrons.

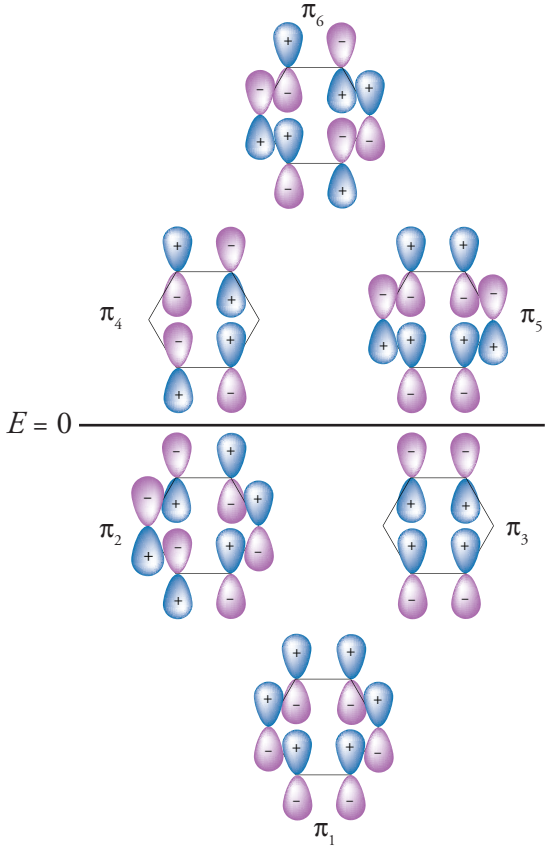


Figure 12.4 Energy Levels and Occupancies of the Molecular Orbitals of Cycloheptatrienyl Cation

The cycloheptatrienyl cation contains $4n + 2 = 6$ π electrons. Therefore, it is aromatic. All three bonding π MOs are fully occupied, and the antibonding orbitals are empty.

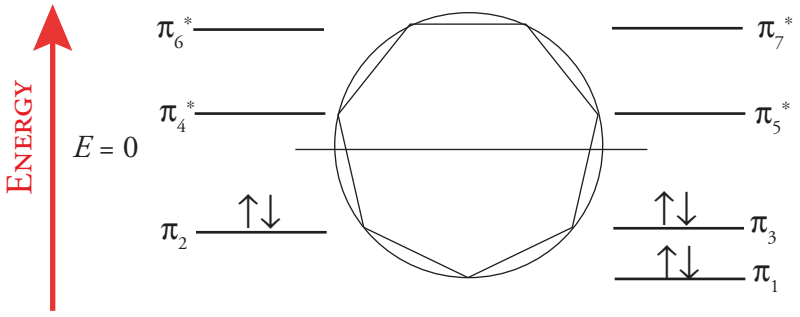
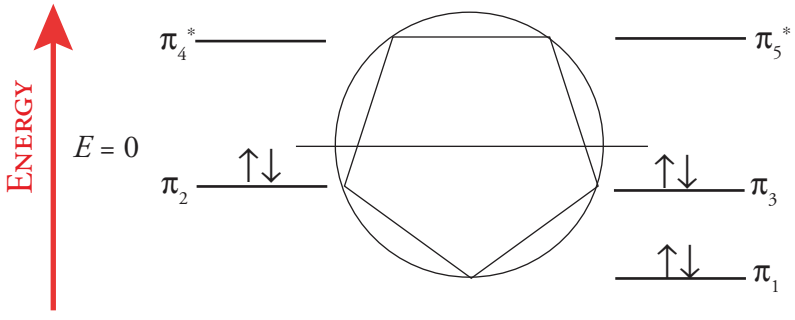


Figure 12.5 Energy Levels and Occupancies of the Molecular Orbitals of Cyclopentadienyl Anion

The cyclopentadienyl anion contains $4n + 2 = 6$ π electrons. Therefore, it is aromatic. All three bonding π MOs are fully occupied, and the antibonding orbitals are empty.



We saw earlier that cycloheptatriene can also be converted to an anion that has several resonance structures, so the negative charge can be delocalized over all seven carbon atoms. However, this anion is quite unstable. The cyclopentatrienyl anion contains eight π electrons. It does not contain the number of π electron required for aromaticity. We have seen that it is antiaromatic because it has $4n$ π electrons; $4n = 8$ where $n = 2$. The energy level diagram for the cyclopentatrienyl anion shows why it is unstable. The "extra" pair of electrons have to go into unstable antibonding orbitals (Figure 12.6).

Figure 12.6 Energy Levels and Occupancies of the Molecular Orbitals of Cycloheptatrienyl Anion

The cycloheptatrienyl anion contains $4n = 8$ π electrons, where $n = 2$. Therefore, it is an unstable antiaromatic species. All three bonding π MOs are fully occupied, but the antibonding π_4^*, π_5^* orbitals each have one electron.

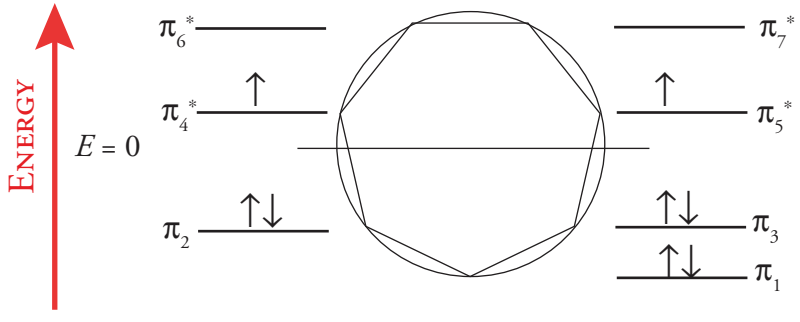


Figure 12.7 shows the energy levels for the stable, aromatic cyclopropenyl cation, and Figure 12.8 shows the energy levels for the unstable, antiaromatic cyclobutadiene molecule.

Figure 12.7 Relative Energy Levels of the Cyclopropenium Ion

The cyclopropenium cation contains $4n + 2 = 2$ π electrons for $n = 0$. Therefore, it is aromatic. Its two bonding π electrons occupy π_1, and the antibonding π_2^*, π_3^* orbitals are empty.

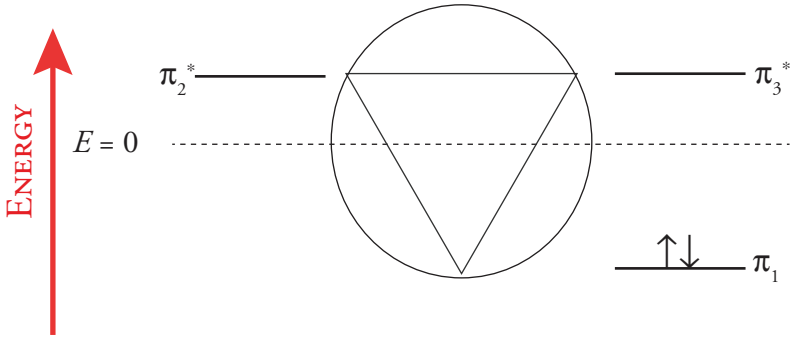
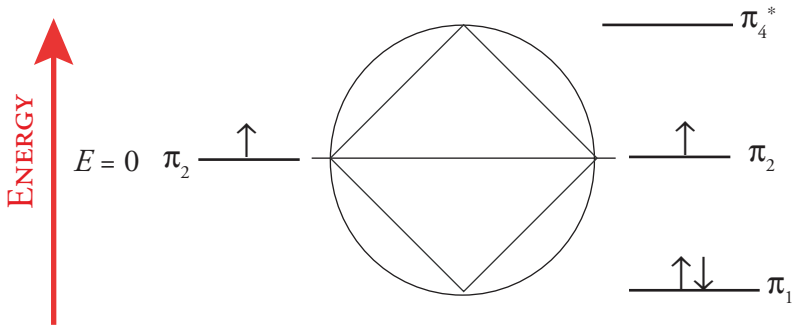
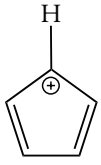


Figure 12.8 Relative Energy Levels of Cyclobutadiene
Cyclobutadiene is a $4n$ π antiaromatic molecule, for $n = 1$. It has two bonding electrons in π_1 and one electron in each of the nonbonding π_2^*, π_3^* orbitals. It is a very unstable diradical.



Problem 12.2
Consider the electronic structure of the carbocation that would result from the loss of a hydride ion from 1,3-cyclopentadiene; that is, cyclopentadienyl cation. How many electrons are in the π system? Are they all paired? Is this ion aromatic? What are the relative energy levels of this ion?

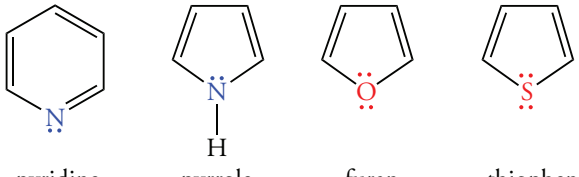


cyclopentadienyl cation

Problem 12.3
Write the resonance structures of the cyclopentadienyl anion to show how the negative charge can be delocalized over five carbon atoms.

12.5 HETEROCYCLIC AROMATIC COMPOUNDS

Cyclic compounds that have one or more atoms other than carbon within the ring are called **heterocyclic compounds**. Those that have $4n + 2$ π electrons are **heterocyclic aromatic compounds**. Nitrogen and oxygen are the most commonly encountered heteroatoms in naturally occurring heterocyclic compounds. Sulfur-containing aromatic compounds also exist. The structures of a few commonly encountered heterocyclic aromatic compounds are shown below.



pyridine pyrrole furan thiophene

In pyridine, two electrons of the nitrogen atom are located in an sp^2 hybrid orbital directed outward from the plane. These electrons are not involved in resonance with the 6 π electrons in the ring. Pyridine resembles benzene:

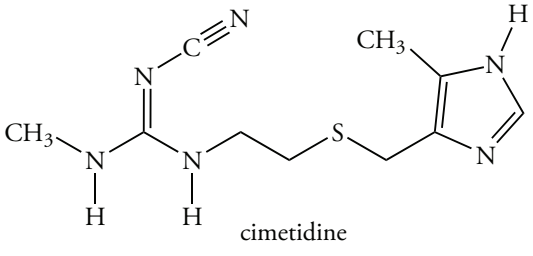
1. Pyridine is planar.
2. Each ring atom of pyridine, including the nitrogen atom, is sp^2 hybridized.
3. Each ring atom contributes one electron in a 2p orbital to an aromatic system of six π electrons.

The sp^2-hybridized nitrogen atom has five valence electrons, one of which contributes to the aromatic sextet. The remaining four valence electrons of nitrogen occupy the three sp^2 orbitals. Two valence electrons form σ bonds to two carbon atoms, and two valence electrons remain as a lone pair in an sp^2 orbital. The lone pair lies in the plane of the ring. This lone pair allows pyridine to act as a base.

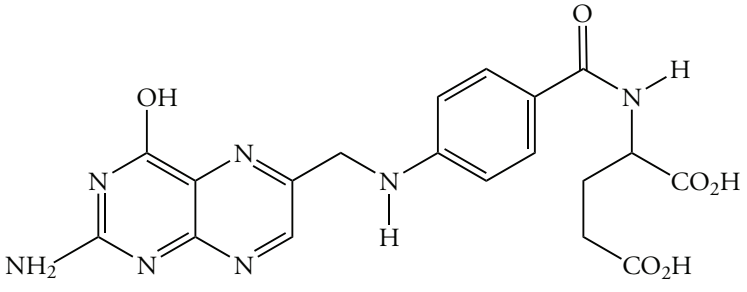
Pyrrole also contains an sp^2-hybridized nitrogen atom. The pyrrole nitrogen atom contributes one electron to each of the three sp^2 orbitals. Two of them form σ bonds with carbon atoms, and the third forms a σ bond with the hydrogen atom. The nitrogen atom's remaining two valence electrons occupy a 2p orbital. These two electrons, plus the four electrons in the 2p orbitals of the four sp^2-hybridized carbon atoms, provide a six-electron π system. Therefore, pyrrole is aromatic. It is isoelectronic with the cyclopentadienyl anion.

Furan and thiophene are similar to pyrrole. Furan has an sp^2-hybridized oxygen atom and thiophene has an sp^2-hybridized sulfur atom. Let's just focus on furan. In furan, two electrons of the oxygen atom are located in a 2p orbital that is part of a 6 π electron, aromatic system. The other four electrons of oxygen are in sp^2 hybrid orbitals. Two of the electrons form π bonds with carbon atoms. The remaining two electrons are located in an sp^2 hybrid orbital directed outward from the plane of the ring.

Many pharmaceutical compounds contain heterocyclic rings. For example, Tagamet (generic name cimetidine), an antiulcer drug, contains a heterocyclic aromatic ring with two nitrogen atoms. Methotrexate, a chemotherapeutic agent used to treat some kinds of cancer, contains four nitrogen atoms in a fused ring system.

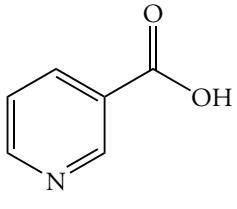


cimetidine

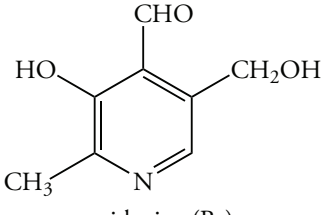


methotrexate

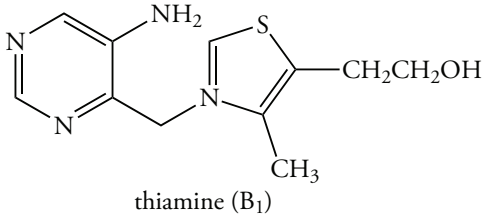
Many naturally occurring, biologically important compounds—such as niacin (vitamin B_1), pyridoxine (vitamin B_3), and thiamine (vitamin B_6)—have one or more aromatic heterocyclic rings of five or six atoms.



niacin (B_3)



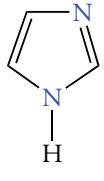
pryidoxine (B_6)



thiamine (B_1)

Problem 12.4

The heterocyclic ring in the drug cimetidine is imidazole. The lone pairs of the two nitrogen atoms are not shown. Which nitrogen atom contributes electrons to the aromatic sextet?



imidazole

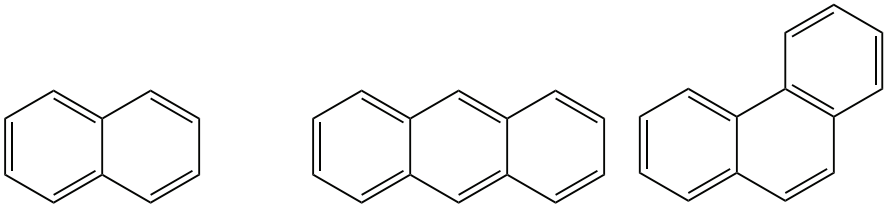
Sample Solution

The nitrogen atom on the bottom of the structure is bonded to a hydrogen atom and resembles the nitrogen atom of pyrrole. Three σ bonds are shown. Each has one valence electron contributed from the nitrogen atom. Thus, the remaining two valence electrons of nitrogen are located in a 2p orbital. These two electrons, along with the four electrons of the two π bonds shown in the imidazole structure, account for six electrons of an aromatic system.

The nitrogen atom on the upper right has one single and one double bond as shown. This nitrogen atom resembles the nitrogen atom of pyridine. Two of its electrons are used to form two σ bonds; one electron is contributed to the π bond with a carbon atom. The remaining two electrons occupy an sp^2 hybrid orbital that lies in the plane of the ring.

12.6 POLYCYCLIC AROMATIC COMPOUNDS

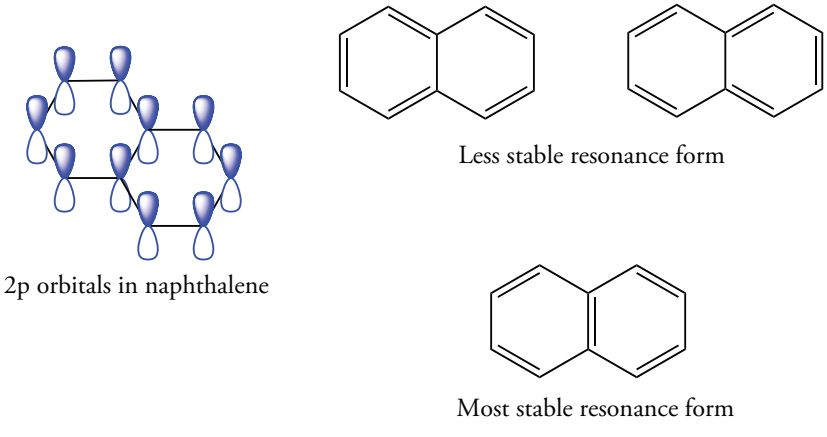
The concept of aromaticity extends to compounds that contain two or more "fused" rings, so called because two carbon atoms are common to two rings. Compounds of this type, called polycyclic aromatic hydrocarbons, have a 2p orbital on every carbon atom. Examples of polycyclic aromatic hydrocarbons include anthracene and phenanthrene. All carbon atoms in naphthalene, anthracene, and phenanthrene are sp^2 hybridized. All atoms in the rings, as well as those directly attached to the rings, are coplanar. Naphthalene, with two fused rings, is the simplest polycyclic aromatic molecule. Note that all the carbon atoms except those at the points of fusion have a bond to a hydrogen atom.



naphthalene anthracene phenanthrene

Naphthalene, which has 10 π electrons, satisfies the Hückel rule for aromaticity. Figure 12.8 shows naphthalene's 2p orbitals. These orbitals contribute to the molecular orbitals of benzene just as the 2p orbitals contribute to the π system of benzene. They overlap around the periphery of the molecule and across the two carbon atoms at the fusion site. Naphthalene has three Lewis resonance forms. Unlike benzene, they are not all equivalent. The most stable resonance form has two Lewis representations of benzene rings. In this contributing structure, both rings share the double bond at the fusion points. The other two contributing structures contain only one Lewis structure of a benzene ring; they have equal energy. In general, the contribution of a resonance form to the resonance hybrid for a polycyclic aromatic hydrocarbon is proportional to the number of Lewis structures that have benzene rings (Figure 12.9).

Figure 12.9 Resonance Structures of Naphthalene
The 10 π electrons of naphthalene are delocalized over both rings. Three resonance forms can be written using localized double bonds.



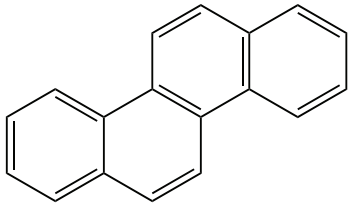
2p orbitals in naphthalene

Less stable resonance form

Most stable resonance form

Problem 12.5

Determine the number of π electrons in chrysene. Is it aromatic?



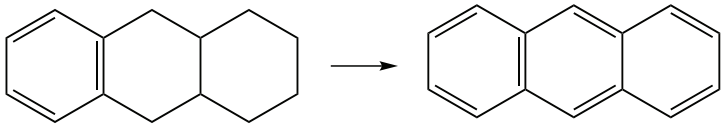
chrysene

Problem 12.6

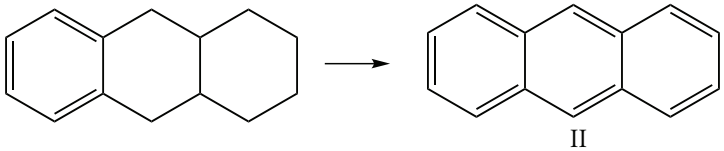
Draw the four resonance forms of anthracene and determine which one(s) make the greatest contribution to the resonance hybrid.

Sample Solution

Start with the two possible Lewis structures for the ring at the left. Then place alternating single and double bonds in the other two rings. Two structures result. Neither structure has a Lewis structure for a "benzene" ring immediately to the right.

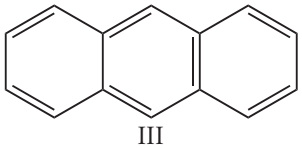


I

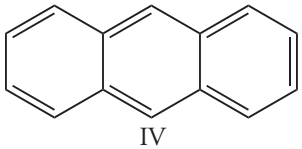


II

We can write two more structures with the same method, starting with the central ring. These contributing structures can also be obtained by rotating the original two structures by 180°.



III



IV

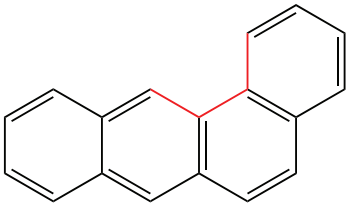
Structures I and III each have two "benzene" rings because the double bond at the fused carbon atoms is shared by the center ring and one terminal ring. These structures contribute more to the resonance hybrid than structures II and IV, which have only one "benzene" ring.

Problem 12.7

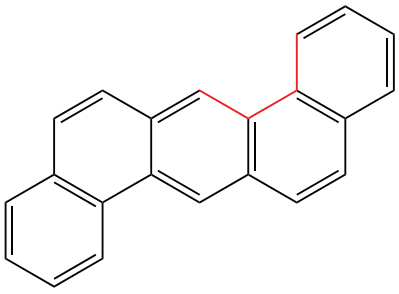
Draw the five contributing resonance forms of phenanthrene. Based on these structures, explain why the C-9 to C-10 bond behaves more like a double bond than the other bonds in the molecule.

Carcinogenic Aromatic Compounds

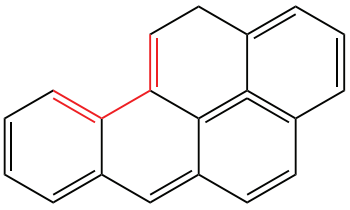
Fused polycyclic aromatic hydrocarbons that contain four or more rings with an angular region are carcinogenic. Their structures resemble phenanthrene. Three of the most potent carcinogens are 1,2-benzanthracene, 1,2,5,6-dibenzanthracene, and 3,4-benzpyrene. The angular region is outlined in red in each structure.



1,2-benzanthracene

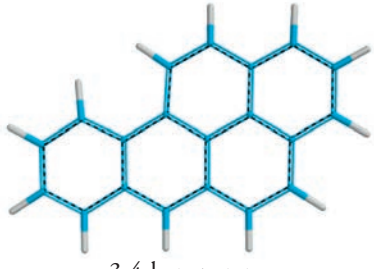


1,2,5,6-dibenzanthracene



3,4-benzpyrene

Small amounts of these angular fused-ring aromatic hydrocarbons cause cancer in about a month when applied to the skin of a mouse. These compounds are present in the effluent from coal-burning power plants and in automobile exhaust. They are also present in tobacco smoke and in meat cooked over charcoal. The incidence of lung cancer among smokers and inhabitants of large urban areas may partly result from inhaling these airborne compounds in minute amounts over time.

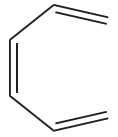
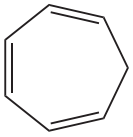
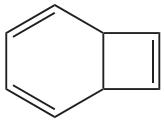
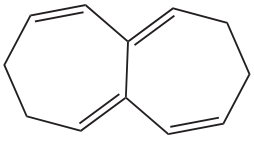


3,4-benzpyrene

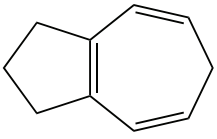
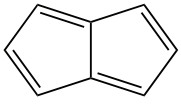
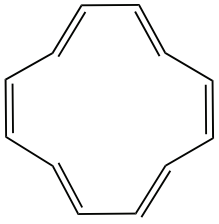
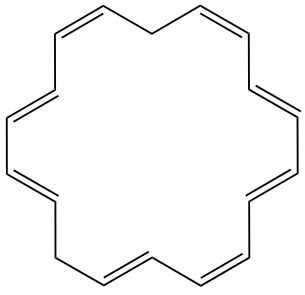
EXERCISES

Criteria for Aromaticity

12.1 Determine whether each of the following is an aromatic compound.

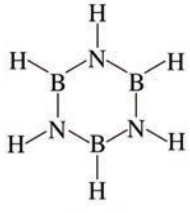
(a)  (b)  (c)  (d) 

12.2 Determine whether each of the following is an aromatic compound.

(a)  (b)  (c)  (d) 

Hückel Rule

12.3 Explain the observation that borazole is an aromatic compound.

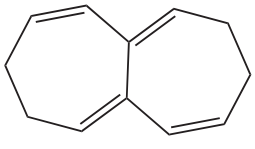
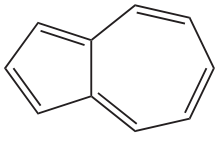
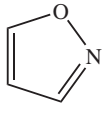


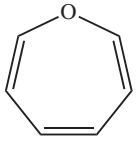
borazole

12.4 Is the following compound aromatic? Explain your answer.

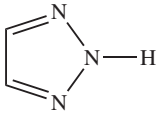


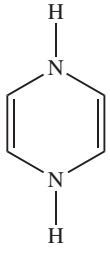
12.5 Are the following compounds aromatic according to the Hückel rule?

(a)  (b)  (c) 

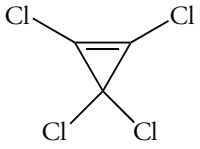
(d) 

12.6 Are the following compounds aromatic according to the Hückel rule?

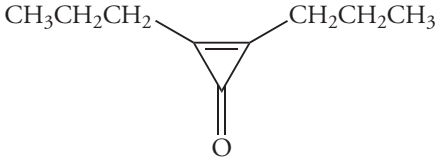
(a) 

(b) 

12.7 1,2,3,3-Tetrachlorocyclopropene reacts with 1 mole of $SbCl_5$ to give the $C_3Cl_3^+$ ion. Draw the structure of the ion and explain why it forms.

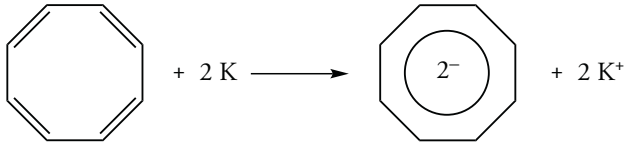


12.8 The dipole moment of dipropylcyclopropenone is 5D. This value is significantly higher than that of acetone, which is 3D. Write a resonance form that accounts for the larger dipole moment of the cyclic ketone.

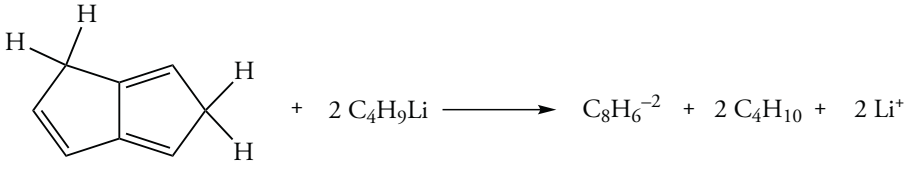


dipropylcyclopropenone

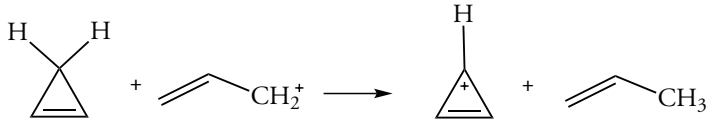
12.9 Cyclooctatetraene reacts with potassium to give a stable dianion. Explain why. Inscribe the dianion in a circle, with one vertex pointed down, and draw a molecular orbital energy diagram for it.



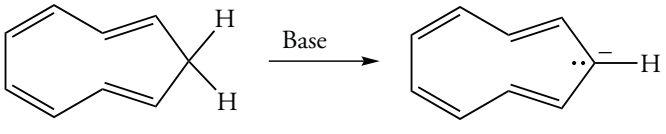
12.10 The following hydrocarbon reacts with 2 moles of butyllithium to form the stable ion $C_8H_6^{2-}$. Draw the structure of this ion. Explain why it is stable.



12.11 Is the following hydride ion transfer reaction favorable in the direction written?

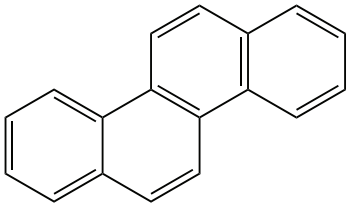


12.12 Is the product of the following reaction aromatic?



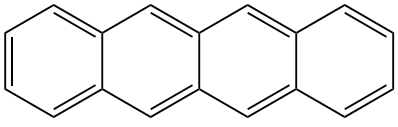
Polycyclic Aromatic Compounds

12.13 Consider the following resonance contributor of chrysene. Draw the most stable resonance contributor.



chrysene

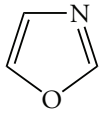
12.14 Draw the most stable resonance contributor of naphthacene.

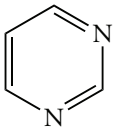


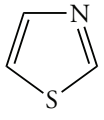
naphthacene

Heterocyclic Aromatic Compounds

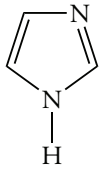
12.15 How many electrons does each heteroatom contribute to the π system in each of the following compounds?

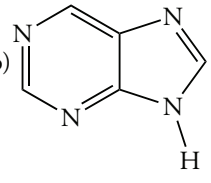
(a) 

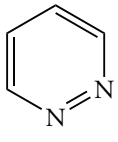
(b) 

(c) 

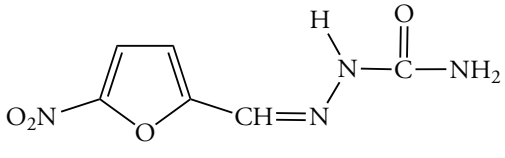
12.16 How many electrons does each heteroatom contribute to the π system in each of the following compounds?

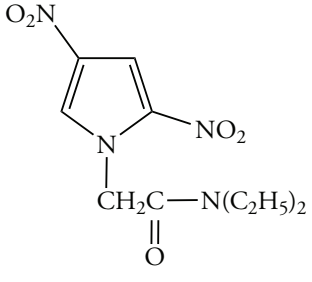
(a) 

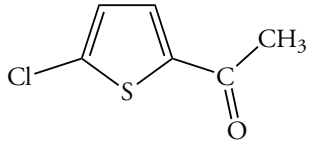
(b) 

(c) 

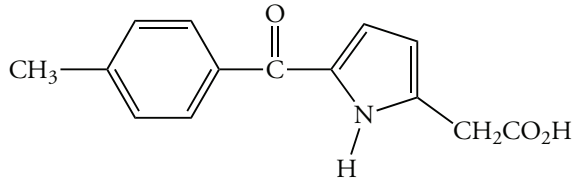
12.17 Identify the heterocyclic ring structure in each of the following compounds.

(a) 

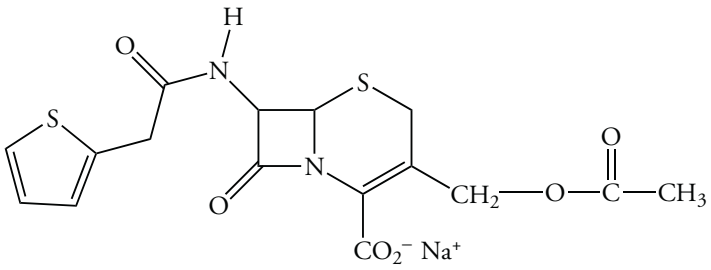
(b) 

(c) 

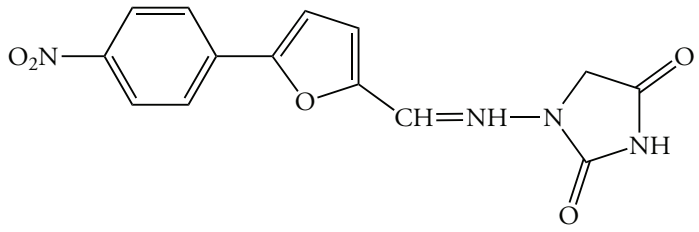
12.18 Identify the aromatic heterocyclic ring structure contained in each of the following compounds.
(a) Tolmetin, a drug used to lower blood sugar levels

(a) 

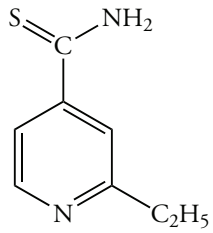
(b) Cephalothin sodium, a broad-spectrum antibacterial



(c) Dantrolene, a muscle relaxant

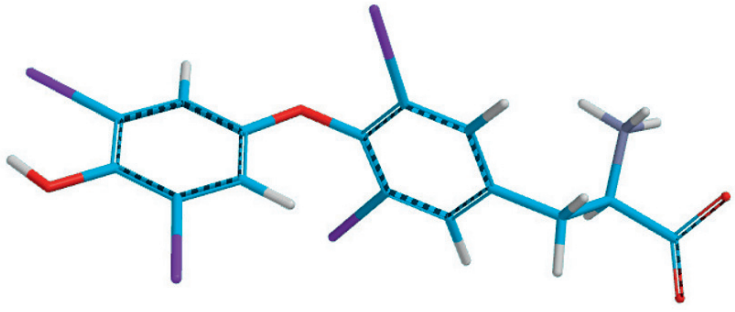


(d) Ethionamide, an antitubercular agent



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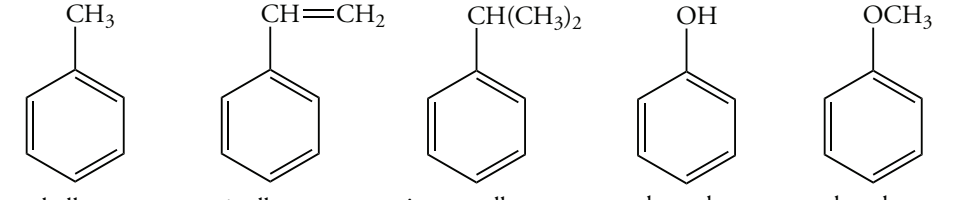
13 Electrophilic Aromatic Substitution



Thyroxine

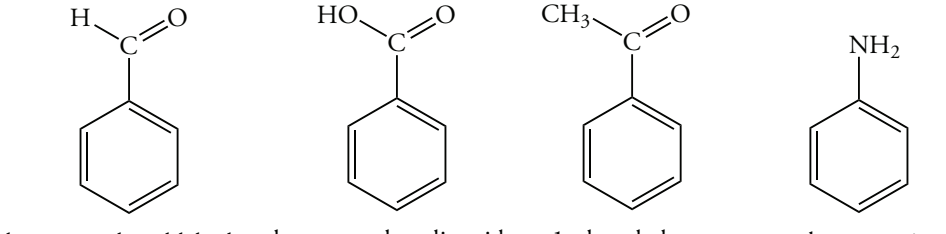
13.1 NOMENCLATURE OF BENZENE DERIVATIVES

Benzene is the "parent" of many aromatic compounds, which have both common and IUPAC names. The common names of substituted benzenes often came from their sources. One example is toluene, which used to be obtained from the South American gum tree, *Toluifera balsamum*. A few benzene compounds are shown below. Their common names are shown in parentheses below their IUPAC names. The common names have been used for so long that they have become accepted by IUPAC.

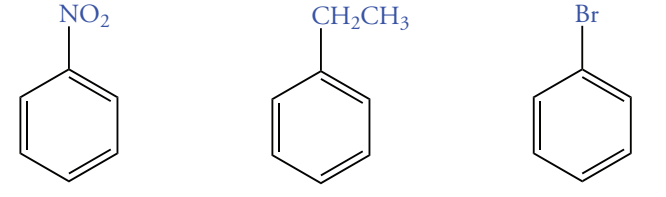


methylbenzene (toluene) | vinylbenzene (styrene) | isopropylbenzene (cumene) | benzol (phenol) | methoxybenzene (anisole)

The IUPAC system of naming substituted aromatic hydrocarbons uses the names of the substituents as prefixes to benzene. Examples include the compounds listed below.



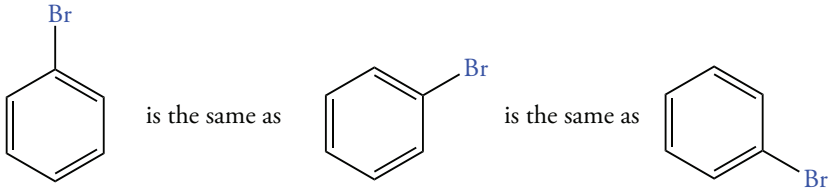
benzenecarboxaldehyde (benzaldehyde) | benzenecarboxylic acid (benzoic acid) | 1-phenylethanone (acetophenone) | benzenamine (aniline)



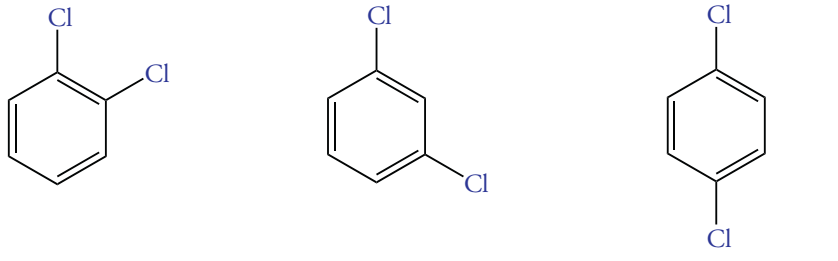
nitrobenzene | ethylbenzene | bromobenzene

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00013-9
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In this section, we will always write a substituent at a "12 o'clock" position. However, the six positions on the benzene ring are equivalent, so if a single substituent is bonded to a benzene ring, it does not matter where we place it.



Many benzene derivatives contain two substituents. They give rise to three isomers. Groups located on adjacent carbons, are ortho (*o*), groups separated by one carbon are meta (*m*), and groups separated by two carbon atoms, which lie at opposite ends of the ring, are para (*p*). That is, ortho compounds are 1,2-substituted, meta compounds are 1,3-substituted, and para compounds are 1,3-substituted.

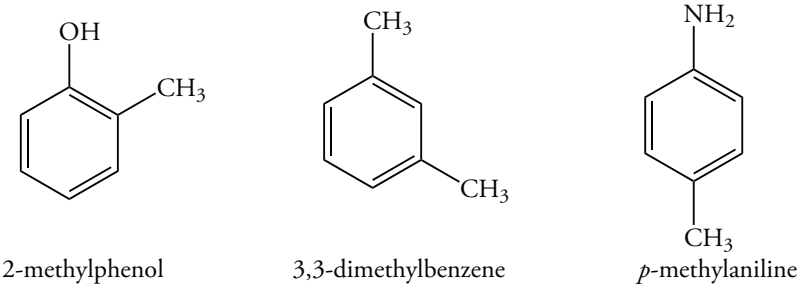


o-dichlorobenzene
(1,2-dichlorobenzene)

m-dichlorobenzene
(1,3-dichlorobenzene)

p-dichlorobenzene
(1,4-dichlorobenzene)

Many disubstituted compounds have common names. Examples include the xylenes, cresols, and toluidines, all of which can be ortho, meta, or para isomers.

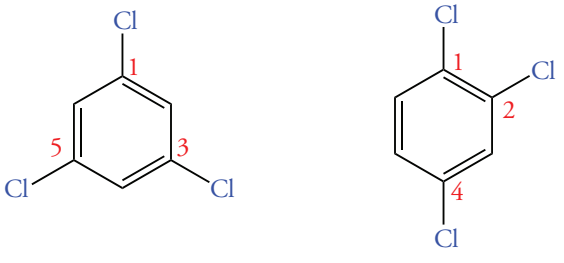


2-methylphenol
(*o*-cresol)

3,3-dimethylbenzene
(*m*-xylene)

p-methylaniline
(*p*-toluidine)

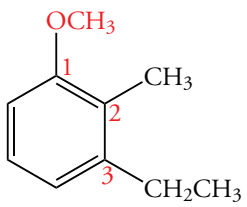
To obtain the IUPAC name of a trisubstituted aromatic compound, we number the benzene ring to give the lowest possible numbers to the carbon atoms bearing the substituents. Thus, each substituent has both a name and a number.



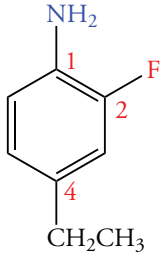
1,3,5-trichlorobenzene

1,2,4-trichlorobenzene

Many derivatives of benzene are named with the common name of the monosubstituted aromatic compound as the parent. The position of the substituent of the parent compound is automatically designated C-1, but the number is not used in the name. The other substituents are prefixes named in alphabetical order along with numbers indicating their locations.



3-ethyl-2-methylanisole



4-ethyl-2-fluoroanline

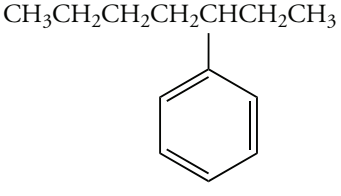
An aromatic ring residue attached to a larger parent structure is called an aryl group. It is abbreviated Ar. The aryl group derived from benzene (C_6H_5—) is a phenyl group. A benzyl group, derived from toluene, has the formula $C_6H_5CH_2$—.



phenyl group

benzyl group

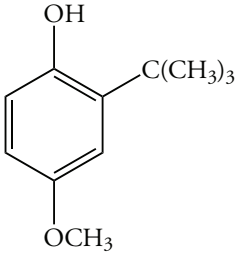
If alkyl groups containing fewer than six carbon atoms are bonded to a benzene ring, the compound is named as an alkyl-substituted benzene. For more complex molecules, the term phenyl is named as a substituent on the parent chain of carbon atoms, as in 3-phenylheptane.



3-phenylheptane

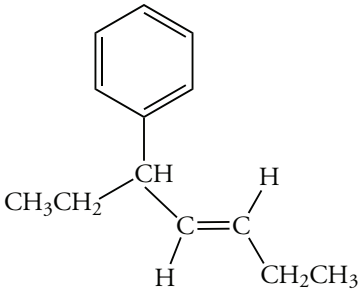
Problem 13.1

What is the name of the following trisubstituted compound?



Problem 13.2

What is the name of the following trisubstituted compound?



Sample Solution

The compound is an alkene with an aromatic ring as a substituent. First, we determine that the chain has seven carbon atoms; it is a heptene. Next, we number the chain from right to left so that the double bond is assigned to C-3. The phenyl group is then located on C-5. Also, we note that the compound is the E isomer. The complete name is (E)-5-phenyl-3-heptene.

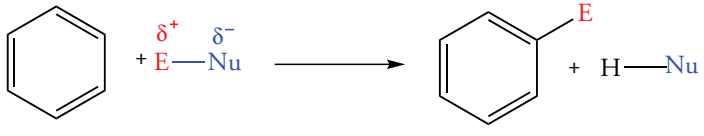
Problem 13.3

Write the structure of each of the following compounds.

(a) 2,4,6-trinitrophenol (b) 3,5-dibromoaniline (c) 2,4-dinitrotoluene
(d) *p*-methylbenzoic acid (e) *p*-chloroanisole (f) *o*-methylacetophenone

13.2 MECHANISM OF ELECTROPHILIC AROMATIC SUBSTITUTION

Aromatic rings do not undergo the electrophilic addition reactions we discussed for alkenes. Instead, they react with electrophiles—and even then only in the presence of a catalyst—to give a substitution product. In these reactions, an electrophile (E^+) substitutes for H^+. The general process is shown below.

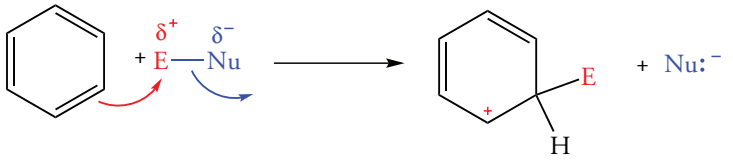


Many electrophiles can replace hydrogen on an aromatic ring. A halogen atom, usually chlorine or bromine, adds to the ring through a halogenation reaction. The nitro group (—NO_2) and the sulfonic acid group (—SO_3H) add in nitration and sulfonation reactions. Alkylation and acylation reactions introduce alkyl (—R) and acyl groups (—COR). These reactions all occur by the same general reaction mechanism.

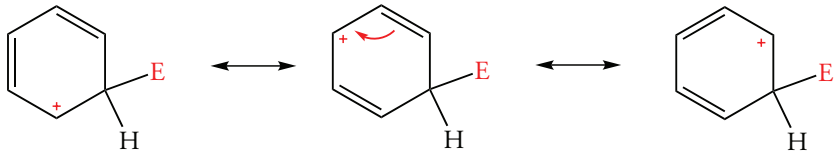
Mechanism of Electrophilic Aromatic Substitution

In the first step of electrophilic aromatic substitution, which resembles the addition of electrophiles to alkenes, the electrophile accepts a pair of electrons from the aromatic ring. However, because this electron pair forms part of a delocalized aromatic sextet, aromatic compounds are significantly less reactive than alkenes. They are so much less reactive that a Lewis acid, such as $FeBr_3$ in bromination, and $AlCl_3$ in alkylation and acylation, is required as a catalyst to generate an electrophile that is potent enough to react with the aromatic ring.

When the electrophile adds to the aromatic ring, it produces a carbocation intermediate. The first step of electrophilic aromatic substitution is usually the rate-determining step. Since a new sigma bond forms in the first step, the intermediate is called a **sigma complex**.



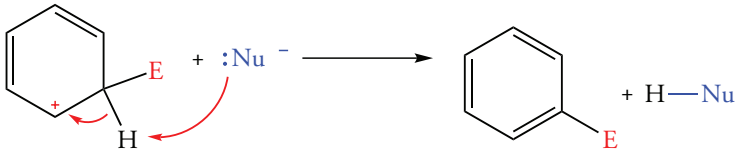
This carbocation is resonance stabilized, but is not aromatic because it has only four π electrons. Therefore, the sigma complex is much more reactive than the original aromatic ring.



resonance forms of a cyclohexadienyl carbocation

The formation of the sigma complex in electrophilic aromatic substitution has a higher activation energy than the formation of a carbocation in electrophilic addition to an alkene (Figure 13.1). Therefore, the rates of electrophilic aromatic substitution reactions are slower than the rates of electrophilic addition reactions to alkenes for the same electrophile. For example, bromine reacts instantly with alkenes, but does not react at all with benzene except in the presence of a strong Lewis acid catalyst.

In the faster second step of the electrophilic substitution mechanism, the proton bound to the sp^3-hybridized ring carbon atom leaves, restoring the aromatic π system. A nucleophile, acting as a base, extracts the leaving proton.



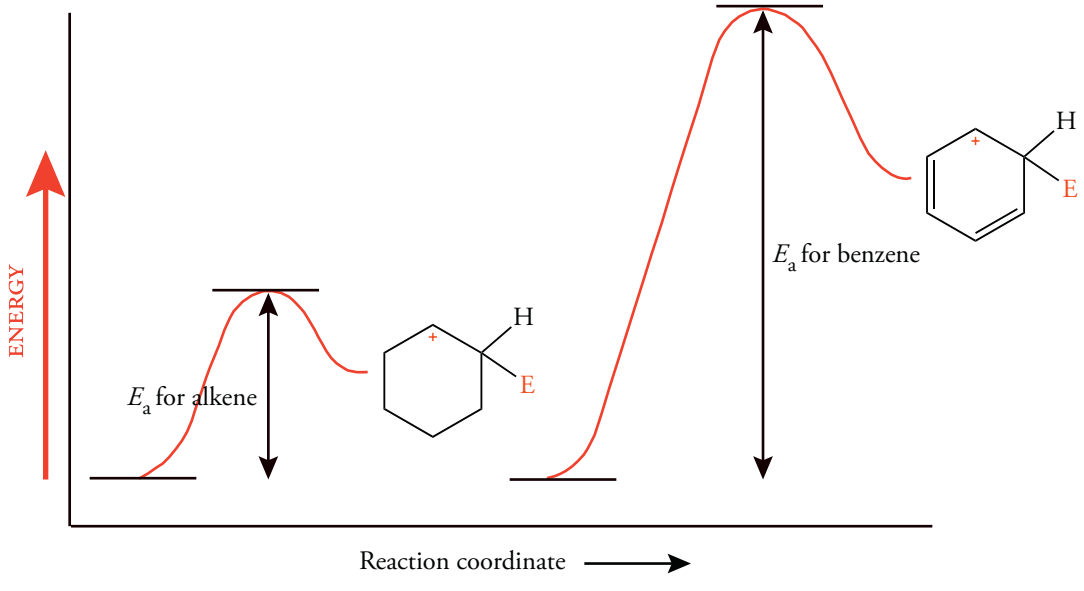
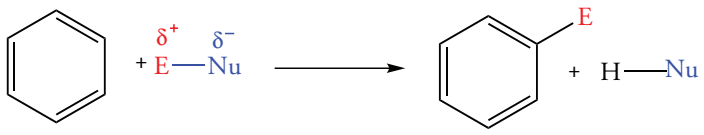


Figure 13.1
Electrophilic Addition to Cyclohexene Compared to Benzene

The activation energy for adding an electrophile to benzene is higher than for the activation energy for adding an electrophilic to an alkene because some of the resonance energy of benzene is lost in the transition state.

13.3 COMMON ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

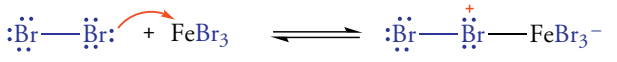
In the preceding discussion, we used a generic electrophile, E^+ in our electrophilic substitution mechanism In this section, we will consider some specific examples of electrophiles that react with aromatic rings.



Many electrophiles can replace hydrogen on an aromatic ring. A halogen atom, usually chlorine or bromine, adds to the ring through a halogenation reaction. The nitro group (—NO_2) and the sulfonic acid group (—SO_3H) add in nitration and sulfonation reactions. Alkylation and acylation reactions introduce alkyl (—R) and acyl groups (—COR). These reactions all occur by the same general reaction mechanism.

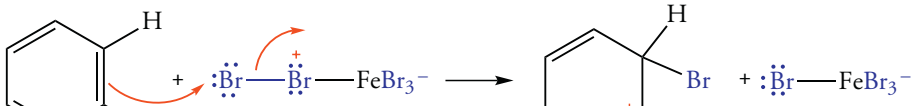
Halogenation

In the presence of a strong Lewis acid, bromine and chlorine halogenate aromatic rings. Bromination requires both Br_2 and a Lewis acid catalyst, $FeBr_3$. The catalyst generates a Lewis acid–Lewis base complex with a weakened Br—Br bond. The bromine atom bonded to iron carries a formal positive charge. It is the electrophile.

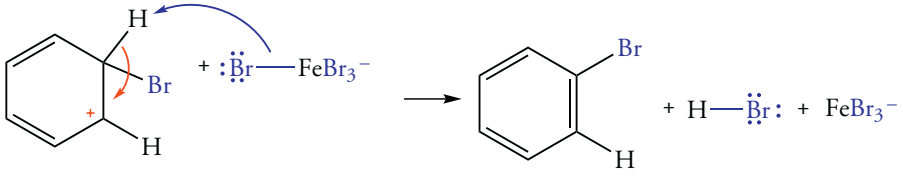


Lewis-acid–Lewis-base complex

The Lewis acid–base complex reacts with the benzene ring to form a cyclohexadienyl ion. This step also forms a tetrabromoferrate ion, which removes a proton from the cyclohexadienyl ion in a subsequent step. This step also regenerates the iron(III) bromide, which continues to act as a catalyst in the reaction.



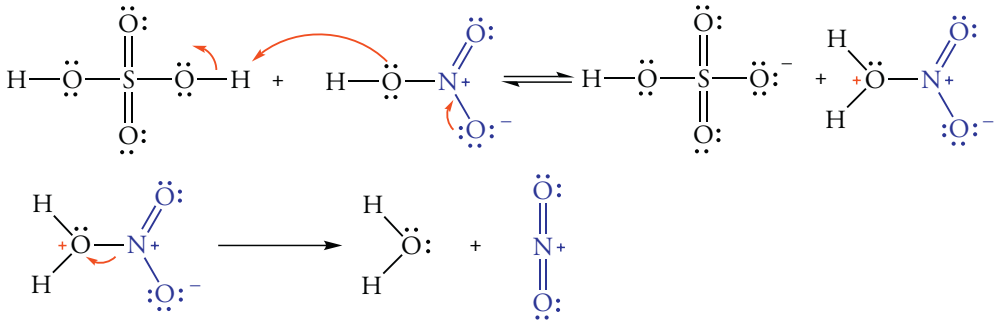
tetrabromoferrate ion



Chlorination, which proceeds in a similar manner, requires $FeCl_3$ as the Lewis acid catalyst. Fluorine reacts so strongly that multiple substitutions occur. Iodine, on the other hand, does not react with benzene by this mechanism. We will discuss alternative methods for aromatic substitution that allow iodination later in this chapter.

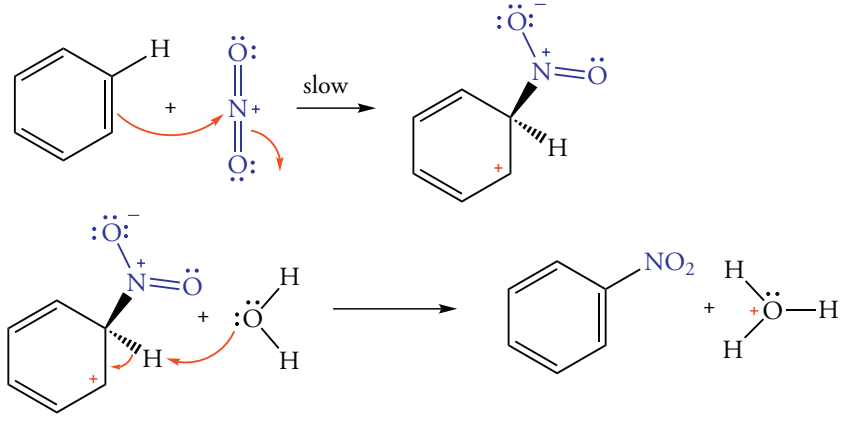
Nitration

Nitration introduces a nitro group (—NO_2) onto an aromatic ring. Electrophilic aromatic substitution requires nitric acid (HNO_3), with sulfuric acid as a catalyst. Nitronium ion, (NO_2^+), is the electrophile. It forms in two steps by the reaction of nitric acid with sulfuric acid.

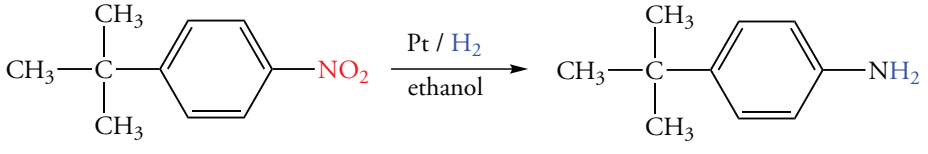


nitronium ion

The nitronium ion reacts with the π system of the aromatic ring to give a sigma complex. A water molecule then extracts a proton from the cyclohexadienyl carbocation to give the product.

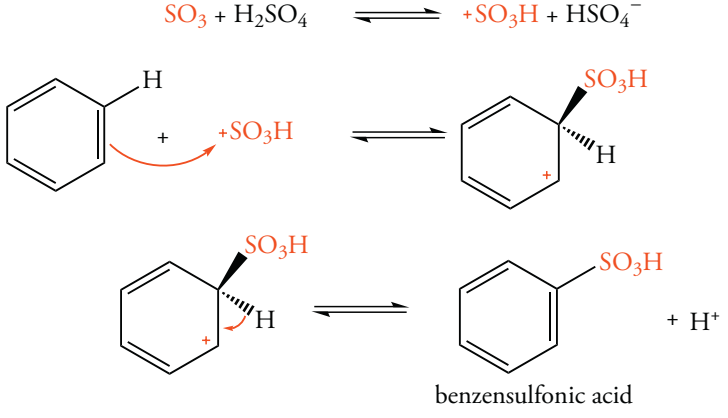


Nitration of aromatic rings is an important reaction because the nitro group can readily be reduced to an amino group, a common functional group required in many pharmaceutical compounds. Other substituents can subsequently replace the amino group (Section 13.8).



Sulfonation

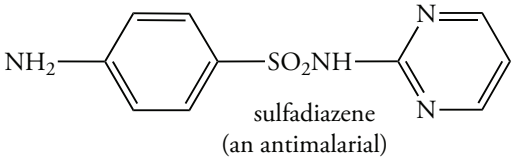
We can add a sulfonic acid group (—SO_3H) to an aromatic ring by an electrophilic aromatic substitution reaction called sulfonation. The reaction requires a mixture of SO_3 and sulfuric acid, called fuming sulfuric acid. The electrophile is $^+SO_3H$.



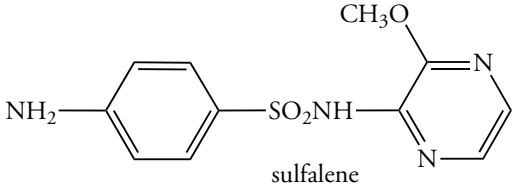
benzensulfonic acid

The sulfonation reaction is less exothermic than halogenation or nitration. Hence, it is reversible, and desulfonation occurs in dilute aqueous acid. The reversibility of sulfonation forms the basis of the synthesis of some aromatic compounds because the sulfonic acid group may block a position on an aromatic ring, preventing substitution at that point. The sulfonic acid group is removed at the end of the synthesis.

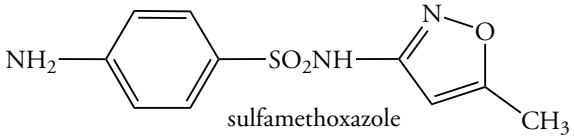
The sulfonic acid functional group, commonly found in azo dyes (Section 27.9), affects both the color of a compound and its solubility in water. A sulfonic acid group can be converted to a sulfonamide group to form sulfa drugs.



sulfadiazene
(an antimalarial)



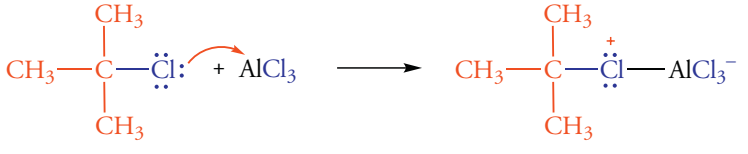
sulfalene
(an antilepral)



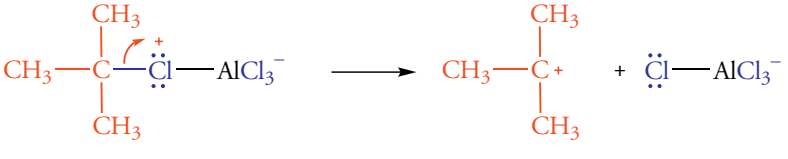
sulfamethoxazole
(an antibacterial)

Alkylation: The Friedel–Crafts Reaction

An alkyl group can replace a hydrogen atom of benzene in the **Friedel–Crafts alkylation** reaction. This reaction requires an alkyl halide, with an aluminum trihalide as the catalyst. The catalyst produces an electrophilic species, which may be a carbocation or a carbocation complexed with a counter ion. For simplicity in writing equations, we will show only the free carbocation. The reaction is commonly carried out only with alkyl bromides or alkyl chlorides. Aryl halides and vinyl halides do not react because the carbocations derived from these compounds do not form under usual reaction conditions. In contrast, tertiary carbocations, such as the *tert*-butyl carbocation, readily form.

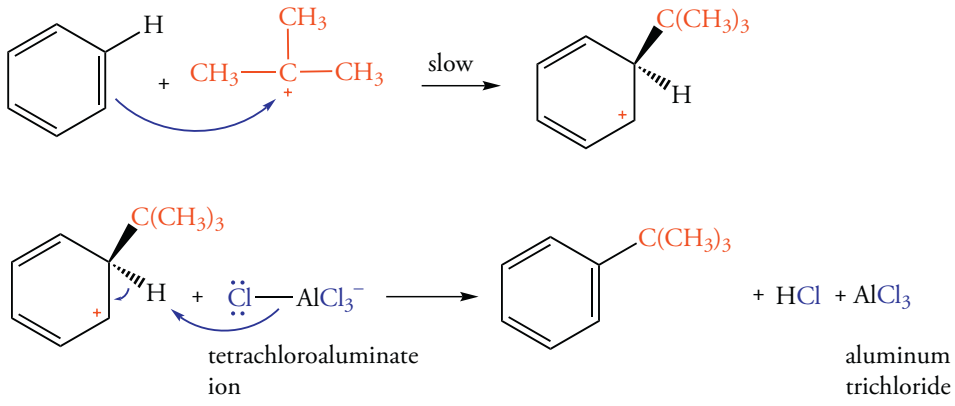


tert-butyl chloride aluminum trichloride Lewis-acid–Lewis-base complex



tert-butyl carbocation tetrachloroaluminate ion

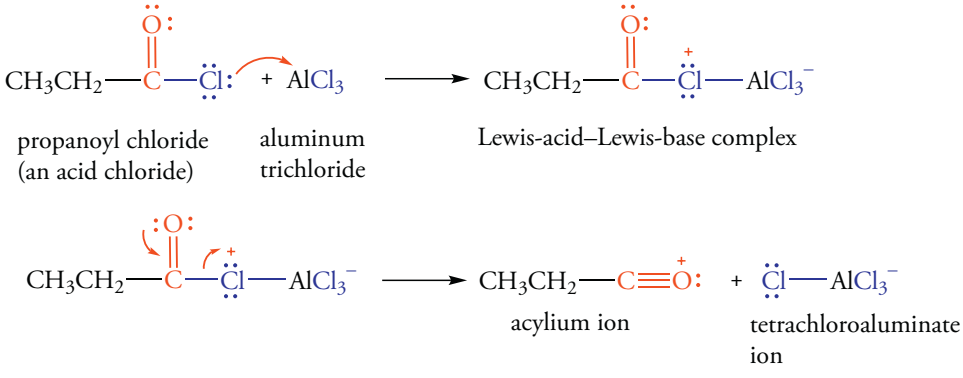
Alkylation of benzene by carbocations such as the *tert*-butyl carbocation occurs by a two-step mechanism similar to those discussed for bromination and nitration.



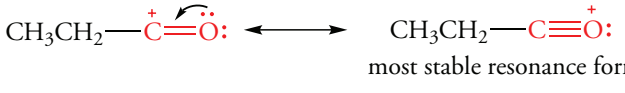
Secondary alkyl halides react with benzene by forming a secondary carbocation. However, primary alkyl halides do not form carbocations under Friedel–Crafts conditions. Instead, the alkyl group transfers directly to the aromatic ring from the Lewis acid–Lewis base complex, which has a highly polarized carbon halogen bond.

Friedel–Crafts Acylation

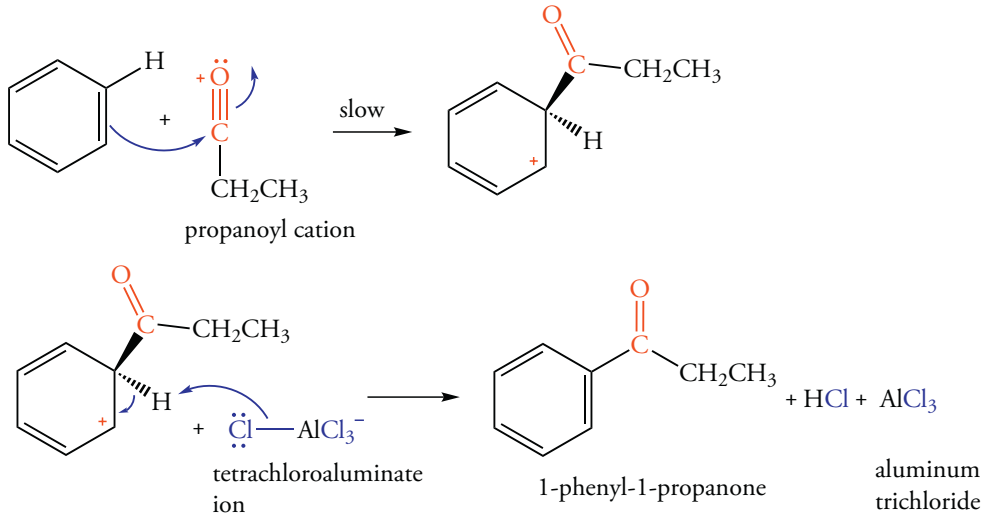
An acyl group can replace hydrogen in an aromatic ring by a reaction called **Friedel–Crafts acylation**. The reaction requires an acyl halide and the corresponding aluminum trihalide. The reaction is commonly carried out only with acyl chlorides. The electrophile is shown as an acyl cation, called an **acylium ion**, forms from a Lewis acid–Lewis base complex of aluminum trichloride and the acyl chloride.



Acyl cations are resonance stabilized. The more stable form has an octet of electrons on both the carbon and oxygen atoms, and a formal positive charge on the oxygen atom. However, to give a stable product, reaction of the acyl cation with an aromatic ring must occur at the acyl carbon atom.



Acylation of benzene by carbocations, such as the propanoyl cation, occurs by a two-step mechanism similar to the mechanism for alkylation.

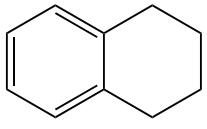


Problem 13.4

Draw the structures of all possible products formed by monosubstitution of *o*-dibromobenzene in a chlorination reaction. Do the same for *m*- and *p*-dibromobenzene.

Problem 13.5

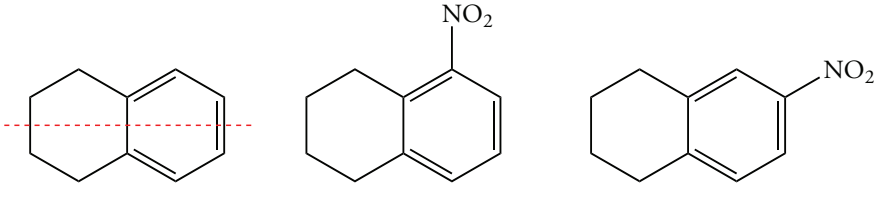
Draw the structures of all possible products formed by mononitration of tetralin.



tetralin

Sample Solution

The molecule has a plane of symmetry perpendicular to the plane of the page that bisects both rings. Two nonequivalent hydrogen atoms lie on either side of the plane. Therefore, only two mononitrated products are possible.

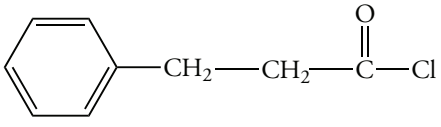


Problem 13.6

Write the structures of the two possible products formed by sulfonation of naphthalene. At 80 °C, isomer I constitutes 96% of the reaction mixture. At 165 °C, isomer II is 85% of the reaction mixture. When isomer I is heated in sulfuric acid at 165 °C, it is converted into isomer II. Explain these observations. Based on steric considerations, which isomer is likely to be more stable?

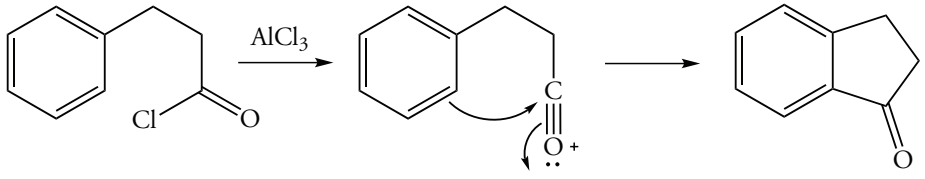
Problem 13.7

Reaction of 3-phenylpropanoyl chloride with $AlCl_3$ yields a compound with the molecular formula C_9H_8O. Write the structure of the compound and explain its origin.



Sample Solution

The Friedel–Crafts reaction we have discussed in this section is an intermolecular reaction between an aromatic compound and an acyl halide. However, if the acyl halide also contains an aromatic ring, an intramolecular reaction can easily occur. Such a unimolecular reaction is favored over a bimolecular reaction when the ring formed contains either five or six atoms. This is a Friedel–Crafts reaction in which the acyl chloride acylates the ortho position.

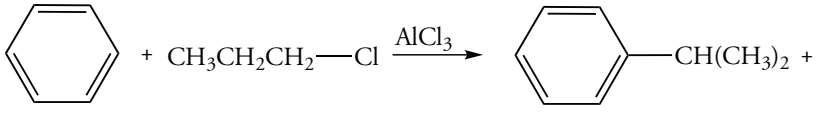


Limitations of the Friedel–Crafts Reaction

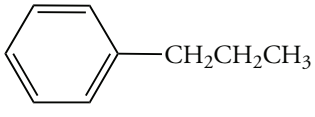
Neither Friedel–Crafts alkylation nor acylation occurs on aromatic rings that have —NO_2, —SO_3H, —C=N, or any carbonyl-containing group that is bonded directly to the aromatic ring. The carbonyl-containing compounds include aldehydes, ketones, carboxylic acids, and esters. All of these substituents make the benzene ring less reactive, as we will shortly discover (Section 13.5).

A second limitation of the Friedel–Crafts alkylation reaction is the difficulty of stopping the reaction after the introduction of a single alkyl group. Alkyl groups make the benzene ring more reactive, so the alkylated product reacts more readily in subsequent substitution reactions than the original reactant. In contrast, Friedel–Crafts acylation yields a less reactive product than the original reactant and multiple acylations do not occur.

The third limitation of Friedel–Crafts alkylation reaction is the structural rearrangement of the alkyl carbocation generated from the alkyl halide. A rearrangement of the alkyl group gives a different product than the one desired. For example, the reaction with 1-chloropropane in the presence of $AlCl_3$ yields a small amount of propylbenzene, but a larger amount of the isomer, isopropylbenzene.

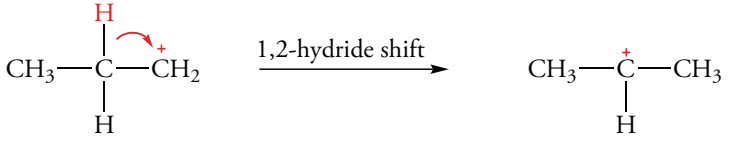


major product



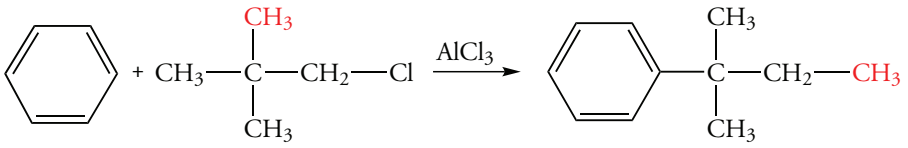
minor product

Carbocations can rearrange in the Friedel–Crafts reaction by a **hydride ($H:^-$) shift**, which converts a less stable carbocation into a more stable one. For example, in a Friedel–Crafts reaction with 1-chloropropane and $AlCl_3$, the Lewis acid–base complex rearranges by a hydride shift from C-2 to C-1.



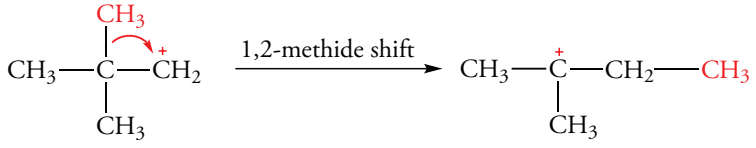
primary carbocation secondary carbocation

Carbocations can also rearrange in the Friedel–Crafts reaction by an **alkyl group shift**. For example, the alkylation of benzene with l-chloro-2,2-dimethylpropane yields only (1,1-dimethylpropyl)benzene.



1-chloro-2,2-dimethylpropane (1,1-dimethylpropyl)benzene

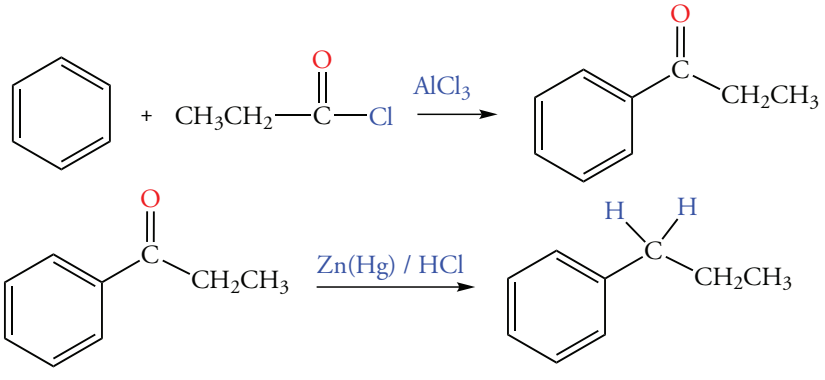
The product results from transfer of a methyl group and its electron pair (a methide ion, CH_3^-) from the quaternary carbon atom to the primary carbon atom. This methide shift converts the primary carbocation to a more stable tertiary carbocation.



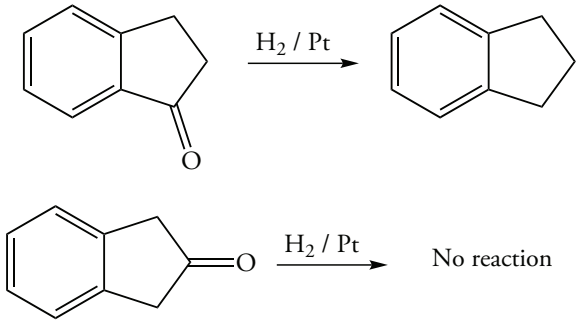
2,2-dimethylpropyl carbocation (1° carbocation)

1,1-dimethylpropyl carbocation (2° carbocation)

Acylium ions produced in the Friedel–Crafts reaction do not rearrange. The acyl group in the product can be reduced using a zinc–mercury amalgam and HCl to produce an alkylbenzene. This reaction is called a Clemmensen reduction. This circumvents the rearrangement of primary alkyl groups that occurs in the Friedel–Crafts alkylation reaction. For example, acylation of benzene with propanoyl chloride followed by a Clemmensen reduction yields propylbenzene.



A carbonyl group bonded to a benzene ring can also be directly reduced by catalytic hydrogenation. This reaction only occurs at the benzylic carbon; if the carbonyl group is elsewhere in the carbon skeleton, it is not reduced.



Problem 13.8
Predict the structure of the major product formed in the Friedel–Crafts alkylation of benzene with 1-chlorobutane.

Problem 13.9
Reaction of 2-methylpropene with benzene in the presence of H_3PO_4 yields *tert*-butyl-benzene. Propose a mechanism for this reaction.

Problem 13.10
Outline a synthesis of 2-methyl-l-phenylpropane (isobutylbenzene) starting from benzene using a Friedel–Crafts reaction.

13.4 SUBSTITUENT EFFECTS ON THE REACTIVITY OF BENZENE RINGS

To this point, we have discussed only electrophilic substitution reactions of benzene itself. Now we will examine the effect that a substituent already bonded to the aromatic ring has on ring attack by an electrophile to attach a second substituent. For a substitution reaction on benzene, only one product results. But if a second substituent adds to a substituted benzene, any of three possible products—the ortho, meta, and para isomers—can result. We would like to know how the original substituent affects (1) the rate of formation of these products and (2) how the substituent affects the product distribution.

Effects of Ring Substituents on Reaction Rate

To examine the effect of a substituent on the rate of electrophilic aromatic substitution, let's compare the rate of nitration of benzene to those of several substituted benzenes. The relative rate of reaction of phenol is 10^{10} faster than that of nitrobenzene. (For comparison, the speed of light is about 10^8 faster than the speed of jogging.)

Table 13.1
Effect of Substituents on Aromatic Substitution

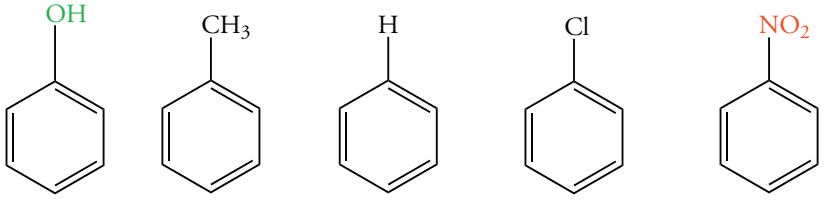
Strongly Activating
—NH_2, —NHR, —NR_2
— OH, —OCH_3

Weakly Activating
—CH_3, —CH_2CH_3, —R

Weakly Deactivating
—F, —Cl, —Br

Strongly Deactivating
—CO—R, —CO_2H
—CN
—NO_2, —CF_3, —CCl_3

Relative rates of nitration of benzene and its derivatives

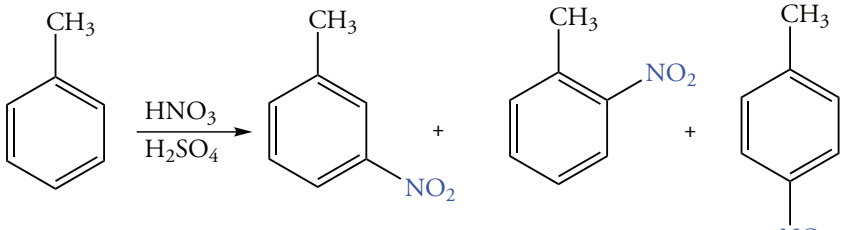


	phenol	toluene	benzene	chlorobenzene	nitrobenzene
rel. rate	10^7	25	1	3×10^{-3}	10^{-7}

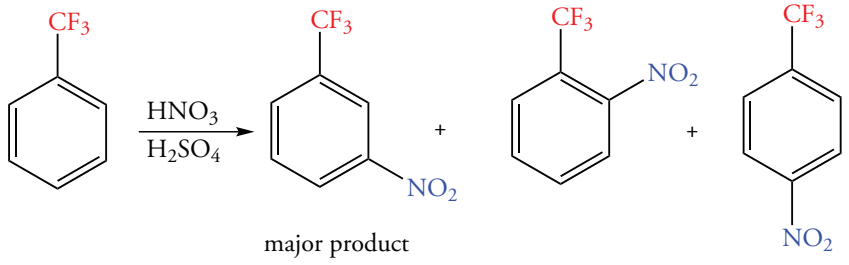
Phenol and toluene are nitrated faster than benzene, whose relative rate of reaction is set at 1. Both a hydroxyl group and a methyl group make the aromatic ring more reactive compared to benzene; they are *activating* groups. On the other hand, chlorobenzene and nitrobenzene react more slowly than benzene. The chloro and nitro groups are *deactivating* groups because they make the aromatic ring less reactive. Table 13.1 lists some common substituents and divides them into activating and deactivating groups with respect to electrophilic aromatic substitution.

Orientation Effects of Ring Substituents

Now let's consider the distribution of products formed in the nitration of toluene. The nitro group that attacks the ring can bond at three nonequivalent sites to give *o*-, *m*-, or *p*-nitrotoluene. When we examine the product distribution, we find that the ortho and para isomers predominate, and that very little of the meta isomer forms. The methyl group directs or orients the incoming substituent into positions ortho and para to itself, and is therefore an **ortho, para director**. All groups that activate the aromatic ring toward further substitution are ortho, para directors. The weakly deactivating halogens also act as ortho, para directors.

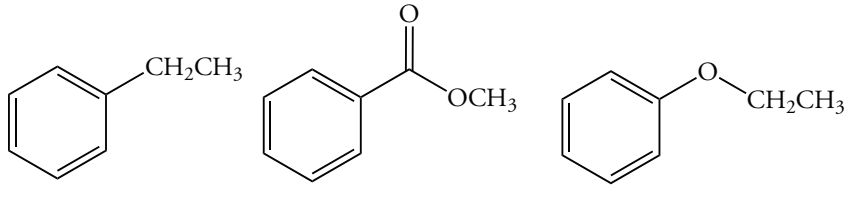


A second class of ring substituents, known as **meta directors**, direct incoming substituents into the meta position. These groups include nitro, trifluoromethyl, cyano, sulfonic acid, and any group with a carbonyl carbon atom bonded directly to the ring. For example, in a nitration reaction, the trifluoromethyl group orients the incoming nitro group to a position meta to itself. Very small amounts of the ortho and para isomers form. All deactivating groups (except halogens) are meta-directing groups.



Problem 13.11

Arrange the following compounds in order of increasing rate of reaction with bromine and $FeBr_3$.



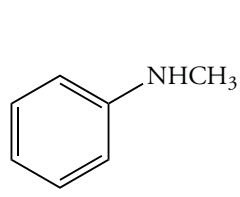
ethyl benzene methyl benzoate ethoxybenzene

Sample Solution

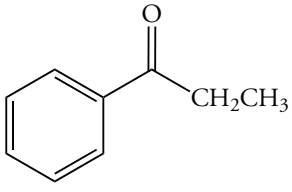
Ethylbenzene contains an alkyl substituent and is slightly more reactive than benzene. Methyl benzoate has a carbonyl carbon atom bonded to the aromatic ring. As a result, its rate of bromination is significantly slower than that of benzene. Ethoxybenzene has an oxygen atom attached directly to the ring, which causes a significant rate increase over that of benzene. Thus, the order of reactivity for the bromination of benzene in an electrophilic aromatic substitution reaction is methyl benzoate < ethylbenzene < ethoxybenzene.

Problem 13.12

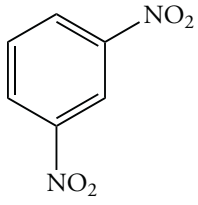
Predict the structure of the product(s) formed in the bromination of each of the following compounds.



N-methylaniline



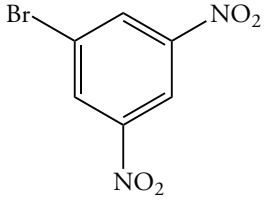
propiophenone



m-dinitrobenzene

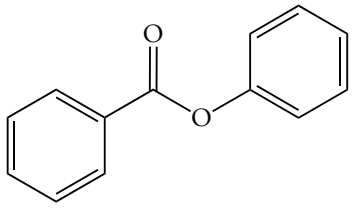
Sample Solution

Propiophenone has a carbonyl group bonded to the benzene ring that directs the bromine to the meta position. *N*-methylaniline resembles aniline, and the bromine will be directed to the ortho and para positions. The third compound has two nitro groups. Each one directs the electrophile onto the ring in positions meta to itself. Thus, both groups direct the bromine into the same position. The product is 3,5-dinitrobromobenzene.



Problem 13.13

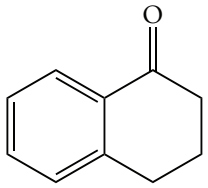
Which of the two aromatic rings of phenyl benzoate would be nitrated? Predict the structure of the product(s) formed.



phenyl benzoate

Problem 13.14

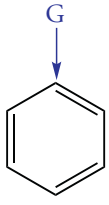
Which two of the four possible products should form in the nitration of tetralone?



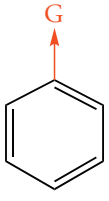
tetralone

13.5 INTERPRETATION OF THE EFFECT OF SUBSTITUENTS ON REACTION RATES

In the preceding section, we saw that a substituent influences both the rate and distribution of products in electrophilic aromatic substitution reactions. The ability of a substituent either to donate or withdraw electron density from the aromatic ring determines both the rate of the reaction and the product distribution. Let's consider the effect of a group, G, on the electron density of the benzene ring.



If G is an electron-donating group, the ring gains electron density

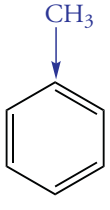


If G is a withdrawing group, the ring loses electron density

Any substituent that donates electron density to the aromatic ring makes the ring more reactive toward attack by an electrophile. A substituent that withdraws electron density from the aromatic ring decreases the electron density in the ring and makes it less reactive toward an attacking electrophile. Therefore, all activating groups listed in Table 13.1 are electron-donating groups. The deactivating groups are electron-withdrawing groups. Substituents can donate or withdraw electron density by inductive or resonance effects.

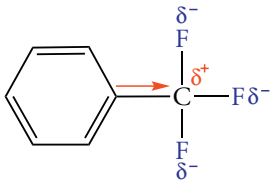
Inductive Effects of Substituents

We have seen that alkyl groups stabilize double bonds and carbocations by an inductive effect. We have also seen that an sp^2-hybridized carbon is electron withdrawing with respect to an sp^3-hybridized carbon. Therefore, it follows that alkyl groups also transfer electron density to a benzene ring by an inductive effect.



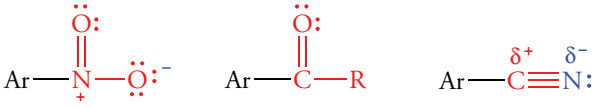
An alkyl group donates electron density to the ring by an inductive effect

The halogens are more electronegative than a benzene ring, so they withdraw electron density from a benzene ring. Any functional group with a partial positive charge on the atom bonded to the aromatic ring also withdraws electron density from the ring by an inductive effect. For example, the fluorine atoms of a trifluoromethyl group pull electrons away from the carbon atom to which they are bonded. To compensate, the carbon atom bearing the fluorine atoms withdraws electron density from the benzene ring.



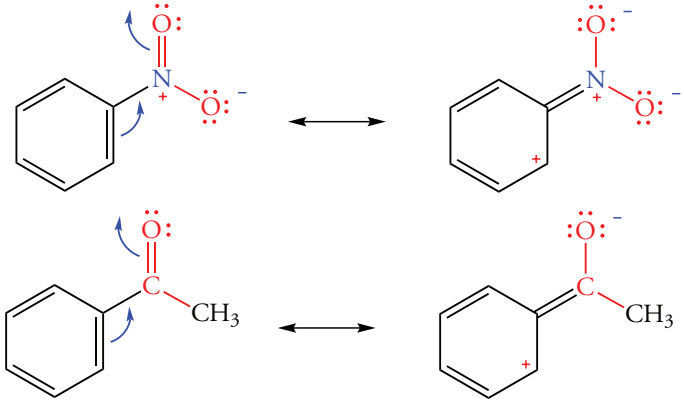
the trifluoromethyl group withdraws electron density from the benzene ring by an inductive effect

Nitro and cyano groups and any group with a carbonyl carbon atom bonded directly to the aromatic ring are electron-withdrawing substituents. The nitrogen atom of the nitro group has a formal positive charge. The carbon atom of a carbonyl or a cyano group has a partial positive charge.

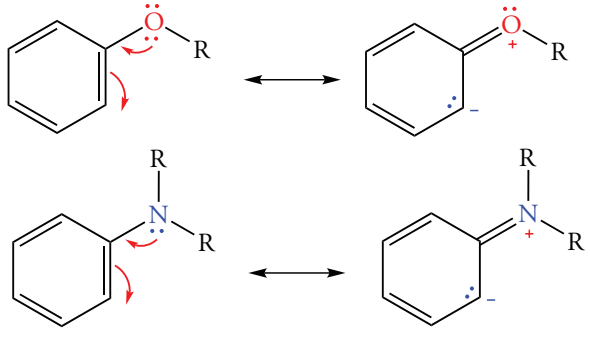


Resonance Effects of Substituents

Nitro, cyano, and carbonyl-containing groups have sp or sp^2-hybridized atoms bonded directly to the benzene ring. These atoms have π orbitals conjugated with the ring. First, consider the resonance effects of the nitro group. Since the carbon atoms of the benzene ring and the nitrogen and oxygen atoms of the nitro group are all sp^2-hybridized, an extended π system is possible. Because oxygen is more electronegative than nitrogen, the electron pair in a nitrogen-oxygen double bond can be delocalized onto the oxygen atom, leaving a positive charge on the aromatic ring. Because of this positive charge, the ring is less reactive toward electrophiles. A similar effect for the acyl group also makes the ring less reactive toward electrophiles.



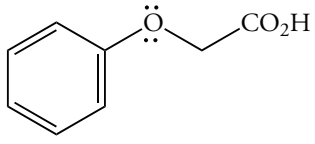
Groups with an unshared electron pair on the atom attached to the ring donate electrons to the aromatic ring by resonance. As a result, the ring develops a partial negative charge and becomes more reactive toward electrophiles. These substituents include hydroxyl (—OH), alkoxy groups such as methoxy (CH_3O—), and amino (—NH_2), or any substituted amino groups (—NHR, —NR_2).



Groups that can donate electrons by resonance are also electronegative. Therefore, they can also withdraw electron density from the ring by an inductive effect. These substituents take electron density from the ring by an inductive effect and give it back by resonance. A group containing a second period element bonded directly to the aromatic ring donates electrons by resonance. Examples include amino and hydroxyl groups. The 2p orbital of these second period atoms effectively overlaps with the 2p orbital of a ring carbon atom. As a result, donation of electrons by resonance is more important than inductive electron withdrawal. This situation, however, does not hold true for chlorine or bromine, which pull electrons out of the aromatic ring by an inductive effect. However, the 3p orbital of chlorine and the 4p orbital of bromine overlap poorly with the 2p orbital of carbon, so electron donation by resonance is less effective than the electron-withdrawing inductive effect.

Problem 13.15

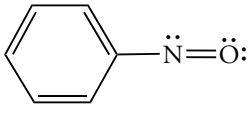
A selective herbicide that kills broad-leaf weeds is made by chlorinating phenoxyacetic acid. Is the substituent an activating or deactivating group?



phenoxyacetic acid

Problem 13.16

Is the nitroso group (—N=O) an activating or deactivating group? Consider both inductive and resonance interactions with the benzene ring.



nitrosobenzene

Sample Solution

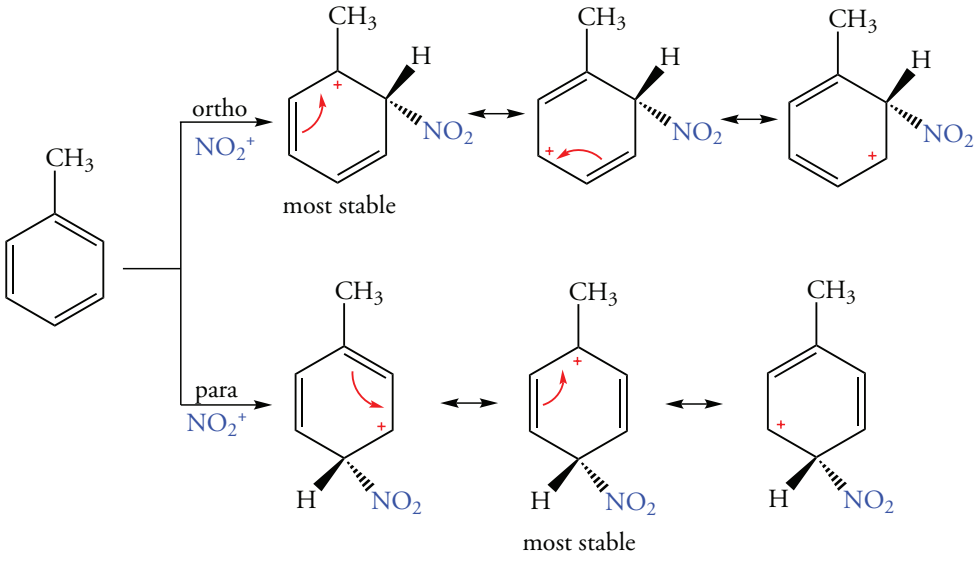
At first glance one might expect the nitroso group to behave like a nitro group. Both have a nitrogen atom directly bonded to the benzene ring and both have the electronegative oxygen atom bonded to it. However, there is no formal charge on the nitrogen atom of the nitroso group as there is in the nitro group. Thus, the nitroso group does not withdraw electrons as strongly as does the nitro group. Based only on inductive effects, the nitroso group should be less deactivating than the nitro group.

The nitroso group has a lone pair of electrons on the nitrogen atom that can be donated into the benzene ring. (The nitro group cannot donate electrons by resonance.) However, this effect is opposed by its electron-withdrawing inductive effect. Therefore, the properties of the nitroso group resemble those of the halogens. In fact, because nitrogen is a second period element, it effectively donates electrons to the ring by resonance.

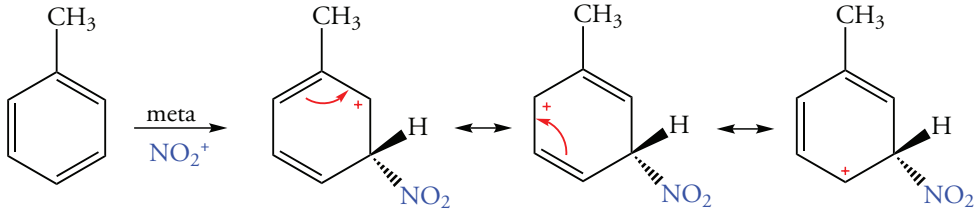
13.6 INTERPRETATION OF DIRECTING EFFECTS

We noted earlier that with the exception of the halogens ortho, para directors activate the ring toward electrophilic substitution by supplying electron density to the ring. But why are the ortho and para positions especially susceptible to attack? To answer this question, consider the stability of the cyclohexadienyl carbocation that forms in the first step of the electrophilic aromatic substitution mechanism. The regioselectivity of the reaction is controlled by the stability of the carbocation. To determine the stability of a cyclohexadienyl carbocation, we must compare all the possible resonance forms. Thus, we compare the stability of the intermediate carbocations resulting from attack at the ortho and para positions with those resulting when an electrophile attacks at the meta position.

First, we will consider the nitration of toluene at the ortho and para positions. Attack at either the ortho or the para position results in one resonance structure with a positive charge on the ring carbon atom bonded to the methyl group. This tertiary carbocation makes a major contribution to the stability of the resonance hybrid.



Now consider nitration at the meta position. The resonance structures show that positive charge cannot reside on the carbon atom attached to the methyl group. Only secondary carbocations are possible, and they are less stable than tertiary carbocations.



Cyclohexadienyl carbocations resulting from ortho or para substitution are more stable and form faster than the cyclohexadienyl carbocation resulting from meta attack. The reaction coordinate diagrams for the formation of all three cyclohexadienyl carbocations are shown in Figure 13.2. The methyl group donates electrons to the ring, making the intermediates more stable than the cyclohexadienyl carbocation derived from benzene. The formation of the ortho- and para-substituted products results from greater stabilization of the related intermediates compared to the intermediate leading to the meta-substituted product.

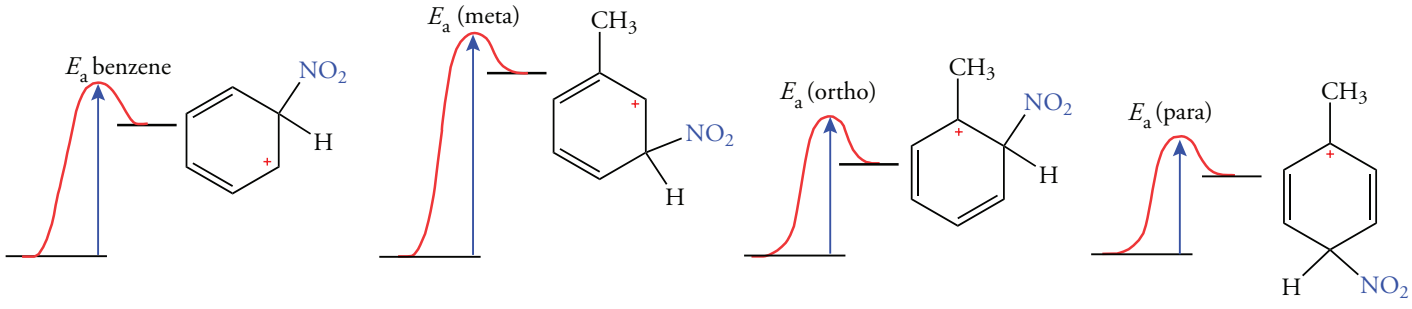
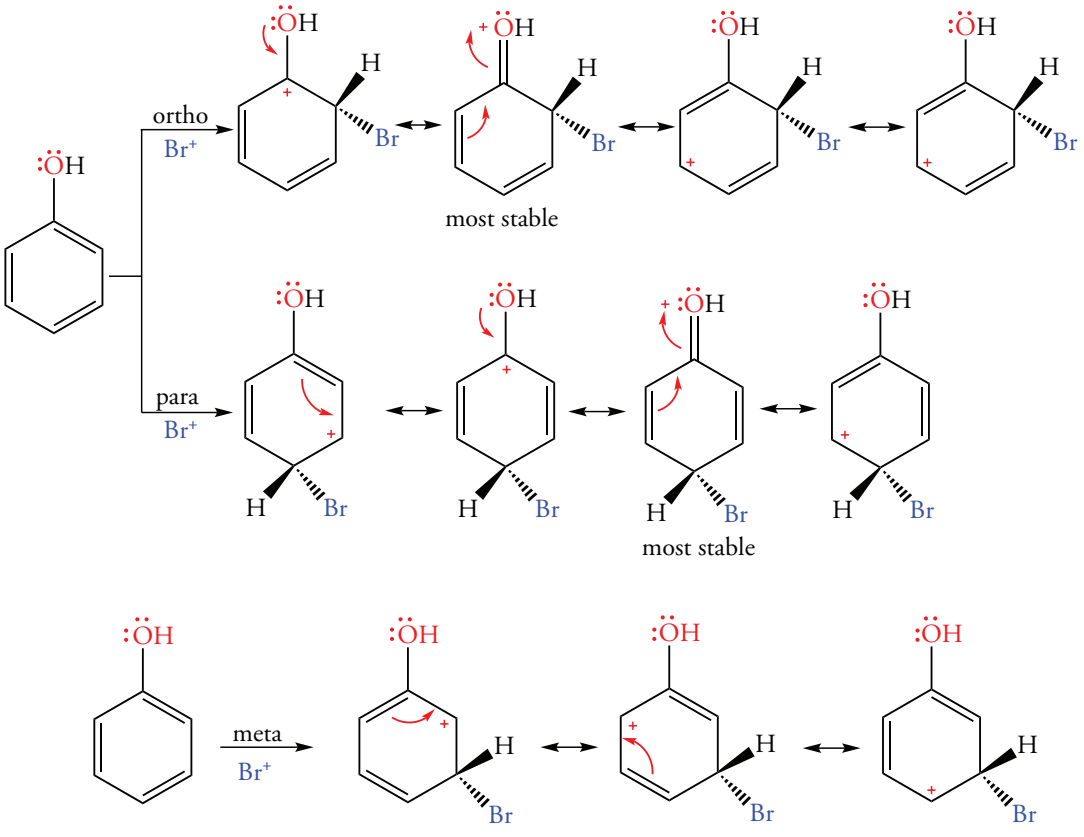
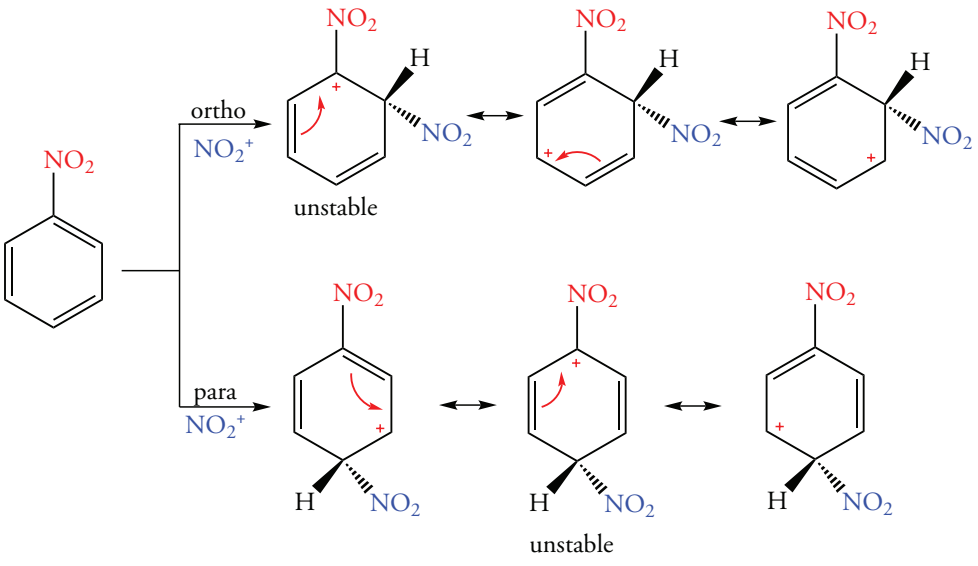


Figure 13.2 Transition State Energies for the Nitration of Toluene
Substitution at any position of toluene occurs at a faster rate than substitution of benzene. However, substitution occurs faster at the ortho and para positions than at the meta position.

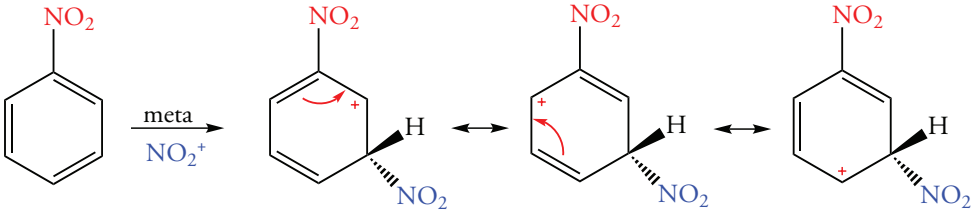
Next, let's consider the ortho, para-directing effect of a hydroxyl group or any other group that can donate an unshared pair of electrons by resonance. An attack either ortho or para to the hydroxyl group leads to an intermediate that is resonance-stabilized by the oxygen atom. As in the case of the methyl group, a contributing structure exists in which the positive charge resides on the carbon atom bonded to the substituent. An electron pair provided by oxygen stabilizes this positive charge. No such stabilization is possible for an electrophile that attacks meta to the hydroxyl group. Hence, ortho or para substitution occurs instead of meta substitution.



We saw in Table 13.1 that some substituents strongly deactivate the ring with respect to electrophilic aromatic substitution. All the strong deactivating groups withdraw electron density from the ring and are meta directors. Where does the preference for attack at the meta position come from in this case? First, let's consider the possible nitration of nitrobenzene at the ortho and para positions. In one of the resonance forms for the cyclohexadienyl carbocation resulting from ortho or para substitution, a positive charge resides on a carbon atom bonded to the original nitro group. The nitrogen atom of the nitro group has a formal positive charge and its proximity to the carbon atom bearing a positive charge makes these resonance forms unstable.



What about attack at the meta position? None of the resonance forms of the intermediate has a positive charge on the carbon atom bonded to the nitro group— whose nitrogen atom, we noted above, has the formal charge of +1. The resonance forms of the intermediates resulting from meta attack are therefore more stable overall than the resonance forms of the intermediates formed from ortho and para substitutions. Hence, meta substitution is favored.



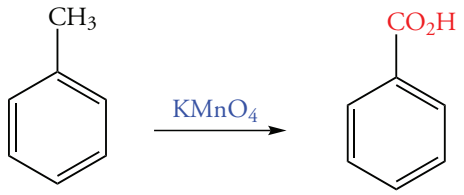
13.7 FUNCTIONAL GROUP MODIFICATION

Functional group modifications are important because electrophilic aromatic substitution can place only a few functional groups directly on an aromatic ring. Modifying a group already bonded to the aromatic ring can produce other groups. When a functional group changes, ortho, para- or meta-directing properties can also change, so functional group modification has wide ranging consequences.

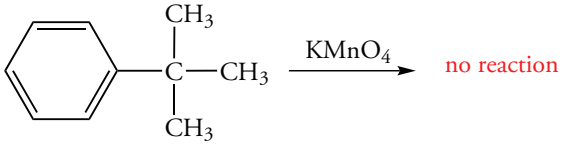
Alkyl Side Chain Oxidation

Although the aromatic ring affects the reactivity of the side chain, the ring itself is quite unreactive toward many reagents and remains intact. Oxidation of the side-chain alkyl groups of alkylbenzenes illustrates the special stability of the aromatic ring. We recall that potassium permanganate reacts with the π bonds of an alkene to give vicinal diols. Potassium permanganate does not oxidize the benzene ring. However, under vigorous conditions, the alkyl side chain is totally oxidized to produce a carboxylic acid at the site of the alkyl group. When two or more alkyl groups are present on a ring, they are all oxidized. The benzene ring, however, remains unscathed!

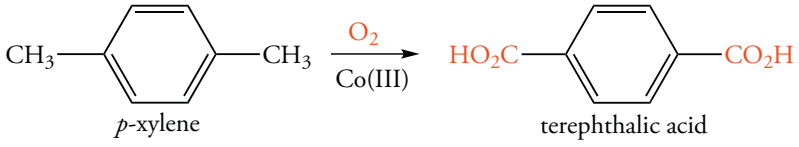
For example, a methyl group introduced by a Friedel–Crafts alkylation can be changed to a carboxylic acid group. This reaction converts an ortho, para-directing methyl group into a meta-directing carboxylic acid group (—CO_2H).



Potassium permanganate does not, however, oxidize tertiary alkyl groups, because they lack the benzylic hydrogen atom required to initiate the oxidation process.

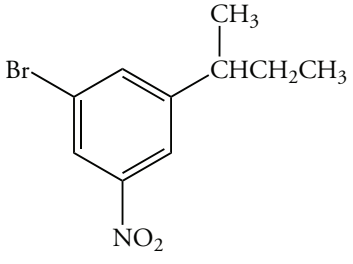


Permanganate is not the only strong oxidizing agent that can oxidize an alkyl group on a benzene ring. For example, the oxidation of *p*-xylene to prepare terephthalic acid, used in production of polyester fibers such as Dacron, is an important industrial process. Air serves as the oxidizing agent in a reaction catalyzed by cobalt(III) salts.



Problem 13.17

What is the product for the oxidation of the following compound with potassium permanganate?

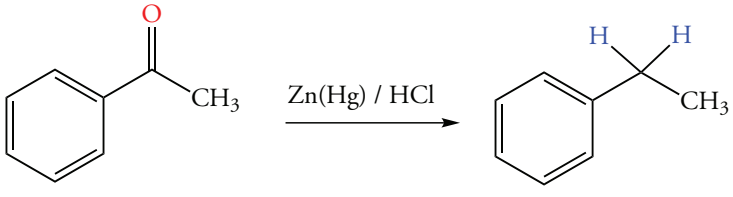


Sample Solution

Potassium permanganate oxidizes the side chain sec-butyl group to give a —CO_2H group. The product of the reaction is 3-bromo-5-nitrobenzoic acid.

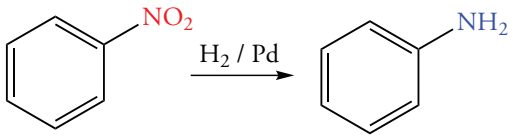
Conversion of an Acyl Group to an Alkyl Group

An acyl group bonded to a benzene ring can be converted into an alkyl group by reduction with a zinc–mercury amalgam in HCl. Since an acyl group has a carbonyl carbon atom directly attached to the ring, it is a deactivating, meta-directing substituent. However, an alkyl group is an activating, ortho, para-directing group.

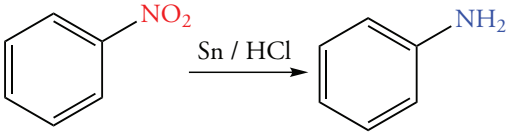


Reduction of a Nitro Group to an Amino Group

Electrophilic aromatic substitution can attach a nitro group directly to a benzene ring, but cannot attach an amino group in one step. However, after a nitro group is introduced, it can easily be reduced to an amino group, producing an aniline. This reaction transforms a strongly deactivating meta-directing nitro group into a strongly activating ortho, para-directing amino group.

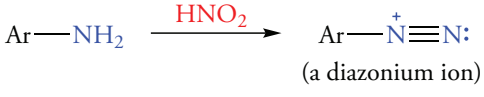


We can also convert a nitro group to an amino group by treating it with tin in the presence of hydrochloric acid.

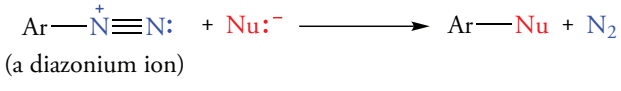


Converting an Amino Group to a Diazonium Ion: The Sandmeyer Reaction

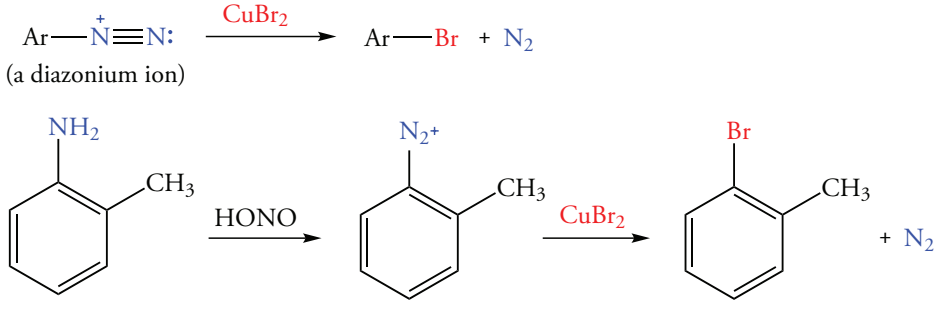
If an aromatic ring has an amino group, the possibilities for further functional group modifications vastly increase. The amino groups of anilines can be converted into many other groups. The door to other functional groups is opened by converting the amino group into an aryl diazonium ion, $Ar—N_2^+$. The diazonium ion results from the reaction of an aniline with nitrous acid (HNO_2), prepared by treating sodium nitrite with sulfuric acid. This step is called **diazotization**.



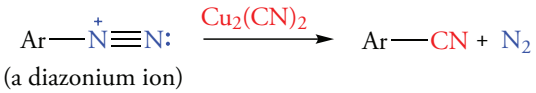
In 1884, the German chemist Traugott Sandmeyer found that diazonium ions react with nucleophiles supplied in the form of a Cu(I) salt. These nucleophiles replace the diazonium group and release nitrogen gas. These reactions are known collectively as the **Sandmeyer reaction**.

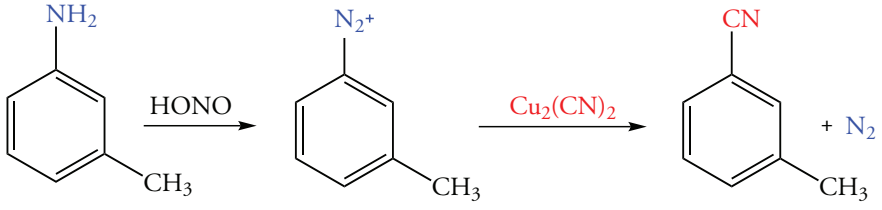


For example, an aromatic diazonium ion can be treated with Cu_2Cl_2 to yield chlorobenzene or with Cu_2Br_2 to give bromobenzene.

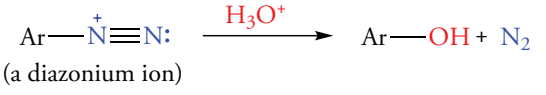


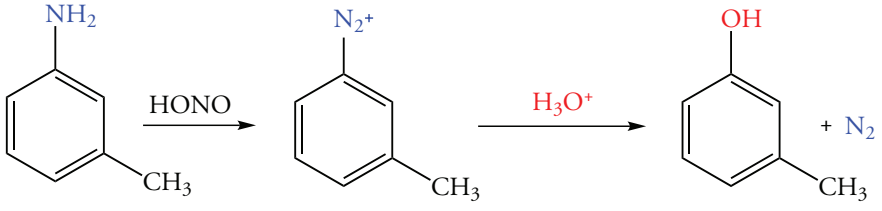
Copper(I) cyanide reacts with aryl diazonium ions to give aryl nitriles.



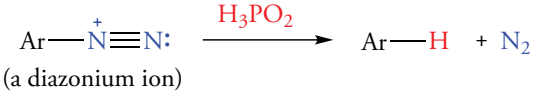


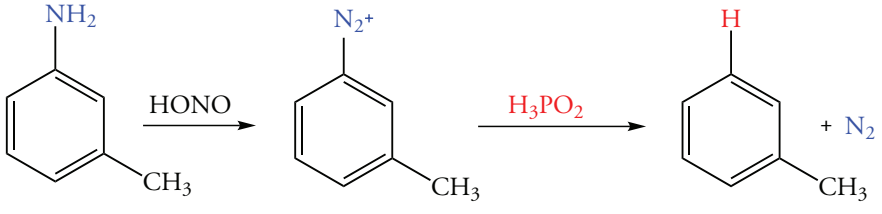
Aryl diazonium compounds react with hot aqueous acid to give phenols. This is the best way to attach an —OH group to an aromatic ring.





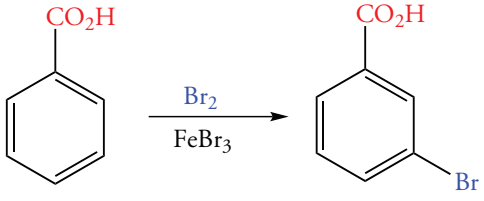
Treating Aryl diazonium compounds with hypophosphorous acid (H_3PO_2) replaces the diazonium group with a proton. This process can be used to remove the amino substituent from the aromatic ring after its role as a directing group in a synthesis concludes.



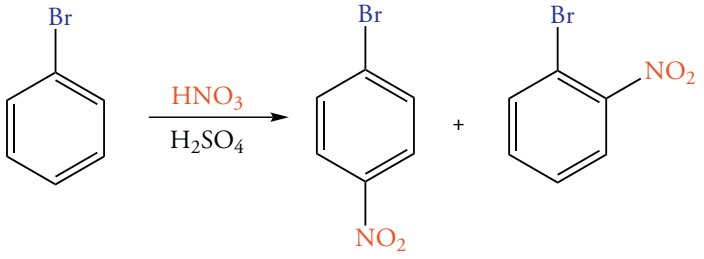


13.8 SYNTHESIS OF SUBSTITUTED AROMATIC COMPOUNDS

The goal of chemical synthesis is preparation of a desired compound in high yield, with minimal formation by-products. The synthesis of aromatic compounds using starting materials with a meta-directing group meets these criteria. For example, we can the convert benzoic acid to *m*-bromobenzoic acid in one step by treating benzoic acid with bromine and iron(III) bromide. The product is a solid (mp 155 °C), which we can separate from the small amounts of ortho- and para-substituted isomers by recrystallization.



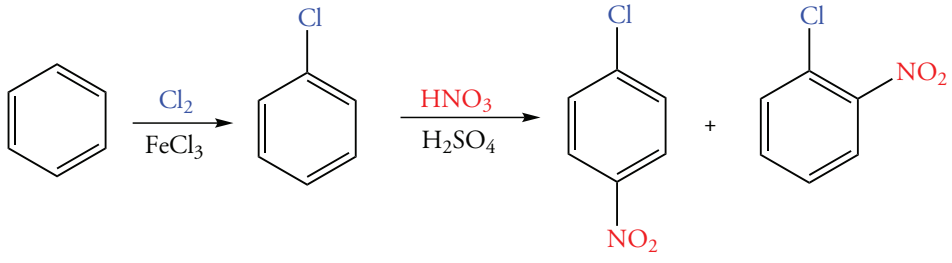
Substitution reactions of compounds having ortho, para-directing groups invariably give mixtures of ortho and para isomers. For example, treating bromobenzene with bromine and iron(III) bromide gives a mixture of *o*- and *p*-bromonitrobenzene. However, para isomers usually have higher melting points and lower solubilities than ortho isomers for any given pair of compounds. The melting point of o-bromonitrobenzene is 43 °C, and the melting point of *p*-bromonitrobenzene is 127 °C, so the less-soluble para isomer can easily be isolated by recrystallization.



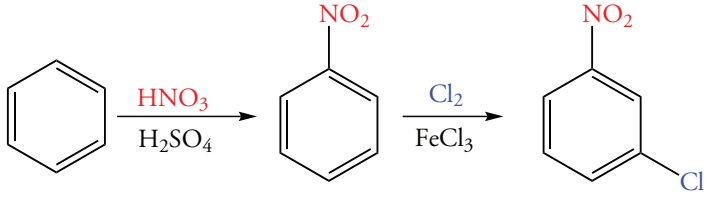
p-bromonitrobenzene *o*-bromonitrobenzene

Strategies for Aromatic Synthesis: Order of Group Substitution

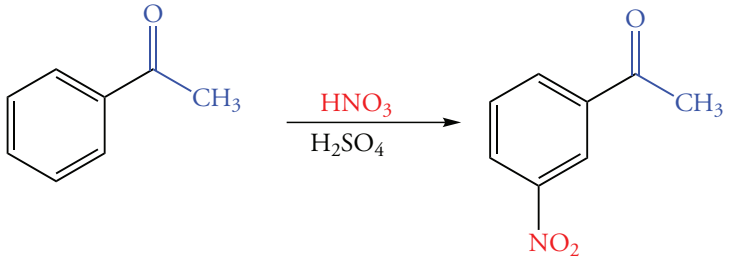
Suppose that we want to prepare an aromatic compound having two or more substituents. We begin with an analysis of the ortho, para- or meta-directing characteristics of the substituents we plan to add. For example, consider the synthesis of *m*-chloronitrobenzene. A nitro group is meta directing, a chloro group is ortho, para directing. The order in which we add these groups is clearly important. If chlorination precedes nitration, the entering nitro group will be directed to form mostly *o*-chloronitrobenzene and *p*-chloronitrobenzene. Very little of the desired meta isomer will form.



Adding the nitro group first and the chloro group second avoids this problem because the nitro group is a meta director, the entering chlorine atom enters at the meta position.

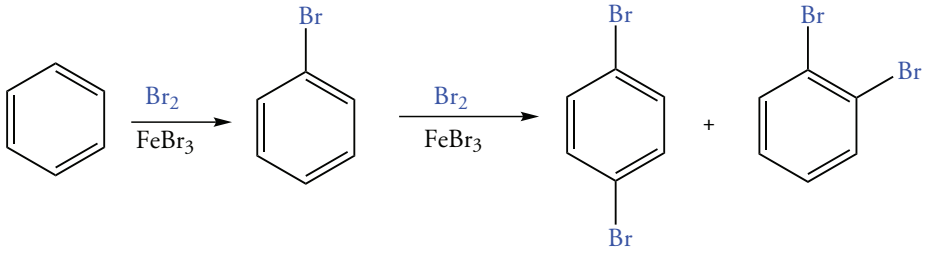


We also have to beware of the limitations of each type of substitution process. We recall that Friedel–Crafts acylation does not occur when the ring contains a meta-directing group. For example, we can make *m*-nitroacetophenone by nitration of acetophenone, but not from Friedel–Crafts acylation of nitrobenzene.

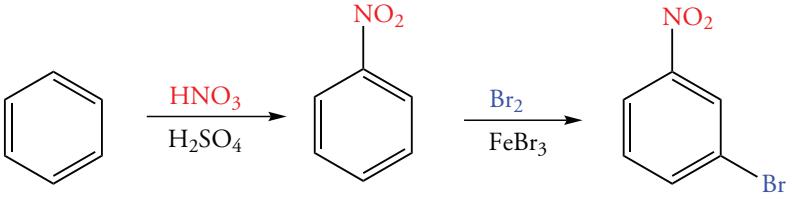


Modifying Ring Substituents

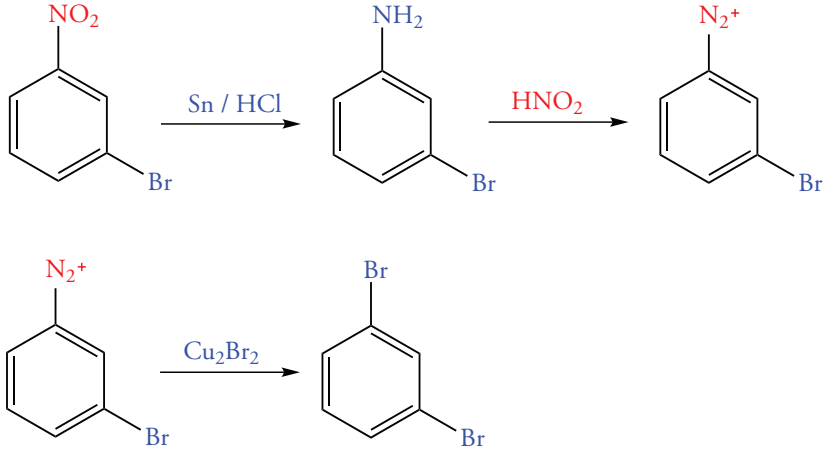
Now we'll examine a task that appears at first glance to be impossible, the synthesis of *m*-dibromobenzene. Why impossible? Because the bromo groups are meta to each other, but bromine is an ortho, para director! Direct bromination of benzene would place the first bromine atom on the ring, and it would then direct the second bromine atom into the ortho or para position.



However, we know that a nitro group is a meta director. So, we first make nitrobenzene, then brominate it to obtain *m*-bromonitrobenzene.



We know that a nitro group can be converted to a bromo group by (1) reducing the nitro group to an amino group, (2) converting the amino group to a diazonium group, and (3) treating the diazonium compound with copper(I) bromide. The procedure requires several steps, but it accomplishes the apparently impossible task of preparing *m*-dibromobenzene.



Problem 13.18

Which of the following procedures will yield 4-chloro-2-ethylnitrobenzene?
(a) chlorination of *o*-ethylnitrobenzene
(b) nitration of *m*-chloroethylbenzene
(c) Friedel–Crafts alkylation of *p*-chloronitrobenzene

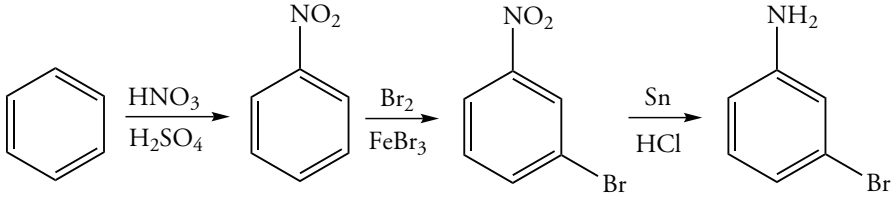
Problem 13.19

Devise a synthesis of *m*-bromoaniline starting from benzene.

Sample Solution

Bromine, which is an ortho, para director, can be introduced directly onto the benzene ring by reaction with bromine and $FeBr_3$. The amino group of aniline is also an ortho, para director, but it can only be introduced by first nitrating benzene and then reducing the nitro compound.

Bromination of benzene followed by nitration gives a mixture of *o*- and *p*-bromonitrobenzene. The meta isomer is not formed. However, nitration gives nitrobenzene, whose substituent directs subsequent electrophiles to the meta position. Thus, bromination of nitrobenzene followed by reduction of the product gives *m*-bromoaniline.



Problem 13.20

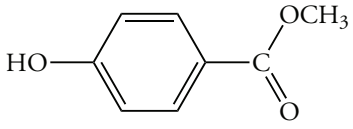
Devise a synthesis of each of the following compounds from benzene.

(a) *p*-Nitrobenzoic acid (b) *m*-Bromophenol (c) *m*-Bromochlorobenzene

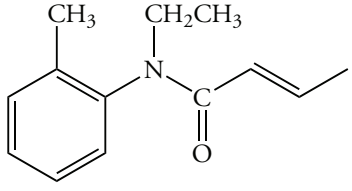
EXERCISES

Nomenclature of Aromatic Compounds

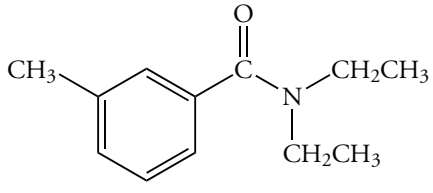
13.1 Identify each of the following as an ortho-, meta-, or para-substituted compound.
(a) Methylparaben, a food preservative used to protect food against molds



(b) Crotamiton, used in creams for topical treatment of scabies

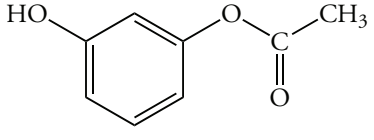


(c) Diethyltoluamide, an insect repellent

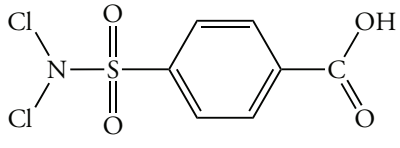


13.2 Identify each of the following as an ortho-, meta-, or para-substituted compound.

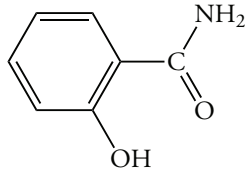
(a) Resorcinol monoacetate, a germicide used to treat skin conditions



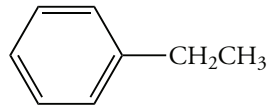
(b) Halazone, used to disinfect water

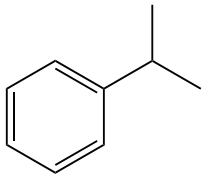


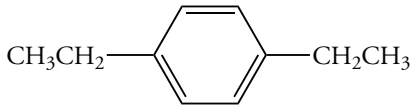
(c) Salicylamide, an analgesic

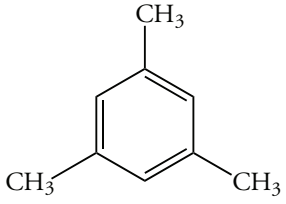


13.3 Name each of the following compounds.

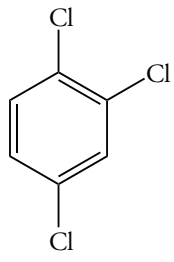
(a) 

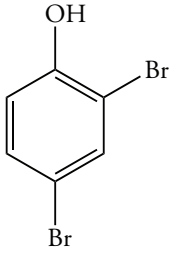
(b) 

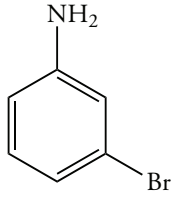
(c) 

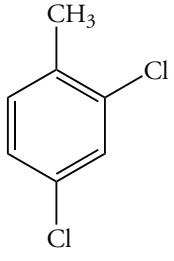
(d) 

13.4 Name each of the following compounds.

(a) 

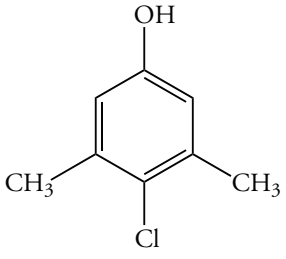
(b) 

(c) 

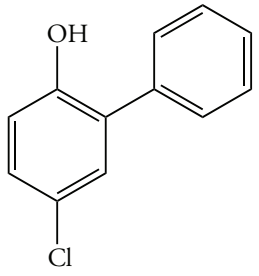
(d) 

13.5 Name each of the following compounds.

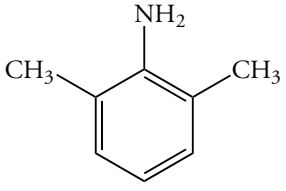
(a) An antiseptic agent used to treat athlete's foot



(b) A disinfectant



(c) A compound used to make a local anesthetic



13.6 Draw the structure of each of the following compounds.
(a) 5-Isopropyl-2-methylphenol, found in oil of marjoram
(b) 2-Isopropyl-5-methylphenol, found in oil of thyme
(c) 2-Hydroxybenzyl alcohol, found in the bark of the willow tree

13.7 Draw the structure of 3,4,6-trichloro-2-nitrophenol, a lampricide used to control sea lampreys in the Great Lakes.

13.8 *N*,*N*-Dipropyl-2,6-dinitro-4-trinuoromethylaniline is the IUPAC name for Treflan, a herbicide. Draw its structure. (The prefix *N* signifies the location of a substituent replacing hydrogen on a nitrogen atom.)

Electrophiles

13.9 Some activated rings may be hydroxylated by reacting hydrogen peroxide (H_2O_2) with acid. What is the formula of the electrophile? How does it form?

13.10 Reactive aromatic rings can be iodinated using iodine monochloride (ICl). What is the electrophile?

13.11 Benzene reacts with mercuric acetate to give phenylmercuric acetate using perchloric acid ($HClO_4$) as a catalyst. What is the electrophile? How does it form?

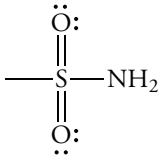
13.12 Treating an aromatic rings with *tert*-butyl alcohol, $(CH_3)_3COH$, in acid solution places a tertiary butyl group on the ring. What is the formula of the electrophile? How does it form?

Properties of Ring Substituents

13.13 Some activated rings may be hydroxylated by reacting hydrogen peroxide (H_2O_2) with acid. What is the formula of the electrophile? How does it form?

13.14 Is the thiomethyl group, —S—CH_3, an activating or deactivating group. Will it be ortho, para directing or meta directing?

13.15 The sulfonamide group is found in sulfa drugs. Is it an activating or deactivating group. Will it be ortho, para directing or meta directing?



13.16 Nitration of *N*,*N*-dimethylaniline, $C_6H_5N(CH_3)_2$, in 85% sulfuric acid gives a meta nitro compound as the major product. What is the structure of the ring substituent responsible for the orientation of the nitro product?

13.17 The percentages of meta nitro product formed in the nitration of benzene compounds containing CH_3—, CH_2Cl—, $CHCl_2$—, and CCl_3— groups are 5%, 16%, 34%, and 64%, respectively. Explain this trend in the data.

Reagents for Electrophilic Substitution

13.18 What reagent is required for each of the following reactions? Write the structure of the major product(s) expected from each reaction.
(a) bromination of anisole (b) sulfonation of toluene
(c) nitration of benzoic acid (d) acetylation of bromobenzene

13.19 What reagent is required for each of the following reactions? Write the structure of the principal product(s) expected from each reaction.
(a) Chlorination of bromobenzene (b) Friedel–Crafts methylation of anisole
(c) Friedel–Crafts acetylation of toluene (d) Nitration of trifluoromethylbenzene

Friedel-Crafts Alkylation and Acylation

13.20 Write the structure of the product resulting from the Friedel–Crafts alkylation of benzene using chlorocyclohexane and aluminum trichloride.

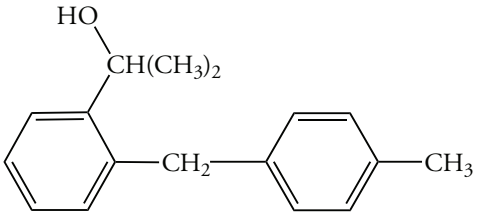
13.21 What product results from the Friedel–Crafts alkylation of benzene using 1-chloro-2-methylpropane and aluminum trichloride?

13.22 Alkylation of benzene can be accomplished using an alkene such as propene and an acid catalyst. Identify the electrophile and the product.

13.23 Write the structure of the product formed by alkylation of *p*-methylanisole using 2-methyl-l-propene and sulfuric acid.

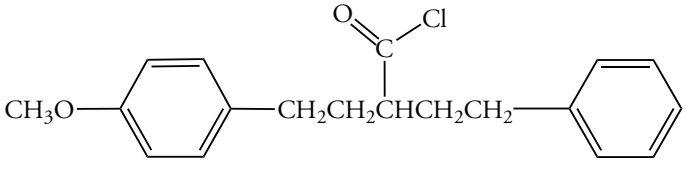
13.24 Reaction of toluene with isopropyl alcohol, $(CH_3)_2CHOH$, using sulfuric acid gives a mixture of two isomers with the molecular formula $C_{10}H_{13}$. Write the structures of these compounds. How does the electrophile form?

13.25 The following compound reacts with sulfuric acid to give a tricyclic hydrocarbon with molecular formula $C_{17}H_{18}$. Write its structure.



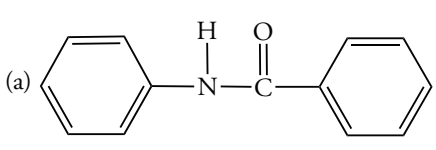
13.26 4-Phenylbutanoyl chloride reacts in carbon disulfide with aluminum trichloride to give a ketone with molecular formula $C_{10}H_{10}O$. Write the structure of the product.

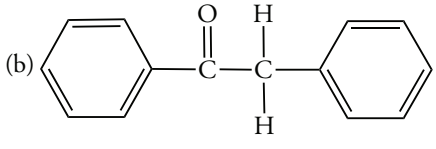
13.27 The following compound undergoes an intramolecular Friedel–Crafts acylation to give a cyclic ketone. Write the structure of the product.



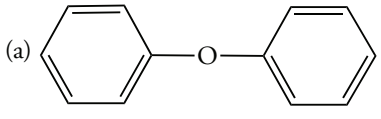
Electrophilic Aromatic Substitution Reactions

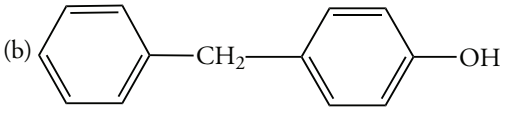
13.28 Indicate on which ring and at what position bromination of each compound will occur.



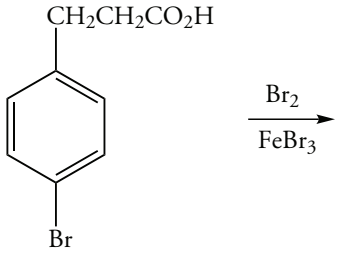


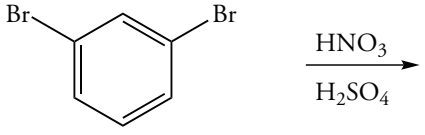
13.29 Indicate on which ring and at what position nitration of each compound will occur.

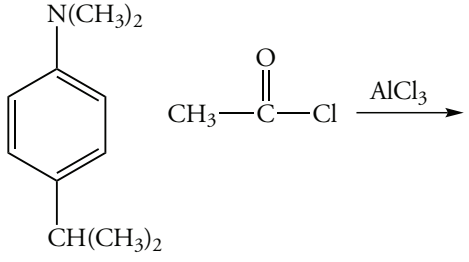




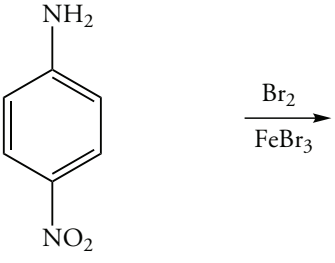
13.30 Write the structure of the major product of each of the following reactions, assuming that only monosubstitution occurs.

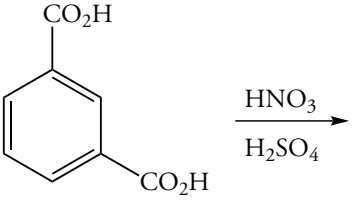
(a) 

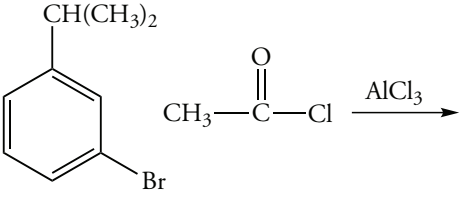
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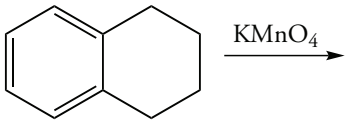
13.31 Write the structure of the major product of each of the following reactions, assuming that only monosubstitution occurs.

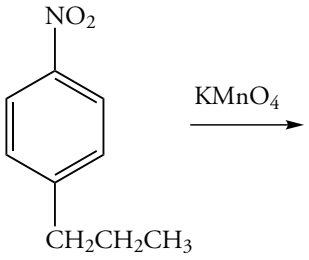
(a) 

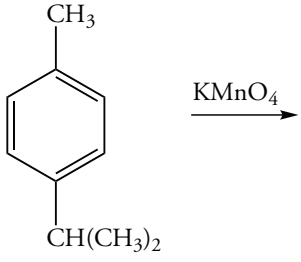
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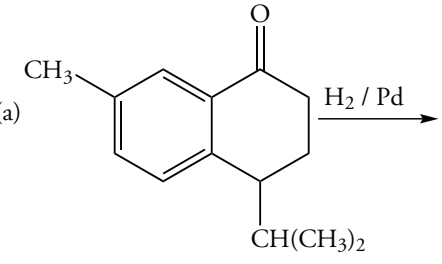
13.32 Write the product of the reaction of each of the following compounds with potassium permanganate.

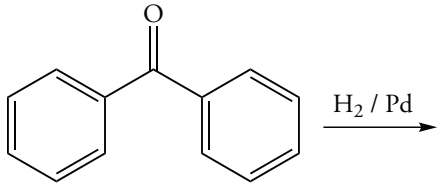
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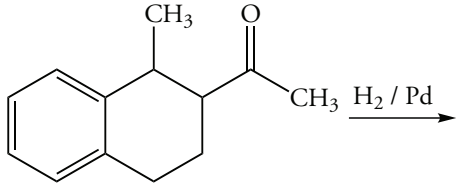
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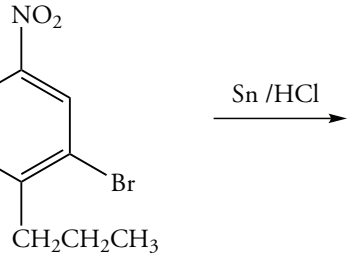
13.33 Write the product of the reaction of each of the following compounds with zinc–mercury amalgam and HCl.

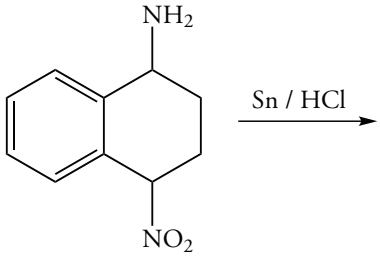
(a) 

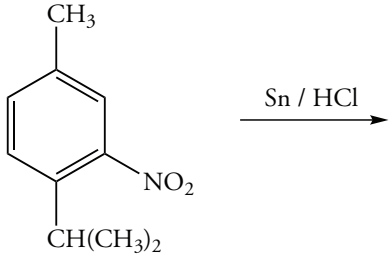
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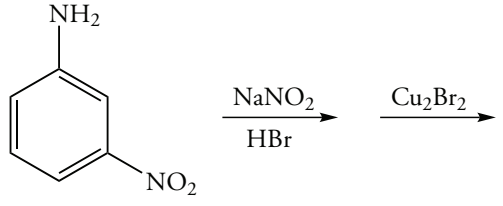
13.34 Write the structure of the major product of each of the following compounds with tin and HCl.

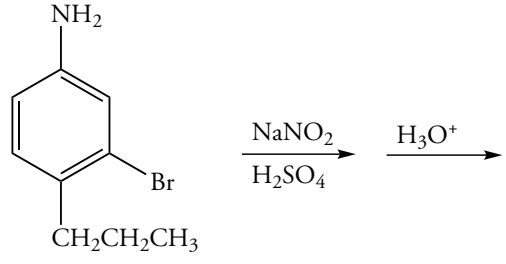
(a) 

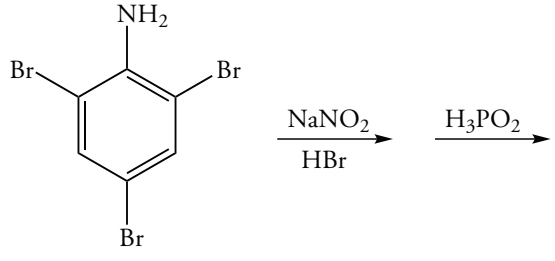
(b) 

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13.35 Write the final product of the sequence of reactions for each of the following compounds.

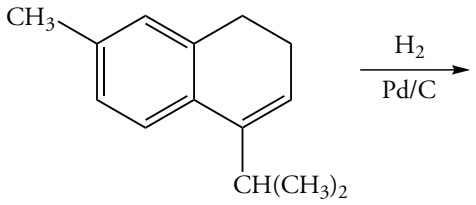
(a) 

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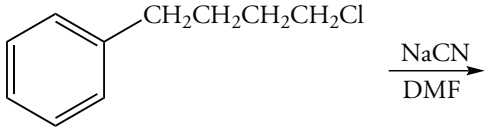
(c) 

13.36 Write the final product for each of the following reactions.

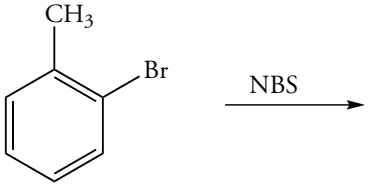
(a)



(b)



(c)



Synthesis of Aromatic Compounds

13.37 What reagent is required for each of the following reactions? Will an ortho and para mixture of products or the meta isomer predominate?
(a) Nitration of bromobenzene (b) Sulfonation of nitrobenzene
(c) Bromination of ethylbenzene (d) Methylation of anisole

13.38 What reagent is required for each of the following reactions? Will an ortho and para mixture of products or the meta isomer predominate?
(a) Bromination of benzoic acid (b) Acetylation of isopropylbenzene
(c) Nitration of acetophenone (d) Nitration of phenol

13.39 Starting with benzene, describe the series of reagents and reactions required to produce each of the following compounds.
(a) *p*-Bromonitrobenzene (b) *m*-Bromonitrobenzene
(c) *p*-Bromoethylbenzene (d) *m*-Bromoethylbenzene

13.40 Starting with benzene, describe the series of reagents and reactions required to produce each of the following compounds.
(a) *m*-Bromobenzenesulfonic acid (b) *p*-Bromobenzenesulfonic acid
(c) *p*-Nitrotoluene (d) *p*-Nitrobenzoic acid

13.41 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(a) 3,5-Dinitrochlorobenzene (b) 2,4,6-Trinitrotoluene (c) 2,6-Dibromo-4-nitrotoluene

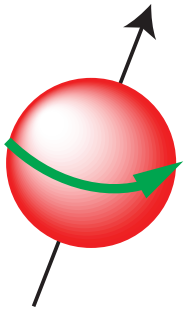
13.42 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(a) 2,4,6-Tribromobenzoic acid (b) 2-Bromo-4-nitrotoluene (c) l-Bromo-3,5-dinitrobenzene

13.43 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(a) *m*-Bromophenol (b) *m*-Bromoaniline (c) *p*-Methylphenol

13.44 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(a) *m*-Bromochlorobenzene (b) *p*-Methylbenzonitrile (c) 3,5-Dibromotoluene

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14 Methods for Structure Determination Nuclear Magnetic Resonance and Mass Spectrometry

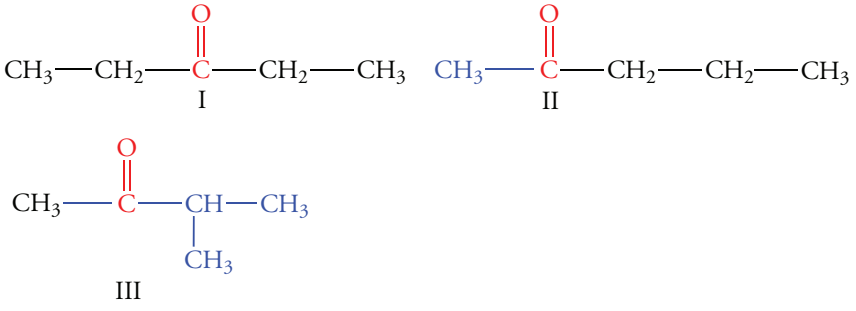


14.1 STRUCTURE DETERMINATION

Of all the tools available to organic chemists, none is more powerful than spectroscopic methods for structure determination. In Chapter 2, we saw that infrared spectroscopy provides us with a rapid way to identify functional groups. In this chapter, we focus upon nuclear magnetic resonance and mass spectrometry. These instrumental methods allow us to determine molecular structures.

At one time, the structures of organic compounds were deduced by chemical reactions that related a compound of unknown structure to compounds whose structures were known. Many chemical reactions had to be carried out to accomplish this task. It was possible to reason backward to postulate what the structure of the original compound must have been to yield the observed products. Structure determination by chemical reactions is a time-consuming process. For example, if we want to determine the structure of a relatively simple compound with molecular formula $C_5H_{10}O$, we will find that 88 isomers are possible, including ethers, alcohols, aldehydes, and ketones. Many chemical reactions would be required to identify the functional group and to determine the hydrocarbon skeleton. Structure determination by chemical reactions also has another severe limitation: each reaction destroys part of the sample of the unknown compound. Spectroscopic structure determination requires only small amounts of a compound, and the experimental methods require very little time compared to the arduous process of determining a molecular structure by a series of chemical reactions.

We know that infrared spectroscopy reveals the functional groups in a compound. For example, if infrared spectroscopy reveals that the structure of a compound with molecular formula $C_5H_{10}O$ is a ketone, the number of possible isomers drops from 88 to a more manageable 3 compounds, which are shown below. These compounds can be easily distinguished by nuclear magnetic resonance spectroscopy, NMR.



Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00014-0
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Mass spectroscopy is also a powerful tool for determining molecular structure. It provides information about molecular structure cannot be obtained by IR or NMR spectroscopy. First and foremost often provides us with the molecular mass of a compound. A compound can be analyzed in the solid, liquid, or gas phase same of a compound by mass spectroscopy, but we will discuss only vapor samples. The basic principles are the same. Taken together, these experimental methods allow us to determine the structure of virtually any compound.

14.2 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Nuclear magnetic resonance spectroscopy provides considerable information about the structure of a compound because it directly probes the nuclei of the entire carbon framework in C-13 NMR or the nuclei of the bonded hydrogen atoms in proton NMR. Nuclear magnetic resonance depends on a property called **nuclear spin**. Nuclear spin varies from element to element and among isotopes of an element. Those nuclei with no nuclear spin, such as ^{12}C and ^{16}O, are NMR inactive, as are all nuclei with both an even number of protons and an even number of neutrons. A nucleus with a spin is characterized by a spin quantum number that may be either a half-integer or an integer. Hydrogen has a spin number of ½. Like the electron, the hydrogen atom can be detected with two different spin orientations in a magnetic field.

Different spin numbers also occur with carbon isotopes. Most carbon atoms in organic molecules are ^{12}C and cannot be detected by NMR spectroscopy. Their locations in a structure must therefore be inferred from the NMR of the hydrogen atoms bonded to them. However, about 1% of carbon atoms are ^{13}C, and they can be detected by NMR. NMR studies of ^{13}C in organic compounds provide confirmatory support for a structure proposed using NMR of hydrogen atoms. Because some carbon atoms are not bonded to hydrogen atoms, the direct detection of carbon using ^{13}C NMR spectroscopy is important. For example, the presence of a carbonyl group may be inferred from the behavior of a hydrogen atom bonded to an adjacent carbon atom. However, ^{13}C NMR spectroscopy "sees" the carbonyl carbon atom itself.

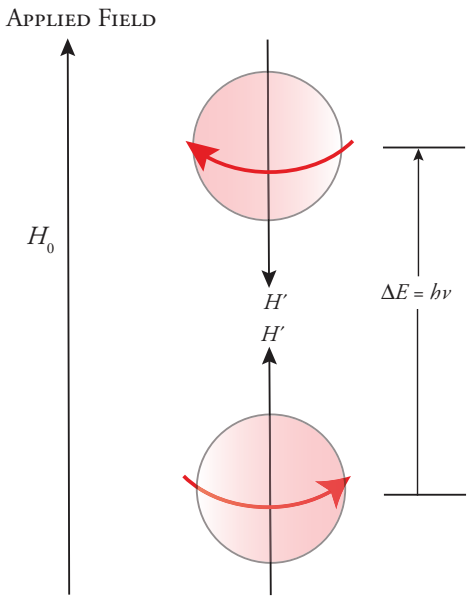
Detecting Nuclear Spin

The magnetic field of an ^{1}H nucleus can spin around its axis in either a clockwise or a counterclockwise direction. Because the nucleus has a positive charge, a magnetic moment results from the spinning nucleus. Thus, hydrogen nuclei are tiny magnets with two possible orientations in the presence of an external magnetic field. They may be aligned with the external magnetic field—the lower energy state—or against it. If a hydrogen nucleus with its magnetic moment aligned with the external field is irradiated with electromagnetic radiation in the radio frequency range, it absorbs energy, and its spin changes so that its magnetic field is opposed to the applied external field (Figure 14.1). Hence, the absorption of energy results in a higher energy state for the hydrogen nucleus.

The energy associated with electromagnetic radiation in the radio-frequency range is very small. For example, the radio frequency required to change the spin of a proton depends on the strength of the external magnetic field. Modern instruments have huge field strengths that can only be achieved by superconducting magnets that operate at the temperature of liquid helium (4 K).

Figure 14.1 Absorption of Electromagnetic Radiation by a Nucleus

When the magnetic moment of a spinning nucleus (H') is aligned with the magnetic field of an NMR spectrometer, (H_0) low energy results. Absorption of specific frequency causes a change in the spin of the nucleus and results in a magnetic moment opposed to the magnetic field of the instrument. This is a higher energy state.

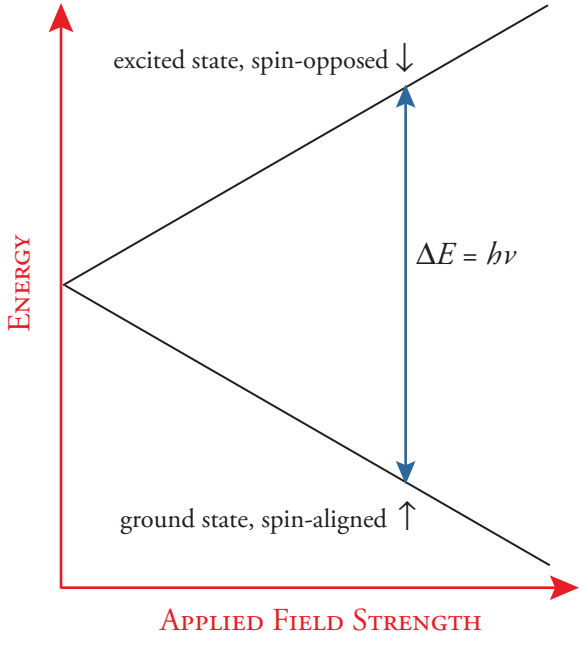


The Role of Magnetic Field Strength in NMR

Since the spin of a proton is ±½, the nucleus has only two orientations with respect to the applied magnetic field. The energy difference between the two spin states—either aligned or opposed to the applied field—varies continuously with energy (Figure 14.2).

Figure 14.2 Effect of Field Strength on Energy Differences

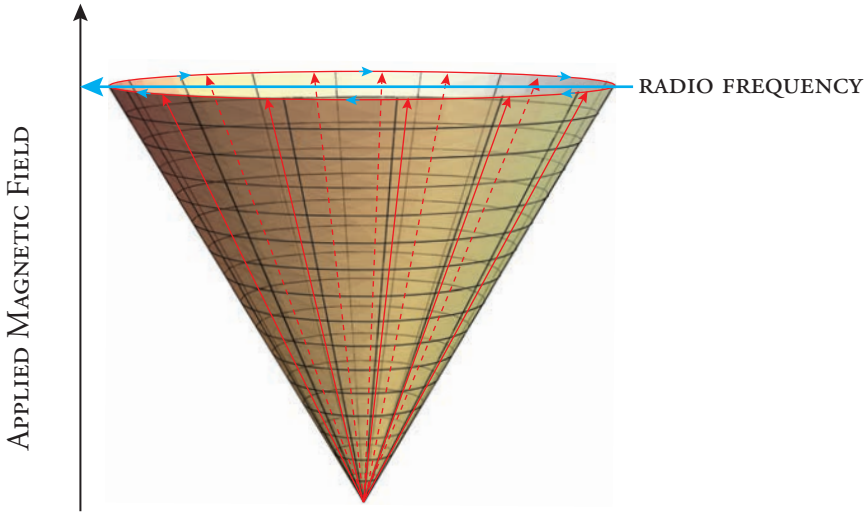
When the magnetic moment of a nucleus is aligned with the applied magnetic field of an NMR spectrometer, the nucleus is in its ground state. When it absorbs energy, its magnetic field opposes that of the applied field, and the nucleus is in an excited state. The energy difference depends on the strength of the applied field. Although only two spin orientations are possible, the energy difference increases continuously as the applied magnetic field increases.



When we look at Figure 14.1, we see a schematic diagram in which the field of the nucleus is spinning around the axis of the applied field, a phenomenon called *precession*. The precessing field sweeps out a cone (Figure 14.3). The precession of the nuclear magnetic field is analogous to the precession of a top that rotates around the axis of the local geometric field. The rate of precession provides the clue to the NMR experiment. If an applied radio frequency is applied to the sample at right angles to the direction of the applied magnetic field, then when the energy of the precession frequency equals the energy difference between the ground and excited states, the system absorbs energy, and there is a transition from the ground to the excited states. This is the *resonance* that gives rise to the name nuclear magnetic resonance spectroscopy. A magnetic field strength of 12.5 T corresponds to a radio frequency of 500 MHz. The instrument detects this transition, which gives a "peak" in the NMR spectrum. How can we distinguish nonequivalent protons and carbons? That story begins to unfold in the following section.

Figure 14.3 The Nuclear Precession Frequency

The applied magnetic field of the instrument interacts with the magnetic field of the nucleus, which causes the nucleus to precess (rotate as a top rotates) around the axis of the applied field. The rate of precession depends on the strength of the applied field. A radio frequency is applied at right angles to the applied field. When the energy difference between the ground and excited states ($\Delta E = h\nu$) of the applied field matches the energy of the radio frequency, the system absorbs energy.



Modern instruments subject the sample to a sequence of electromagnetic pulses across the range of energies required to obtain absorptions for the protons in a molecule. This process is analogous to striking a bell with a mallet. All of the vibrations of the bell, which give it a unique musical signature, are excited in the process. The frequencies responsible to the sound are analyzed by a mathematical method called Fourier transform analysis. Similarly, an NMR spectrum is generated by Fourier transform analysis of the nuclear responses of the hydrogens in the molecule to the sequence of electromagnetic pulses.

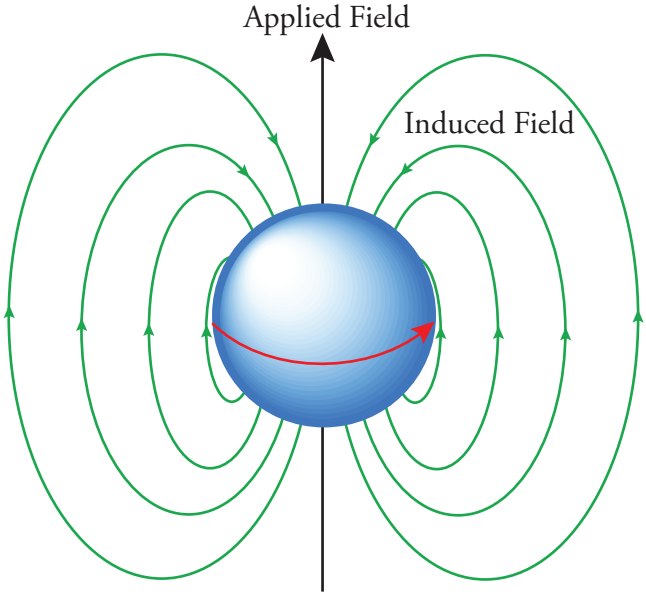
14.3 THE CHEMICAL SHIFT

At any given radio frequency, the magnetic field strength required for a given hydrogen atom in a molecule to absorb energy depends upon its chemical environment. If all hydrogen atoms absorbed the same electromagnetic radiation in an NMR experiment at the same magnetic field strength, then only a single absorption would be observed. As a consequence, we would only know that the molecule contained hydrogen atoms, and we would learn nothing about the molecule's structure.

The hydrogen nuclei in molecules are surrounded by electrons. The circulation of electrons around a nucleus sets up a small, induced, *local* magnetic field opposite to the applied external magnetic field (Figure 14.4). The local field alters the magnetic environment of the hydrogen nuclei. When a local field opposes the external magnetic field, we say that the nucleus is *shielded*. The effective field "felt" by the nucleus in a chemical bond is the applied magnetic field *minus* the local magnetic field generated by the electrons in the bond.

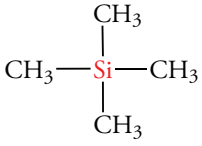
Figure 14.4 Shielding of Nucleus by Electrons

The applied magnetic field induces electron circulation about the nucleus of the hydrogen atom. This generates a small, local magnetic field around the proton that is opposed to applied magnetic field. The induced field shields the nucleus from the applied field.



The Delta Scale

The induced local magnetic fields that result from the electrons in chemical bonds differ throughout the molecule because the number and types of bonds differ. As a result, the shielding of each hydrogen nucleus is unique, and distinct resonances called **chemical shifts** occur for each structurally nonequivalent hydrogen atom in a molecule. Chemical shifts are measured relative to a reference compound, which is usually tetramethylsilane (TMS) in proton NMR. At a constant radio frequency, the external magnetic field required to change the spin of a hydrogen atom is larger for more shielded nuclei. The hydrogen atoms of TMS are more shielded from the applied magnetic field than the hydrogen atoms bond to carbon in other organic compounds. Since the electronegativity of silicon (1.9) is less than the electronegativity of carbon (2.5), carbon withdraws electron density from silicon. As a result, the C—H bond of the carbon in TMS is more shielded than the hydrogen in the C—H bond of nearly all other organic compounds. TMS is an internal standard, and its chemical shift, δ, is set at zero.



tetramethylsilane
(TMS)

The strengths of the local magnetic fields for various hydrogen atoms are miniscule, only about 10^{-6} times that of the applied magnetic field. *Therefore, the magnetic fields required to invert the nuclear spin of a hydrogen atom various structurally different hydrogen nuclei in a molecule differ by parts per million (ppm)*. Rather than using absolute values of the field strength, chemists use a relative scale termed the **delta scale**. An NMR chart is labeled on the horizontal axis with the delta scale in which one delta unit (δ) is 1 ppm of the magnetic field of the instrument. The chemical shift is independent of the strength of the applied field. The mathematical basis for the delta scale is given by the following equation:

$$\delta = \frac{\text{chemical shift (Hz)}}{\text{frequency of NMR (Hz)}} = \frac{\upsilon_{\text{sample}} - \upsilon_{\text{TMS}}}{\upsilon_0} \times 10^6$$

The equation is usually written using Hertz (Hz), a unit of frequency, rather than Tesla, a magnetic field unit. The numerator gives the differences between the resonance position of hydrogen atoms in the sample and those in tetramethylsilane (TMS), whose chemical shift is set at zero. This value is about 10^{-6} that of the frequency of the NMR spectrometer. Hence, the quotient is multiplied by 10^6 to obtain delta units.

The Operating Radio Frequency and the Chemical Shift

The difference between the resonances of a sample and TMS varies directly with the operating frequency of the NMR spectrometer. For example, if the resonance of a nucleus in a sample differs from the resonance of TMS by 720 Hz for an NMR spectrometer operating at 360 MHz, the δ value is 2. If the operating frequency of another NMR spectrometer is 720 MHz, we find that the difference between the resonances of the sample and the reference is 1440 Hz. The delta value is still 2. *The delta scale is therefore independent of the operating frequency (and field) of the instrument.*

The chemical shift of TMS is defined as 0 δ, an absorption that occurs at lower field than tetramethylsilane (TMS) appears to the left of the TMS absorption, has a positive δ value. The scale is labeled with δ units or ppm increasing from right to left with $\delta = 0$ for TMS on the right side of the spectrum. Figure 14.5 shows the chemical shift scale for a series of compounds that have only a single type of hydrogen atom. These hydrogen atoms are chemically equivalent, and therefore, they have the same chemical shift.

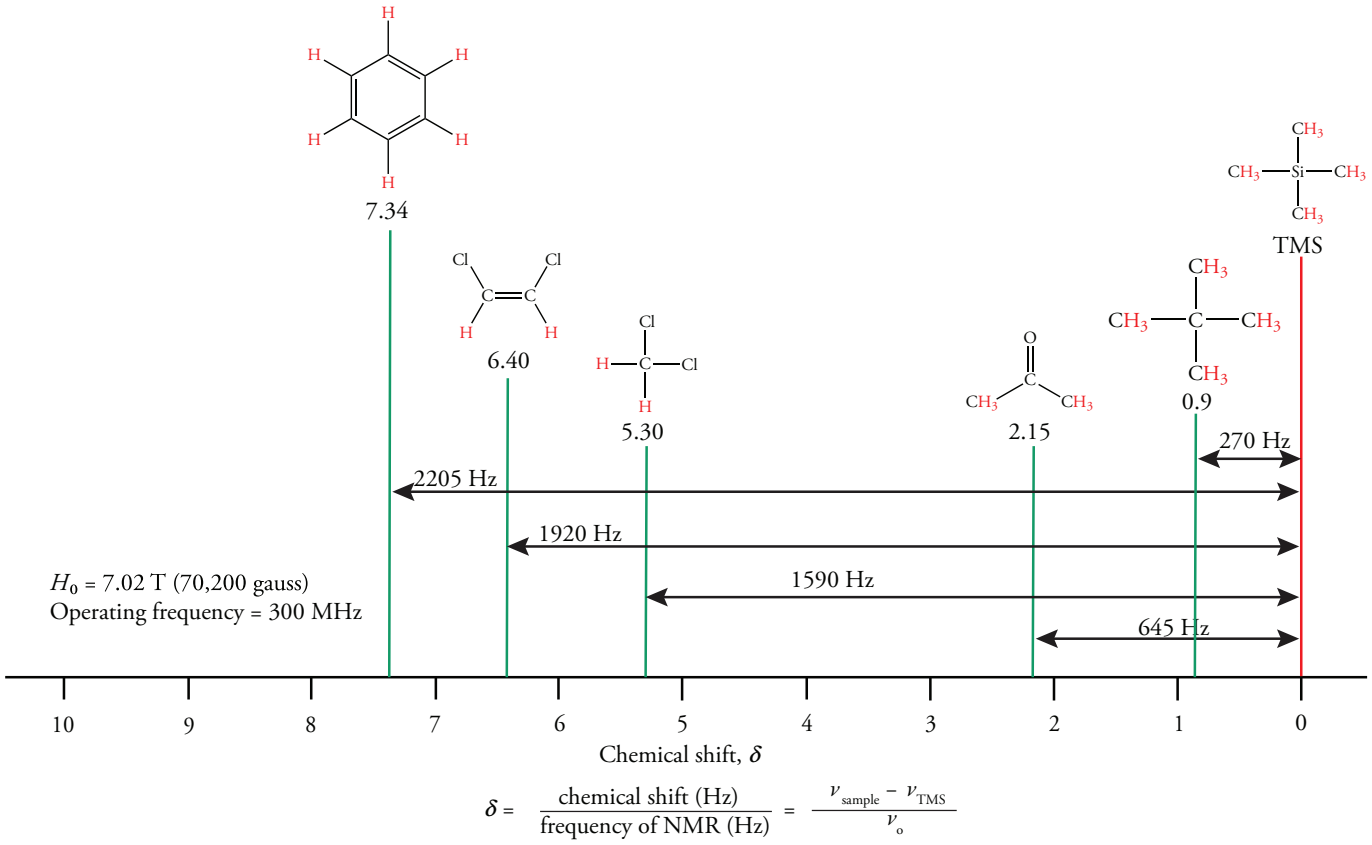
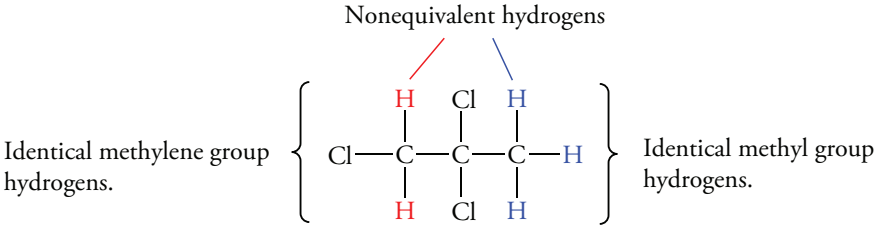


Figure 14.5 Chemical Shifts of Equivalent Hydrogens
The chemical shift of a given hydrogen atom depends upon the extent to which it is shielded from the applied magnetic field. All of the hydrogens in each compound are equivalent in these examples.

14.4 DETECTING SETS OF NONEQUIVALENT HYDROGEN ATOMS

Nuclear magnetic resonance spectroscopy provides the most information about the structure of a compound because it directly probes all of the bonded hydrogen atoms. When we examine the NMR spectrum, we can tell how many sets of structurally equivalent hydrogen atoms are contained in a molecule. The hydrogens in each compound in Figure 14.12 are equivalent. Of course, in most compounds, this is not the case. In this section, we begin to consider nonequivalent hydrogens. Our first example is the NMR spectrum of 1,2,2-trichloropropane shown in Figure 14.6. The spectrum consists of peaks at 2.2 and 4.0 δ. There are two different sets of hydrogen atoms in 1,2,2-trichloropropane. Each set of hydrogen atoms contains equivalent hydrogens and gives rise to one peak. We will outline the reasons for the specific assignment of the individual resonances to each type of hydrogen in Section 14.6.



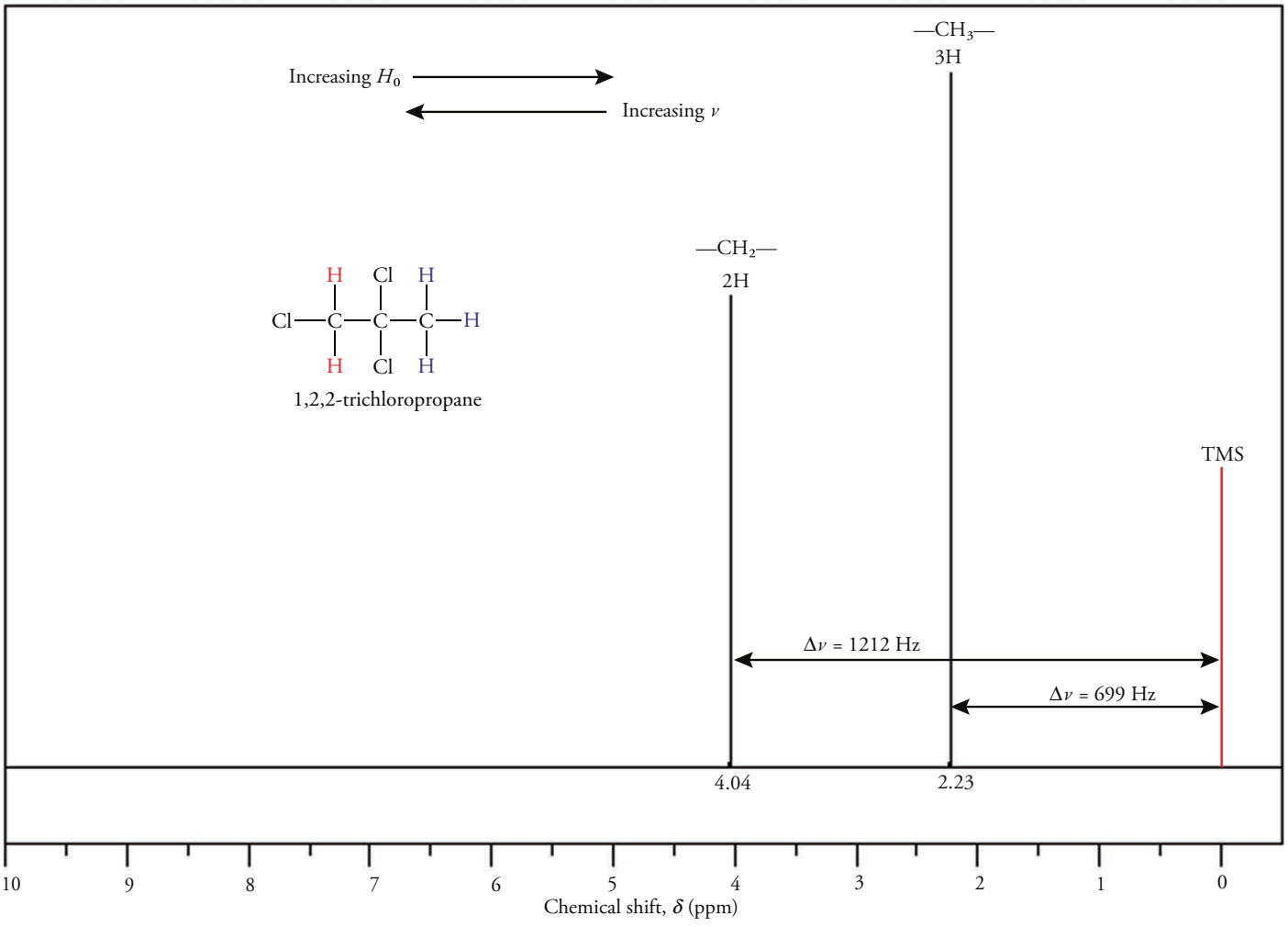
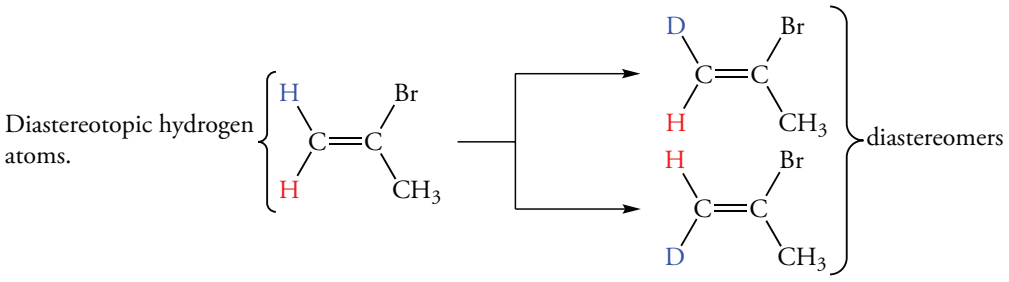


Figure 14.6 NMR Spectrum of 1,2,2-Trichloropropane
The three equivalent hydrogen atoms bonded to C-3 have a chemical shift of 2.23 δ. The two equivalent hydrogen atoms bonded to C-1 have a chemical shift of 4.04 δ.

We can deduce the structure of the compound from its NMR spectrum because the number of sets of equivalent hydrogen atoms in a molecule and the number of resonances in its spectrum are related. The two hydrogen atoms bonded in a methylene unit of 1,2,2-trichloropropane are equivalent because they are in the same local magnetic environment. The three hydrogen atoms of the methyl group are also equivalent. The NMR spectrum not only tells how many set of nonequivalent hydrogens are present, but it also gives us the *ratio* of these hydrogens. It does this by integrating the area under the peaks. The ratios of these areas equal the ratios of the number of hydrogen atoms in each peak, commonly given as 1H, 2H, 3H, and so forth (see Section 14.7).

Diastereotopic and Enantiotopic Hydrogen Atoms

Some hydrogen atoms may appear to be equivalent because they are bonded to the same carbon atom, yet they are not equivalent. Such hydrogen atoms are often **diastereotopic** (Section 8.12), and they have different chemical shifts. We can determine if two hydrogen atoms are diastereotopic by replacing either one by a deuterium atom. For example, the two geminal hydrogen atoms of 2-bromopropene are diastereotopic.



Replacing the hydrogen atom *cis* to the bromine atom with deuterium gives the *Z* isomer, but replacing a hydrogen atom *cis* to the methyl group with deuterium gives the *E* isomer. The hydrogen atoms are diastereotopic because their environments differ. As a result, their chemical shifts differ. The hydrogen atom *cis* to the bromine atom appears at 5.3 δ. The other hydrogen atom bonded to the same carbon atom has 5.5 δ. The difference in chemical shift is small. Some diastereotopic hydrogen atoms "accidentally" have the same chemical shift or differ too little to detect experimentally. Nevertheless, the hydrogen atoms are still diastereotopic. We must recognize diastereotopic hydrogen atoms to interpret an NMR spectrum correctly.

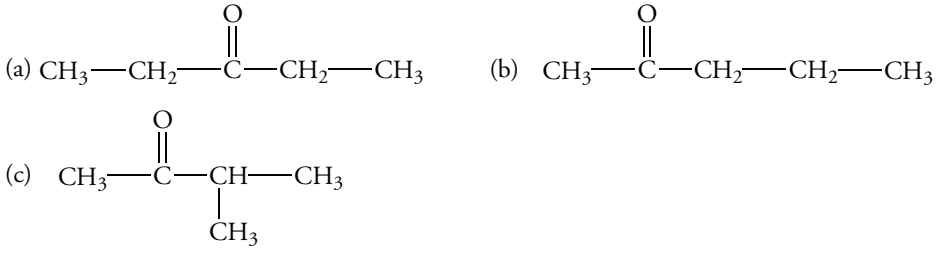
Protons that are in mirror image environments are **enantiotopic** (Section 8.12). The methylene protons of 1,2,2-trichloropropane are enantiotopic. Replacing one hydrogen atom with deuterium gives a chiral compound, the enantiomer of the compound formed by replacing the other hydrogen atom with deuterium. Enantiotopic hydrogen atoms have the same chemical shift, as we see in Figure 14.6.

Problem 14.1

The chemical shift of methylene chloride as measured with a 300 MHz instrument is 5.30 δ. What is the separation in Hz from TMS? What is the δ value when measured with a 400 MHz instrument?

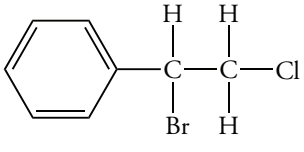
Problem 14.2

How many sets of nonequivalent hydrogen atoms are contained in each of the following ketones?



Problem 14.3

Classify the two hydrogen atoms bonded to the chlorine-bonded carbon atom of the following compound.



Sample Solution

The benzylic carbon atom is a chiral center. Thus, the two hydrogen atoms bonded to the adjacent carbon atom are diastereotopic. These hydrogen atoms do not have the same chemical shift.

14.5 EFFECTS OF STRUCTURE ON CHEMICAL SHIFT

The chemical shifts of hydrogen atoms appear between 0 and 10 δ for most organic molecules. This range is conveniently divided into regions that reflect certain structural characteristics. The electronegativity of atoms directly bonded to the carbon bearing the hydrogen atom and a magnetic field generated by π systems both affect chemical shifts.

Electronegativity Effects

As noted above, electronegative atoms, such as chlorine, **deshield** the hydrogen atom of a Cl—C—H unit. The degree of deshielding, as measured by a shift to lower field (larger δ value), increases with the electronegativity of the atom. The trend within the group of halogens is shown below.

	CH_3I	CH_3Br	CH_3Cl	CH_3F
chemical shift δ:	2.1	2.7	3.1	4.3

A similar effect of the electronegativity of the atom on the chemical shift occurs within a row of the periodic table.

	CH_3CH_3	$(CH_3)_3N$	$(CH_3)_2O$	CH_3F
chemical shift δ:	0.9	2.2	3.1	4.3

The effects of several groups bonded to a common atom are cumulative and often additive. For example, the chlorinated methanes show a nearly linear shift to lower field with increased numbers of chlorine atoms.

	CH_4	CH_3Cl	CH_2C1_2	$CHCl_3$
chemical shift δ:	0.9	3.1	5.3	7.3

Effect of π Electrons

Hydrogen atoms bonded to sp^2-hybridized carbon atoms absorb energy at lower fields than hydrogen atoms bonded to saturated sp^3-hybridized carbon atoms. For example, hydrogen atoms in alkenes absorb energy in the 5–6 δ region. The hydrogen atoms bonded to an aromatic ring absorb energy in the 7–8 δ region. The reason for these substantial shifts to low field is related to the magnetic fields associated with the motion of electrons in the molecular orbitals of these compounds. Figure 14.7 shows the magnetic field generated by circulating π electrons in benzene. A deshielding effect is "felt" by any hydrogen atoms located in the same plane as the benzene ring. A related phenomenon also affects the hydrogen atoms bonded to the sp^2-hybridized carbon atoms of alkenes.

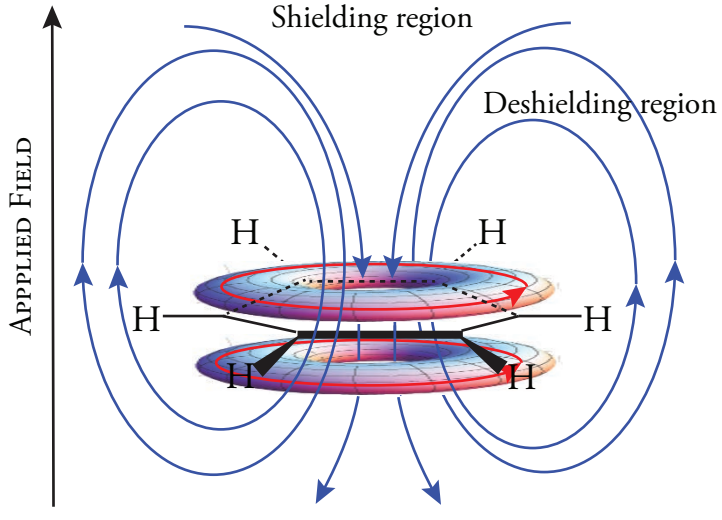
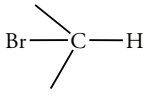
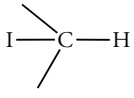
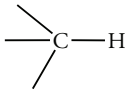
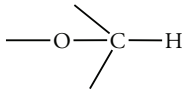
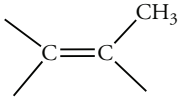
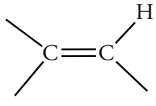
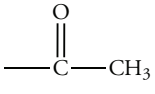
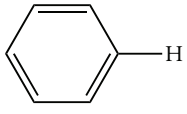
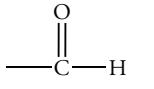
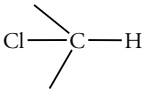
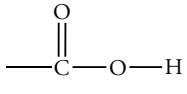


Figure 14.7 Effect of π Electrons on Chemical Shift of Benzene Hydrogens
The circulation of the π electrons of benzene results in a substantial ring current that induces a local magnetic field. The induced magnetic field reinforces the external magnetic field. Thus, a lower magnetic field is required to change the spin orientation of the hydrogen atoms that are coplanar with the aromatic ring, and the chemical shift is larger than it is for alkyl hydrogens.

Chemical Shifts of Hydrogen Atoms

The position of absorption for hydrogen atoms bonded to a variety of functional groups such as carbonyl groups can be calculated. However, such theoretical treatments are not required to use NMR data to determine structure. It is only necessary to accumulate data from a few model compounds to identify group structural contributions to the chemical shift. Groups such as halogen atoms, carbonyl carbon atoms, and aromatic rings affect chemical shifts, and several features can simultaneously influence the chemical shift. The effects are cumulative, but not necessarily additive. Table 14.1 lists examples of group contributions to chemical shifts.

Table 14.1
Chemical Shifts of Hydrogen Atoms

Partial Structural Formula	*Chemical Shift (ppm)*	*Partial Structural Formula*	*Chemical Shift (ppm)*
—CH_3	0.7–1.3		2.5–4.0
—CH_2—	1.2–1.4		2.0–4.0
	1.4–1.7		3.3–4.0
	1.6–1.9		5.0–6.5
	2.1–2.4		6.5–8.0
	2.5–2.7		9.7–10.0
	3.0–3.4		10.5–13.0

Problem 14.4

Explain why the chemical shift of the hydrogen atoms of $(CH_3)_4Sn$ appears at higher field than TMS.

Problem 14.5

1,3-Dichlorobutane has resonances 1.60, 2.15, 3.72, and 4.27 ppm downfield from TMS. Assign each resonance to the individual hydrogen atoms.

14.6 RELATIVE PEAK AREAS AND PROTON COUNTING

The set of hydrogen atoms bonded to C-1 of 1,2,2-trichloropropane has a chemical shift at 4.05 δ, and the set of hydrogen atoms bonded to C-3 has a chemical shift of 2.2 δ. This assignment can be made because hydrogen atoms bonded to a carbon atom that is also bonded to an electronegative atom absorb energy at a lower field. However, "proton counting" is another method to confirm this assignment. The area of each resonance is proportional to the relative numbers of hydrogen atoms of each kind.

The relative area of a resonance is obtained from an electronic integrator used after the spectrum has been recorded. The integrated area is equal to the vertical displacement of a "stair step" superimposed on the resonance peak. These vertical distances have ratios equal to the ratios of the number of hydrogen atoms. For example, the ratio of the integrated intensities of the two resonances of 1,2,2-trichloropropane is 3:2 (Figure 14.8).

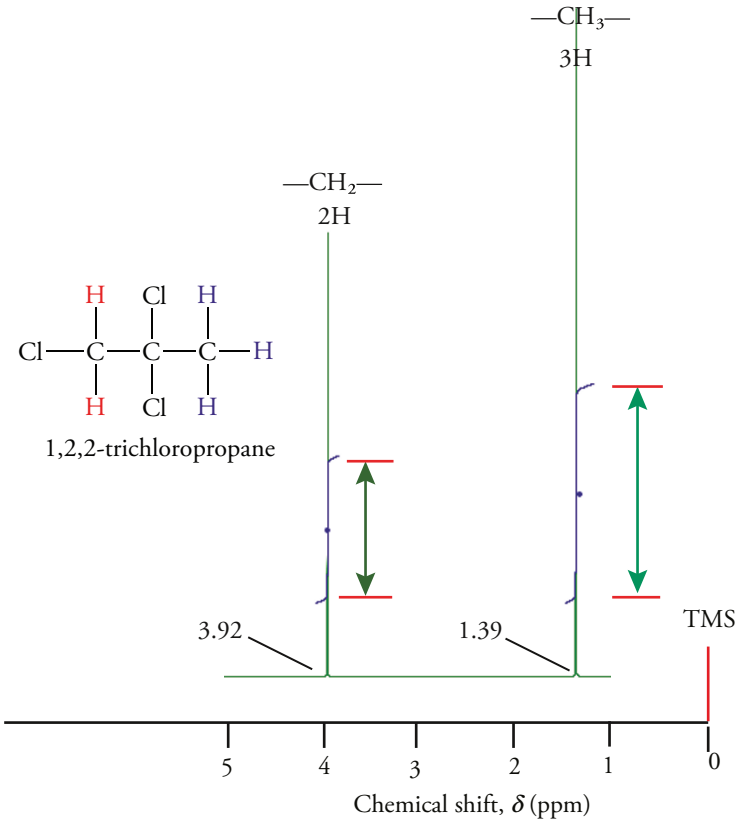


Figure 14.8 Integrated Intensities of an NMR Spectrum
The area of each resonance is proportional to the number of hydrogen atoms. The vertical distances of the "stair steps" shown is a measure those areas. The ratio of peak heights, represented by the green arrows, 3:2, corresponds to the three hydrogen atoms bonded to C-3 and the two hydrogens bonded to C-1 in 1,2,2- trichloropropane.

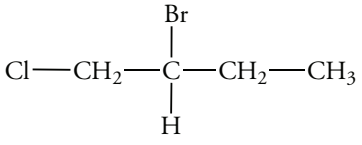
Problem 14.6

What are the relative integrate areas of the absorptions of each of the following compounds?

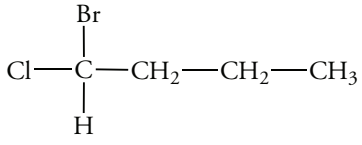
(a) 1,2-dichloro-2-methylpropane (b) 1-bromo-2,2-dimethylpropane
(c) 1,4-cyclohexadiene

Problem 14.7

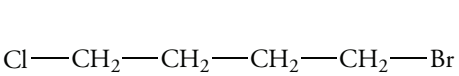
Which of the following isomers can be distinguished from the others solely on the basis of the number of NMR absorptions and their intensities?



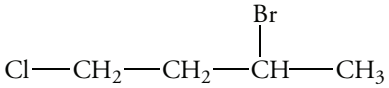
I



II



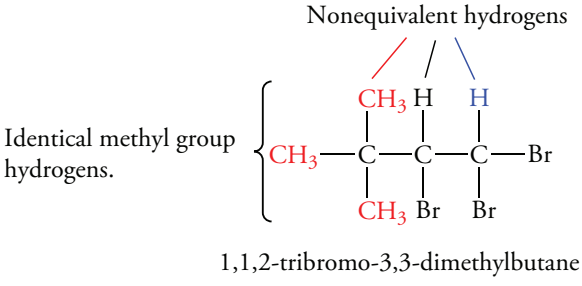
III



IV

14.7 SPIN–SPIN SPLITTING

In 1,2,2-trichloropropane, each of the two sets of hydrogen atoms produces a single peak, called a **singlet**. This is by no means always the case; in fact, the NMR spectra of most organic compounds contain many sets of peaks. The spectrum of 1,1,2-tribromo-3,3-dimethylbutane provides an example (Figure 14.9).

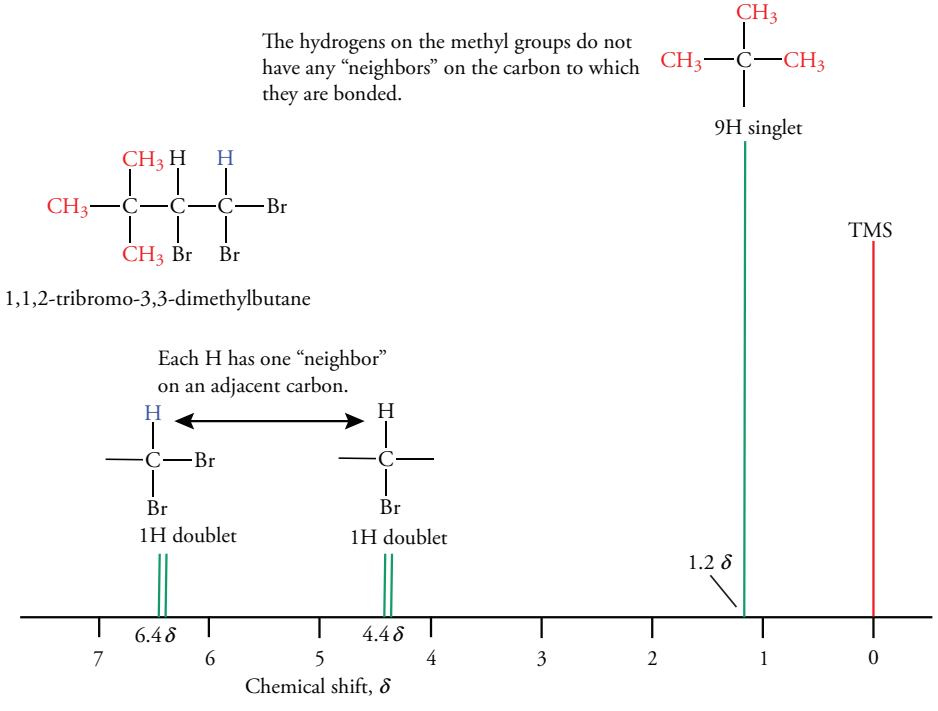


1,1,2-tribromo-3,3-dimethylbutane

The nine equivalent hydrogen atoms of the three equivalent methyl groups give rise to the intense peak at 1.2 δ. The hydrogen atoms bonded to C-1 C-2 atoms are nonequivalent. The resonance of the hydrogen atom at C-1 is located at 6.4 δ. It is downfield from the methyl hydrogens because two electronegative bromine atoms are bonded to C-1. The resonance of the hydrogen atom at C-2 is located at 4.4 δ, upfield from the hydrogen at C-1, because only one bromine atom is bonded to C-2. The intensities of the absorptions and the chemical shifts of the hydrogen atoms appear as predicted from molecular structure.

Figure 14.9 NMR Spectrum of 1,1,2-Tribromo-3,3-dimethylbutane

The areas under the peaks are in the ratio of 9:1:1, which corresponds to the ratio of hydrogens at C-3, C-2, and C-1. The hydrogen atoms at C-1 and C-2 each have one "neighbor." The nine hydrogens in the methyl groups attached to C-3 do not have any neighboring hydrogen atoms on the quaternary carbon.



Both the 4.4 and 6.4 δ absorptions of 1,1,2-tribromo-3,3-dimethylbutane are "split" into two peaks called **doublets**. Multiple peaks are common in NMR spectroscopy. Other common multiplets include **triplets** that are split into three peaks and **quartets** that are split into four peaks.. We will see that the number of peaks, or **multiplicity**, of a resonance helps us to determine structure by NMR spectroscopy.

Multiple absorptions for a set of equivalent hydrogen atoms are known as **spin–spin splitting**. The splitting results from the interaction of *nonequivalent* nuclear spins of either geminal or vicinal hydrogens. Typically, these are either geminal hydrogens or vicinal hydrogens. The small magnetic field of nearby hydrogen atoms affects the magnetic field felt by other hydrogen atoms. Thus, the local induced field on one hydrogen atom induces an induced field on the neighboring hydrogens. This effect is transmitted through the sigma bonding network (Figure 14.10).

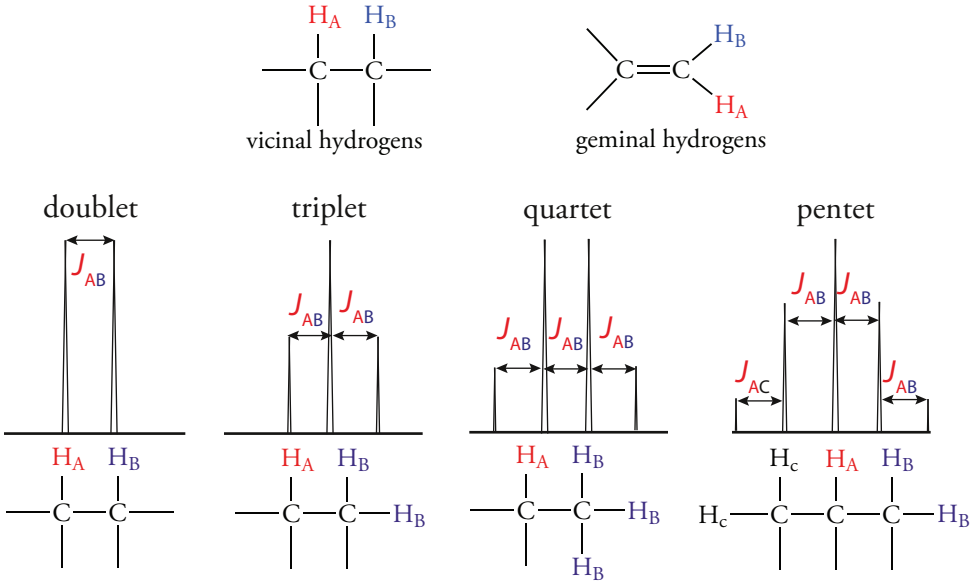


Figure 14.10 NMR Splitting Pattern for Vicinal Hydrogens
The resonance of one hydrogen atom (H_A) with neighboring hydrogens is shown. The number of equivalent neighboring hydrogen atoms is responsible for the multiplicity of the resonance. The number of peaks for H_A equals the number (n) of vicinal hydrogens +1.

The interaction between a given hydrogen (for example, H_A in Figure 14.10) and its neighbors depends only on the interacting nuclei and the bonds connecting them. Therefore, the magnitude of the interaction is *independent* of the field strength of the NMR spectrometer. Spin–spin splitting occurs between geminal and vicinal nonequivalent nuclei. The coupling interaction is usually restricted to two or three bonds, although we will encounter exceptions to this generalization when we consider aromatic compounds in Section 14.9. The resonance for the nine methyl hydrogen atoms of 1,1,2-tribromo-3,3-dimethylbutane is not "split" because the neighboring quaternary carbon atom has no hydrogen atoms. This is not the case for the hydrogen atom on the C-1 atom of 1,1,2-tribromo-3,3-dimethylbutane. There is a vicinal hydrogen atom at C-2 that can couple to the spin of the hydrogen at C-1 either of two directions. In molecules in which the hydrogen atom at the C-2 atom is spinning clockwise, the hydrogen atom at hydrogen atom at C-2 is spinning clockwise, its local field adds to the local field of the hydrogen at C-1, further shielding it from the applied magnetic field. This shifts the resonance line up field. If the hydrogen atom at C-2 is spinning counterclockwise, the hydrogen atom at C-1 experiences a deshielding effect, and its resonance shifts down field. Therefore, the vicinal hydrogen atoms **couple** with each other. A doublet results. The distance between the lines is the **coupling** constant, J, which is reported in Hz. The same explanation accounts for the doublet for the hydrogen atom at C-2 in 1,1,2-tribromo-3,3-dimethylbutane. In general, if hydrogen A is coupled to hydrogen B, hydrogen B is also coupled to hydrogen A; each interacts with its neighbor. The spectrum for 1,1,2-tribromo-3,3-dimethylbutane thus contains two doublets. We know that these two hydrogen atoms are coupled because the coupling constants are the same for both peaks.

Since each hydrogen sees the vicinal hydrogens to which it is coupled in either of two spin states—either aligned or opposed to the applied magnetic field—the number of lines in a resonance increases as $(a + b)^n$. This is the equation for a binomial expansion, and the coefficients of a binomial expansion are famously given by Pascal's triangle (Figure 14.11).

Why a binomial expansion? The spin of a hydrogen atom can be either aligned or opposed to the applied field. Therefore, if there is one hydrogen on each of two bonded atoms, as in 1,1,2-tribromo-3,3-dimethylbutane (Figure 14.9), each can see the other as either "spin-up" or "spin-down" with equal probability. Therefore, each appears in the spectrum as a doublet.

Figure 14.11 Ratios of Peak Heights for NMR Resonances
The ratios of peak heights in NMR multiplets are given by Pascal's triangle.

Singlet			1				
Doublet			1	1			
Triplet		1	2	1			
Quartet		1	3	3	1		
Pentet	1	4	6	4	1		
Sextet	1	5	10	10	5	1	
Septet	1	6	15	20	15	6	1

Pascal's triangle

Characteristics of Multiplets

A set of one or more hydrogen atoms with n equivalent neighboring hydrogen atoms have $n + 1$ peaks in the NMR spectrum. To understand the relative peak areas of multiplets resulting from more than one neighboring hydrogen atom, we'll examine the spectrum of 1,1,2-trichloroethane (Figure 14.12).

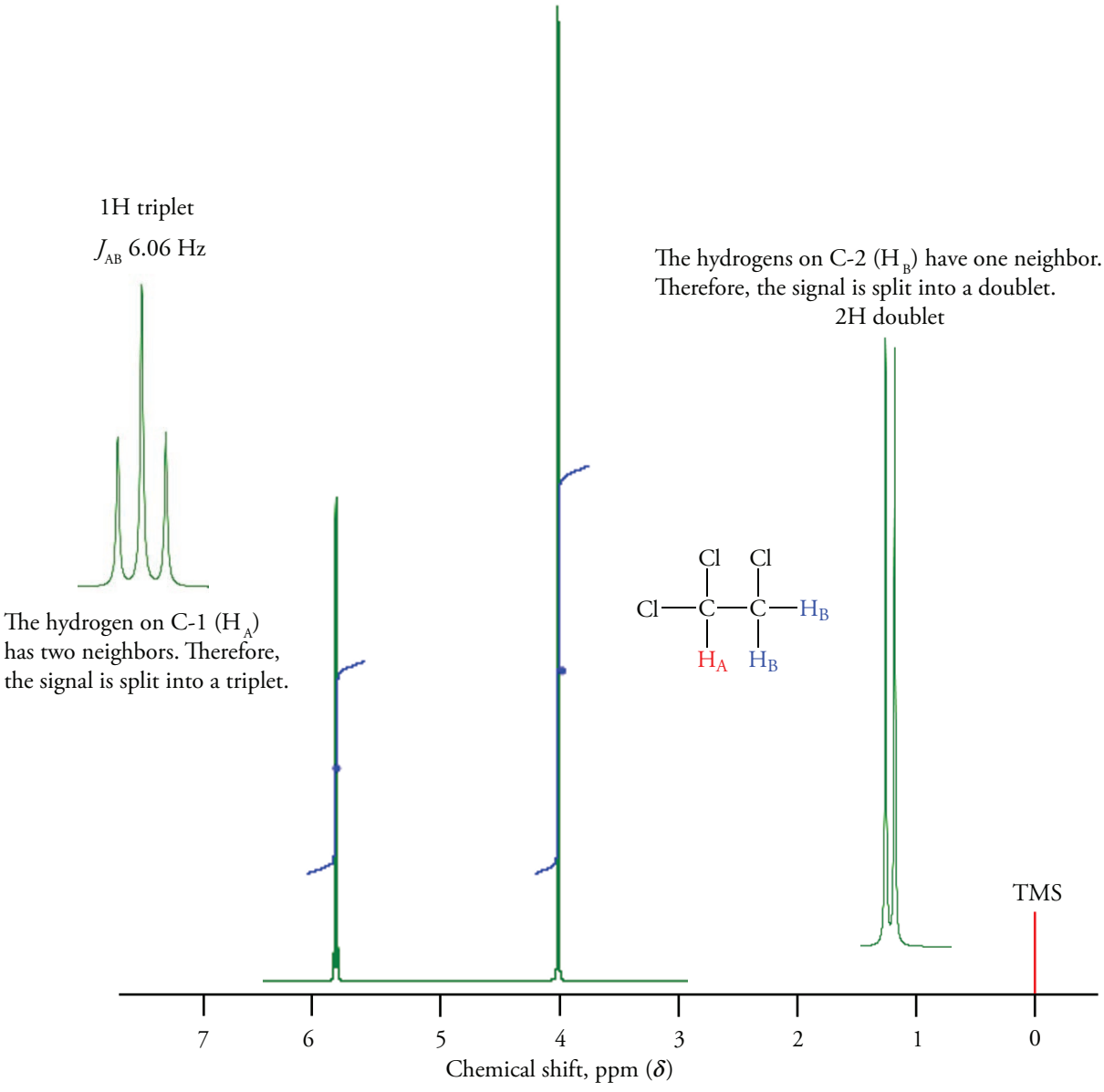


Figure 14.12 NMR Spectrum of 1,1,2-Trichloroethane
The spectrum consists of two multiplets: a doublet at 3.96 δ that integrates to two hydrogens, and a triplet centered at 5.782 δ that integrates to one hydrogen. The insert shows the triplet for the resonance centered at 5.782 δ for H_A. The two chlorine atoms at C-1 deshield H_A relative to H_B, so the H_A resonance has a larger chemical shift.

Splitting Patterns of the Ethyl Group and the Isopropyl Group

Now let's consider systems containing many more hydrogen atoms. The analysis of an apparently complex spectrum is often made easier if we recognize characteristic patterns associated with a structural unit. One such pattern is due to the ethyl group (CH_3CH_2—). The pattern consists of a high-field triplet corresponding to the three hydrogen atoms of the methyl group. The resonance of the methylene group is at lower field because it is invariably bonded to a deshielding group. This group is a quartet with an integrated intensity of the two hydrogens of the methylene group. Thus, the triplet–quartet pattern is characteristic of an ethyl group. The spectrum of chloroethane illustrates this pattern (Figure 14.13).

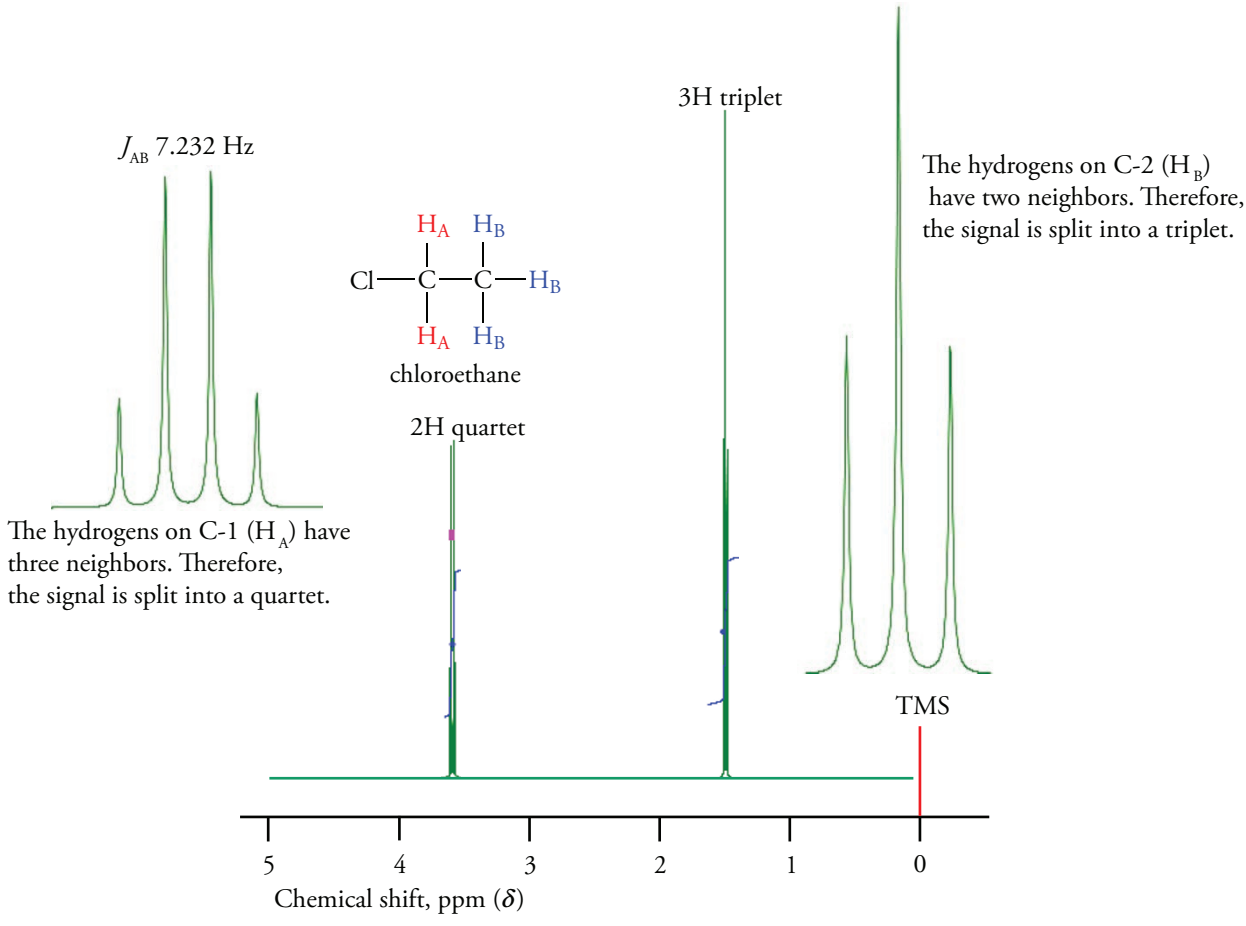


Figure 14.13 NMR Spectrum of Chloroethane
The spectrum of chloroethane consists of two multiplets: a triplet centered at 1.488 δ for H_B that integrates to three hydrogens, and a quartet centered at 3.505 δ for H_A that integrates to two hydrogens. The insert shows the quartet for H_A. The chlorine atom at C-1 deshields the two H_A protons, so the H_A protons have a larger chemical shift than the H_B protons at C-2.

Another common pattern occurs with isopropyl groups, $(CH_3)_2CH$—. The six equivalent methyl hydrogen atoms are split into a doublet by the methine proton. The methine hydrogen atom is split by all six of the methyl hydrogen atoms, and a septet results. The doublet–septet pattern identifies an isopropyl group. However, the total intensity of the septet is only one-sixth that of the total intensity of the doublet. The entire septet is not always visible because the outermost lines of the septet have such a small intensity. As a result, the methine absorption may appear as a quintet. Figure 14.14 shows the nmr spectrum of 2-chloropropane. The outer peaks are indeed not well resolved.

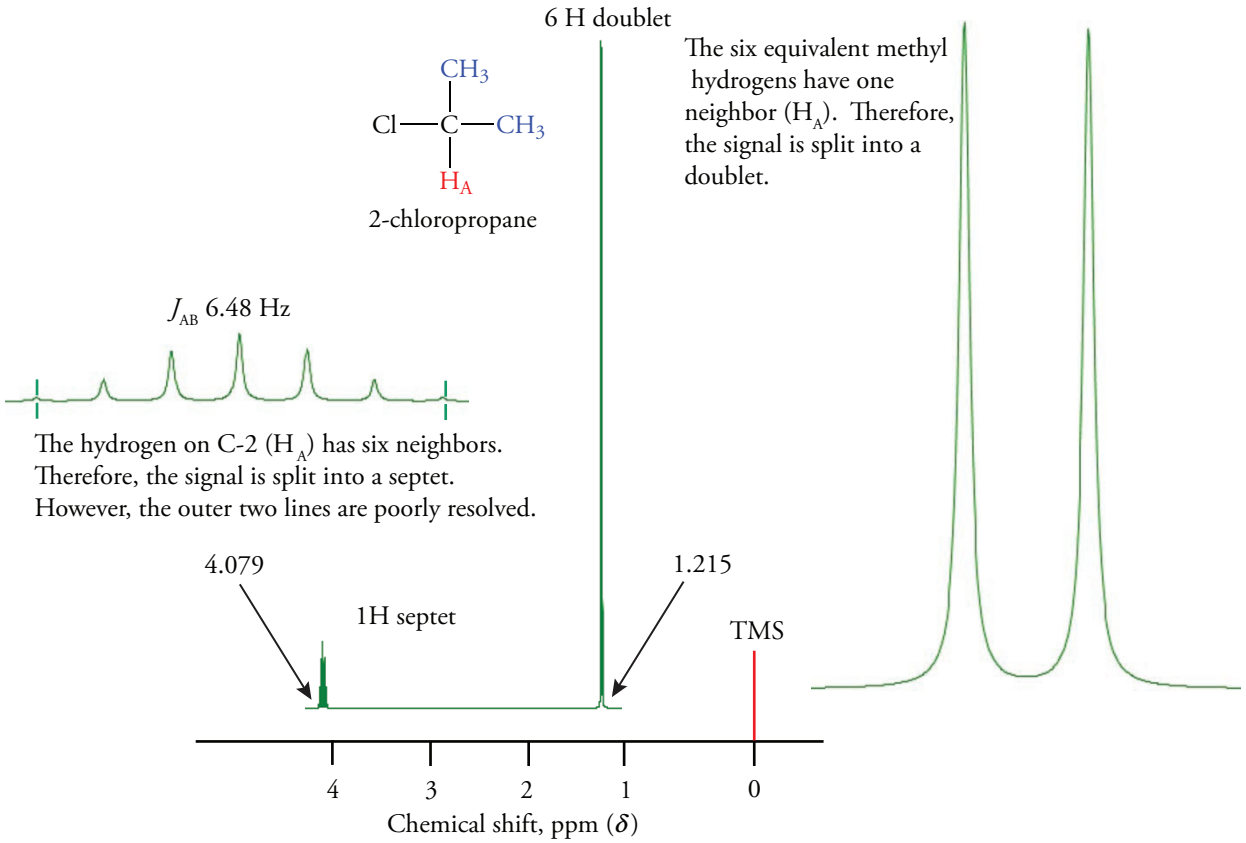
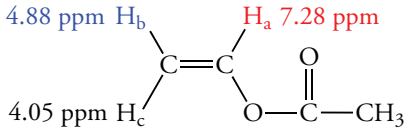


Figure 14.14 NMR Spectrum of 2-Chloropropane
The spectrum consists of two multiplets: a doublet at 1.444 δ that integrates to two hydrogens, and a septet centered at 3.735 δ that integrates to one hydrogen. The insert shows the septet. However, the outer peaks are not highly resolved, so the resonance appears to be a pentet rather than a septet. The chlorine atom at C-2 deshields H_A relative to the methyl hydrogens, so the H_A resonance has a larger chemical shift.

Multiple Splitting: The Vinyl Group

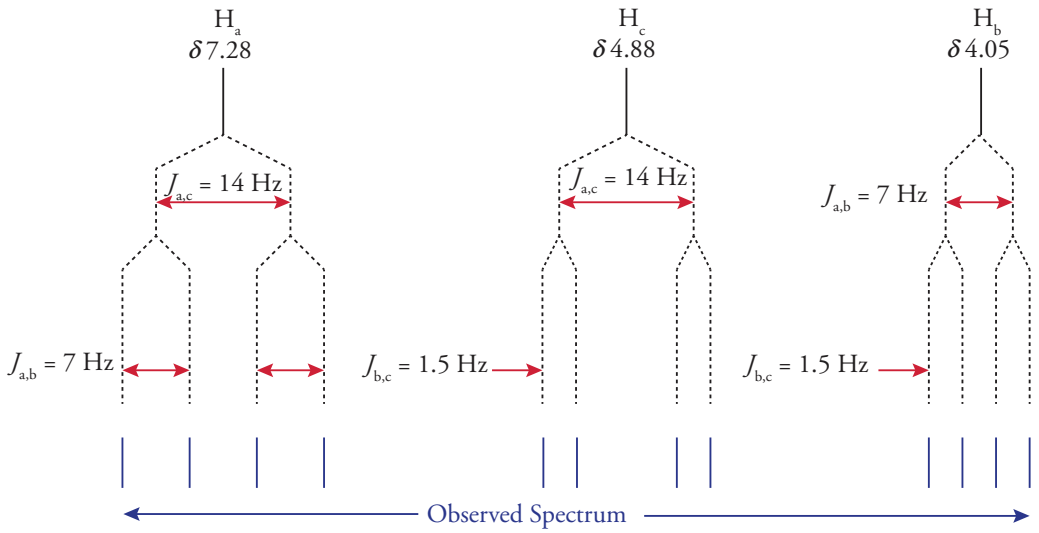
When a hydrogen atom has more than one type of neighboring hydrogen atom, it is split into multiple peaks. The vinyl group is an example.



The alkene hydrogen atoms of a vinyl group have different chemical shifts. The hydrogen at lowest field (H_a) is deshielded by the ethanoate group. H_a, H_b, and H_c are coupled to one another. Thus, the resonance of each hydrogen atom is split separately by the other two. The magnitude of each coupling constant is characteristic of vinyl systems. Geminal coupling of the hydrogen atoms of the CH_2 unit is the smallest with J_{gem} (1–2 Hz). Vicinal couplings are larger; J_{trans} (12–16 Hz) is greater than J_{cis} (6–8 Hz). We will discuss this relationship further in the next section.

To analyze spectra with multiple coupling constants, we consider each hydrogen atom, and split its resonance successively by each of the other hydrogen atoms coupled to it. This process leads to a splitting diagram. For the three-hydrogen vinyl system cited above, the H_a resonance is split into a doublet with J = 14 Hz by H_c which is *trans* to it (Figure 14.15). Then each line of the doublet is further split into doublets with J = 7 Hz by H_b. A doublet of doublets results. Note that we could have constructed this splitting diagram by considering the coupling constants in reverse order. The result would be the same. However, it is usually simpler to apply the coupling constants in the order of decreasing value of J.

Figure 14.15 Splitting Pattern of a Vinyl Group

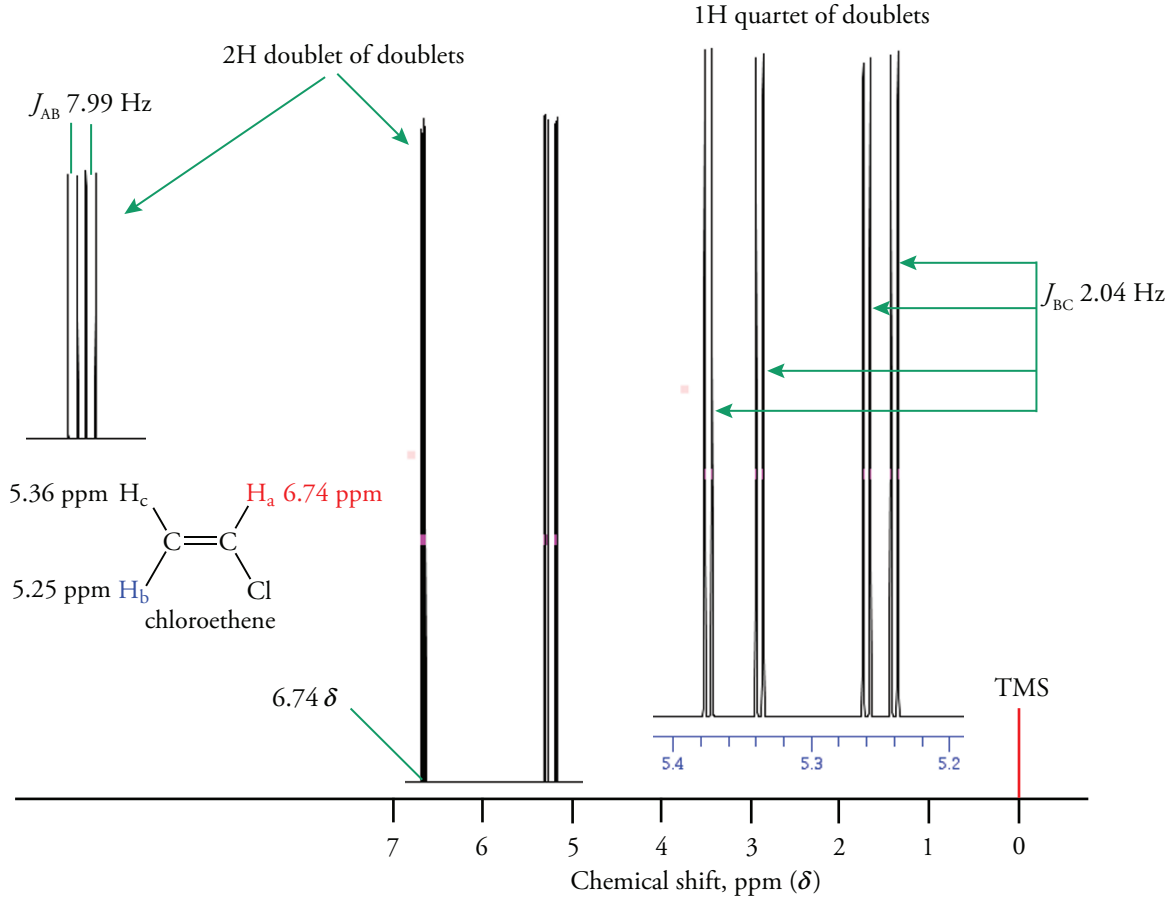


There is no doubt about the assignment of the doublet of doublets centered at 7.28 δ because the oxygen atom causes a substantial deshielding of this hydrogen atom.

The hydrogen atom labeled H_c shows the same large coupling constant as H_a because these atoms are situated *trans* to each other. The splitting of the resonance centered at 4.88 δ corresponds to J_{trans} (Figure 14.15). Each part of this doublet is further split into closely spaced doublets by the geminal hydrogen atom H_b (J_{gem} = 1.5 Hz). Thus, a second doublet of doublets results, but one of its two coupling constants is different than for the doublet of doublets of H_a.

Finally, the complete assignment of the vinyl resonances is confirmed by the splitting diagram of H_b (Figure 14.15). It has the same 7 Hz coupling constant associated with H_a because they are *cis* to each other. Each part of this doublet is further split into closely spaced doublets by the geminal hydrogen atom H_c. Yet another doublet of doublets results in the general area of that for H_c, but this one has the small coupling constant of J_{cis} rather than J_{trans}. These general ideas are illustrated in the NMR spectrum of chloroethene (Figure 14.16).

Figure 14.16 NMR Spectrum of Chloroethene

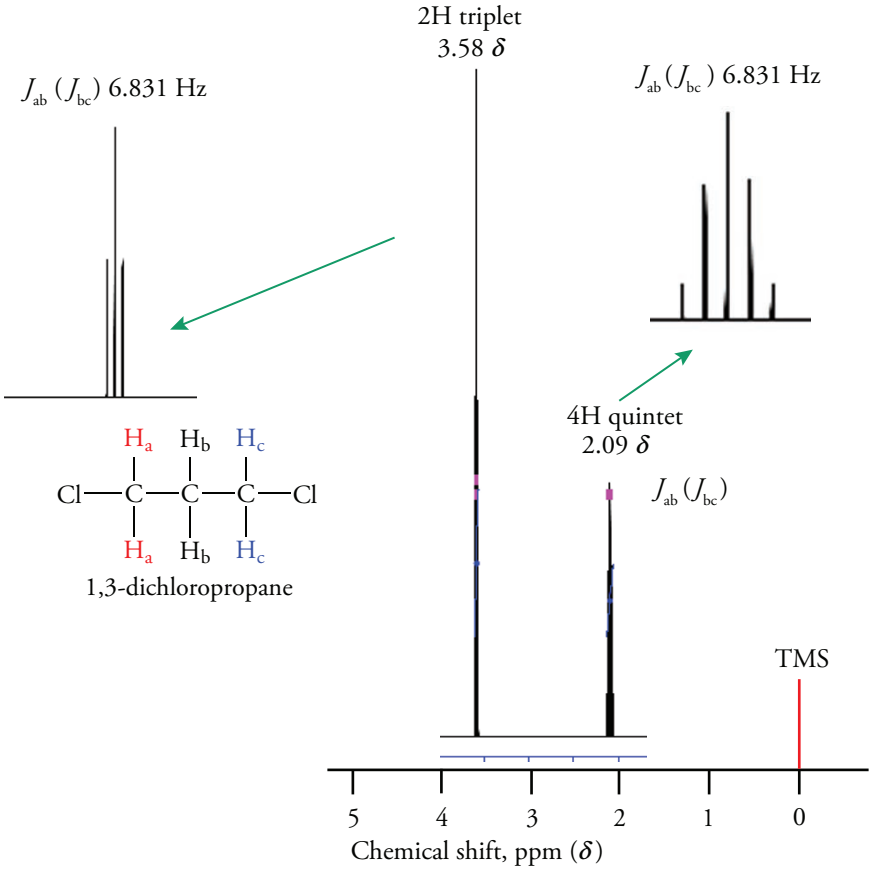


Problem 14.11

Describe the NMR spectrum of 1,3-dichloropropane.

Sample Solution

The methylene protons of C-1 and C-3 are equivalent and appear in the 3–4 δ region with a total intensity of 4H. The methylene protons of the C-2 atom appear at higher field with intensity 2H. The low-field resonance is a triplet because the protons at either C-1 or C-3 are coupled with the two protons at C-2. The high-field resonance is a pentet because the C-2 methylene protons are coupled to a total of four equivalent protons at C-1 and C-3.



Problem 14.12

Describe the NMR spectrum of each of the following compounds.

(a) 2-chloropropane (b) 1,1,1,2-tetrachloropropane
(c) 2,2-dibromobutane (d) 1-bromo-l-chloroethene

14.8 EFFECT OF STRUCTURE ON COUPLING CONSTANTS

The coupling of two nuclei results from an interaction passed through the network of bonding electrons. This interaction is not like the flow of electricity though a wire. Instead, a conformational effect provides information about the geometry of the coupled nuclei in space.

Effect of Dihedral Angle on Coupling Constants

The stereochemistry of some saturated cyclic compounds can be established by determining some of the vicinal coupling constants. The value of J for vicinal hydrogen atoms depends on their dihedral angle, 0. We recall that *anti* periplanar arrangements have θ = 180°, and gauche arrangements have θ = 60°.

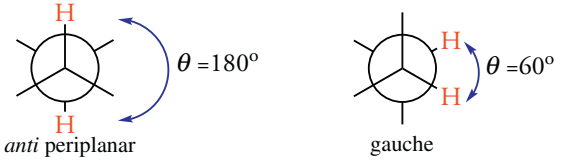
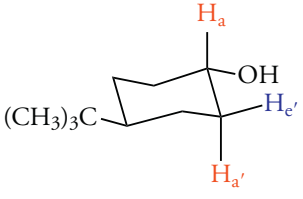


Table 14.2 shows the relationship between the vicinal coupling constant and the dihedral angle.

Table 14.2
Relation of Coupling Constants to Dihedral Angle

Dihedral Angle, θ (degree)	*Coupling Constant, J (Hz)*
0	8.5
60	3–4
90	0
180	9–14

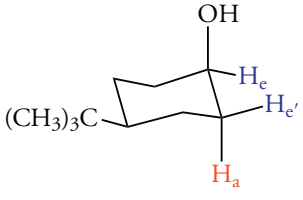
The coupling constants in the *cis*- and *trans*-4-*tert*-butylcyclohexanol reveal these relationships. The *trans* isomer has an equatorial hydroxyl group. Thus, the hydrogen atom at C-1 is axial. It has a large coupling constant to the axial hydrogen atoms at C-2 and C-6 because $\theta = 180°$. It is also coupled to equatorial hydrogen atoms at C-2 and C-6 with $\theta = 60°$. The *cis* isomer has an equatorial hydrogen atom at C-1. It is coupled to axial and equatorial hydrogen atoms at C-2 and C-6. The dihedral angles are 60° for both sets of interacting protons. The sets of coupling constants for the *cis* isomer are therefore smaller than for the *trans* isomer.



trans-4-*tert*-butylcyclohexanol

$J_{aa'} = 13.1$ Hz

$J_{ae'} = 4.3$ Hz



cis-4-*tert*-butylcyclohexanol

$J_{ee'} = 2.7$ Hz

$J_{ae'} = 3.0$ Hz

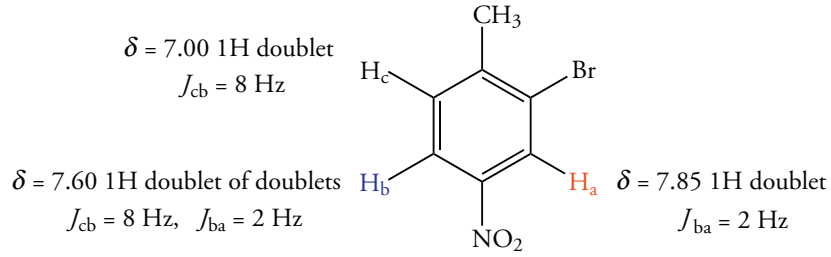
Long-Range Coupling in Aromatic Compounds

In our discussion of coupling constants in vinyl systems, we saw that geminal hydrogens couple across two double bonds, and that vicinal hydrogens couple across three bonds. Spin–spin coupling across four or more bonds is called **long-range coupling**. Long-range coupling occurs between *ortho*, *meta*, and *para* hydrogen atoms in aromatic compounds. The coupling between *ortho* hydrogen atoms is vicinal, and the coupling constant is in the 6–10 Hz range. Coupling between *meta* hydrogens occurs across four bonds, with coupling, J_{meta}, of 1–3 Hz. Coupling of *para* hydrogens occurs across five bonds. The range of values and J_{para} is very small, 0–1 Hz.

Determining the structure of an aromatic compound by NMR is often possible by counting the number of different resonances that correspond to the number of nonequivalent hydrogen atoms. Assignment of each resonance can often be done using reference compounds that provide information about the effect of substituents on *ortho* hydrogen atoms. The assignment is confirmed from the multiplicity of each resonance. The largest coupling constant is for *ortho* hydrogen atoms. Smaller splitting occurs for coupling with a *meta* hydrogen atom.

Long-range coupling constants and chemical shifts in 2-bromo-4-nitrotoluene are shown below. The assignments are made using the knowledge that the deshielding effect of substituents on *ortho* hydrogen atoms is $NO_2 >> Br > CH_3$.

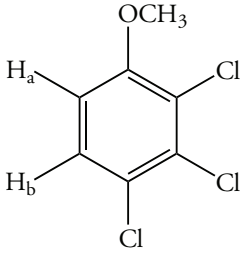
The lowest field resonance is for the hydrogen atom at C-3, which is *ortho* to both the bromine atom and the nitro group. The resonance of the hydrogen atom at C-5 is close to the C-3 hydrogen resonance. However, it is a doublet of doublets because it is coupled to the *ortho* hydrogen atom at C-6 and the *meta* hydrogen atom at C-3.



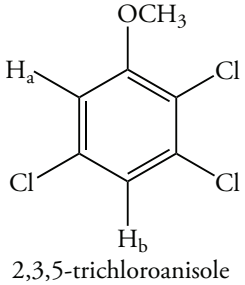
2-bromo-4-nitrotoluene

Problem 14.13

Explain how 2,3,4-trichloroanisole, 2,3,5-trichloroanisole can be established using the coupling constants of the two doublets in the NMR spectrum of each compound.



2,3,4-trichloroanisole



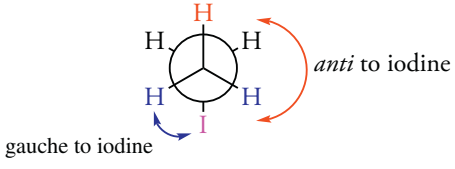
2,3,5-trichloroanisole

14.9 EFFECT OF DYNAMIC PROCESSES

A specific hydrogen atom has a unique chemical shift because it maintains its position in space long enough to be detected. If a rapid exchange process occurs, the NMR experiment detects a *time average* of all the species in equilibrium. To illustrate this principle as it applies to NMR spectroscopy, we will use the movement of an airplane propeller as an analogy. If the propeller is not moving, we can clearly see each blade. As the engine starts, we still might be able to see each blade, but the images blur as the propeller accelerates, and we see the time average of the motion, which is a disk. Thus, there is a relationship between the rate of the process and our ability to see that motion. Let's now apply that concept to NMR spectroscopy. The motion is that of conformational changes or chemical equilibrium. The "seeing" is related to the conditions under which the NMR spectrum is obtained.

Conformational Changes

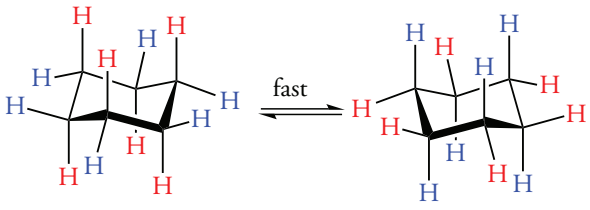
Consider the three hydrogen atoms of the methyl group of iodomethane.



If this specific conformation of a single molecule could be "seen" by the NMR instrument, then the three methyl hydrogen atoms would not be equivalent. The two hydrogen atoms that are gauche to the iodide are equivalent, but different from the hydrogen atom that is *anti* to the iodide atom. As a result, the methyl group would appear as two chemical shifts, and more resonances would appear. However, we know that the methyl hydrogen atoms are equivalent. This equivalence results from a rapid rotation around the σ bond much like that of a propeller. Because the rotation is too fast for the NMR spectrometer to "see," the result is a time average, which appears as a single chemical shift.

A similar effect occurs for the observed coupling constant for the interaction between the methyl and methylene hydrogen atoms. Only a time average coupling constant appears. The protons that are *anti* to each other have J_{vic} in the 12–16 Hz range. Those that are gauche to each other have J_{vic} = 3–4 Hz. The time average coupling constant is 6–7 Hz because more gauche arrangements exist than *anti* arrangements.

Conformational changes of cyclic systems also lead to time-averaged chemical shifts. We know that the equatorial and axial hydrogen atoms of cyclohexane have different structural environments. However, we also know that the cyclohexane ring undergoes a chair–chair interconversion, and that the equatorial and axial hydrogen atoms exchange positions. This process is so rapid that the NMR cannot detect the individual conformations, and the hydrogen atoms in the two different environments at room temperature. As a result, cyclohexane appears as a single resonance at 1.4 δ.

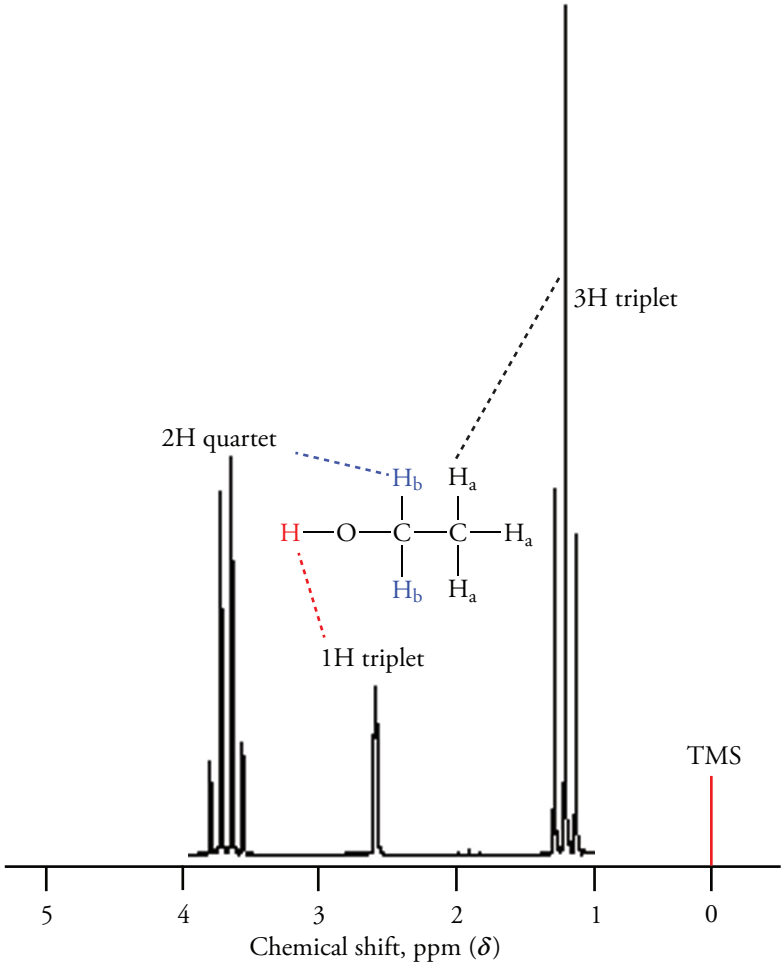


Hydroxyl Hydrogens

The resonance of a hydroxyl hydrogen atom is characterized by a variability of its chemical shift and in many cases by the absence of any splitting. For example, the chemical shift of the hydroxyl hydrogen atom of ethanol "moves" depending on experimental conditions, but the chemical shift of the methylene and methyl hydrogen atoms remains unchanged.

The chemical shift varies with solvent, temperature, and concentration because as the degree of aggregation of the hydrogen-bonded species changes, the environment of the hydrogen atom changes. The chemical shift may vary from 4–5 δ in concentrated solutions to about 1 δ in dilute solutions (Figure 14.17).

Figure 14.17
NMR Spectrum of Ethanol



14.10 CARBON-13 NMR SPECTROSCOPY

Carbon-13 (^{13}C) has a nuclear spin of ½, and it can be detected by ^{13}C-NMR experiment. ^{13}C NMR allows us to detect the structural environment of carbon atoms. This is often an advantage, especially for carbon atoms that are not bonded to hydrogen atoms, and thus cannot be detected by hydrogen NMR.

NMR spectra can be easily obtained for many isotopes with half integer spins, such as ^{19}F and ^{31}P, because their natural abundance is 100%. The detection of the isotope ^{13}C is more difficult because it has an abundance of only 1%. However, ^{13}C NMR spectra are easily obtained. Let's consider the location of ^{13}C in a compound such as 2-butanol. Most of the carbon atoms are ^{12}C, which has no nuclear spin. The probability is equal for the location of ^{13}C at any of the positions in a molecule. The probability of finding a ^{13}C at C-1 of a molecule is 1%. The probability of finding a ^{13}C at C-2 is also 1% and so on. The probability of finding two or more ^{13}C in the same molecule and simultaneously bonded to each other is very low. For example, the probability of finding ^{13}C in the same molecule at both C-1 and C-2 is only 0.01%. As a result, a ^{13}C NMR spectrum shows a sum of the signals generated by individual atoms at all of the possible sites in a collection of isotopically substituted molecules.

Characteristics of ^{13}C Spectra

The ^{13}C spectra of organic compounds is shown using a δ scale relative to the resonance of ^{13}C in TMS. The chemical shift of ^{13}C shows many of the same trends as hydrogen chemical shifts. However, the range of chemical shifts for ^{13}C is much larger, on the order of 200 ppm (Table 14.3). Thus, the chemical shifts of ^{13}C are very sensitive to changes in structural environment. As a result, it is usually possible to "see" distinct signals for every nonequivalent ^{13}C in a molecule.

The resonances for ^{13}C are split by hydrogen atoms. The rules for the multiplicity of a ^{13}C resonance split by hydrogen are the same as for hydrogen coupled to hydrogen. The multiplicity is $n + 1$ for n equivalent neighboring hydrogen atoms. The largest coupling is observed for ^{13}C directly bonded to hydrogen—that is, a one-bond coupling. Coupling of ^{13}C with hydrogen atoms farther away is small. By using specialized experimental methods, all splitting by hydrogen atoms can be eliminated, as we will shortly see. This greatly simplifies the spectrum since *each chemically unique* carbon atom appears as a single line in the spectrum.

The ^{13}C spectrum of 2-butanol is shown in Figure 14.18: the four nonequivalent carbon atoms. The signal at lowest field is assigned to C-2 because it is deshielded by an oxygen atom. The line at 32.0 δ is assigned to C-1 because it is bonded to C-1, but not to an alkyl group. The line at 10.0 δ is assigned to C-4 because it is furthest from C-2, and thus the least deshielded by the oxygen atom. We know that a methyl group is electron releasing relative to hydrogen. Therefore, the line at 22.8 δ is assigned to C-3. The line at 32, δ is assigned to C-1.

Figure 14.18
^{13}C NMR Spectrum of 2-Butanol

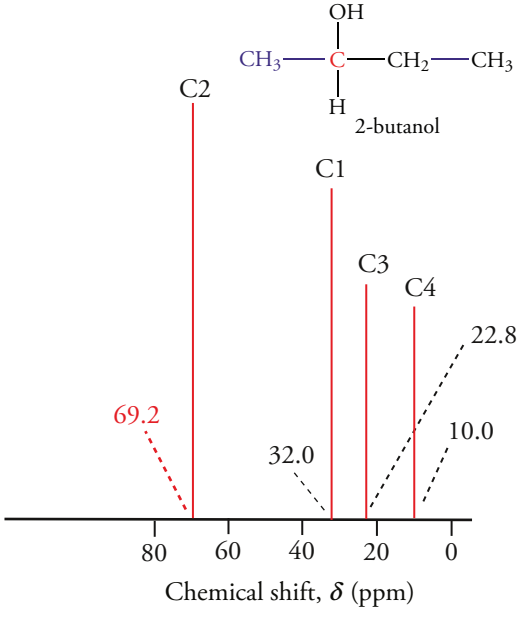
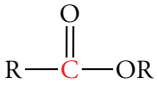
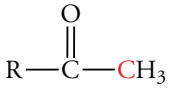
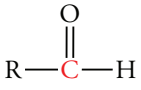
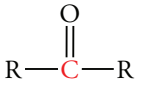
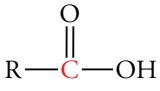


Table 14.3
Chemical Shifts of ^{13}C Atoms

^{13}Carbon Atom	*Chemical Shift (ppm)*	*^{13}Carbon Atom*	*Chemical Shift (ppm)*
RCH_2CH_3	12–15	$RCH{=}CH_2$	115–120
R_2CHCH_3	16–25	$RCH{=}CH_2$	125–140
R_3CH	12–35		170–175
	30		190–200
RCH_2Cl	40–45		205–220
RCH_2Br	27–35		180
RCH_2OH	50–65	benzene	128

Proton-Decoupled Spectra

We noted above that "special techniques" can be used to generate ^{13}C spectra that consist of single lines rather than as multiplets. The splitting of a resonance for a ^{13}C atom by hydrogen can be eliminated to generate a singlet by a technique called **proton decoupling**. The resulting spectrum is called a **proton-decoupled NMR spectrum**. While the spectrum of ^{13}C is being obtained over at one magnetic field strength and frequency, a high-intensity source of radio frequency that detects protons is simultaneously used to irradiate the sample. This combination of field and radio frequency causes changes in spin states of hydrogen nuclei. Because the intensity of the radio frequency is so high, the nuclei rapidly change their spin states. Hence, they do not spend sufficient time in specific arrangements to couple with the ^{13}C nucleus. As a result of this averaging, no coupling is observed.

The proton-decoupled ^{13}C spectrum of 2-butanol consists of four signals corresponding to the four nonequivalent carbon atoms, as we saw in Figure 14.18. We can eliminate the isomers 2-methyl-1-propanol (Figure 14.19) and 2-methy1-2-propanol (Figure 14.20) as possible structures because the spectra of these compounds would show three and two signals, respectively.

Figure 14.19
^{13}C NMR Spectrum of 2-Methyl-1-propanol

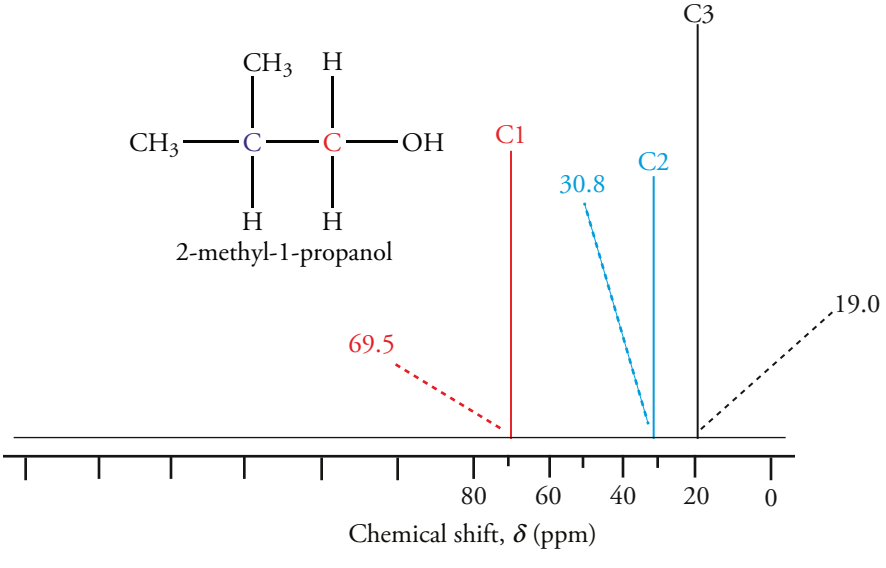
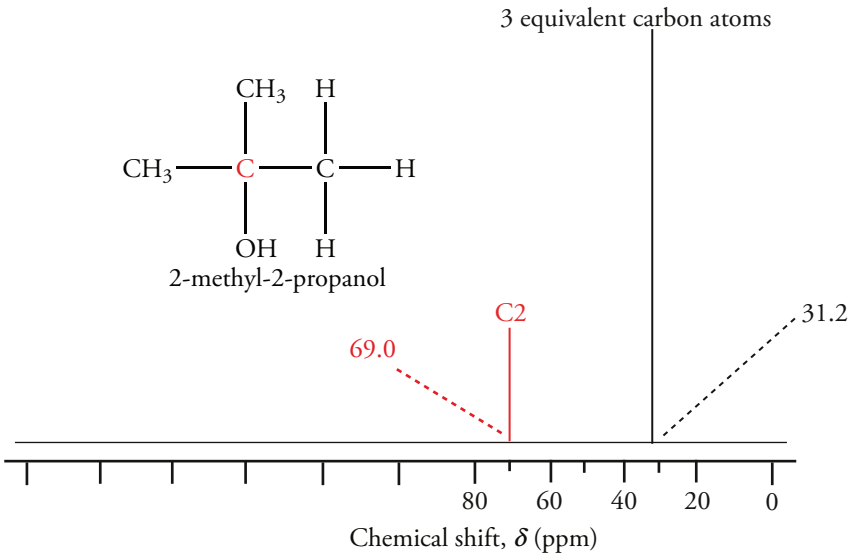


Figure 14.20
^{13}C NMR Spectrum of
2-Methyl-2-propanol



Counting Carbon Atoms in ^{13}C Spectra

In the spectra of 2-butanol, methyl-1-propanol, and 2-methyl-2-propanol, we see that the intensities of the nonequivalent carbon atoms are not equal. Unlike proton NMR spectroscopy, the method used to obtain ^{13}C spectra gives peak intensities that are not proportional to the number of carbon atoms. The signals for carbon atoms bearing more hydrogen atoms tend to be larger than for carbon atoms bearing fewer hydrogen atoms. Carbon atoms without hydrogen atoms, such as quaternary carbon atoms and ketone carbonyl carbon atoms, have the lowest intensity. However, substituents also affect the intensity of the carbon atom. As a result, we cannot accurately count the number of equivalent carbon atoms responsible for a resonance.

The number of equivalent carbon atoms can be determined by comparing the number of signals in a ^{13}C spectrum with the number of carbon atoms in the molecular formula. If some of the carbon atoms in a molecule are equivalent, the number of signals is reduced. As a result, ^{13}C spectroscopy is quite useful in determining the symmetry of a molecule.

The structures of two diastereomers: 1-*cis*-3-*cis*-5-trimethylcyclohexane and 1-*cis*-3-*trans*-5-trimethylcyclohexane. The isomer that has all-*cis* methyl groups is more symmetrical than the diastereomer with one *trans* methyl group.

The three methyl groups of the all-*cis* isomer are located in equatorial positions and are equivalent. Therefore, the methyl groups give one signal. The equivalence of the methyl groups is related to the equivalence of other sites in the structure. The three methine carbon atoms bonded to the methyl groups are also equivalent, as are the three methylene carbon atoms. Therefore, the nine carbon atoms of the molecule consist of three sets of three carbon atoms each. The spectrum consists of three resonances (Figure 15.21).

Now let's consider the spectrum of the diastereomeric 1-*cis*-3-*trans*-5-trimethylcyclohexane. The two equatorial methyl groups are equivalent, but different from the axial methyl group. Likewise, the two methine carbon atoms containing equatorial methyl groups are equivalent, but different from the methine carbon atom containing the axial methyl group. Finally, two methylene carbon atoms are equivalent and different from the third methylene carbon atom. Hence, the nine carbon atoms are divided into six groups. Three of the groups contain two carbon atoms each, and the other three groups contain one carbon atom each. The spectrum consists of six signals, of which three are approximately twice the intensity of the other three. Figures 14.21 and 14.22 show the spectra of the *cis* and *trans* isomers. Determining a structure using ^{13}C NMR depends on a one-to-one correspondence between the number of sets of equivalent carbon atoms and the number of signals in the spectrum.

Figure 14.21
^{13}C NMR Spectrum of 1-*cis*-3-*cis*-5-trimethylcyclohexane

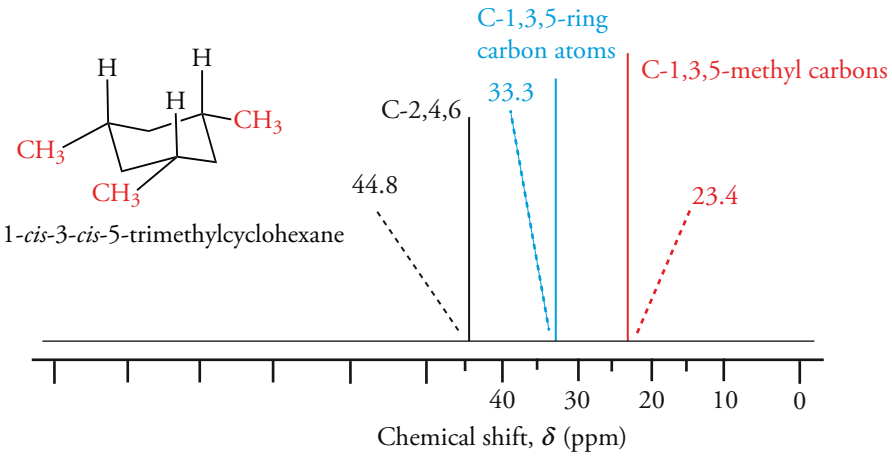
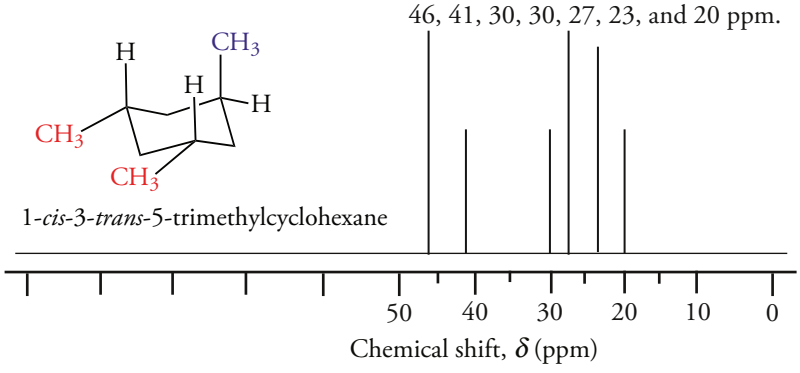


Figure 14.22
^{13}C NMR Spectrum of 1-*cis*-3-*trans*-5-trimethylcyclohexane



Problem 14.14
How can a compound of molecular formula $C_4H_{10}O$ be established as an ether or an alcohol using ^{13}C NMR spectroscopy?

Problem 14.15
The isomeric alcohols 3-heptanol and 4-heptanol cannot be easily distinguished by hydrogen NMR spectroscopy. Describe how ^{13}C NMR spectroscopy can be used to distinguish between these isomers.

14.11 INTRODUCTION TO MASS SPECTROMETRY

In this section, we introduce a powerful and complex experimental method called mass spectrometry. In mass spectrometry, a compound is ionized in the gas phase—although liquids and solids can be studied we will not consider them— and the ions are then sorted by mass. The combination of fragmentation sorting process produces a "spectrum" of fragments derived from the ion that forms in the initial ionization. This is the parent ion. The gas phase chemistry that produces these fragments— the "daughter ions," we might say— is very different in many ways from the reactions we have already discussed. However, one principle links this chemistry to reactions with which we are familiar: Most of the time, *the fragmentation of an ion in a mass spectrometer occurs to give the most stable daughter ions.* Thus, we can apply our previous discussions of bond dissociation energies, radical stability, and carbocation stability to the gas phase reactions in a mass spectrometer. A caveat is required here: the ions that form in a mass spectrometer have very high energies, and sometimes they fragment by processes that do not occur in solution. We will focus upon basis principles, and the cases we will describe fall into patterns of ions stability that we have seen before.

In this chapter, we will discuss the mass spectra of alkanes, halogen-containing compounds, alcohols, and amines. We will discuss the mass spectra of other functional groups when we consider them in later chapters.

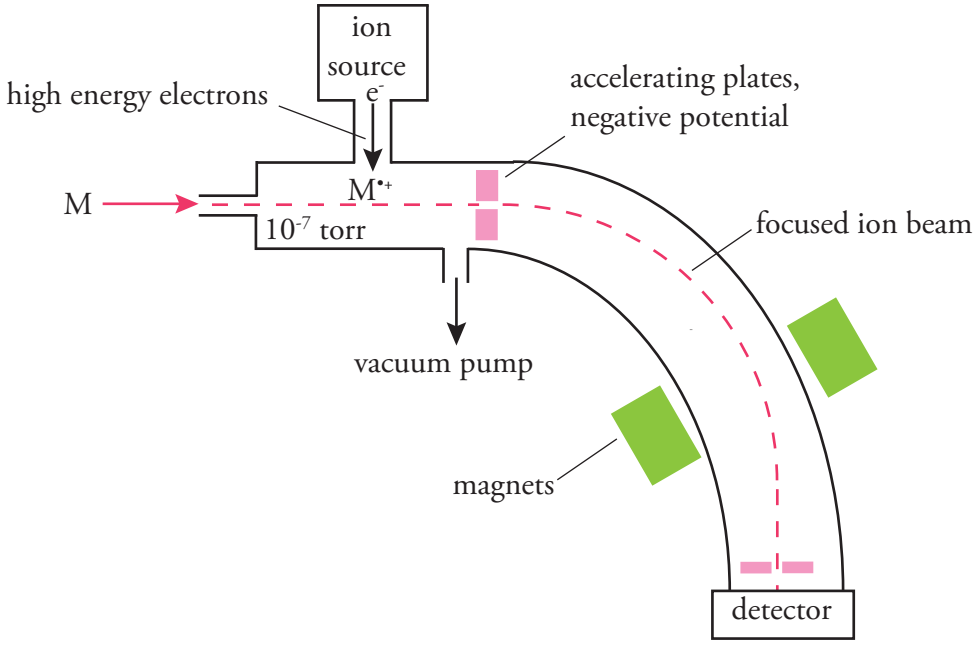
The Mass Spectrometer

A mass spectrometer has three major components (Figure 14.23).

1. The ion source. In an **electron impact mass spectrometer**, a sample of the compound is bombarded by electrons. The collision of a high-energy electron with a sample molecule converts it into a **radical cation**.
2. The mass analyzer. The mass analyzer separates the fragments produced during and after the initial ionization process.
3. The detector. The fragments that have been sorted are displayed on a computer monitor or printed as a **mass spectrum** that gives the mass of each fragment, and the relative abundance of the fragments.

The ions produced in a mass spectrometer have exceedingly short lifetimes. They are very reactive and can survive only in a high vacuum. The pressure in a mass spectrometer is on the order of 10^{-7} torr. The ions are accelerated by a set of electrically charged plates that focus them into a beam. An applied magnetic field acts upon the ion beam and deflects the ions in an arc whose radius is inversely proportional to the mass of each ion. Thus, lower mass ions travel in a more curved arc than more massive ones. The strength of the magnetic field is varied so that ions of different masses are focused at different times on a detector located at the end of a curved tube. Only ions having a single mass number pass through the slit and reach the detector.

Figure 14.23
Block Diagram of a Mass Spectrometer



The Production of Ions in a Mass Spectrometer

Highly energetic electrons emitted by the ion source bombard sample molecules. The collision of a high-energy electron with a sample molecule produces an ion by ejecting a bonding or nonbonding electron from the sample molecule. This method of producing ions is called electron impact mass spectrometry. The ion that forms in this process is a **radical cation**, $M^{+\cdot}$. The radical cation that forms initially is called the **parent ion**. Since the charge of the parent ion is +1, and since the mass of an electron is much smaller than the mass of a proton or neutron, the ratio of the mass of the parent ion, $M^{+\cdot}$, to its charge, m/z, equals the molecular mass of the compound.

$$M + e^- \longrightarrow \underset{\text{Molecular ion (parent ion)}}{M^{\cdot +}} + 2\,e^-$$

The parent ion has very high-energy, and it fragments in the instrument before it reaches the detector. Sometimes, the parent ion accounts for as little as 0.1% of the mass spectrum. If there is no $M^{+\cdot}$ peak, determining the molecular weight becomes more difficult since the molecule has to be reconstructed from its fragments. The peak for the most abundant ion is assigned an arbitrary intensity of 100; this is the **base peak**. The parent ion, $M^{+\cdot}$, fragments to give two products: one is a cation or a radical cation and the other is neutral. The detector responds only to positively charged species. We can identify the mass of the neutral particle that forms when the parent ion disintegrates by subtracting the mass of the base peak from the mass of the parent ion. When we construct the structure of a compound from its mass spectrum, we are essentially solving a "molecular jig-saw puzzle."

$$M^{\bullet +} \longrightarrow M'^{\bullet +} + N^{\bullet}$$

Parent ion — Most stable ion (base peak) — Neutral fragment (not detected)

We saw earlier, in our discussion of NMR, that 1% of carbon atoms exist as the stable isotope ^{13}C. If the parent ion has very low intensity, then the peak for ^{13}C is likely to be below the level of detection. However, if the parent ion is sufficiently intense, then a **P+1 ion** will be present in the mass spectrum. The probability that a molecule will contain ^{13}C increases with the number of carbons in the compound. Thus, for a compound with 10 carbons, there is a 10% chance that one of the carbons will be ^{13}C. In general, then, we have to be careful not to confuse the parent ion with its sibling, the P+1 peak.

Mass Spectrometry of Hydrocarbons

We will begin with the mass spectrum of *n*-pentane. Although it is a simple molecule, it reveals some important information about the mass spectra of hydrocarbons that can be extended to more complex molecules (Figure 14.24).

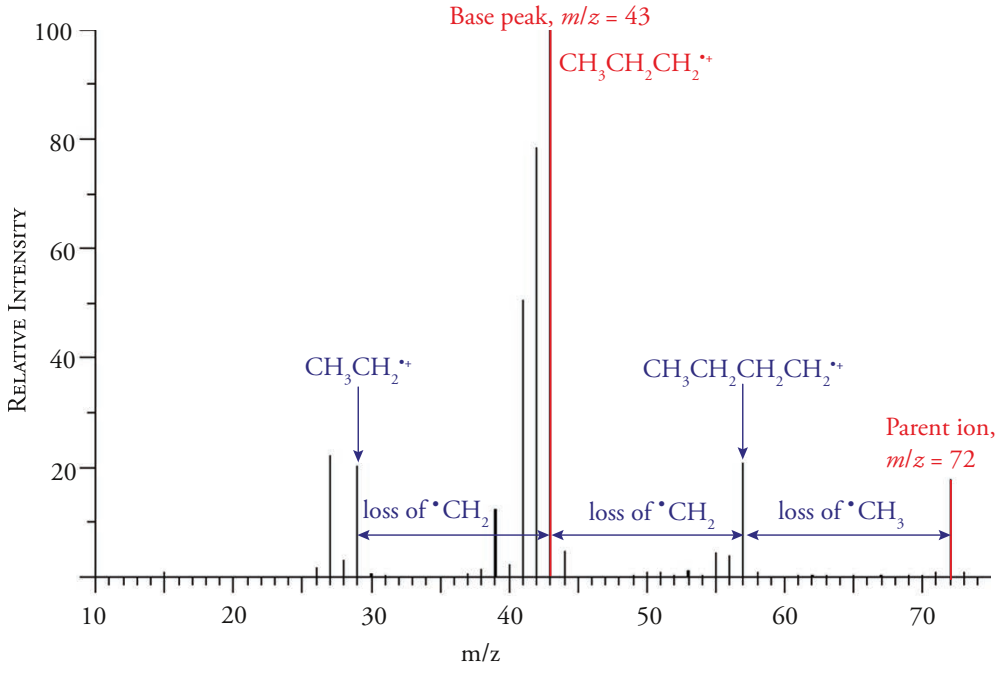


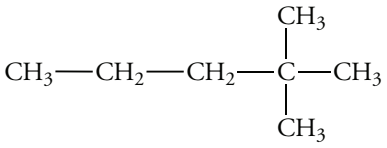
Figure 14.24 Mass Spectrum of *n*-Pentane

n-Pentane ionizes to give a parent ion whose m/z = 72. The parent ion loses a methyl radical to give a peak at m/z = 57. This peak loses a neutral CH_2· group to give the base peak at m/z = 43. The general pattern for *n*-alkyl groups is loss of a CH_3· group first, followed by successive loss of CH_2· groups.

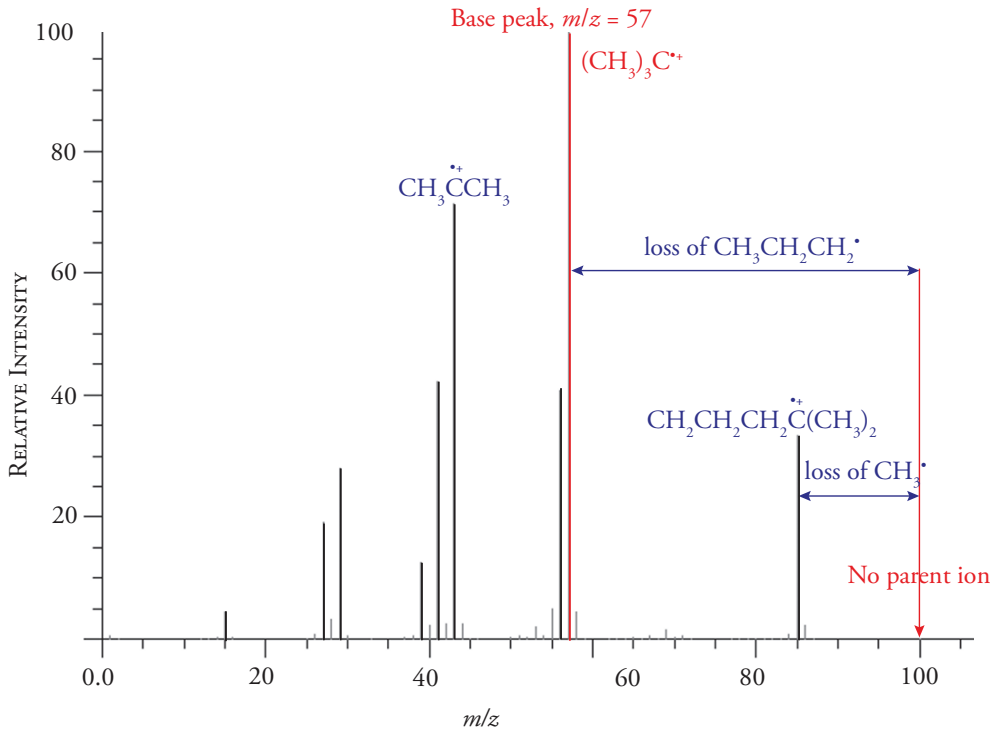
The parent ion of a normal alkane or *n*-alkyl group fragments in a characteristic pattern. The first fragmentation step forms a neutral methyl, CH_3·, and a primary radical cation. This species continues to fragment by losing successive CH_2· groups. The base peak typically has a mass of $CH_3(CH_2)_n^{+}$.

When we examine the mass spectrum of a branched hydrocarbon such as 2,2-dimethylpentane, we do not find a parent ion (Figure 14.25). The ion in the spectrum with the largest mass forms when the parent ion fragments to give a tertiary 2-methylpentyl carbocation and a neutral methyl radical. Alternatively, the parent ion can fragment to give a *tert*-butyl carbocation and an *n*-propyl radical. The *tert*-butyl carbocation (m/z 57) is the base peak. It in turn fragments to form an isopropyl carbocation (m/z 43) and a methyl radical.

Figure 14.25 Mass Spectrum of 2,2-Dimethylpentane



2,2-dimethylpentane
MW 100

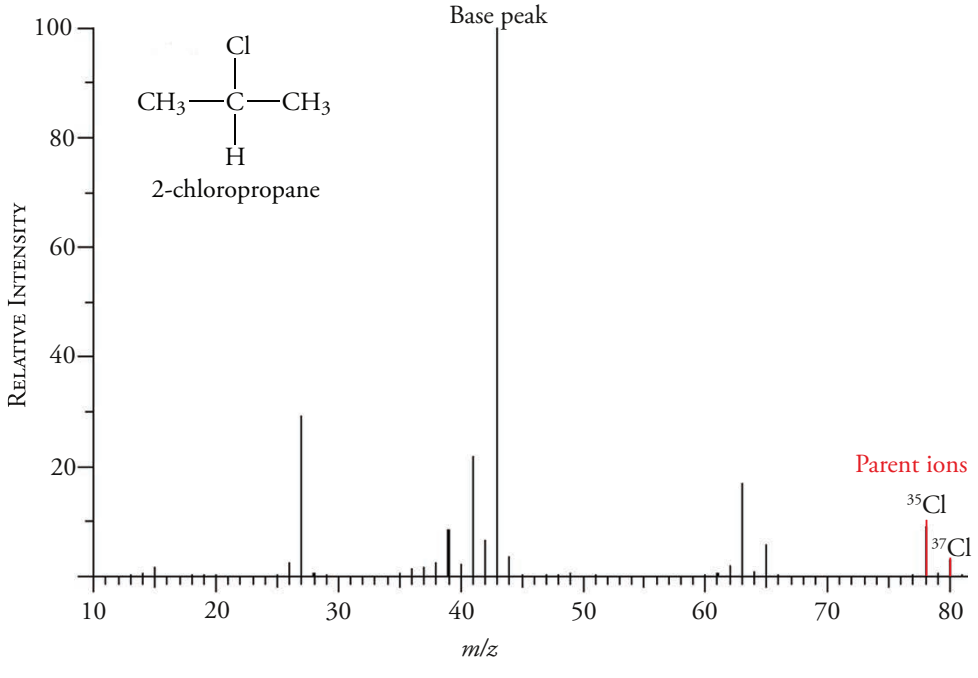


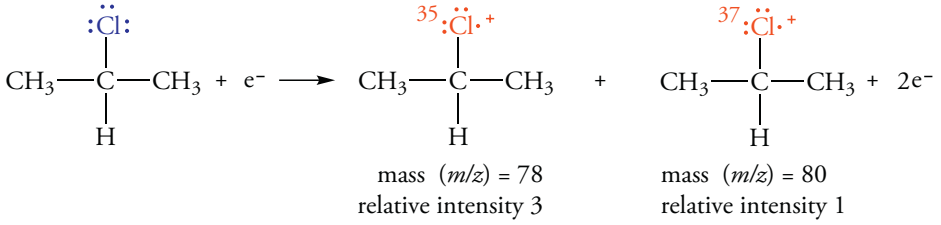
Identifying Chlorine and Bromine-Containing Compounds in a Mass Spectrum

Mass spectrometry is particularly valuable in identifying chlorine and bromine by their isotopic abundances. The atomic mass of chlorine is 35.5. Chlorine has two isotopes, ^{35}Cl and ^{37}Cl. The atomic mass corresponds to an isotopic ratio $^{35}Cl/^{37}Cl$ of 3:1. For example, the mass spectrum of 2-chloropropane has two parent ions that differ by two mass units. The ratios of the intensities of these peaks are 3:1, confirming the presence of chlorine (Figure 14.26).

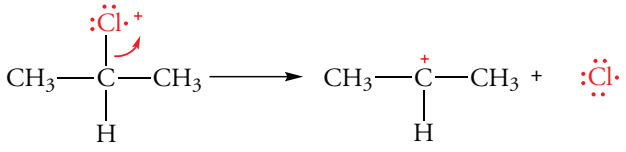
Figure 14.26 Mass Spectrum of 2-Chloropropane

2-Chloropropane ionizes to give two parent ions that differ by two mass units. The ratio of the peak intensities is 3:1, showing that one parent ion contains ^{35}Cl and the other one contains ^{37}Cl. Fragmentation of either parent peak by loss of ^{35}Cl or ^{37}Cl gives the base peak of mass 43. It is an isopropyl cation, $C_3H_7^+$.

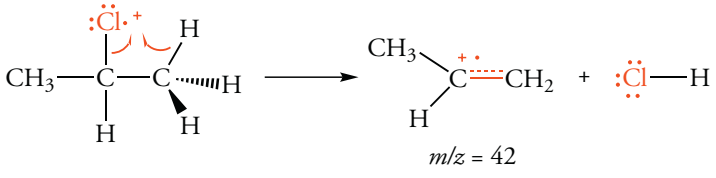




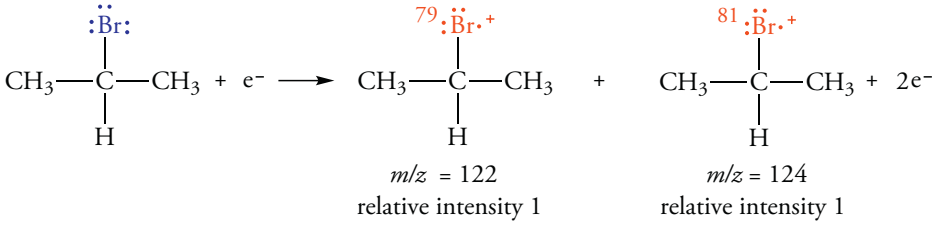
The parent ion can lose a chlorine atom to give an isopropyl carbocation in a process called α-cleavage. The resulting ion has an *m/z* of 43. This process produces the base peak.



The parent ion can also lose HCl to a propenyl radical cation. The resulting ion has an *m/z* of 42.

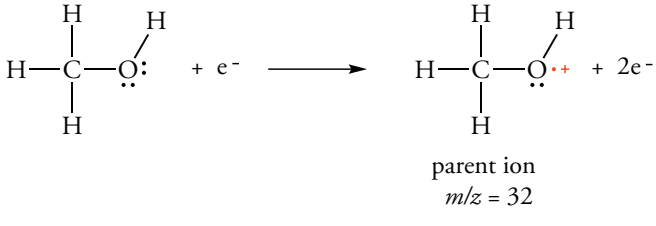


Bromine-containing compounds form molecular ions and fragment in similar ways. In the case of bromine, the relative intensities of the parent ions are the same, corresponding to the 1:1 isotope ratio of $^{79}Br/^{81}Br$.



Mass Spectrometry of Alcohols

We have seen that we can identify alcohols by IR spectroscopy and by proton NMR spectroscopy. The mass spectra alcohols also have characteristic fragmentation patterns. Alcohols lose a hydrogen atom to give a radical cation whose *m/z* is one unit less than the parent ion. Methanol is the simplest example, but it illustrates a basic principle (Figure 14.27).



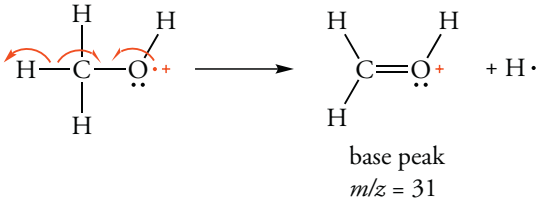
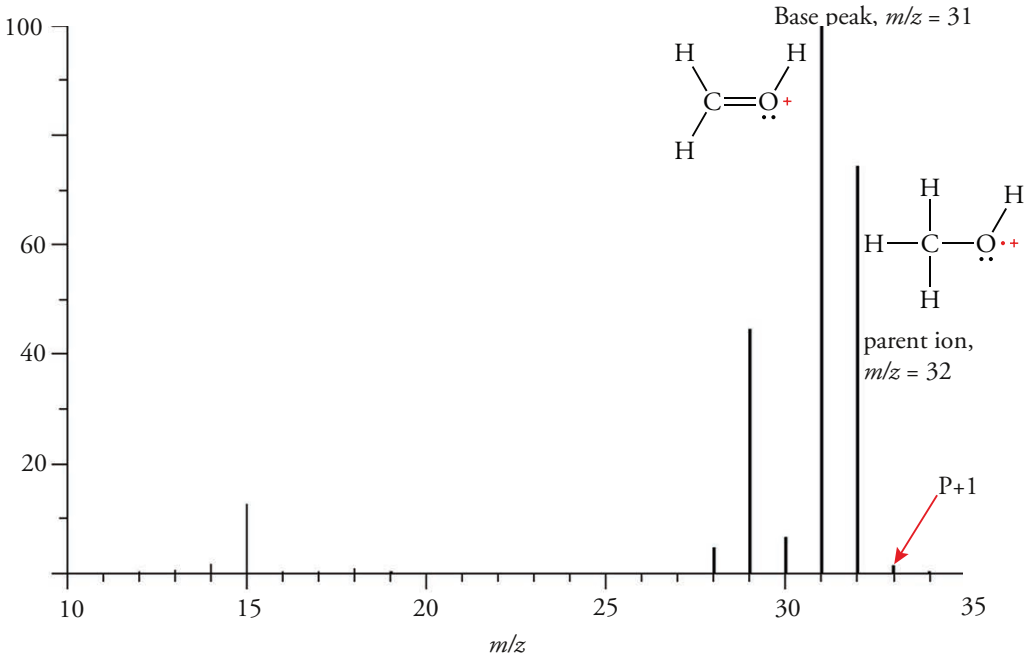
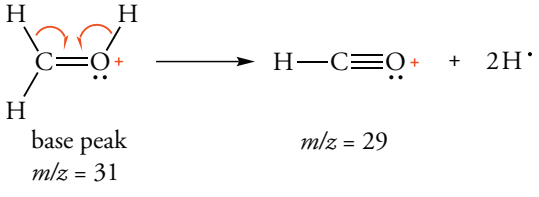


Figure 14.27 Mass Spectrum of Methanol

Methanol ionizes to give a molecular ion whose *m*/*z* is 32. The small peak at *m*/*z* = 33 is the P+1 ion. The parent ion loses a hydrogen atom to give the base peak, a protonated carbonyl group of ethanal.



The fragmentation of the base peak results from cleavage of the C—H bond rather than the C—O bond because the C—O bond is stronger. We can see this effect from the mass spectrum: The peak at *m*/*z* = 15 is a methyl carbocation. It is only about 12% as intense as the base peak. The P+1 peak is the radical cation of the $^{13}CH_3OH$ (the oxygen bears the positive charge, as in the parent peak). The peak at *m*/*z* 29 results from loss of two hydrogen atoms from the base peak, as shown below.



Identifying of Nitrogen-Containing Compounds in a Mass Spectrum

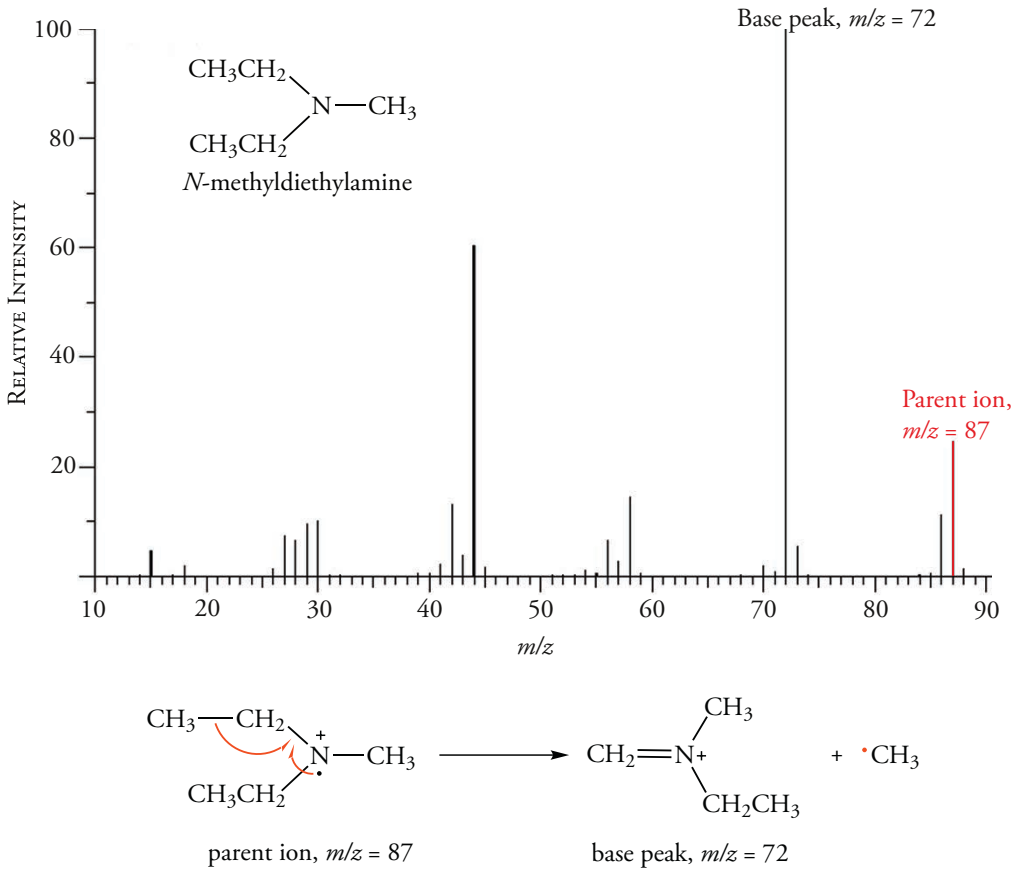
The mass spectrum of a compound provides clues about the presence or absence of nitrogen. If a compound contains a single nitrogen atom, or in fact any odd number of nitrogen atoms, its mass is an odd number. If the mass spectrum of a compound is an even number, then either it has an even number of nitrogen atoms, or none (Table 14.4). Figure 14.28 shows the mass spectrum of *N*,*N*-diethylmethylamine, whose mass is 87.

Table 14.4
Molecular Mass as a Function of the Presence of Absence of Nitrogen

Number of Nitrogen Atoms in Ion	*MW*
One or any odd number	Odd
Two or any even number	Even
None	Even

Figure 14.28 Mass Spectrum of *N*-Methyl-diethylamine

This compound has one nitrogen atom, and therefore the parent ion has an odd molecular mass of 87. Loss of a methyl group as a radical gives the base peak, whose mass is 72.



EXERCISES

Calculation of Chemical Shift

14.9 The hydrogen NMR spectrum of $CHCl_3$, measured with a 360-MHz spectrometer, is a singlet that is 2622 Hz downfield from TMS. Calculate δ.

14.10 The hydrogen NMR spectrum of CHI_3, measured with a 360-MHz spectrometer, is a singlet at 5.37 δ. Calculate the chemical shift in Hz relative to TMS.

Chemical Shifts and Structure

14.11 How many NMR signals should be observed for the hydrogen atoms in each of the following compounds?
(a) 2,2-dimethylpropane (b) 2-methyl-l-propene (c) 1,3,5-trimethylbenzene

14.12 How many NMR signals should be observed for the hydrogen atoms in each of the following compounds?
(a) 1,1-dichloroethene (b) vinyl chloride (c) allyl bromide (d) 1-bromo-l-chloroethene

14.13 How can the compounds of each pair be distinguished using hydrogen NMR spectroscopy?
(a) isopropyl ethyl ether and *tert*-butyl methyl ether
(b) cyclohexane and *cis*-3-hexene
(c) 2,2-dimethyloxirane and *cis*-2,3-dimethyloxirane

14.14 How can the compounds of each pair be distinguished using hydrogen NMR spectroscopy?
(a) 1,3-dibromopropane and 2,2-dibromopropane
(b) 1,1-dichlorobutane and 1,4-dichlorobutane
(c) *cis*-2-butene and 2-methyl-l-propene

14.15 Draw the structure of each of the following hydrocarbons whose hydrogen NMR spectrum consists of a singlet with the indicated chemical shift.

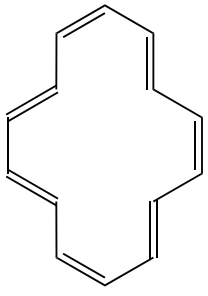
(a) C_5H_{10} ; $\delta = 1.5$ (b) C_8H_{18}; $\delta = 0.9$ (c) $C_{12}H_{18}$; $\delta = 2.2$ (d) C_8H_8; $\delta = 5.8$

14.15 Draw the structure of each of the following hydrocarbons whose hydrogen NMR spectrum consists of a singlet with the indicated chemical shift.

(a) C_5H_{10} ; $\delta = 1.5$ (b) C_8H_{18}; $\delta = 0.9$ (c) $C_{12}H_{18}$; $\delta = 2.2$ (d) C_8H_8; $\delta = 5.8$

14.17 The hydrogen NMR spectrum of [18]annulene consists of signals at $\delta = 8.8$ and -1.9 ppm. The negative value of δ corresponds to an "unusual" chemical shift that is upfield from TMS. The ratio of intensities of the 8.8 to -1.9 ppm resonances is 2:1. Explain these data.

14.18 The hydrogen NMR spectrum of [14]annulene consists of signals at $\delta = 7.8$ and -0.6 ppm. Assign the resonances and predict the relative intensities of each.



[14]annulene

Multiplicity and Structure

14.19 Describe the multiplicity of each of the signals corresponding to a set of equivalent hydrogen atoms in each of the following ethers.

(a) $CH_3CH_2OCH_2CH_3$ (b) $CH_3OCH(CH_3)_2$ (c) $ClCH_2OCHClCH_3$ (d) $Cl_2CHOCHClCHCl_2$

14.20 Describe the multiplicity of the lowest field resonance of each of the following alkyl halides.

(a) 1-chloropentane (b) 1-chloro-2,2-dimethylpropane (c) 3-chloropentane (d) 1-chloro-2-methyl-2-butene

14.21 Using a 400-MHz NMR spectrometer, the chemical shifts of the C-1, C-2, and C-3 hydrogen atoms of chloropropane are 5.82, 4.40, and 1.78 ppm. The coupling constant of the C-2 and C-3 hydrogen atoms is 6.0 Hz and that of the C-2 and C-1 hydrogen atoms is 3.5 Hz. Draw the splitting diagram for the C-2 hydrogen atom.

14.22 Assume that the coupling constants for three nonequivalent hydrogen identified as H_a, H_b, and $H_{a,b}$ are $J_{a,b}$ = 6 Hz, $J_{a,c}$ =2 Hz, and $J_{b,c}$ = 6 Hz. Draw the splitting diagram for H_b. What is the appearance of this resonance?

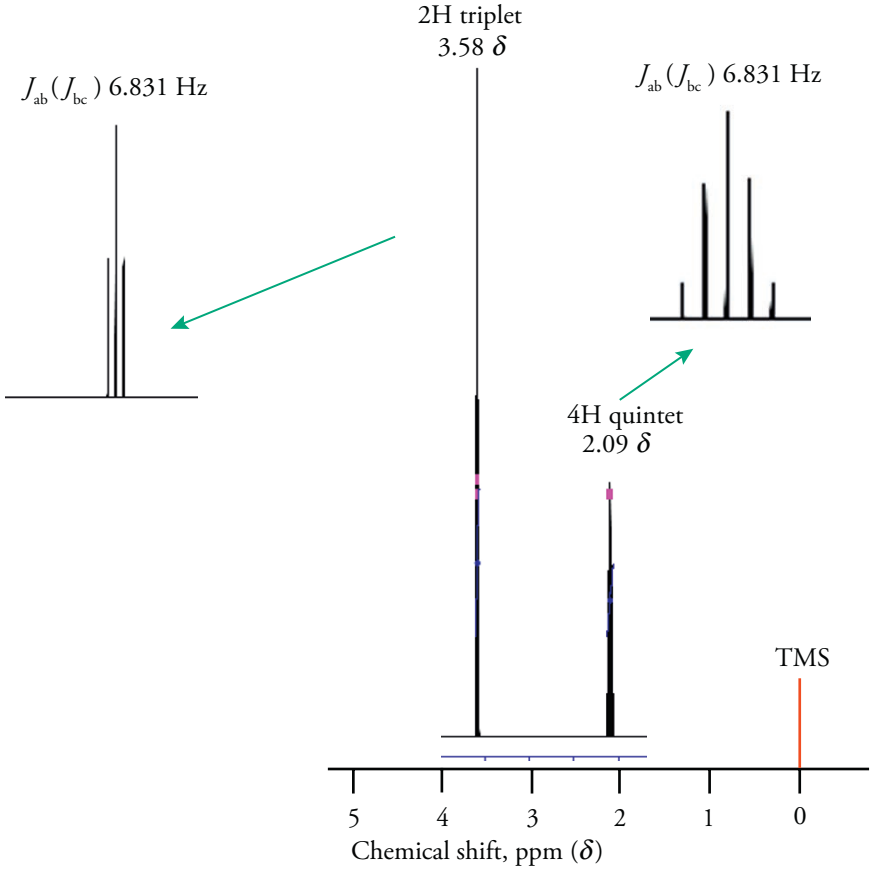
14.23 Hydrogen bromide adds to 3-bromopropene under certain experimental conditions to give a compound whose NMR spectrum is a quintet at 2.10 δ and a triplet at 3.60 δ. The ratio of the total intensity of the quintet to that of the triplet is 1:2. What is the structure of the compound?

14.24 The spectrum of a compound with molecular formula $C_3H_3Cl_5$ consists of a triplet at 4.5 δ and a doublet at 6.0 δ. The intensity ratio of the high-field to low-field signal is 1:2. What is the structure of the compound?

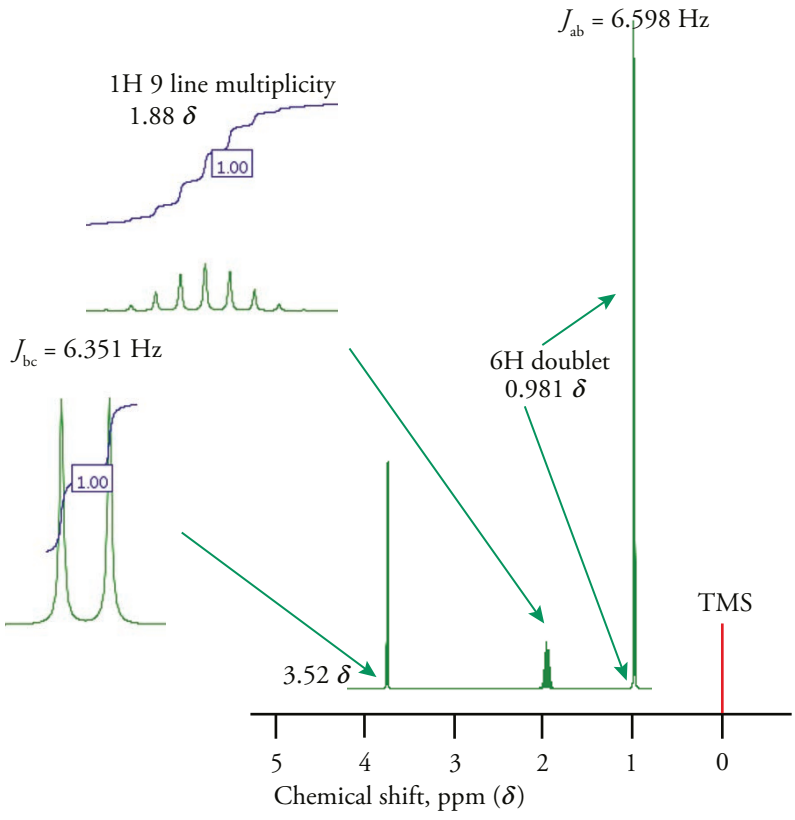
Analysis of Spectra

14.25 Determine the structure of the compound corresponding to each of the following hydrogen NMR spectra.

(a) $C_3H_6Cl_2$

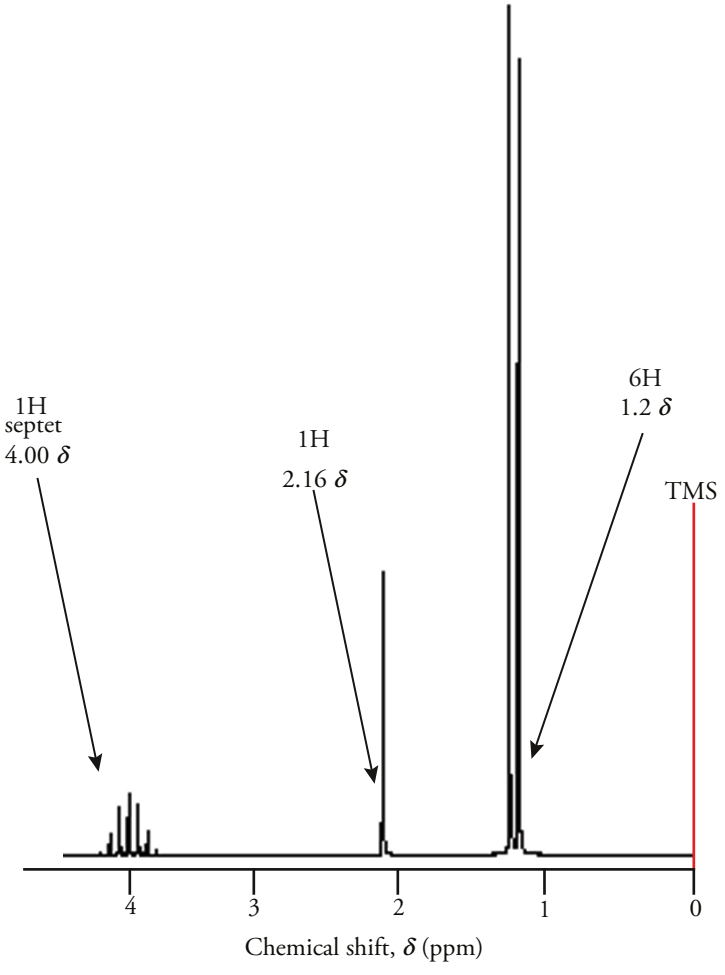


(b) C_4H_9Cl

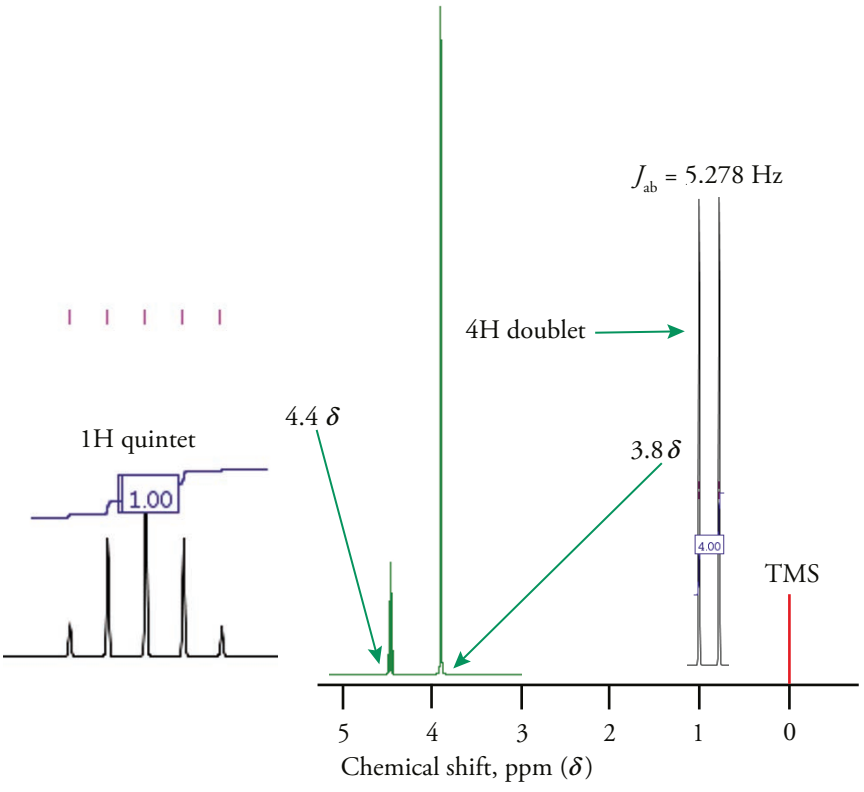


14.26 Determine the structure of the compound corresponding to each of the following hydrogen NMR spectra.

(a) C_3H_8O



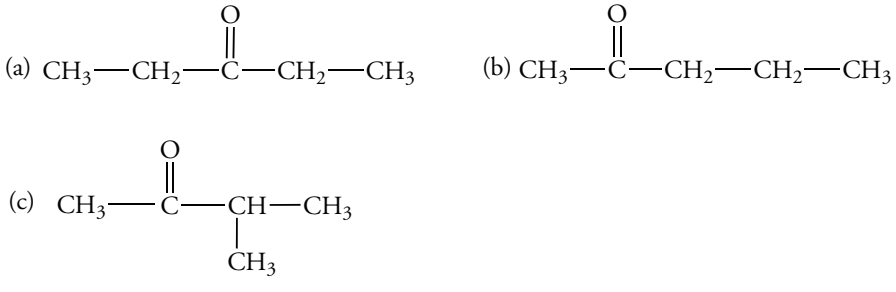
(b) $C_3H_5Cl_3$



Carbon-13 NMR

14.27 Determine the number of signals in the ^{13}C NMR spectrum of each of the following aromatic compounds.
(a) naphthalene (b) 1,2,3-trimethylbenzene (c) 1,3,5-trimethylbenzene (d) 1,4-dimethylbenzene

14.28 Determine the number of signals in the ^{13}C NMR spectrum of each of the following ketones.



Dynamic Processes

14.29 Explain why the ^{13}C NMR spectrum of *trans*-1,4-dimethylcyclohexane contains only one methyl resonance.

14.30 The hydrogen NMR of 2,2,3,3-tetrachlorobutane has a single resonance, a singlet, at 25 °C. Decreasing the temperature to –50 °C yields a spectrum with two singlets of unequal intensity. What structures account for the low temperature spectrum?

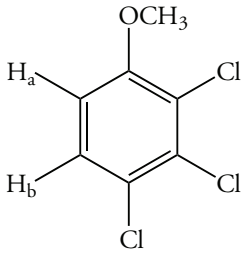
14.31 The hydrogen NMR of 1,1-dibromo-2,2-dichloroethane has a doublet of doublets with a coupling constant of 3.88 Hz. What does this coupling constant indicate about the predominant conformation?

Mass Spectrometry

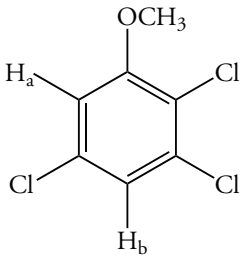
14.32 The mass spectrum of a compound whose IR spectrum has an intense peak at ~3350 cm^{-1} is shown below. (a) Identify the parent peak. (b) Identify the peak compound.

Problem 14.14 Explain how 2,3,4-trichloroanisole and 2,3,5-trichloroanisole can be established using the coupling constants of the two doublets in the NMR spectrum of each compound.

Answer: The coupling constant, J_{ab}, for 2,3,4-trichloroanisole is 8.23 Hz. The coupling constant, J_{ab}, for 2,3,5-trichloroanisole is 8.23 Hz.

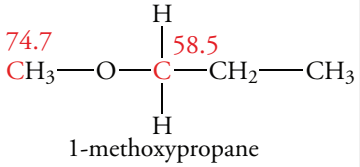


2,3,4-trichloroanisole

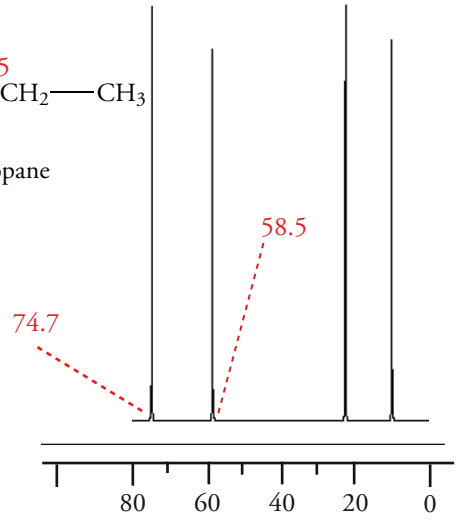


2,3,5-trichloroanisole

Problem 14.15 How can a compound of molecular formula $C_4H_{10}O$ be established as an ether or an alcohol using ^{13}C NMR spectroscopy?

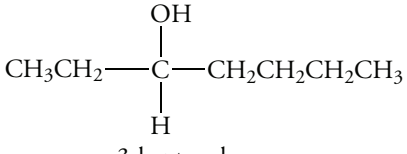


1-methoxypropane

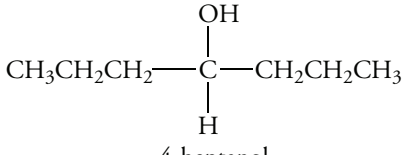


Answer: If we compare ^{13}C NMR spectra of an alcohol and an ether with the same formula, we find that the alcohol has one carbon with a high chemical shift (see Figure 14.24), but an ether has two low-field resonances, as shown above for 1-methoxypropane. This feature allows us to distinguish the two compounds.

Problem 14.16 The isomeric alcohols 3-heptanol and 4-heptanol cannot be easily distinguished by hydrogen NMR spectroscopy. Describe how ^{13}C NMR spectroscopy can be used to distinguish between these isomers.



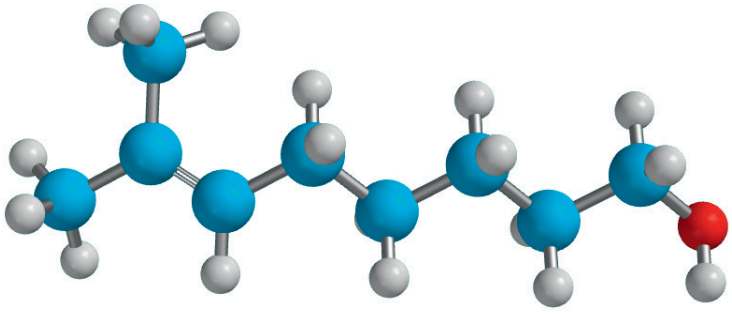
3-heptanol



4-heptanol

Answer: 4-Heptanol, which is highly symmetrical, has only four nonequivalent carbon atoms, and therefore only four ^{13}C NMR resonances. In contrast, 3-heptanol has seven ^{13}C NMR resonances.

15 Alcohols: Reactions and Synthesis

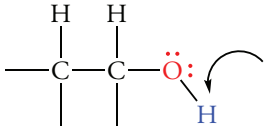


Citronellol

15.1 OVERVIEW OF ALCOHOL REACTIONS

Alcohols can be converted into many classes of oxygen-containing compounds including ethers, esters, aldehydes, ketones, and carboxylic acids. They can also be converted into haloalkanes by substitution reactions, and into alkenes by elimination reactions.

We classify reactions of alcohols according to the different bonds that are broken. Considering only the bonds of the hydroxyl oxygen atom, two types of reactions occur, those involving the O—H bond and those involving the C—O bond. We have already considered the loss of a proton from the O—H bond in acid–base reactions. These are not synthetic reactions. However, replacing the hydrogen atom of the O—H bond by a carbon-containing group is a synthetic procedure used to form more complex structures.

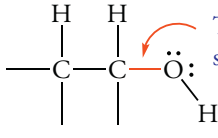


Replacing the alcohol hydrogen with an alkyl group gives an ether. Replacing it with a carbonyl carbon atom yields an ester.

The reaction of the oxygen atom with the electrophilic center of alkyl groups bonded to good leaving groups yields ethers. We will discuss the synthesis of ethers in Chapter 16. Many of the reactions of alcohols yield an ester either as a reaction intermediate or as a stable product. Ester-forming reactions fall into three broad classes:

1. The synthesis of esters of inorganic or organic acids.
2. The formation of ester intermediates that contain a transition metal.
3. The formation of ester intermediates in the conversion of alcohols into alkyl halides.

We will briefly review the conversion of alcohols into alkyl halides that we described in Chapter 9 in this chapter. The conversion of alcohol to alkyl chlorides and alkyl bromides is accomplished using thionyl chloride and phosphorus tribromide, respectively. The C—O bond breaks in these nucleophilic substitution reactions.

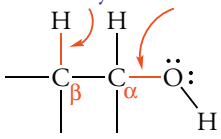


The carbon–oxygen bond breaks in a nucleophilic substitution reaction, which is often acid-catalyzed.

In some reactions in which either the C—O or the O—H bond breaks, a C—H bond also breaks. That C—H bond may be on the β carbon atom or on the carbon atom bearing the hydroxyl group. The dehydration reaction of alcohols results in the cleavage of both the C—O bond and the C—H bond of the β carbon atom. We discussed this process, a β-elimination reaction that results in net dehydration, in Section 9.20.

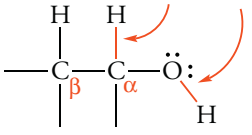
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00015-2
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The carbon–oxygen and carbon–hydrogen bonds break in a dehydration reaction, often acid-catalyzed.



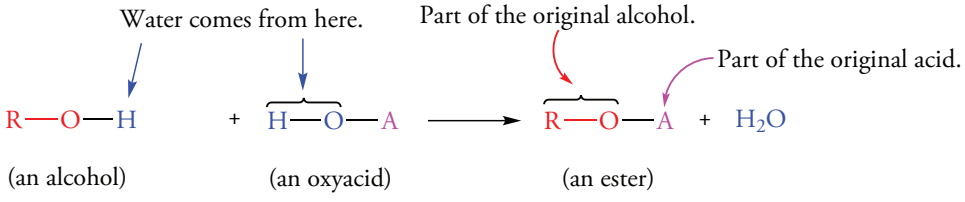
Breaking both the O—H bond and the C—H bond at the carbon atom bearing the hydroxyl group is an oxidation reaction. We will consider this α-elimination reaction in detail in this chapter. The oxidation reactions convert alcohols into aldehydes and ketones or, by further oxidation, into carboxylic acids.

The oxygen–hydrogen and carbon–hydrogen bonds break in an oxidation reaction, an α-elimination,



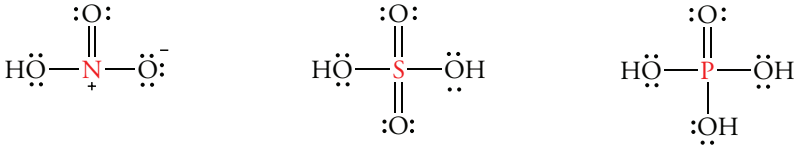
15.2 CONVERTING ALCOHOLS INTO ESTERS

The reaction of an oxyacid, represented as HOA, with an alcohol can yield an ester. The ester forms by the nucleophilic attack of the alcohol oxygen atom on the central atom of the oxyacid bearing the hydroxyl group. Thus, the ester contains the oxygen atom of the alcohol.



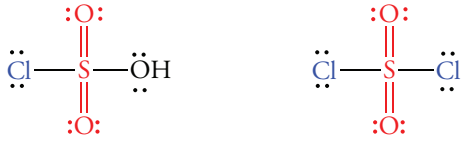
Esters of Nitric, Sulfuric, and Phosphoric Acid

The structures of nitric, sulfuric, and phosphoric acid are shown below. The polyprotic acids, sulfuric acid and phosphoric acid, contain two and three hydroxyl groups, respectively. Thus, mono- and diesters can form from sulfuric acid and mono-, di-, and triesters from phosphoric acid.



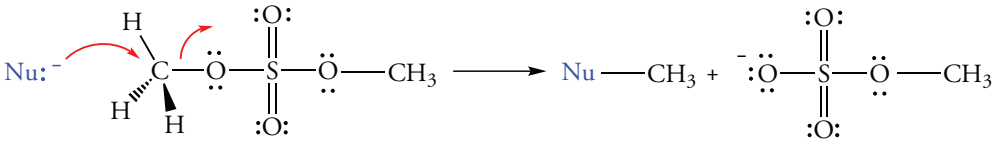
nitric acid | sulfuric acid | phosphoric acid

Although esters can be formed by direct reaction of an acid with an alcohol, they are more commonly formed using a derivative of an acid called an **acid chloride**. Two acid chlorides of sulfuric acid- chlorosulfonic acid and sulfuryl chloride- are used to prepare esters.



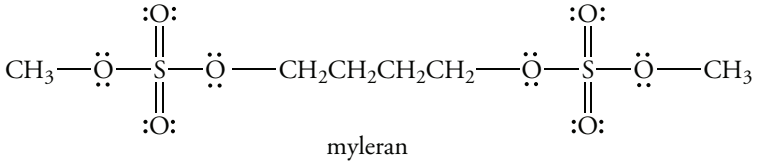
chlorosulfuric acid | sulfuryl chloride

Dimethyl sulfate, a diester of sulfuric acid, is a commercially available liquid used as a methylating agent. Nucleophiles readily attack the electrophilic methyl carbon atom by an S_N2 reaction to give methylated products. The methyl sulfate ion is an excellent leaving group because it is resonance stabilized, and only weakly basic.



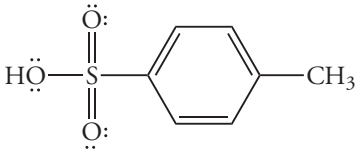
dimethyl sulfate methyl sulfate

Highly active methylating agents such as dimethyl sulfate must be used with great care because they react with cellular molecules, which all contain nucleophilic sites. Some alkylating agents act as antineoplastic agents, slowing the growth of some cancers. For example, myleran is used in the treatment of myelogenous leukemia.

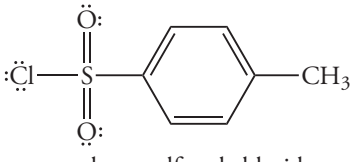


myleran

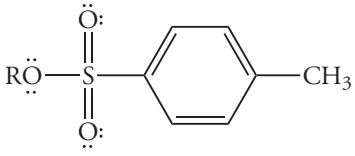
We recall that alcohols react with sulfonyl chlorides—the acid chlorides of sulfonic acids—to form sulfonates (Section 9.3). We now recognize that these alcohol derivatives are esters of an organic analog of sulfuric acid.



p-toluenesulfonic acid

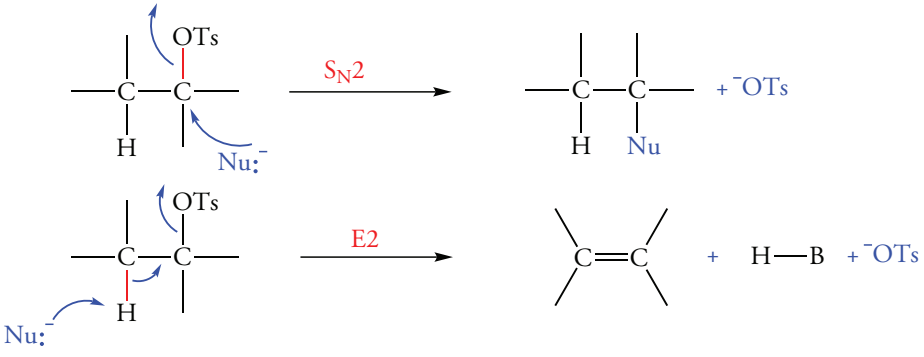


p-toluenesulfonyl chloride
(tosyl chloride)



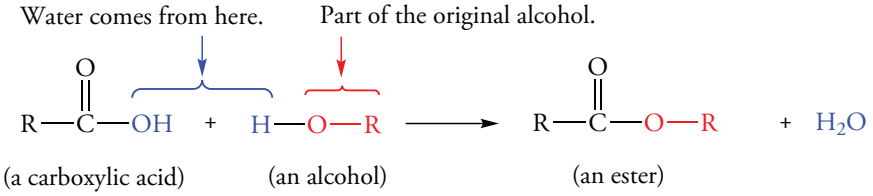
alkyl *p*-toluenesulfonate
(alkyl tosylate)

Alcohols react with *p*-toluenesulfonyl chloride to give useful synthetic intermediates called *p*-toluenesulfonates, or tosylates. The *p*-toluenesulfonate ion, a weak base, is an excellent leaving group. Methyl, primary, and secondary tosylates undergo S_N2 displacement reactions with nucleophiles. They also react with strong bases in E2 reactions.

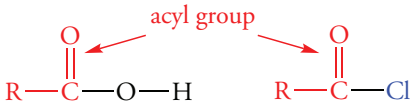


Esters of Carboxylic Acids

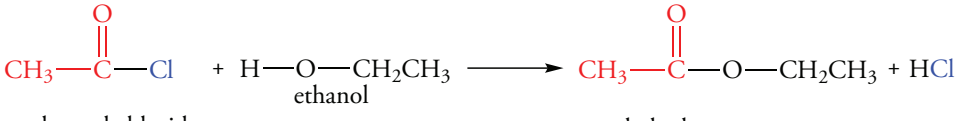
If the nucleophilic oxygen atom of an alcohol attacks the carbonyl carbon atom of the carboxylic acid, the result is an ester that contains the oxygen atom of the alcohol.

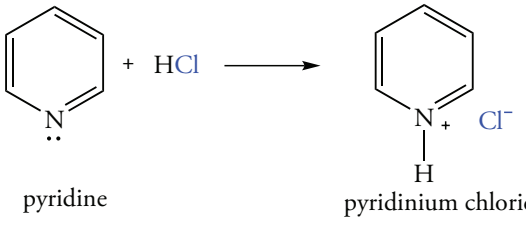


As in the case of inorganic acids, a derivative of a carboxylic acid called an **acid chloride** or **acyl chloride** is often the preferred reagent to form esters.

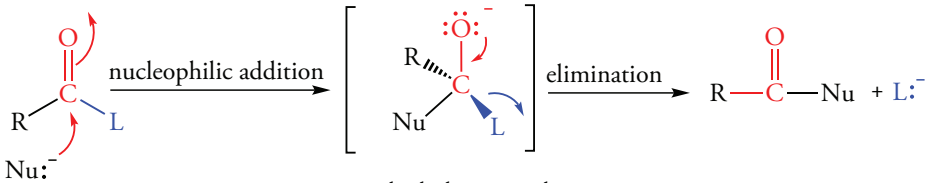


The reaction of an alcohol with an acid chloride produces an organic ester. The reaction releases HCl, which is neutralized with a base such as pyridine.





This reaction, in which a halide ion is formally replaced by an alkoxy group, is an example of **nucleophilic acyl substitution**. A general representation of this mechanism using $Nu:^-$ as the nucleophile and $Nu:^-$ as the leaving group is shown below.



The net result is a substitution reaction in which the stoichiometry resembles that of an S_N2 substitution reaction of haloalkanes. However, an S_N2 reaction occurs in a single step in which the nucleophile bonds to the carbon atom as the leaving group leaves. Nucleophilic acyl substitution occurs in two steps, and the rate-determining step is usually nucleophilic attack at the carbonyl carbon atom to form a tetrahedral intermediate. The loss of the leaving group occurs in a second, faster step.

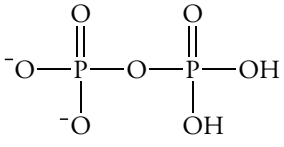
We recall that the size of the nucleophile strongly affects the rate of an S_N2 reaction. Thus, *tert*-butoxide is a poorer nucleophile than ethoxide ion (Section 9.1). For the same steric reasons, the order of reactivity of an alcohol with an acyl chloride (or carboxylic acid) decreases in the order primary > secondary > tertiary.

The chemistry of organic esters differs substantially from that of inorganic esters. The conjugate base of a carboxylic acid—the carboxylate ion—is a stronger base than the conjugate bases of inorganic acids. Hence, a carboxylate ion is not a good leaving group and the alkyl carbon atom is not

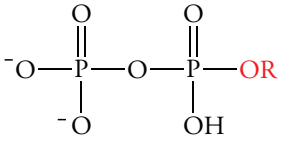
nearly as susceptible to nucleophilic substitution reactions. Also, the carbonyl carbon atom of the ester is much more susceptible to attack by a nucleophile (Chapter 20). The chemistry of organic esters differs substantially from that of inorganic esters. The conjugate base of a carboxylic acid—the carboxylate ion—is a stronger base than the conjugate bases of inorganic acids. Hence, a carboxylate ion is not a good leaving group and the alkyl carbon atom is not nearly as susceptible to nucleophilic substitution reactions. Also, the carbonyl carbon atom of the ester is much more susceptible to attack by a nucleophile (Chapter 20).

Phosphate and Pyrophosphate Esters

Many cellular reactions that occur by displacement of a hydroxyl group by a nucleophile. Although the hydroxyl group of an alcohol is not a good leaving group, it can be converted into a phosphate or a pyrophosphate ester. Both phosphoric and pyrophosphoric acids are stronger acids than water. Thus, the related conjugate bases—phosphate ion and pyrophosphate ion—are weaker bases than hydroxide ion. Both conjugate bases are then excellent leaving groups. We will focus on the pyrophosphates.

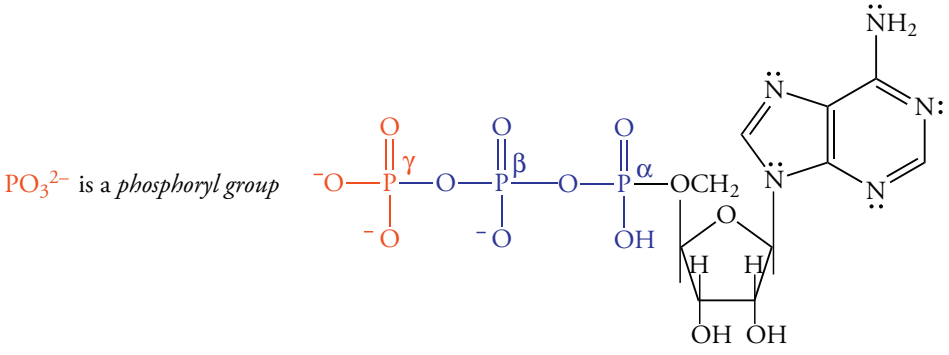


dihydrogen pyrophosphate

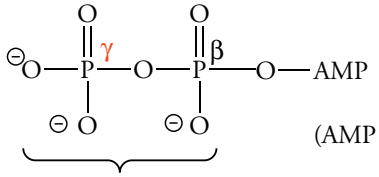


monohydrogen pyrophosphate ester

The concentration of pyrophosphate ion in cells is very low, and the conversion of alcohols to pyrophosphates does not occur by itself. So, how are alcohols converted to pyrophosphates in cells? The answer is that the source of pyrophosphate is not the pyrophosphate ion or phosphoric acid, but adenosine 5′-triphosphate (ATP), which contains a pyrophosphoryl group.



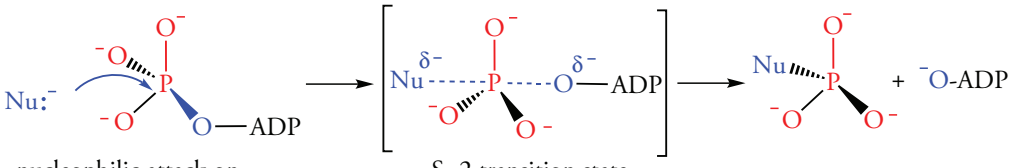
Adenosine-5′-phosphate (ATP^{3-})



(AMP is adenosine monophosphate.)

Pyrophosphoryl group of ATP

The phosphorus atoms are very susceptible to attack by nucleophiles because of the inductive electron withdrawal by oxygen atoms. The leaving group is a phosphate or diphosphate derivative, depending on which phosphorus atom the nucleophile attacks. For example, attack at the terminal phosphorus, the γ phosphorus, releases ADP as the leaving group.

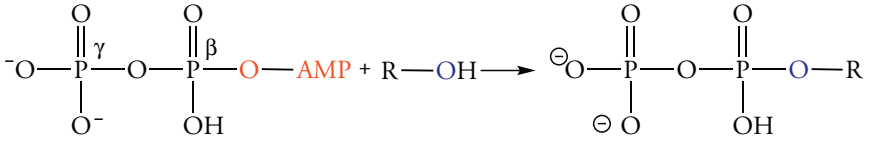


nucleophilic attack on tetrahedral phosphorus

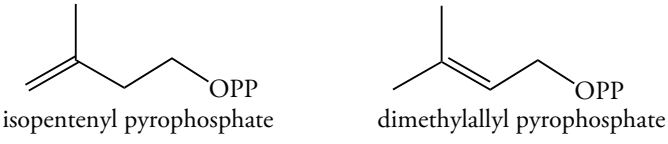
S_N2 transition state

The hydrolysis of ATP is one example of nucleophilic attack at a phosphoryl group. Either of the P—O—P bonds of adenosine triphosphate can be hydrolyzed. Nucleophilic attack by water at a terminal, γ, phosphorus atom displaces adenosine 5′-diphosphate (ADP). Attack at the internal phosphorus atom displaces adenosine 5′-monophosphate (AMP) and forms pyrophosphate. The equilibrium constants for both hydrolysis reactions are much greater than 1.0. The large equilibrium constant partly results from the electrostatic repulsion among the negatively charged oxygen atoms on neighboring phosphorus atoms. The separated product ions are better solvated than ATP, and this also favors the reaction.

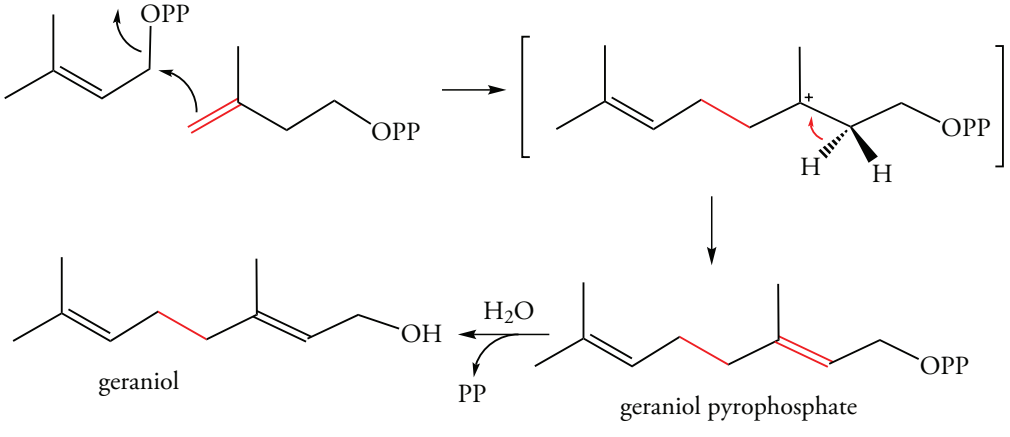
Alcohols react with ATP in enzyme-catalyzed reactions to produce phosphate and pyrophosphate esters. The reaction occurs by nucleophilic attack of the alcohol hydroxyl group on phosphorus. The net enzyme-catalyzed reaction for formation of a pyrophosphoryl group is shown below.



Pyrophosphate derivatives of alcohols participate in the biosynthesis of many molecules, including cholesterol and steroid hormones. The biosynthesis of these molecules begins with a nucleophilic substitution reaction between two five-carbon isoprenoid pyrophosphates called isopentenyl pyrophosphate and dimethylallyl pyrophosphate. An enzyme-catalyzed reaction interconverts the two isomers. The pyrophosphoryl groups are abbreviated—OPP.



They combine in a nucleophilic substitution reaction in which the π electrons of isopentenyl pyrophosphate act as a nucleophilic center to displace a pyrophosphoryl group from dimethylallyl pyrophosphate. The nucleophilic substitution reaction produces a new carbon–carbon bond, leaving a carbocation in the isopentenyl group.



Loss of a proton at the C-2 atom yields geraniol pyrophosphate. This product then reacts with water, which displaces the pyrophosphate group and produces a terpene alcohol, geraniol.

Although the reactions become more complicated, the mechanisms for the formation of other terpenes, both cyclic and acyclic, are similar.

Problem 15.1

Write the Lewis structure of phosphorus oxychloride ($POCl_3$) the acid chloride of phosphoric acid. Write the structure of the product formed when excess methanol reacts with phosphorus oxychloride.

Problem 15.2

Write the structure of the product formed in the reaction of chlorosulfonic acid with (*S*)-2-butanol. What is the configuration of this product?

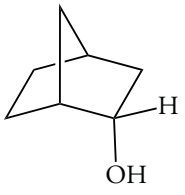
Problem 15.3

Silicic esters, $(RO)_4Si$, form in the reaction of alcohols with $SiCl_4$. They react with water to form silica and an alcohol. Mechanisms for the hydrolysis can be written that involve S_N2 attack of water on silicon or at the carbon atom of the R group. Suggest an experiment using isotopes that would distinguish between these two possible mechanisms.

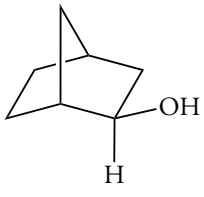
$$(RO)_4Si + 4H_2O \rightarrow 4ROH + Si(OH)_4$$

Problem 15.4

The rates of reaction of ethanoyl chloride CH_3COCl, acetyl chloride with *exo*- and *endo*-bicyclo[2.2.1] heptan-2-ol, are different even though both are secondary alcohols. Examine molecular models of these compounds to determine why. Which compound reacts at the faster rate?



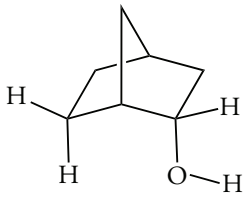
endo-bicyclo-[2.2.1]heptan-2-ol



exo-bicyclo-[2.2.1]heptan-2-ol

Sample Solution

The hydroxyl group of the *endo* compound is in a more sterically crowded environment. There are 1,3 diaxial interactions, much like those in the axial position of a cyclohexane ring.



We recall that the rate of reaction of nucleophiles decreases with increased steric size of the nucleophile (Section 9.1). Thus, the *endo* compound should react at a slower rate than the *exo* compound.

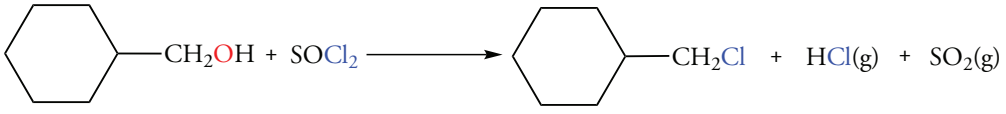
15.3 CONVERSION OF ALCOHOLS TO HALOALKANES

Alcohols are starting materials for the synthesis of many functional groups, and a synthetic scheme might very well begin with conversion of an alcohol to a chloroalkane. The reaction of an alcohol with a hydrogen halide, however, often produces carbocations that undergo elimination reactions that often compete with substitution reactions. To avoid this competing reaction, synthetic methods have been developed that do not use strongly acidic reagents.

Reaction of Alcohols with Thionyl Chloride

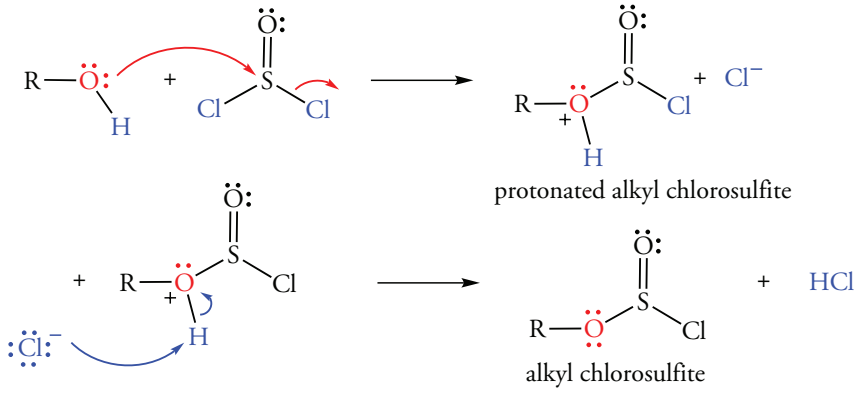
We recall that alcohols react with HCl to give alkyl chlorides. The negatively charged hydroxide ion, a strong base, is a poor leaving group. The first step in these reactions is protonation of the alcohol to give its conjugate acid. Protonation of the alcohol converts the —OH group into a good leaving group, water. Substitution of water by chloride or bromide ion occurs by an S_N2 process for primary and secondary alcohols and an S_N1 process for tertiary alcohols. The order of reactions rates for alcohols is 3° > 2° > 1°. We also recall that primary and secondary alcohols react readily with thionyl chloride ($SOCl_2$) to give alkyl chlorides. The reaction of thionyl chloride gives the by-products hydrogen chloride and sulfur dioxide, which are released from the reaction as gases. The chloroalkane remains in solution.

$$CH_3(CH_2)_4CH_2OH + SOCl_2 \longrightarrow CH_3(CH_2)_4CH_2Cl + HCl(g) + SO_2(g)$$



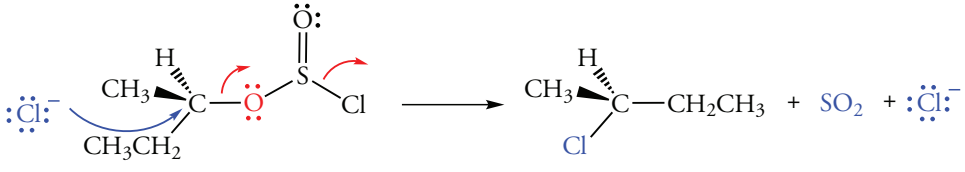
Mechanism of the Reaction of Alcohols with Thionyl Chloride

The reaction mechanism by which thionyl chloride reacts an alcohol occurs in several steps. First, a nucleophilic oxygen atom of the alcohol displaces a chloride ion from thionyl chloride to form an a protonated alkyl chlorosulfite intermediate. Subsequent deprotonation of this intermediate by a base yields the alkyl chlorosulfite, an inorganic ester.

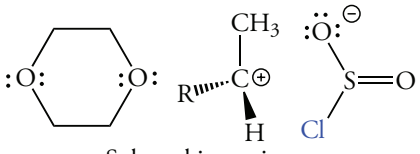


The next step of the reaction may occur by either of two mechanisms, depending on the reaction conditions.

1. If a base such as pyridine is present to neutralize the HCl generated in the steps leading to the alkyl chlorosulfite, a substitution reaction occurs with inversion of configuration.

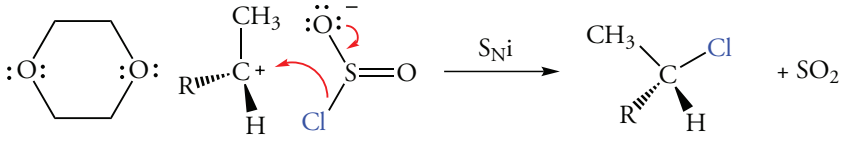


2. In dioxane as solvent, the substitution reaction occurs with retention of configuration. The alkyl chlorosulfite undergoes heterolytic cleavage of its C—O bond to give a pair of oppositely charged ions. These ions, a carbocation and chlorosulfite, remain together as an ion pair. Dioxane solvates the carbocation on the side opposite the chlorosulfite.



Solvated ion pair

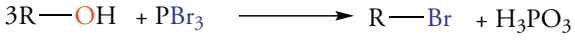
The ion pair can react by transfer of chloride ion to the same face of the carbocation as the original C—O bond. The process is called **internal return**, and the mechanism is called S_Ni, where the i refers to *internal*.

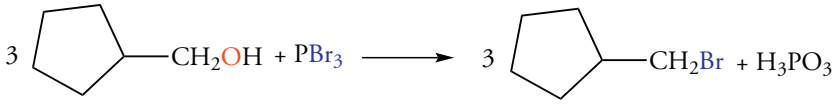


Solvated ion pair Retention of configuration

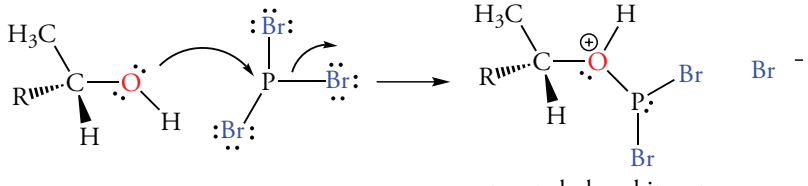
Reaction of Alcohols with Phosphorus Tribromide

The reaction of alcohols with phosphorus tribromide produces an alkyl halide plus phosphorous acid, which has a high boiling point and is water soluble. Therefore, the bromoalkane can be separated from the reaction mixture by distillation or by adding water.



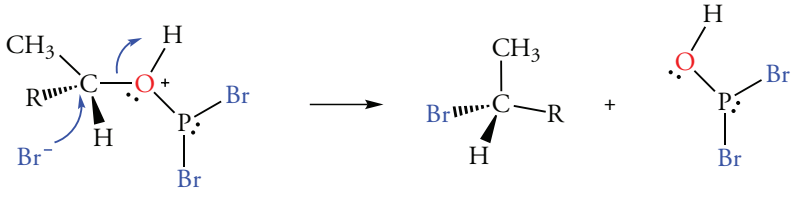


In the first step of this reaction, the nucleophilic oxygen atom of the alcohol displaces a bromide ion from the phosphorus tribromide to form the conjugate acid of a phosphite ester, $ROPBr_2$.



protonated phosphite ester

Continued reaction, and successive displacement of bromide ion on the $ROPBr_2$ intermediate, yields esters having the general formulas $(RO)_2PBr$ and $(RO)_3P$. These esters react with bromide ion to form the alkyl bromide product. For the sake of simplicity, we will only show the reaction of the $ROPBr_2$ intermediate.



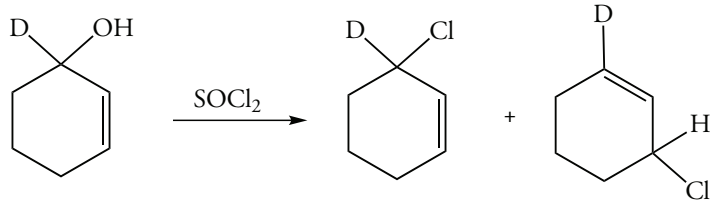
In the second step of the reaction, the C—O bond of the phosphite ester breaks, with predominant inversion of configuration. Some loss of optical activity and a small amount of rearrangement may occur. For example, 2-bromobutane formed from optically active 2-butanol is about 80% optically pure. About 2% of the product is 2-bromo-2-methylpropane.

Problem 15.5

The reaction of 3-pentanol with phosphorus tribromide yields a mixture of 3-bromopentane and 2-bromopentane in approximately a 9:1 ratio. Explain the source of each product.

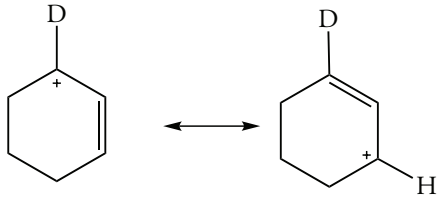
Problem 15.6

The reaction of l-deuterio-2-cyc1ohexen-1-ol with thionyl chloride in dioxane as solvent yields a mixture of two isomeric 3-chlorocyc1ohexenes with the deuterium distributed as indicated. Suggest a mechanism that accounts for the formation of the two products. Predict the ratio of the two products formed.



Sample Solution

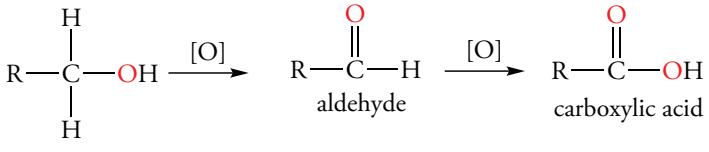
The chlorosulfite derived from the alcohol is an allyl derivative that is prone to react by an S_N1 mechanism. Two resonance forms can be written for the carbocation, which are equal in energy, but nonequivalent because of the deuterium atom.



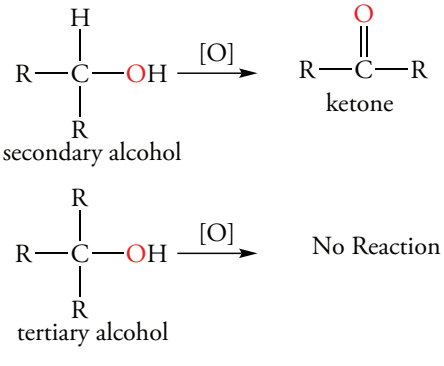
Capture of the carbocation by a chloride ion can occur at either of two sites, giving two isomeric 3-chlorocyclohexenes in equal amounts.

15.4 OXIDATION OF ALCOHOLS

Many oxidizing agents react with primary and secondary alcohols. Primary alcohols can be oxidized to aldehydes. Aldehydes are easily oxidized and, depending upon the reaction conditions, may react to produce carboxylic acids. The symbol [O] in the reactions shown below denotes an oxidation reaction. In each case, the hydrogen bound to oxygen leaves as H^+, and a hydrogen bound to oxygen departs with its electron pair, formally as "H^-." In the conversion of an aldehyde to a carboxylic acid, the second oxygen comes from the solvent.

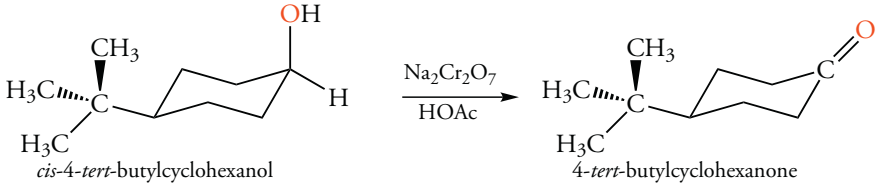


Secondary alcohols are oxidized to form ketones, which are not easily oxidized because there is no hydrogen atom on the carbonyl carbon atom of the ketone. Tertiary alcohols are not oxidized because the carbon atom bearing the hydroxyl group does not have a hydrogen atom.



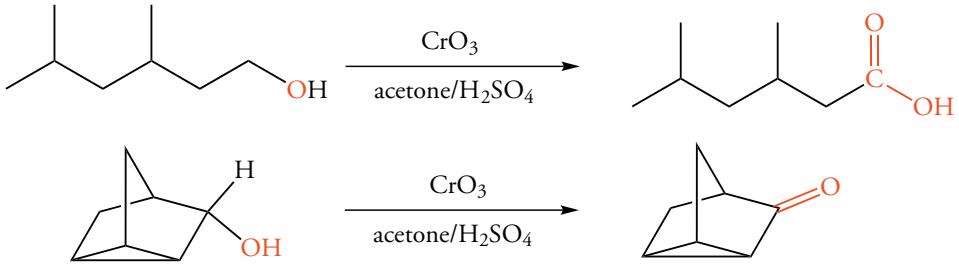
Oxidizing Agents for Alcohols

Alcohols are often oxidized with chromium(VI) compounds. When the alcohol is oxidized, Cr(VI) is reduced in several steps to Cr(III). The specific Cr(VI) species used depends on the scale of the process, the cost of reagents, and limitations that result from the presence of other functional groups in the reactant. For example, the inexpensive reagent sodium dichromate ($Na_2Cr_2O_7$) oxidizes secondary alcohols to ketones. It also oxidizes primary alcohols to aldehydes and then to carboxylic acids. Sodium dichromate in acetic acid (HOAc) is used in large-scale reactions to convert secondary alcohols to ketones.



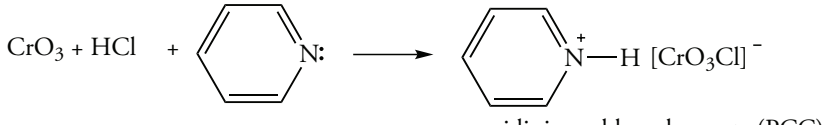
cis-4-*tert*-butylcyclohexanol — 4-*tert*-butylcyclohexanone

In small-scale reactions, the Jones reagent, which consists of chromium trioxide (CrO_3) in a solution of aqueous acetone and sulfuric acid, is used to oxidize alcohols. The Jones reagent converts primary alcohols to aldehydes and then immediately oxidizes the aldehydes to carboxylic acids. It also converts secondary alcohols to ketones.



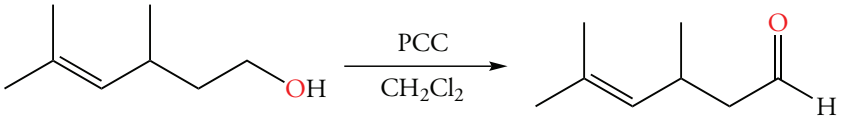
Oxidation by the Jones reagent occurs rapidly at or below room temperature. A simple alcohol with no other functional groups is easily oxidized to give a good yield of oxidized product.

Alcohols are also oxidized with a milder oxidizing agent consisting of pyridinium chlorochromate (PCC) in methylene chloride (CH_2Cl_2) as solvent. PCC is made by dissolving CrO_3 in HCl and then adding pyridine to obtain a solid, which is isolated and then dissolved in methylene chloride. The reagent is anhydrous, so a primary alcohol can be converted to an aldehyde without further oxidation to a carboxylic acid.



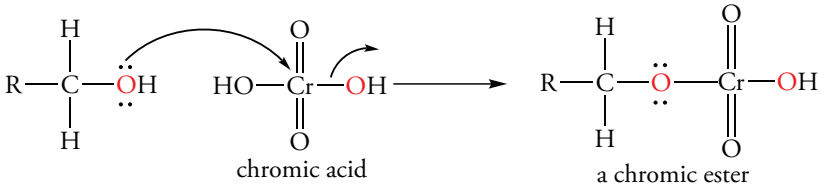
pyridinium chlorochromate (PCC)

Because the PCC reaction occurs under basic conditions, functional groups such as carbon–carbon double bonds do not react during the time required for oxidation of the alcohol. But, the principal advantage of PCC is that primary alcohols are converted to aldehydes without continued oxidation to carboxylic acids.

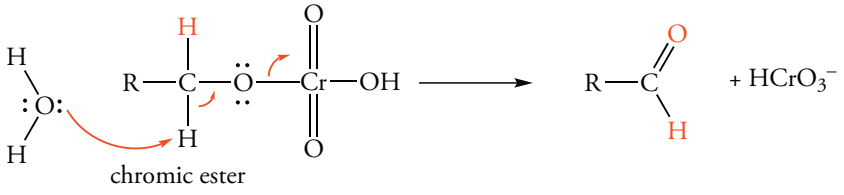


Mechanism of Oxidation by Chromium(VI)

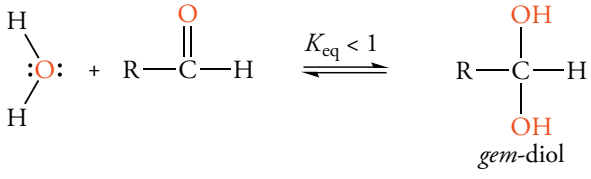
Chromic acid (H_2CrO_4) reacts with alcohols to form a chromic ester in which the alcohol oxygen atom bridges the carbon and chromium atoms. The ester forms by nucleophilic attack of the alcohol oxygen atom on the chromium atom. This reaction is analogous to an S_N2 reaction with a—OH group of chromic acid as the leaving group.



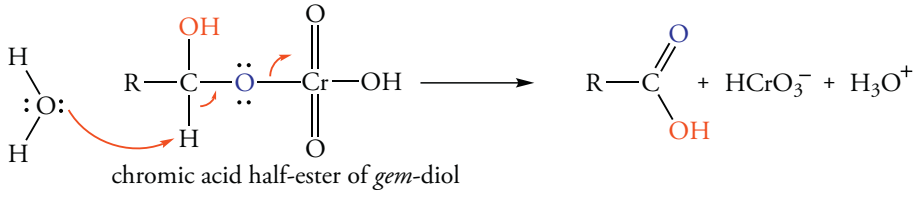
In the second step of the reaction, water extracts a hydrogen atom from the alcohol carbon, the electron pair in the C—H bond acts as a nucleophile, and the O—Cr bond in the chromic ester breaks to form a carbon–carbon double bond.



In an aqueous acid solution, chromic acid converts aldehydes to carboxylic acids. Before this second occurs, the aldehyde reacts with water to give a 1,1-diol, called a *gem-diol*. *gem*-diols result from an addition reaction to the carbonyl group, a process that we will discuss in Chapter 18.



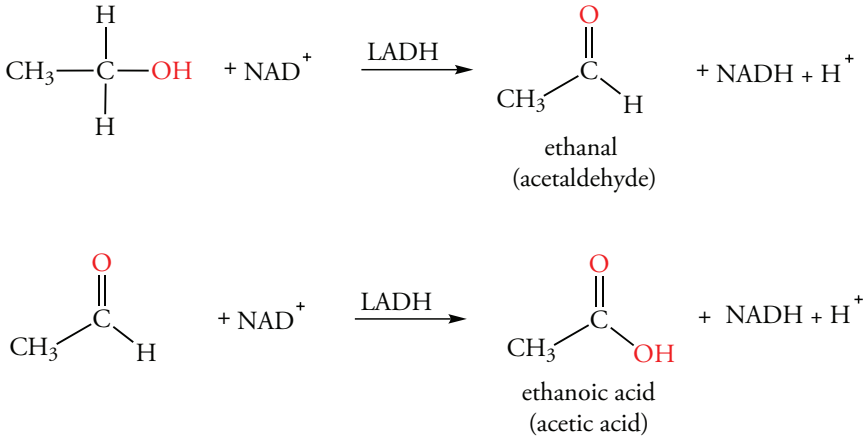
The *gem*-diol is an alcohol. One of its hydroxyl groups is oxidized by way of a chromic half-ester in the same manner as alcohols. The resulting compound retains the hydroxyl group of the original chromic half-ester and is a carboxylic acid.



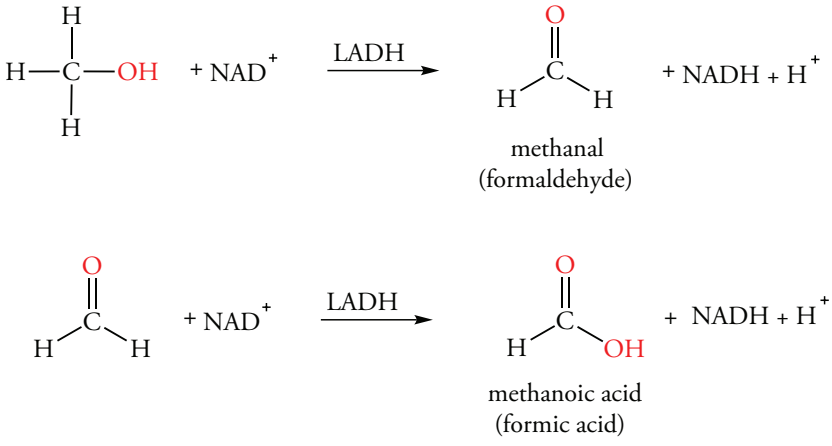
gem-diols form in low concentration in equilibrium with the aldehyde. However, when they are converted into chromic acid half-esters and oxidized, they continue to form until the oxidation is complete. When a primary alcohol is oxidized by PCC, water is absent. So, a *gem*-diol cannot form, and the aldehyde is not further oxidized.

Toxicity of Alcohols

Methanol is highly toxic. Drinking as little as 15 mL of pure methanol can cause blindness; 30 mL will cause death. Prolonged breathing of methanol vapor is also a serious health hazard. Although ethanol is the least toxic of the simple alcohols, it is still a poisonous substance and must be oxidized in the liver to prevent high blood alcohol levels, which can poison the brain. The liver enzyme alcohol dehydrogenase (LADH) oxidizes methanol and ethanol. LADH requires a coenzyme, nicotinamide adenine dinucleotide (NAD^+), as an oxidizing agent. The coenzyme can exist in an oxidized form, NAD^+, and a reduced form, NADH. NAD^+-dependent LADH oxidizes ethanol to ethanal (acetaldehyde). Subsequent oxidation of ethanal yields ethanoic acid (acetic acid), which is nontoxic in small concentrations.

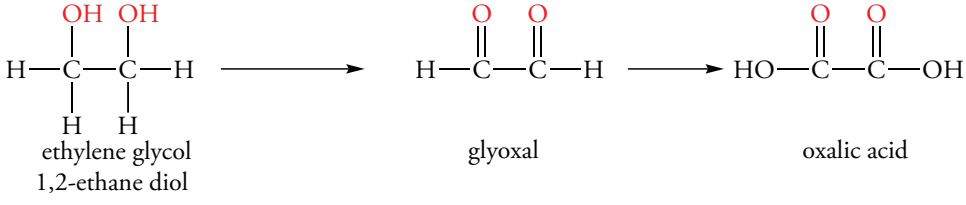


The oxidation products of some other alcohols are toxic. In the case of methanol, oxidation catalyzed by LADH gives methanal (formaldehyde) and then methanoic acid (formic acid).



Formaldehyde travels in the blood throughout the body and reacts with proteins, destroying their biological function. Methanol causes blindness because formaldehyde destroys an important visual protein. Formaldehyde reacts with an amine functional group of the amino acid lysine in a protein, called rhodopsin. Formaldehyde also reacts with amino groups in other proteins, including many enzymes, and the loss of the function of these biological catalysts causes death.

Ethylene glycol is also toxic. If this sweet-tasting is left in open containers, oxidation occurs to give oxalic acid, which causes kidney failure.



Physicians treat methanol or ethylene glycol poisoning with intravenous injections of ethanol before substantial oxidation has occurred. LADH binds more tightly to ethanol than to methanol or ethylene glycol, and the rate of oxidation of ethanol is about six times faster than that of ethylene glycol. The ethanol concentration can be kept higher because it is directly injected. As a result, neither methanol nor ethylene glycol is competitively oxidized to toxic products, and the kidneys can slowly excrete them.

Problem 15.7

Which of the isomeric C_4H_{10} alcohols reacts with the Jones reagent to produce the ketone C_4H_8O?

Problem 15.8

Potassium permanganate ($KMnO_4$) oxidizes alcohols, but is a less selective reagent than chromium(VI) reagents. Write a reasonable multistep mechanism involving a manganate ester that accounts for the oxidation of a secondary alcohol to a ketone.

Problem 15.9

The Jones reagent oxidizes isomeric alcohols at different rates. For example, *cis*-4-*tert*-butyl-cyclohexane reacts faster than the *trans* isomer. Considering the steric effects of these two compounds, which step of the mechanism is rate determining?

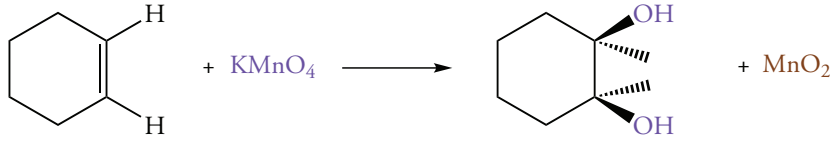
Sample Solution

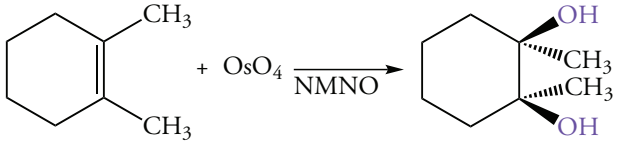
The formation of a chromic ester should be sensitive to the steric environment of the oxygen atom, which acts as a nucleophile in forming the Cr—O bond. Because an axial hydroxyl group is in a more hindered position than an equatorial hydroxyl group, we would expect the *cis* isomer to react more slowly than the *trans* isomer if ester formation were the rate-determining step. The second step involves removal of hydride at the α carbon atom. In the *cis* isomer, the carbon–hydrogen bond is equatorial, a position that is more sterically accessible to base than is the axial carbon–hydrogen bond of the *trans* isomer. This order of reactivity observed, which is consistent with the removal of hydride as the rate-determining step

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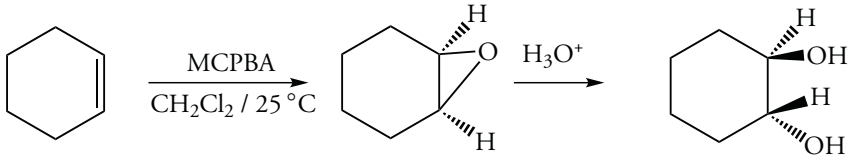
15.5 REACTIONS OF VICINAL DIOLS

Vicinal diols can be prepared from alkenes using potassium permanganate or osmium tetraoxide (Section 6.9). We recall that these reactions occur by *syn* addition to give *cis* 1,2-diols.



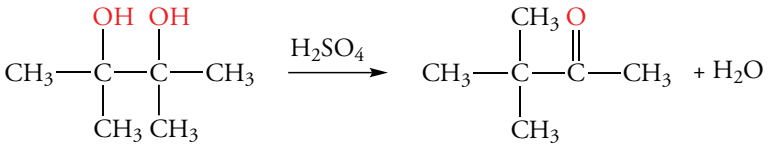


Vicinal diols also occur in which the OH groups are *trans*. Net anti dihydroxylation occurs in a multistep process with an epoxide intermediate. The acid-catalyzed hydrolysis of epoxides yields a ring-opened product by S_N2 attack of the nucleophilic water molecule on the protonated epoxide. We will discuss the ring-opening reactions of expoxides in the next chapter.



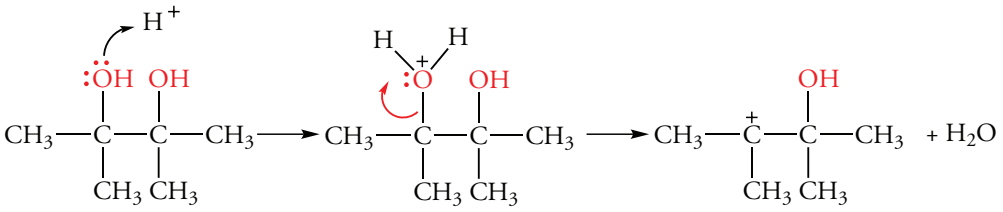
The Pinacol Rearrangement

A vicinal diol reacts with sulfuric acid to give a rearranged dehydration product. The reaction of 2,3-dimethyl-2,3-butanediol (pinacol) to 3,3-dimethyl-2-butanone (pinacolone) is an example of this process, generally known as the **pinacol rearrangement**.

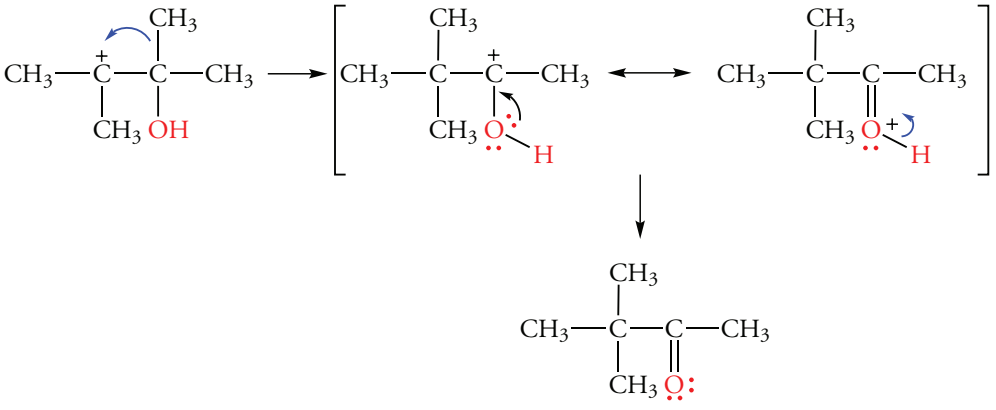


2,3-dimethyl-2,3-butanediol
(pinnacol)

The first step of the pinacol rearrangement is protonation of one of the two hydroxyl oxygen atoms. Then water leaves, yielding a tertiary carbocation.



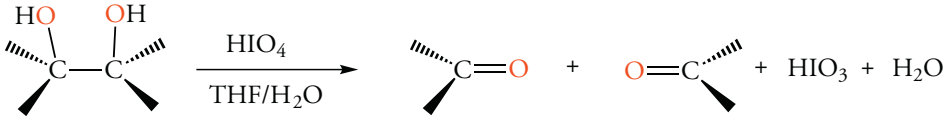
In the dehydration of alcohols, we recall that a methyl group can migrate to an adjacent electron-deficient center if a more stable carbocation results (Section 9.19). In this case, the rearrangement of a methyl group yields a carbocation that is formally a secondary ion. However, it is a stabilized hydroxy carbocation, or oxonium ion. The nonbonded electron pair on the oxygen atom is delocalized to the positive carbon atom.



Because the oxonium ion resonance form has an octet of electrons around each of the atoms, it is the most important contributor. The resultant stabilization of the ion compared to a typical carbocation is part of the reason for the rearrangement reaction. (We recall that the cyclohexadienyl cation intermediates formed in aromatic substitution reactions are also stabilized by the resonance donation of electrons from the oxygen atom of phenols and anisoles.) Loss of the hydrogen atom bonded to oxygen from the resonance-stabilized cation yields the final product, 3,3-dimethyl-2-butanone, pinacolone.

Oxidative Cleavage of Vicinal Diols

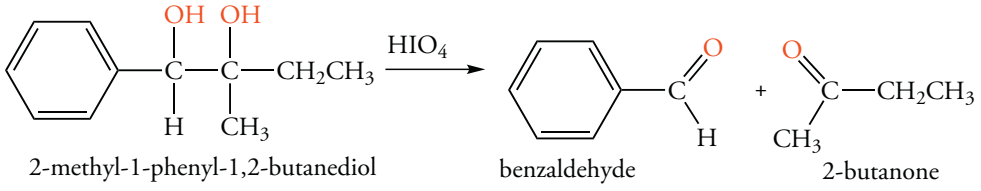
Vicinal diols are cleaved by periodic acid to yield aldehydes or ketones, depending on the number of substituents on the carbon atoms bearing the hydroxyl groups. The periodic acid is reduced to iodic acid (HIO_3).



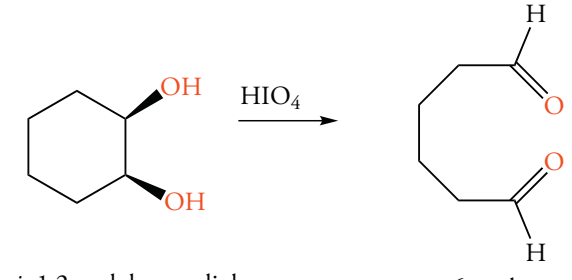
vicinal diol

Because vicinal diols are obtained from alkenes, the combination of dihydroxylation followed by oxidative cleavage of a diol provides an alternative method to ozonolysis of alkenes to yield the same products. We can deduce the structure of the starting diol from the structures of the carbonyl compounds.

If the vicinal diol is contained in an acyclic portion of a molecule, two carbonyl compounds result—unless the vicinal diol is a symmetrical molecule, in which case it yields two equivalents of a carbonyl compound. If the two hydroxyl groups are on a ring, a ring-opened product containing two carbonyl groups forms.

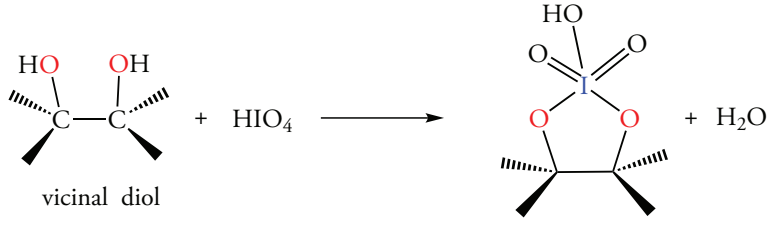


2-methyl-1-phenyl-1,2-butanediol benzaldehyde 2-butanone



cis-1,2-cyclohexanediol 6-oxohexanal

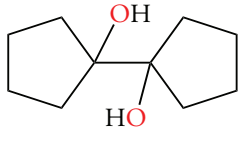
The cleavage reaction occurs by way of a cyclic periodate intermediate, which may formally be considered a diester of an inorganic acid. The cyclic ester forms more easily for *cis* diols than for *trans* diols, so the rate of cleavage of *cis* diols is faster than the rate of cleavage of *trans* diols.



vicinal diol cyclic periodate ester

Problem 15.10

Reaction of the following diol with sulfuric acid yields a ketone with the molecular formula $C_{10}H_{16}O$ Write the structure of the product



Problem 15.11

A compound with the formula $C_{12}H_{22}O_2$ reacts with periodic acid to give cyclohexanone. Write the structure of the reactant.

15.6 SYNTHESIS OF ALCOHOLS

Alcohols are important synthetic intermediates because they can be transformed into many other functional groups. Fortunately, they can also be synthesized from several classes of compounds, some of which contain oxygen and some of which do not. We will find that each method for the synthesis of alcohols has certain limitations that determine the scope of the reaction. Thus, it is important to learn what can and cannot be done with each set of reagents.

To synthesize an alcohol (or any other compound), conditions must be chosen that produce only the correct compound with a minimum of by-products in the smallest number of steps. As the number of steps in a synthetic sequence increases, the chance of obtaining a high yield of the end product decreases.

The selection of a given reaction to synthesize an alcohol is often based on a knowledge of the mechanisms of the various potential reactions. For that reason, we have to understand how differences in molecular structure can affect the final yield of product. We can't simply select a reagent because it works for some other compound. We must always ask whether the reaction will occur in good yield for the selected compound.

Overview of Synthetic Methods

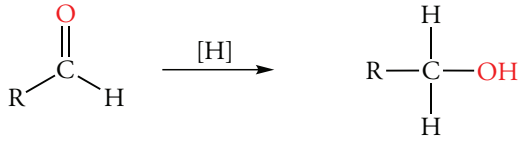
We saw in Chapter 9 that an alcohol can be obtained by substituting a halide ion in an alkyl halide with hydroxide ion. However, in Chapter 10, we found that a competing elimination reaction diminishes the yield in the substitution reaction because the nucleophilic hydroxide ion is also a strong base. In Section 15.7, we will examine an alternative substitution reaction that takes into account this potential competing reaction.

We have previously discussed the hydration of alkenes as a method for the synthesis of alcohols (Section 6.5). The reaction is easily reversible, and poor yields of product may result. Furthermore, even if the reaction is "pushed" by the selection of optimal reaction conditions, there is a competing reaction. Hydration is an electrophilic addition reaction that occurs by way of a carbocation, and can yield rearranged products. Therefore, direct hydration is not the preferred method of synthesis of most alcohols. In Section 15.8, we will examine alternate addition reactions that have no competing rearrangement reactions, and give good yields of alcohols.

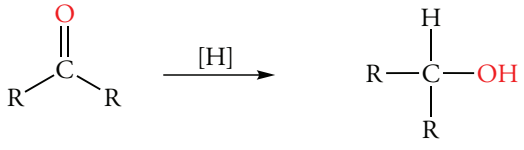
Reductive Synthetic Methods

Both the nucleophilic substitution of halide by an oxygen nucleophile and the hydration of alkenes start with substrates that do not contain oxygen. However, the synthesis of alcohols from compounds with functional groups that already contain oxygen has an obvious advantage. The presence of oxygen in a functional group at the very site where the hydroxyl group is desired is a synthetic opportunity of immense value.

Carbonyl compounds such as aldehydes and ketones contain a carbon–oxygen double bond that can be reduced to yield an alcohol.



aldehyde primary alcohol



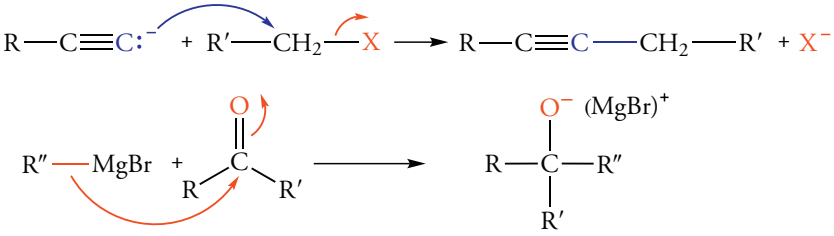
ketone secondary alcohol

In Section 15.9, we will consider reducing agents and their regioselectivity. The reduction of carbonyl groups is sometimes accompanied by reduction of other functional groups. We will find that many synthetic variations are possible because several reducing agents with different reactivities and regioselectivities have been developed.

In Section 15.9, we will consider reducing agents and their regioselectivity. The reduction of carbonyl groups is sometimes accompanied by reduction of other functional groups. We will find that many synthetic variations are possible because several reducing agents with different reactivities and regioselectivities have been developed.

Alkylation Synthetic Methods

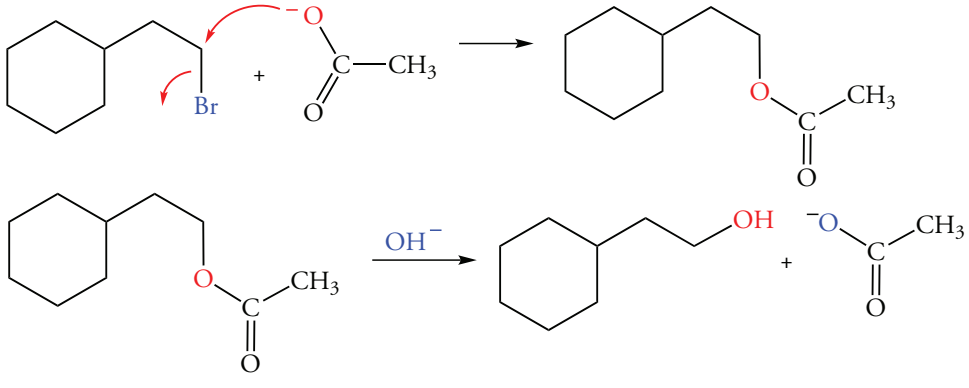
Organic synthetic methods must be able to accomplish more than just functional group transformations. We also need methods that form carbon–carbon bonds so that complex structures can be made from simpler structures. One example of this method is the formation of complex alkynes by alkylation of alkyl halides using alkynide ions. We recall that the reaction occurs by nucleophilic attack of the alkynide ion at the electrophilic carbon atom of the alkyl halide (Section 11.8). The carbanion available from a Grignard reagent reacts with certain electrophilic carbon atoms, such as a carbonyl carbon atom of either an aldehyde or a ketone. A new carbon–carbon bond results, and an alcohol forms. We will see that this use of Grignard reagents to form alcohols is one of the powerful synthetic methods in organic chemistry.



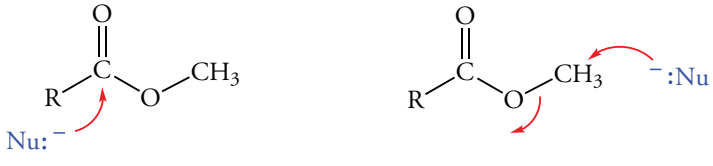
alkoxide ion,
(salt is neutralized to give alcohol)

15.7 SYNTHESIS OF ALCOHOLS FROM HALOALKANES

To avoid competition between substitution and elimination, we can select a nucleophilic oxygen source that is not a strong base. One such source is the ethanoate ion (acetate ion). It is a weaker base than the hydroxide ion because ethanoic acid (acetic acid) is a stronger acid than water. It will displace a halide such as bromide ion in an S_N2 process. The resulting ester can then be cleaved by aqueous base in a process called *saponification* to give the desired alcohol.



We will discuss the details of the mechanism of this second reaction, a nucleophilic acyl substitution, in Chapter 20. At present, we will only note that the nucleophilic hydroxide ion cleaves the carbonyl carbon–oxygen bond, and that a competing elimination reaction does not occur. Although the equation may look like a typical nucleophilic substitution reaction in which hydroxide ion displaces the ethanoate ion, the reaction does *not* occur by way of an S_N2 mechanism. The ether oxygen atom (shown in red) of the ester remains bonded to the alkyl group. In general, attack of nucleophiles on esters occurs at the carbonyl carbon atom, not at the sp^3-hybridized carbon atom of the alkyl group.



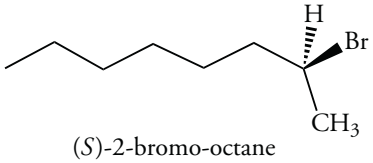
favored mode of attack

less favored mode of attack

What are the limitations of this two-step procedure to produce alcohols from alkyl halides? First, we need an appropriate alkyl halide. Second, the displacement of halide ion by acetate occurs by an S_N2 process, which is efficient for primary alkyl halides, but occurs at a slower rate for secondary alkyl halides. The process fails for tertiary alkyl halides, which are too sterically hindered to react.

Problem 15.12

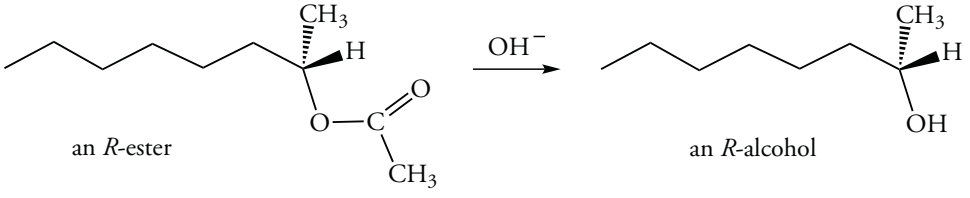
Write the structures of the products of the reaction of (*S*)-2-bromooctane with sodium acetate followed by hydrolysis with hydroxide ion. What is the configuration of each compound?



(*S*)-2-bromo-octane

Sample Solution

An S_N2 reaction gives a product with inverted configuration with respect to the reactant. The ester formed has the *R* configuration. The hydrolysis reaction does not occur at the chiral center, and thus the configuration of the alcohol is the same as for the ester.



an *R*-ester an *R*-alcohol

Problem 15.13

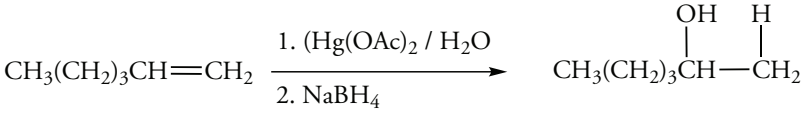
Which of the two compounds should react faster with sodium acetate in DMF, *cis*- or *trans*-4-methyl-1-chlorocyclohexane?

15.8 INDIRECT HYDRATION METHODS

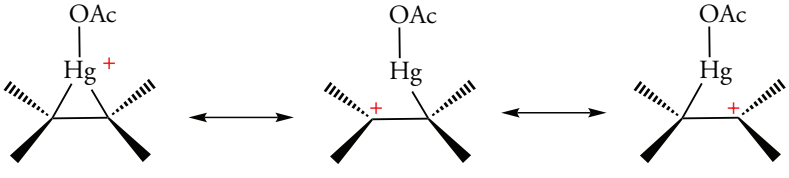
We can bypass the problems encountered in the hydration of alkenes by using either of two indirect hydration reactions. These methods use reagents that react mechanisms that do not give rearranged products. The reagents have different regioselectivities. One method, **oxymercuration–demercuration**, indirectly gives net Markovnikov addition of water. The second method, **hydroboration–oxidation**, gives net *anti*-Markovnikov addition of water.

Oxymercuration–Demercuration

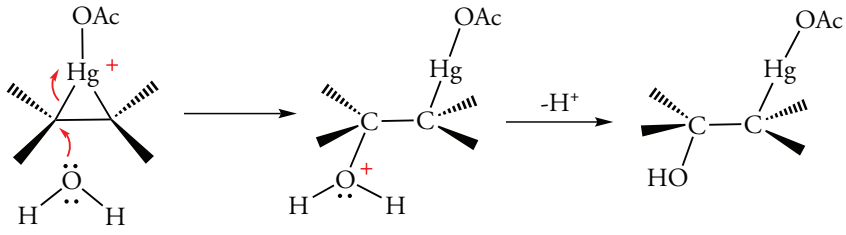
In an oxymercuration–demercuration reaction, an alkene is treated with mercury(II) acetate, $Hg(OAc)_2$, and the product is treated with sodium borohydride. The net result is a Markovnikov addition product in which the OH group bonds to the more substituted carbon atom of the alkene.



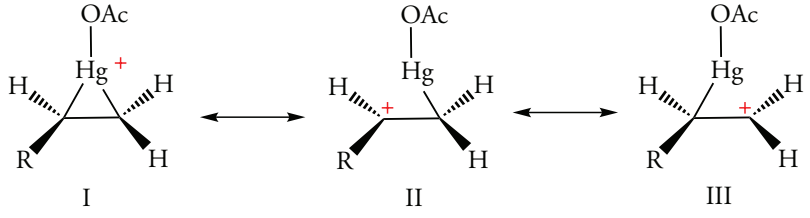
In the first step, an electrophilic $HgOAc^+$ ion adds to the double bond to give a mercurinium ion whose structure is similar to that of a bromonium ion (Section 6.5). Like the bromonium ion, the mercurinium ion is a hybrid of three contributing resonance structures.



This species subsequently reacts with a nucleophilic water molecule. This results in the bonding of an HgOAc group and a hydroxyl group on adjacent carbon atoms, with net *anti* addition.

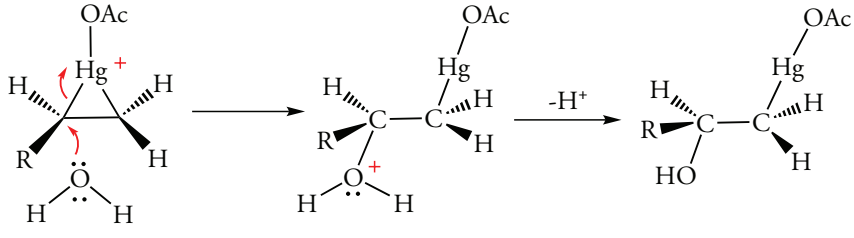


Why does Markovnikov addition occur as a result of the attack of water on the mercurinium ion? If the alkene is not symmetric, then neither is the mercurinium ion. In the most important resonance contributor to the ion, the mercury atom has the positive charge. Of the other two contributors, the one with the charge on the more substituted carbon atom is more stable. That is, resonance structure II is more stable than structure III.



mercurinium ion of a terminal, monosubstituted alkene

The structure of the transition state for nucleophilic attack of water on the mercurinium ion is closely related to the structure of this intermediate. Thus, the energy barrier is lower for attack of water at the more positive carbon atom of the intermediate. For a mercurinium ion of a terminal monosubstituted alkene such as 1-hexene, attack occurs at C-2, the more substituted site.



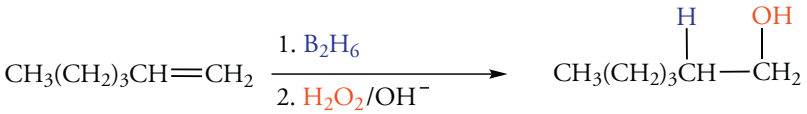
The organomercury compound is reduced with sodium borohydride, and the HgOAc group is replaced by a hydrogen atom. The mechanism is not well established, but is thought to involve free radicals. Thus, the reaction is not necessarily stereospecific. Only the location of the hydroxyl group can be predicted from knowledge of the formation of the mercurinium ion and the direction of attack of water on that ion.

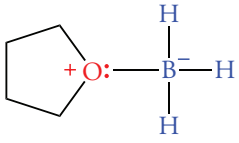
Oxymercuration–demercuration gives the product that would result from direct hydration of an alkene. However, the reactions occur with a higher yield than the direct hydration reaction because the competing reverse reaction, dehydration, does not occur. Because most of the positive charge in the mercurinium ion is on the mercury atom, the mercurinium ion has little carbocation character, and rearrangement reactions do not occur.

Hydroboration–Oxidation

Hydroboration–oxidation of alkenes also requires two steps. The sequence of reactions adds the hydrogen and hydroxyl of water to a double bond to give a product that corresponds to *anti*-Markovnikov addition.

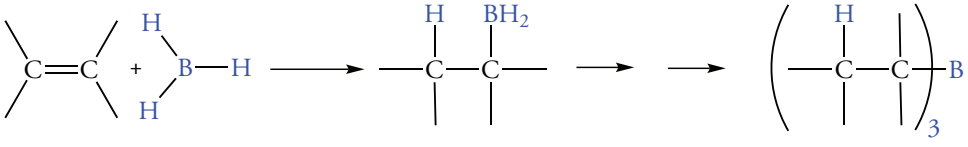
In the first step, hydroboration, an alkene is treated with diborane $(BH_3)_2$ or B_2H_6. Diborane acts as if it were the monomeric species called borane, (BH_3). The boron reagent is usually prepared in an ether solvent such as diethyl ether or tetrahydrofuran.



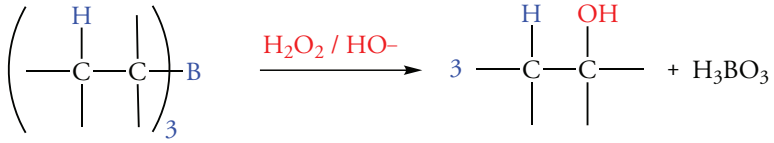


BH_3-tetrahydrofuran complex

Borane adds to the carbon–carbon double bond of one alkene and then adds successively to two more alkenes, producing a trialkylborane, R_3B. These steps are hydroboration reactions.

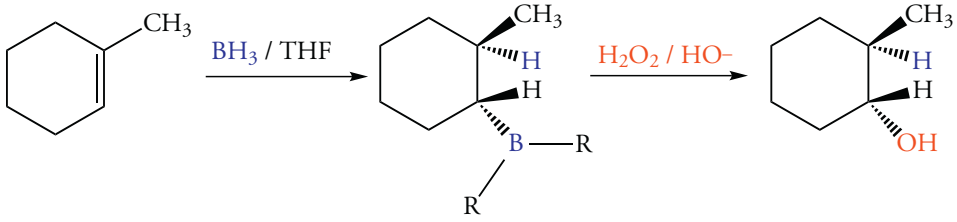


In the oxidation step, the trialkylborane is treated with hydrogen peroxide and base to oxidize the trialkylborane to an alcohol.



trialkylborane

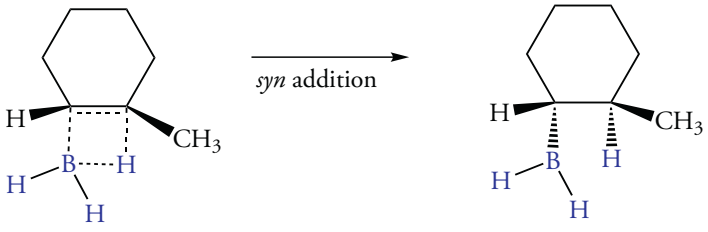
The result of the hydroboration–oxidation of 1-methylcyclohexene reveals information about the stereochemistry of the reaction. The overall addition of water is *anti*-Markovnikov. That is, the hydrogen atom adds to the more substituted carbon atom, and the hydroxyl group to the less substituted carbon atom. The hydrogen atom and hydroxyl group are introduced from the same side of the double bond. In the oxidation step, a hydroxyl group replaces the boron with retention of configuration. Therefore, the net addition of water is *syn*.



trialkylborane

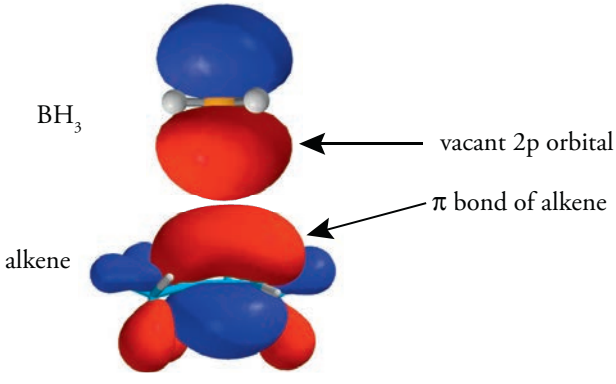
syn addition

This mode of addition occurs because hydroboration is a concerted *syn* process. That is, the carbon–boron and carbon–hydrogen bonds form at the same time that the boron–hydrogen bond breaks. Borane reacts with alkenes for two reasons. First, the boron atom in borane is an electron-deficient species with only six electrons. Thus, the boron atom has a vacant 2p orbital and is an electrophilic Lewis acid. Because boron is electrophilic, it bonds to the least substituted carbon atom much like a proton. Second, boron is more electropositive than hydrogen. Therefore, the hydrogen atom of the boron–hydrogen bond has a partial negative charge. This hydrogen atom behaves like a hydride ion, not like a proton.



The boron and hydrogen atom add to the same face of the double bond. The resulting product has the groups *cis* to each other. The dotted lines represent bonds formed and broken in the transition state of the concerted reaction. In summation, two properties of BH_3, the electrophilic character of the boron atom and the hydride character of the hydrogen atom, account for *anti*-Markovnikov addition of BH_3 to alkenes. The regioselectivity also reflects some steric control in which the boron adds to the less substituted carbon atom. Figure 15.1 shows the transition state for hydroboration in greater detail.

Figure 15.1
Transition State Structure for Hydroboration

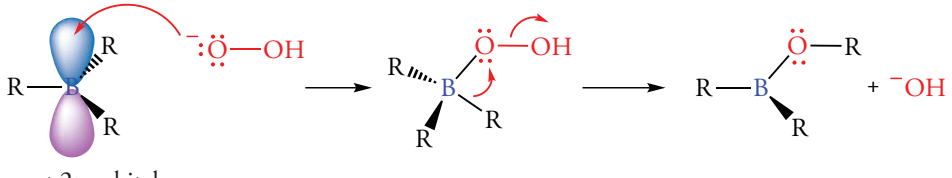


(a) Orbital interaction in the transition state of 1-methylcyclopentene hydroboration



(b) Tube model of the transition state of alkene hydroboration

In the next step of the reaction, the trialkyl borane reacts with hydrogen peroxide and base. In this step, a hydroxyl group replaces boron with retention of configuration. The nucleophilic hydroperoxide ion attacks the electron-deficient borane to give an intermediate with a weak O—O bond. Although the hydroxide ion is a poor leaving group, a concerted intramolecular migration of an alkyl group occurs.



vacant 2p orbital

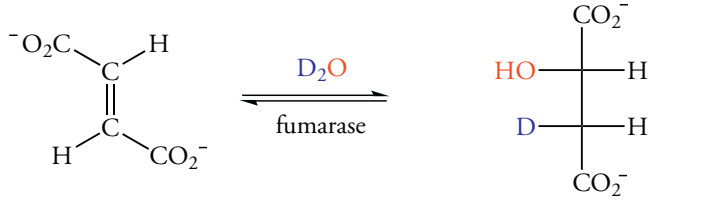
This migration resembles those we described for the migrations of hydrogen and alkyl groups in carbocations. In both cases, the group moves with its bonding electron pair in a concerted process to an adjacent site. The configuration of the alkyl group is retained in this transfer process.

The initial product formed from the migration of an alkyl group has the formula R_2BOR. It continues to react with hydroperoxide ion to give $RB(OR)_2$ and eventually the trialkyl borate, $(RO)_3B$. Subsequent hydrolysis of the borate in basic solution gives the alcohol and sodium borate.

$$(RO)_3B + 3NaOH \longrightarrow 3ROH + Na_3BO_3$$

Problem 15.14

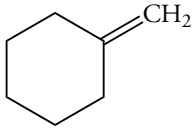
Hydration of alkenes occurs stereospecifically in biological systems. Hydration of fumarate by D_2O catalyzed by fumarase yields (2*S*,3*R*)-3-deuteriomalate. Determine the stereochemistry of addition.



fumarate (2*S*,3*R*)-3-deuteromalate

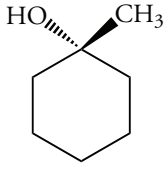
Problem 15.15

What product forms from the following methylenecyclohexane by oxymercuration–demercuration? What product forms in hydroboration–oxidation?

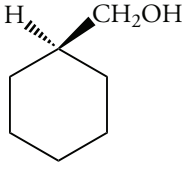


Sample Solution

Both alkyl groups of this disubstituted alkene are part of the ring and are bonded to the same carbon atom. The CH_2 unit has the less substituted carbon atom. An oxymercuration–demercuration reaction places a hydrogen atom at the CH_2 site and a hydroxyl group on the ring carbon atom. This product is the predicted Markovnikov product of indirect hydration of an alkene



The hydroboration–oxidation product has a hydroxyl group at the CH_2 site and a hydrogen atom at the ring carbon atom. This process is equivalent to *anti*-Markovnikov addition of water to an alkene.

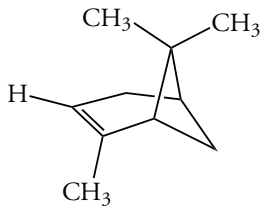


Problem 15.16

Write the structure of the product of oxymercuration–demercuration of 3,3-dimethyl-l-butene. Is this product the same as would be obtained by the acid-catalyzed hydration of the alkene?

Problem 15.17

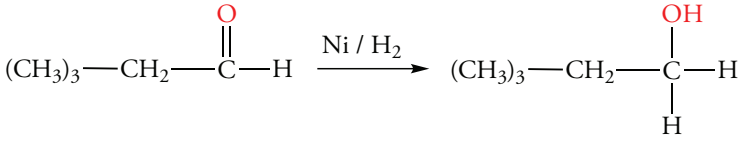
Write the structure, showing the stereochemistry, of the product of hydroboration–oxidation of 2,6,6-trimethyl-2-bicyclo[3.1.1]heptene (α-pinene).



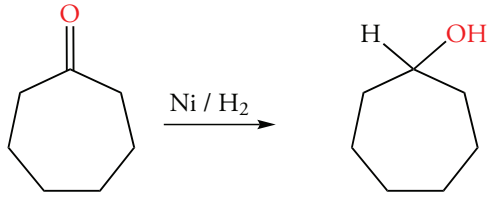
α-pinene

15.9 REDUCTION OF CARBONYL COMPOUNDS

Alcohols can be made by reducing the carbonyl group of aldehydes and ketones with hydrogen gas in the presence of a metal catalyst such as palladium, platinum, or Raney nickel. Aldehydes yield primary alcohols; ketones yield secondary alcohols.

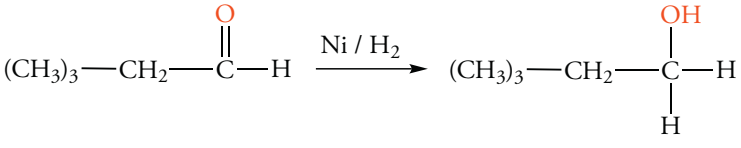


3,3-dimethylbutanal 3,3-dimethylbutanol

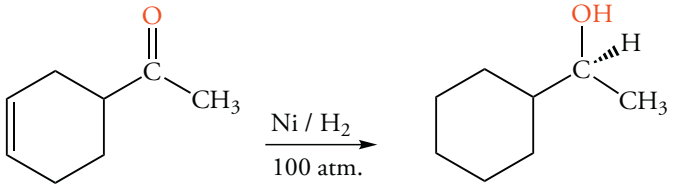


cycloheptanone cycloheptanol

The reduction reaction occurs by the transfer of hydrogen atoms bound to the surface of the metal catalyst to the carbonyl oxygen and carbon atoms. We recall that the same types of catalysts are used for the hydrogenation of alkenes, a much faster reaction. Alkenes can be reduced at room temperature under 1 atm. pressure of hydrogen gas. Carbonyl compounds require higher temperatures and pressures as high as 100 atm. Therefore, transition metal-catalyzed reduction of carbonyl compounds that also have a carbon–carbon double bond results in reduction of both functional groups.



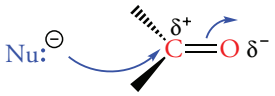
3,3-dimethylbutanal 3,3-dimethylbutanol



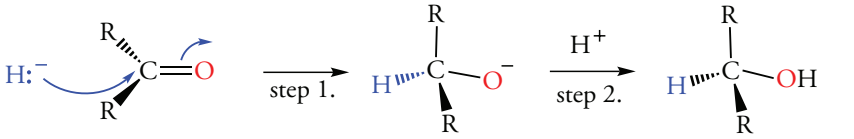
At high pressure, both the vinyl and the carbonyl groups are reduced.

Reduction by Metal Hydrides

The carbonyl group is highly polar. The carbonyl carbon atom has a partial positive charge that reacts with nucleophiles.

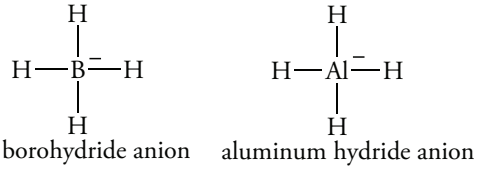


Hence, a hydride anion reacts with a carbonyl group, reducing it to an alkoxide anion, which is protonated to give an alcohol in a second step.



ketone alkoxide ion secondary alcohol

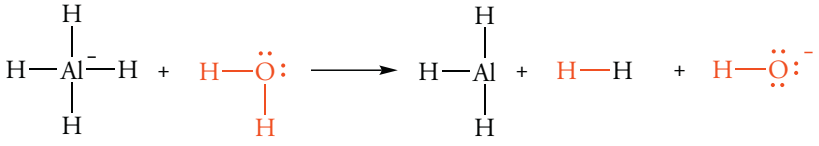
Although hydride anion is an excellent nucleophile, it is also an extremely strong base, which reacts with far too many other functional groups to be a useful reagent for the reduction of carbonyl compounds. However, the basicity of the hydride ion is greatly diminished in sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$). Borohydride and aluminum hydride are excellent sources of hydride anions for the reduction of carbonyl compounds.



borohydride anion aluminum hydride anion

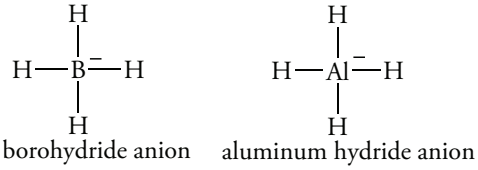
Solvents for Lithium Aluminum Hydride and Sodium Borohydride

Both aluminum hydride and borohydride react with protic solvents such as water and ethanol. Lithium aluminum hydride reacts violently with water to form hydrogen gas, which may burn explosively because of the heat generated in the reaction. Therefore, lithium aluminum hydride can only be used in aprotic solvents such as diethyl ether.



$$AlH_4^- + 4H_2O \longrightarrow [Al(OH_4)]^- + 4H_2$$

The borohydride anion is much less reactive than aluminum hydride. It reacts only slowly with protic solvents such as water. It can be used in a basic aqueous solution or in a solvent such as ethanol. It reacts with these solvents at a much slower rate than with an aldehyde or a ketone.



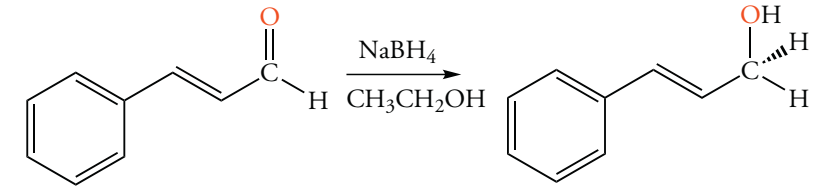
borohydride anion aluminum hydride anion

$$NaBH_4 + 4CH_3CH_2OH \xrightarrow{\text{slow}} Na^+ [B(OCH_2CH_3)_4]^- + 4H_2$$

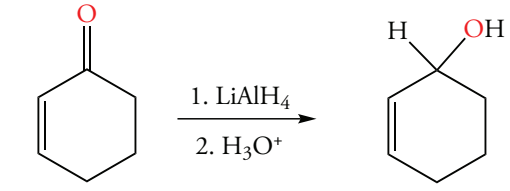
$$LiAlH_4 + 4CH_3CH_2OH \xrightarrow{\text{fast}} Li^+ [B(OCH_2CH_3)_4]^- + 4H_2$$

Regioselectivity of Hydride Reduction

The carbon–carbon double bond of alkenes is not polar; therefore, alkenes do not react with nucleophiles. This difference in reactivity accounts for the regioselectivity of sodium borohydride or lithium aluminum hydride reduction. Neither reagent reduces alkenes; both reduce aldehydes and ketones.

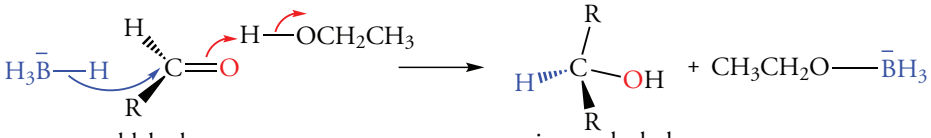


(*E*)-3-phenyl-2-propenal (*E*)-3-phenyl-2-propen-1ol



3-cyclohexenone 3-cyclohexenol

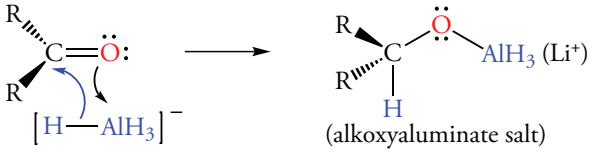
In the reduction of an aldehyde by sodium borohydride in ethanol, a hydride is transferred to the carbonyl carbon atom, and the carbonyl oxygen atom is protonated by ethanol.



aldehyde primary alcohol

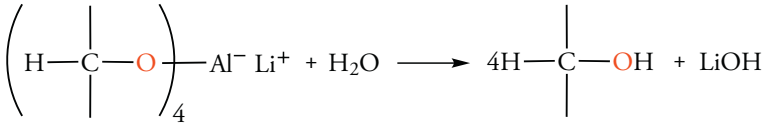
The ethoxyborohydride product in the above reaction has three remaining hydride ions available for further reduction reactions, and the ultimate boron product is tetraethoxyborohydride, $(RO)_4B^-$. Thus, one mole of $NaBH_4$ reduces four moles of a carbonyl compound. A dilute solution of acid is used to destroy any excess reagent as part of the standard work-up procedure.

When lithium aluminum hydride is used to reduce carbonyl compounds, an ether, such as diethyl ether, $(CH_3CH_2)_2O$, is used as the solvent. The reduction of a carbonyl group by lithium aluminum hydride occurs by transfer of a hydride anion from AlH_4^- to the carbonyl carbon atom. The carbonyl oxygen atom forms an alkoxyaluminate salt.



(alkoxyaluminate salt)

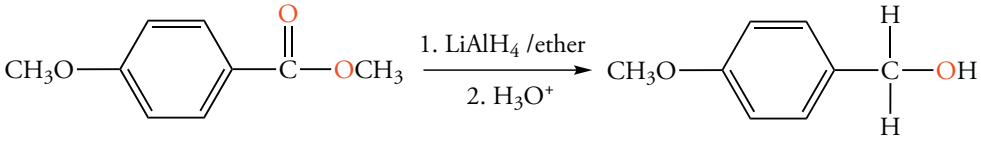
The initial alkoxyaluminate has three remaining hydride ions available for further reduction reactions, and the ultimate aluminum product is tetraalkoxyaluminate, $(RO)_4Al^-$. Thus, one mole of $LiAlH_4$ reduces four moles of a carbonyl compound. The tetraalkoxyaluminate is hydrolyzed with aqueous acid in a separate, second step.



(alkoxyaluminate salt)

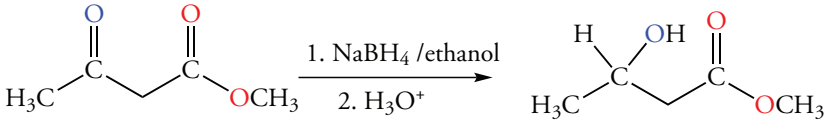
Reduction of Other Carbonyl Compounds

Many carbonyl compounds, including aldehydes and ketones, acids, esters, acid halides, and amides, can be reduced with lithium aluminum hydride. For example, lithium aluminum hydride reduces esters to primary alcohols.



methyl *p*-methoxybenzoate — *p*-methoxybenzyl alcohol

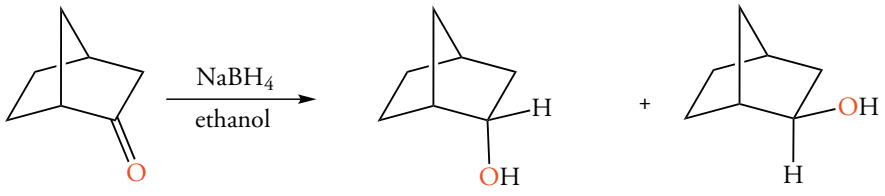
Sodium borohydride is less reactive than lithium aluminum hydride. It reduces only aldehydes or ketones. Therefore, if both a ketone and an ester functional group are present in a molecule, and the goal is to reduce only the ketone, only sodium borohydride gives the required result.



Only the ketone is reduced.

Stereoselectivity of Metal Hydride Reduction

Sodium borohydride and lithium aluminum hydride have only moderate stereoselectivity. The anions tend to attack sterically hindered compounds from the least sterically hindered side. For example, reduction of bicyclo[2.2.1]heptan-2-one yields a mixture of two alcohols in which the *endo* compound predominates. The *exo* face of the carbonyl group is more open to attack by the nucleophilic hydride reagent, and as a result the *endo* alcohol is the major product.

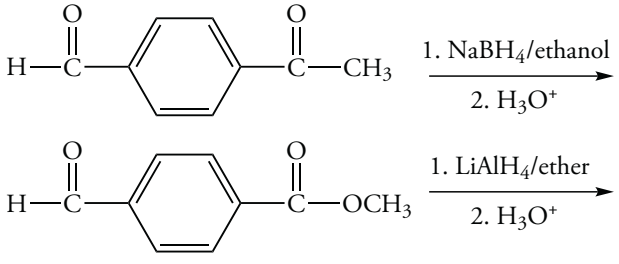


endo 86% bicyclo[2.2.1]heptan-2-ol — *exo* (14%) bicyclo[2.2.1]heptan-2-ol

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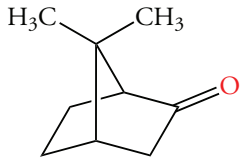
Problem 15.18

Write the structure of the product of each of the following reactions, assuming an excess of each metal hydride.



Problem 15.19

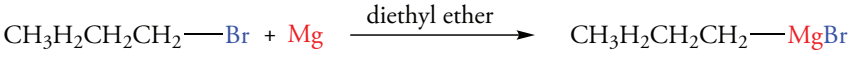
Reduction of 7,7-dimethylbicyc1o[2.2.1]heptan-2-one with sodium borohydride yields two isomeric alcohols in a 6:1 ratio. Considering the effect of the methyl groups, write the structures of the products.



7,7-dimethylbicyclo[2.2.1]heptan-2-one

15.10 ALCOHOL SYNTHESIS USING GRIGNARD REAGENTS

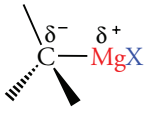
Haloalkanes and aryl and vinyl halides react with magnesium metal to yield organomagnesium halides called **Grignard reagents**. An ether solvent, usually diethyl ether, is required for preparation of Grignard reagents. The French chemist Victor Grignard discovered this reaction over a century ago in 1900. Grignard reagents are powerful tools for the synthesis of alcohols.



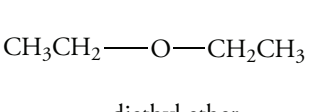
1-bromobutane

1-butylmagnesium bromide
(a Grignard reagent)

A Grignard reagent has a very polar carbon–magnesium bond in which the carbon atom has a partial negative charge and magnesium has a partial positive charge. Because the carbon atom in a Grignard reagent has a partial negative charge, it resembles a carbanion, and it reacts with electrophilic centers such as the carbonyl carbon atom of aldehydes, ketones, and esters. We will discuss this chemistry in the next section.



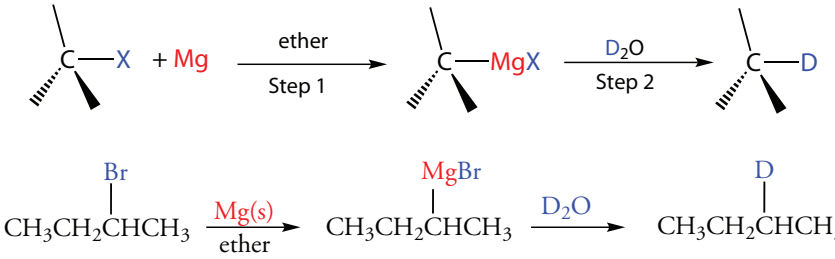
Grignard reagents form easily from 1°, 2°, and 3° alkyl halides. Aryl and vinyl halides react somewhat more slowly, and the cyclic ether tetrahydrofuran (THF) is often used to prepare Grignard reagents of these compounds. The higher boiling point of the cyclic ether provides more vigorous reaction conditions, but the rate of the reaction is also increased because THF solvates the Grignard reagent better than diethyl ether. The solvent, either diethyl ether or THF, is an essential component of the reaction.



diethyl ether
bp 35 °C

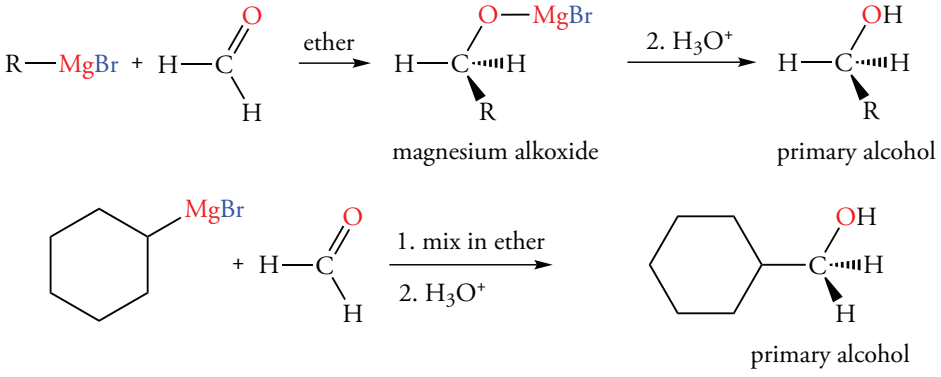
tetrahydrofuran
bp 65 °C

Grignard reagents react rapidly with acidic hydrogen atoms in molecules such as alcohols and water. When a Grignard reagent reacts with water, a proton replaces the halogen, and the product is an alkane. The Grignard reagent therefore provides a pathway for converting a haloalkane to an alkane in two steps. If the second step of this process is carried out in D_2O, deuterium is introduced into the compound at the position initially occupied by the halogen.

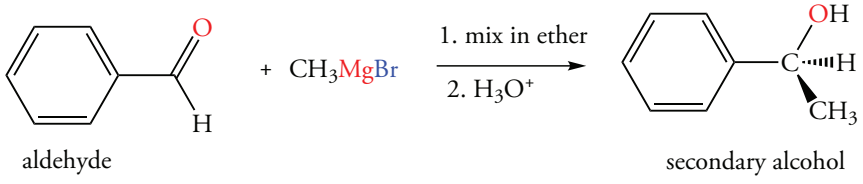


Synthesis of Alcohols Using Grignard Reagents

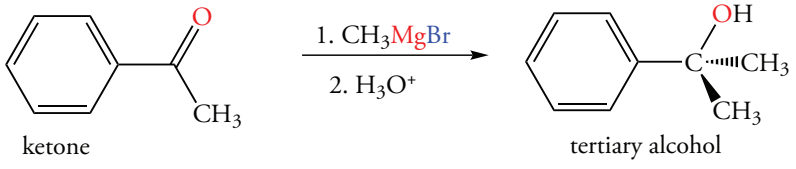
Grignard reagents add to carbonyl compounds to give primary, secondary, and tertiary alcohols. A primary alcohol is synthesized by reacting the Grignard reagent, R′—MgX, with formaldehyde.



Reacting a Grignard reagent with an aldehyde gives a secondary alcohol.



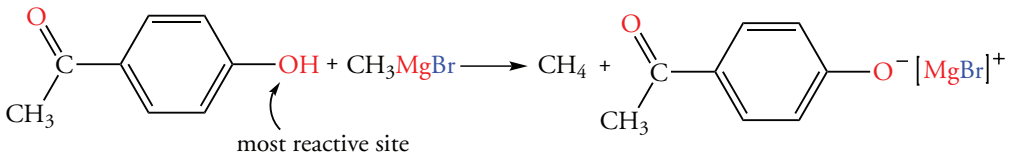
Reacting a Grignard reagent with a ketone gives a tertiary alcohol.



Limitations of the Grignard Reaction

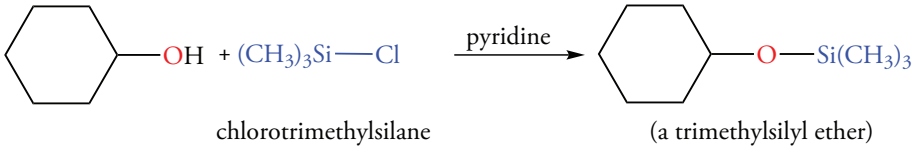
We recall that Grignard reagents cannot be made if acidic functional groups are also present in the halogen compound. The Grignard reagent is destroyed by reaction with acidic hydrogen atoms of water, alcohols, phenols, or carboxylic acid groups.

For the same reason, we must consider the structure of the carbonyl compound selected for reaction with a Grignard reagent. If the carbonyl compound also contains a hydroxyl group, the fastest reaction will be the destruction of the added Grignard reagent by protonation.



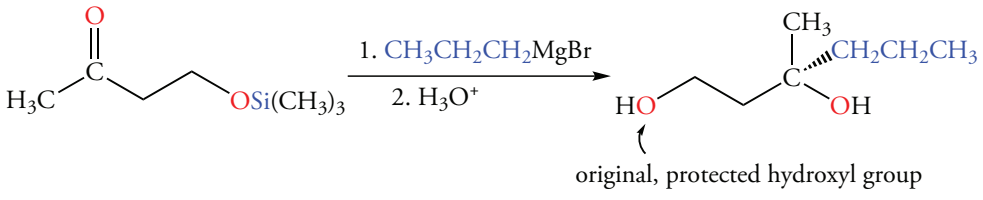
Alcohol Protecting Groups

Many ways have been devised to protect acidic groups, such as an hydroxyl group, that would interfere with Grignard reactions. One of the simplest is conversion of an alcohol to a silyl ether.



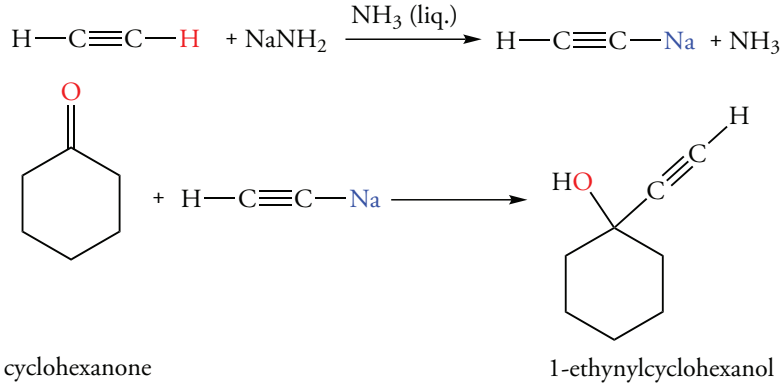
To prevent the production of HCl, the reaction is carried out along with an amine catalyst, which is converted to an ammonium salt.

After the alcohol has been protected, a Grignard reaction is possible. In the second step of the reaction, when the magnesium salt is hydrolyzed, the silyl ether is hydrolyzed too.

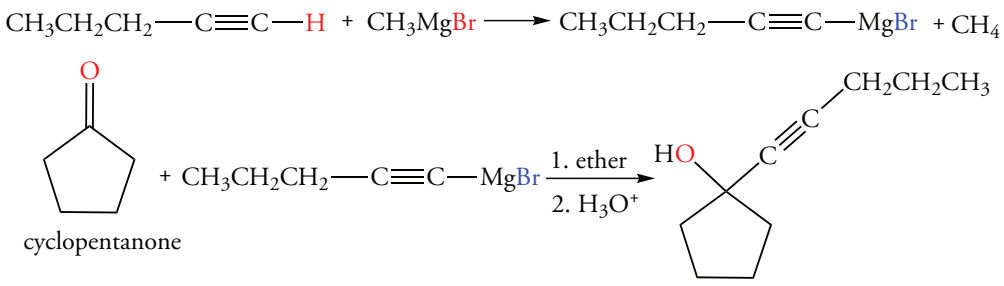


Acetylenic Alcohols

Alkynide ions react with carbonyl groups in much the same way as Grignard reagents do. We recall that these ions are effective nucleophiles that will displace a halide ion from an alkyl halide to give an alkylated alkyne. The alkynides are prepared in an acid–base reaction with acetylene or a terminal alkyne using sodium amide in ammonia. If a carbonyl compound is then added to the reagent, an alcohol forms after acid work-up. If the alkynide is derived from acetylene, an acetylenic alcohol forms.

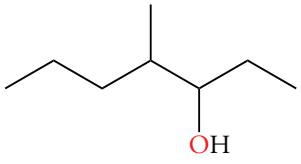


We can also produce alkynides without using liquid ammonia. We recall that alkynes are more acidic than alkanes. Therefore, the acid–base reaction of an alkyne with a readily available Grignard reagent gives a Grignard reagent of the alkyne. This alkynide ion of the Grignard reagent reacts with carbonyl compounds.



Problem 15.20

The European bark beetle produces a pheromone that causes beetles to congregate. Describe two ways that the compound could be synthesized by a Grignard reagent.



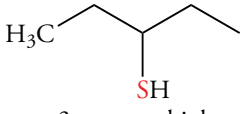
4-methyl-3-heptanol

Problem 15.21

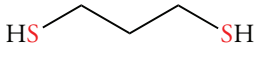
Write the structures of the two products obtained by reaction of 4-*tert*-buty1cyc1ohexanone with sodium acetylide. Predict which one is obtained in the larger amount.

15.11 THIOLS AND THIOETHERS

Sulfur is in the same group of the periodic table as oxygen and forms compounds structurally similar to alcohols. Compounds containing an —SH group, called a **sulfhydryl group**, are named as **mercaptans** or **thiols**. The nomenclature of these compounds resembles that of alcohols, except that the suffix -thiol replaces the suffix -ol and the -e of the alkane name is retained.



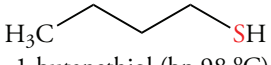
3-pentanethiol



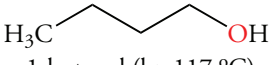
1,3-propanedithiol

Physical Properties of Thiols

Alcohols and thiols resemble each other in many ways, but they also differ in some significant respects. For example, thiols have lower boiling points than the corresponding alcohols because sulfur does not form intermolecular hydrogen bonds.



1-butanethiol (bp 98 °C)



1-butanol (bp 117 °C)

Some alcohols have rather sweet odors, but one of the distinguishing properties of thiols is their strong, disagreeable odor. The odor of the striped skunk (*Memphitis mephitis*) is due to 3-methyl-1-butanethiol. The human nose can detect thiols at a few parts per billion in air. There is a positive side to the obnoxious odors of thiols: Small amounts of thiols are added to natural gas to aid in easy detection of leaks.

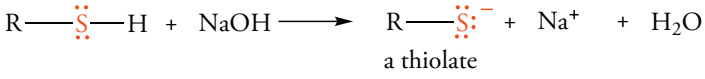
Reactions of Thiols

Although thiols are weak acids, they are far stronger acids than alcohols. The sulfur atom of a thiol is sp^3-hybridized, and orbital overlap between this orbital and the 1s orbital of hydrogen is poor. As a result, the S—H bond is nonpolar, and it is much weaker than the short, polar, O—H bond of alcohols.

$$CH_3CH_2SH + H_2O \rightleftharpoons CH_3CH_2S^- + H_3O^+ \quad pK_a = 8$$

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+ \quad pK_a = 17$$

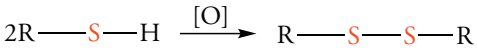
The sulfhydryl group reacts with hydroxide ions to form thiolate ions, which are excellent nucleophiles.



a thiolate

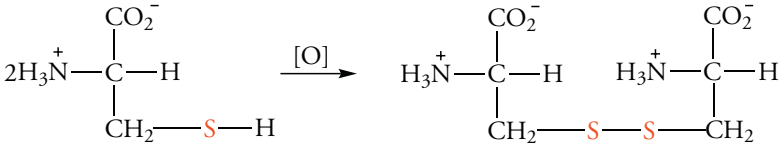
The oxidation of alcohols occurs at the carbon bound to oxygen atom and gives compounds with a carbon–carbon double bond. The oxidation reactions of thiols are very different. Although sulfur analogs of aldehydes, ketones, and carboxylic acids exist, they are not obtained by the direct oxidation of thiols.

Thiols are easily oxidized, but oxidation occurs at the sulfur atom rather than the carbon atom. Mild oxidation agents such as bromine and iodine convert thiols into disulfides. In the following equation, the symbol [O] represents an unspecified oxidizing agent that removes hydrogen atoms.



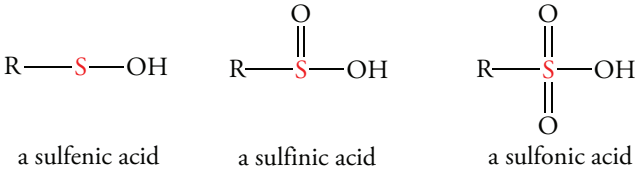
a disulfide

This reaction is of great biochemical importance because many proteins contain the amino acid cysteine. Oxidation of the sulfhydryl group gives a disulfide bond in an amino acid called cystine.



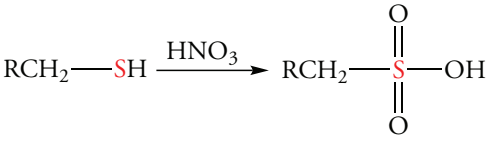
cysteine cystine

Oxidation with stronger oxidizing agents converts thiols to a series of acids with oxygen atoms bonded to sulfur.



a sulfenic acid a sulfinic acid a sulfonic acid

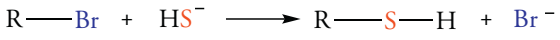
Sulfonic acids, the most highly oxidized product of thiols, are obtained by vigorous oxidation by concentrated nitric acid.

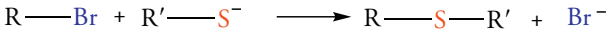


a sulfonic acid

Synthesis of Thiols

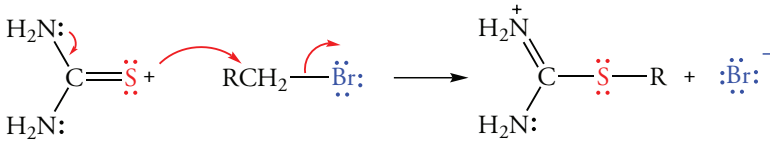
Thiols can be made from haloalkanes by nucleophilic substitution of the halide ion by the sulfhydryl ion (HS^-), which is an excellent nucleophile. Because thiolate ions are also excellent nucleophiles, thioethers can react again to give a thioether. To limit this competing second reaction, a large excess of HS^- must be used.



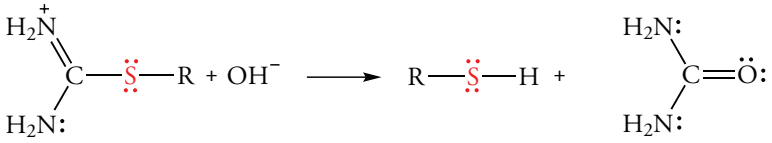


a thioether

The sulfur atom of thiourea is a better source of a sulfur nucleophile in a reaction that will convert a alkyl halide to a thiol. Thiourea reacts with alkyl halides to give an isothiouronium salt. Subsequent hydrolysis of this salt in the same reaction vessel yields a thiol.



thiourea isothiouronium ion



urea

The overall driving force for this reaction is the formation of urea, whose carbonyl bond is much stronger than the C=S bond of thiourea.

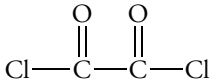
EXERCISES

Formation of Esters

15.1 Write the structural formula of each of the following esters.
(a) ethyl sulfate (b) dimethyl phosphate (c) propyl nitrate (d) 2-propyl methanesulfonate

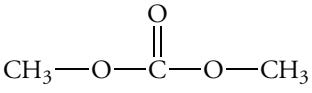
15.2 Write the structural formula of each of the following esters.
(a) trimethyl phosphate (b) dipropyl sulfate (c) 2-propyl nitrate (d) l-butyl-*p*-toluenesulfonate

15.3 Oxalyl chloride is a diacid chloride having the following structure. Draw the structure of the related diacid. Draw the structure of the product from reaction of one equivalent of benzyl alcohol with oxalyl chloride. Draw the structure of the product from the reaction of two equivalents of methyl alcohol with oxalyl chloride.

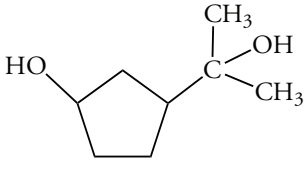


oxalyl chloride

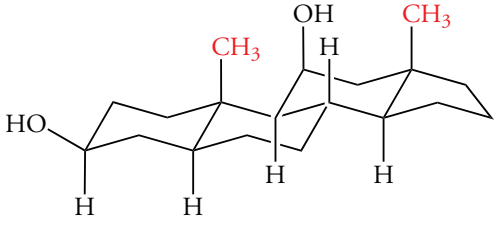
15.4 What acid is contained in the following diester? Write the structure of an acid chloride that could be used to synthesize the diester.



15.5 The following diol reacts with one equivalent of tosyl chloride to give a single ester in good yield. Write the structure of the ester. Explain why the reaction is regioselective.



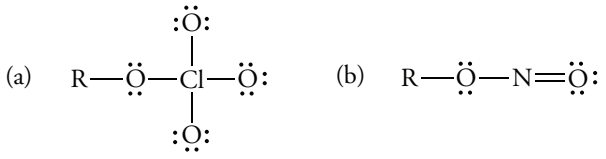
15.6 The following diol reacts with one equivalent of tosyl chloride to give a single ester in good yield. Write the structure of the ester. Explain why the reaction is regioselective.



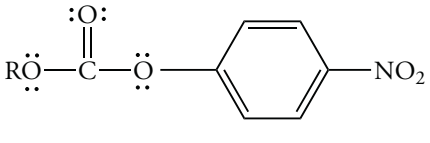
Reactivity of Esters

15.7 Are alkyl esters of triftuoromethylsulfonic acid expected to be more or less reactive in S_N1 reactions than alkyl esters of methanesulfonic acid?

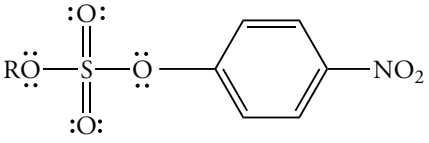
15.8 Describe the expected reactivity of the following compounds in S_N2 reactions compared to methanesulfonate esters.



15.9 The relative reactivities of alkyl *p*-nitrobenzoates and alkyl *p*-nitrobenzenesulfonates in S_N2 reactions relative to the reactivity of alkyl chlorides are 10^{-5} and 10^{5}, respectively. Explain the difference in the relative rates of reaction of the two esters.



an alkyl *p*-nitrobenzoate



an alkyl *p*-nitrobenzenesulfonate

15.10 Predict whether *p*-bromobenzenesulfonate is a better or worse leaving group than *p*-toluenesulfonate.

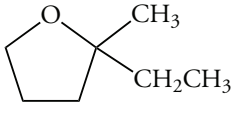
Reactions of Alcohols with Acid

15.11 Explain why (*R*)-2-butanol in aqueous acid gradually loses its optical activity.

15.12 Explain why l-phenyl-2-propen-1-ol rearranges to an isomer in the presence of a catalytic amount of H_2SO_4.

15.13 *cis*-2-Buten-1-ol isomerizes to form a mixture that contains an isomeric alcohol when treated with dilute sulfuric acid. Write the structure of this alcohol.

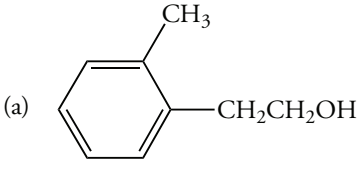
15.14 When (*S*)-4-methyl-1,4-hexanediol is heated with acid, optically inactive 2-ethyl-2-methyltetrahydrofuran results. Write a mechanism for the reaction that accounts for the formation of the product and its lack of optical activity.

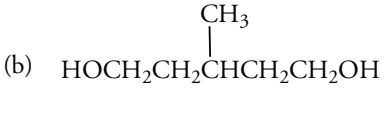


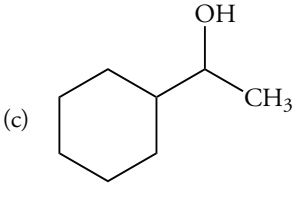
2-ethyl-2-methyltetrahydrofuran

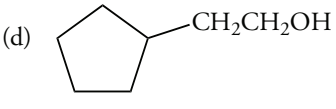
Formation of Alkyl Halides

15.15 Draw the structure of the product of reaction for each of the following compounds with PBr_3.

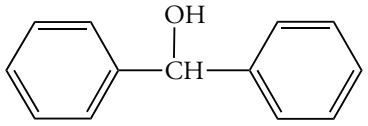


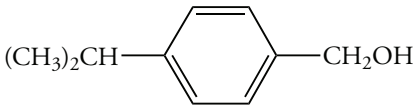


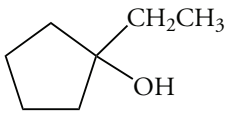


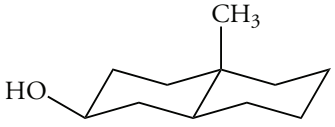


15.16 Draw the structure of the product of the reaction for each of the following compounds with $SOCl_2$ and pyridine.

(a) 

(b) 

(c) 

(d) 

15.17 Both 2-methyl-2-buten-l-ol and 3-methyl-2-buten-1-ol are converted to chlorides using concentrated HCl. Which compound reacts at the faster rate?

15.18 3-Methyl-3-cyclopentenol reacts with aqueous HBr to yield a mixture of two isomeric bromo compounds. Draw the structures of the two products. Predict the major isomer, assuming the reaction is not reversible. How might the data be different if the products can equilibrate?

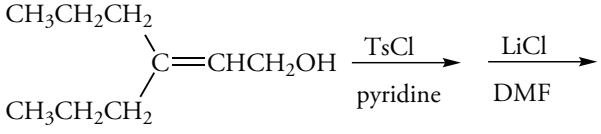
15.19 The yields of alkyl bromides obtained by reaction of an alcohol with PBr_3 are reduced if some of the HBr formed escapes from the reaction. In what alternate product would the alkyl groups be found under these conditions?

15.20 The yields of alkyl bromides in the reaction of alcohols with PBr_3 are increased if HBr is bubbled into the reaction vessel after the PBr_3 and alcohol are mixed. Explain why.

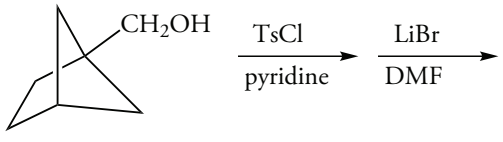
15.21 How could *trans*-4-*tert*-butylcyclohexanol be converted into *trans*-4-chloro-l-*tert*-butylcyclohexane? How could *trans*-4-*tert*-butylcyclohexanol be converted into *cis*-4-chloro-l-*tert*-butylcyclohexane?

15.22 What is the product of the reaction of (*R*)-2-octanol with thionyl chloride in pyridine? What is the product in diethyl ether as solvent?

15.23 Draw the structure of the product of the following series of reactions. What product would result if the alcohol reacted with HCl?



15.24 Draw the structure of the product of the following series of reactions. What product would result if the alcohol reacted with HBr?



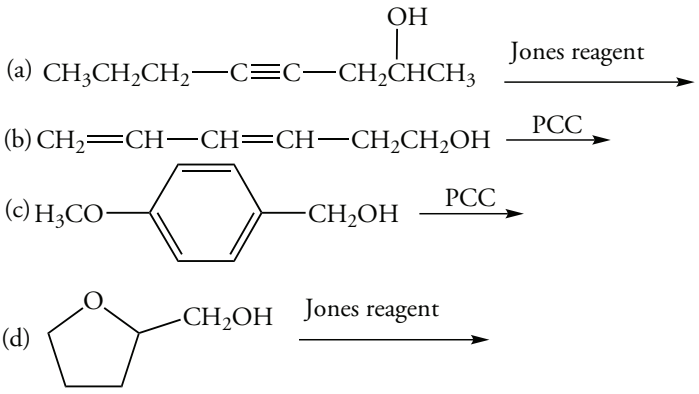
15.25 Sterically hindered alcohols react with phosphorus tribromide, but tend to give large quantities of rearranged product. The product mixture obtained from 2,2-dimethyl-l-propanol (neopentyl alcohol) contains 63% 1-bromo-2,2-dimethylpropane, 26% 2-bromo-2-methylbutane, and 11 % 2-bromo-3-methylbutane. Explain the origin of the products. Why are sterically hindered alcohols more prone to give rearranged products?

15.26 Both 2-chloropentane and 3-chloropentane are converted to a mixture of the two compounds in a concentrated HCl solution containing zinc chloride. The ratio of the 2-chloro to the 3-chloro compound is 2:1. Write a mechanism that explains how the zinc chloride accounts for the equilibration. Why does the observed ratio occur?

Oxidation of Alcohols

15.27 Both l-octanol and 2-octanol react with aqueous basic potassium permanganate. The product of the reaction of 2-octanol is not soluble in aqueous base, but the product of reaction of l-octanol is soluble. What are the products? Explain the difference in solubility.

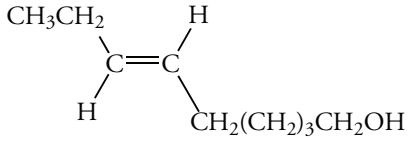
15.28 Draw the structure of the product of each of the following reactions.



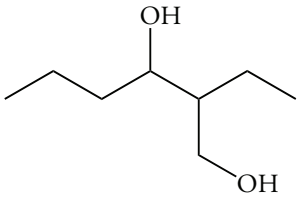
15.29 Write the product formed from the oxidation of each of the compounds in Exercise 15.15 using PCC.

15.30 Write the product formed from the oxidation of each of the compounds in Exercise 15.16 using the Jones reagent.

15.31 Write the product formed from the oxidation of the fruit fly repellent by PCC.



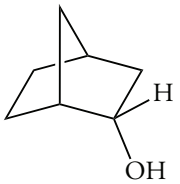
15.32 Write the product formed by oxidation of the following mosquito repellent with PCC.



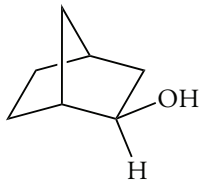
15.33 Consider the relative rates of oxidation of the following three compounds by chromium(VI). What do these data reveal about the rate-determining step of the reaction?

Compound	$CH_3CH(OH)CH_3$	$CH_3CD(OH)CH_3$	$CD_3CH(OH)CH_3$
Relative rate	1.0	0.16	1.0

15.34 The rate of oxidation of *endo*-bicyclo[2.2.1]heptan-2-ol is faster than the rate of oxidation of the *exo* isomer. What does this fact indicate about which step in the mechanism determines the reaction rate?



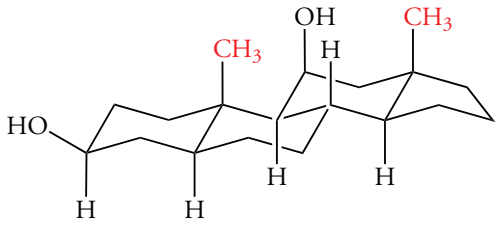
endo-bicyclo[2.2.1]hepan-2-ol



exo-bicyclo[2.2.1]hepan-2-ol

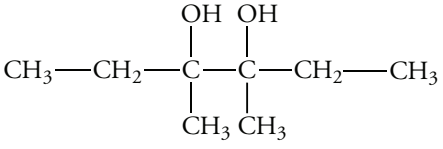
15.35 Write a mechanism of the oxidation of an alcohol by chromium(VI) that uses only an intramolecular process for the abstraction of the a hydrogen atom. Considering the size of the ring in the cyclic process, how likely is it that this process will occur?

15.36 Which of the two sites within the following structure will be oxidized at the faster rate when only one equivalent of a chromium(VI) oxidizing agent is available?

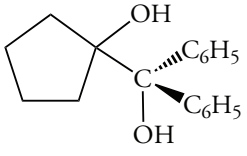


Reactions of Vicinal Diols

15.37 Draw two possible structures of products formed by treating the following vicinal diol with sulfuric acid.

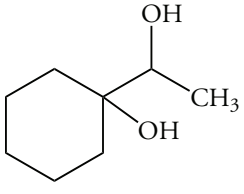


15.38 Only one product is formed by treating the following vicinal diol with sulfuric acid. Draw its structure. Why is it formed rather an isomeric product?

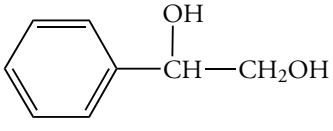


15.39 Draw the structure of the product(s) of the reaction of each of the following compounds with periodic acid.

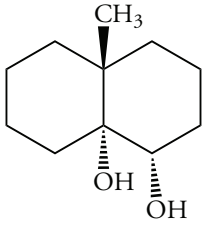
(a)



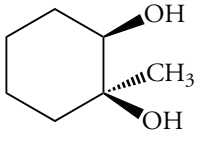
(b)



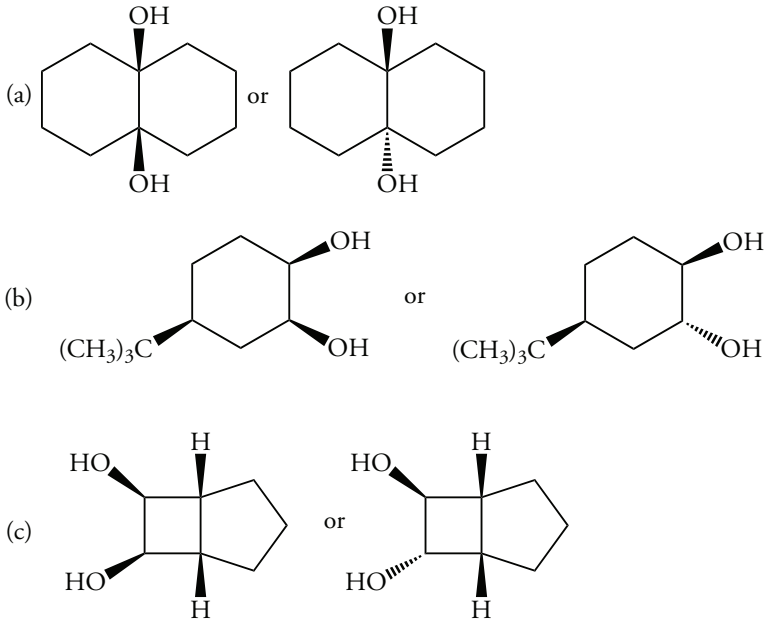
(c)



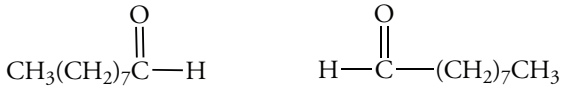
(d)



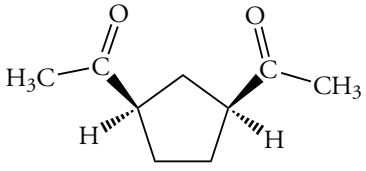
15.40 Which compound in the following pairs reacts fastest with periodic acid?



15.41 The reaction of oleic acid ($C_{18}H_{34}O_2$) with osmium tetraoxide followed by reaction with periodate yields the following two compounds. Draw the structure of oleic acid.



15.42 A hydrocarbon of molecular formula C_9H_{14} is found in sandalwood oil. Reaction of the compound with osmium tetraoxide followed by reaction with period ate yields the following compound. Draw the structure of the hydrocarbon.

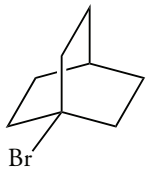


Synthesis of Alcohols from Alkyl Halides

15.43 Which compound of each of the following pairs will react with ethanoate ion at the faster rate?
(a) 1-iodohexane or l-bromohexane
(b) l-bromo-l-phenylethane or l-bromo-2-phenylethane
(c) l-bromo-2,2-dimethylpropane or 1-bromopentane

15.44 Would DMF or ethanol be the better solvent for the displacement of halide ions from alkyl halides by ethanoate ion?

15.45 Attempted synthesis of bicyclo[2.2.2]octan-l-ol by reaction of ethanoate with l-bromobicyclo[2.2.2]octane fails. Why?



1-bromobicyclo[2.2.2]octane

15.46 Predict the stereochemistry of the alcohols obtained by the reaction of *cis*-1-bromo-4-*tert*-butylcyclohexane with ethanoate followed by hydrolysis under basic conditions.

Hydration of Alkenes

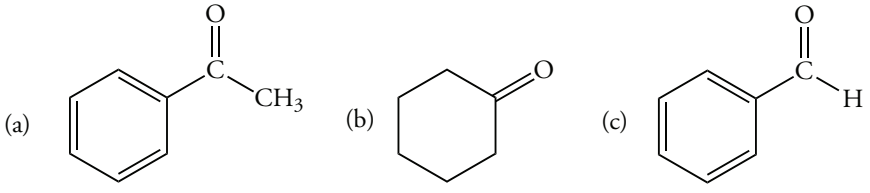
15.47 Which of the isomeric $C_4H_{10}O$ alcohols can be produced by an acid-catalyzed hydration reaction of an alkene?

15.48 The acid-catalyzed hydration of 3,3-dimethyl-l-pentene gives a mixture of two tertiary alcohols. Draw the structures and write a mechanism for their formation.

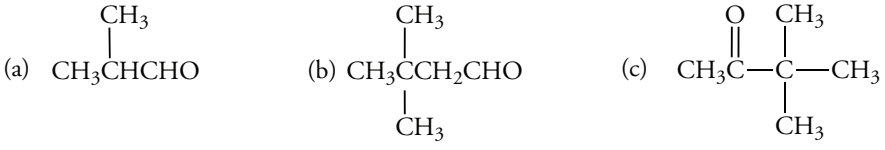
15.49 The acid-catalyzed hydration of 4-*tert*-butylcyclohexene gives a mixture of four secondary alcohols. Draw the structures and write a mechanism for their formation.

Reduction of Carbonyl Compounds with Metal Hydrides

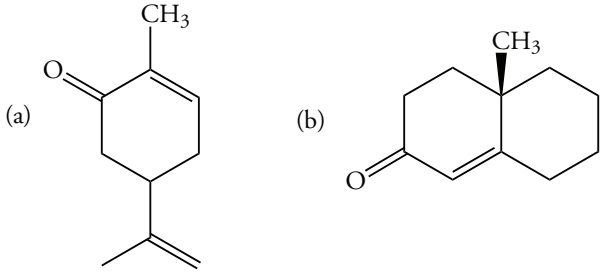
15.50 What is the product when each of the following reacts with lithium aluminum hydride?



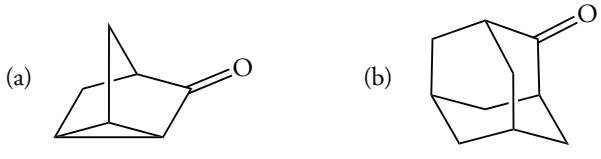
15.51 What is the product when each of the following reacts with sodium borohydride?



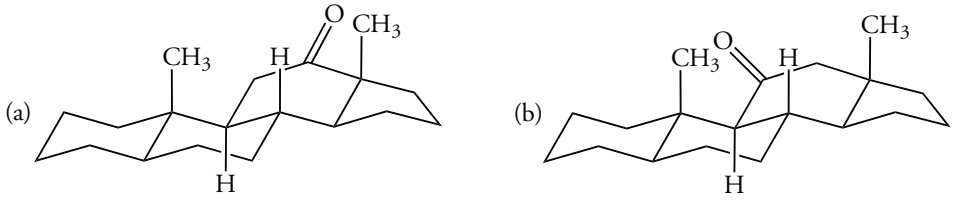
15.52 The reduction of each of the following compounds by lithium aluminum hydride yields two products. Explain why.



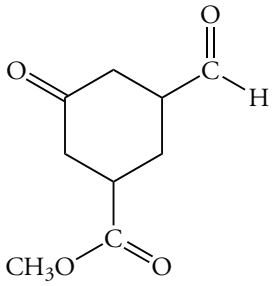
15.53 The reduction of each of the following compounds by sodium borohydride yields only one product. Explain why.

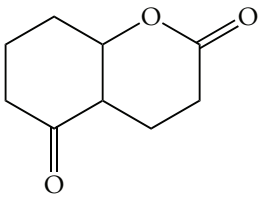


15.54 Assuming that steric factors control the reduction by sodium borohydride, what stereoisomer should predominate for the reduction of each of the following compounds?



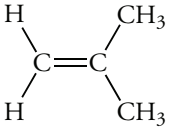
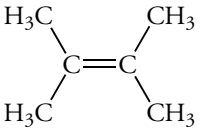
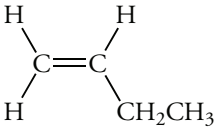
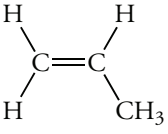
15.55 What is the product of the reaction of each of the following compounds with sodium borohydride and also with lithium aluminum hydride?

(a) 

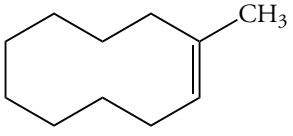
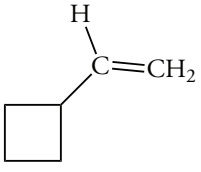
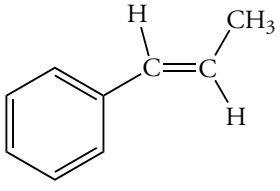
(b) 

Oxymercuration–Demercuration

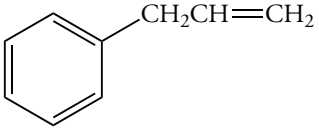
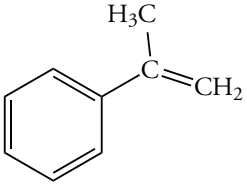
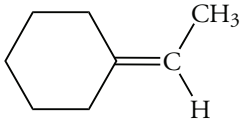
15.56 Name the final product of oxymercuration–demercuration of each of the following compounds.

(a)  (b)  (c)  (d) 

15.57 Draw the structure of the oxymercuration–demercuration product of each of the following compounds.

(a)  (b)  (c) 

15.58 Draw the structure of the oxymercuration–demercuration product of each of the following compounds.

(a)  (b)  (c) 

15.59 How many products should be formed in the oxymercuration–demercuration of 4-*tert*-butylcyclohexene?

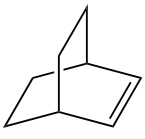
Hydroboration–Oxidation

15.60 Draw the final product of hydroboration–oxidation of each of the compounds in Exercise 15.56.

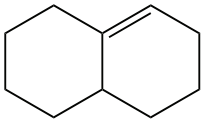
15.61 Draw the final product of hydroboration–oxidation of each of the compounds in Exercise 15.57.

15.62 Draw the final product of hydroboration–oxidation of each of the compounds in Exercise 15.58.

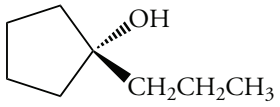
15.63 Draw the structure of the hydroboration–oxidation product of the following bicyclic hydrocarbon.



15.64 Draw the structure of the hydroboration–oxidation product of the following bicyclic hydrocarbon.

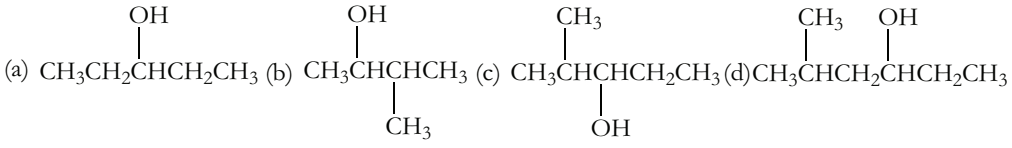


15.65 Can the following compound be synthesized by hydroboration–oxidation from 1-propylenecyclopentene?

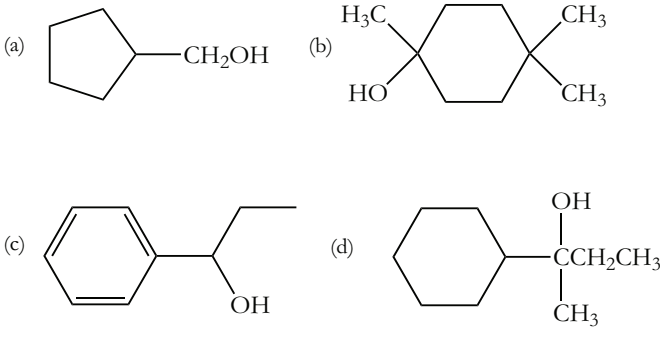


Grignard Reactions

15.66 What carbonyl compound and Grignard reagent are required to produce each of the following compounds?



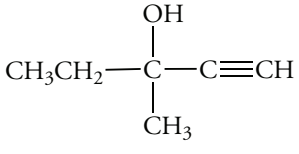
15.67 What carbonyl compound and Grignard reagent are required to produce each of the following compounds?



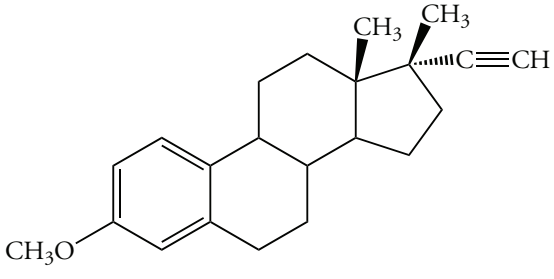
15.68 Outline how each of the following alcohols could be made from the indicated starting material and other necessary compounds using the Grignard synthesis.
(a) 2-cyclopentyl-2-propanol starting from bromocyclopentane
(b) l-cyclopentyl-1-ethanol starting from ethanal (CH_3CHO)
(c) l-nonanol starting from 1-bromooctane.
(d) 3-heptanol starting from pentanal $CH_3(CH_2)_3CHO$

15.69 Using bromobenzene, outline how each of the following alcohols could be made using the Grignard synthesis.
(a) 1-phenylcyclopentanol
(b) 3-phenyl-3-hexanol
(c) 1-phenyl-l-octanol
(d) benzyl alcohol

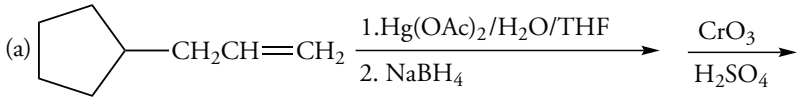
15.70 What carbonyl compound and Grignard reagent are required to produce each of the following compound?

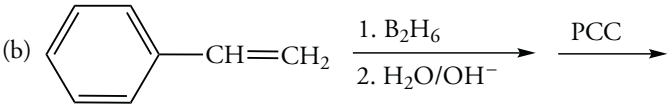


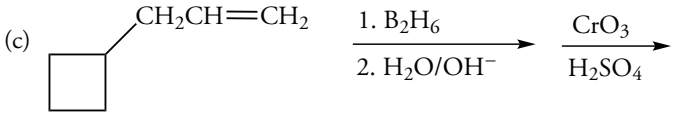
15.71 Mestranol, a component of oral contraceptive drugs, is made by reaction of ethynyl Grignard with a ketone, explain why the indicated stereochemistry is observed.



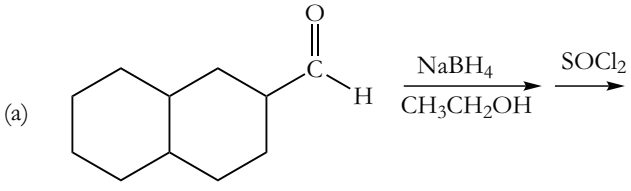
15.72 Write the structure of the final product of each of the following sequences of reactions.

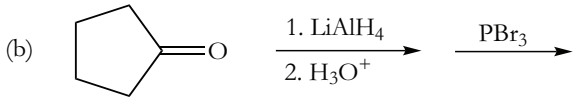
(a) 

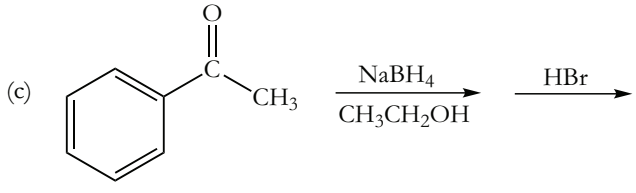
(b) 

(c) 

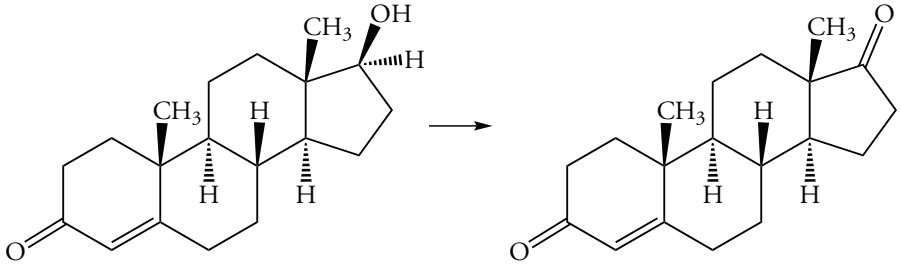
15.73 Write the structure of the final product of each of the following sequences of reactions.

(a) 

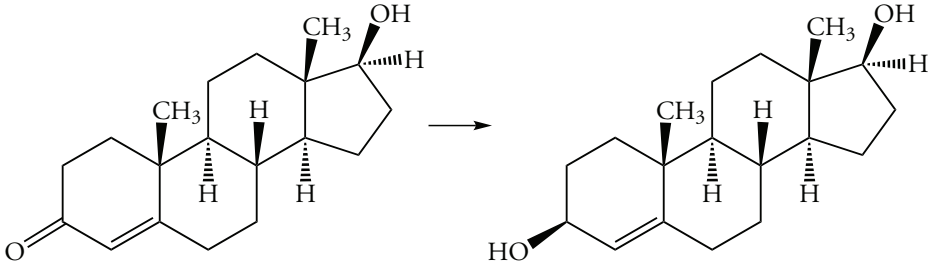
(b) 

(c) 

15.74 Outline the steps required to convert testosterone into the indicated steroid structure.

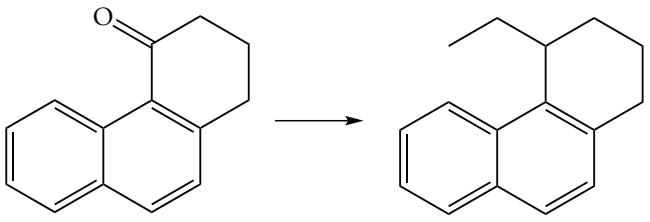


15.75 Outline the steps required to convert testosterone into the indicated steroid structure.



15.76 Propose a sequence of reactions that could be used to convert cyclohexanone into l-methylcyclohexene.

15.77 Propose a sequence of reactions that could be used to accomplish the following conversion.



Sulfur Compounds

15.78 There are four isomeric compounds $C_4H_{10}S$ with an —SH group. Draw the structures of the compounds.

15.79 There are three isomeric compounds C_3H_8S. Draw their structures.

15.80 Draw the structure of each of the following compounds.
(a) l-propanethiol
(b) 2-methyl-3-pentanethiol
(c) cyclopentanethiol

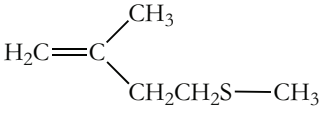
15.81 Draw the structure of each of the following compounds.
(a) 2-propanethiol
(b) 2-methyl-1-propanethiol
(c) cyclobutanethiol

15.82 Addition of sodium hydroxide to an aqueous solution of $CH_3CH_2CH_2SH$ eliminates the odor. Explain why.

15.83 The boiling points of ethanethiol and dimethyl sulfide are 35 and 37 °C, respectively. Why are the boiling points similar? What types of intermolecular forces are responsible for this similarity?

$CH_3—CH_2—SH$	$CH_3—S—CH_3$
ethanethiol	dimethyl sulfide

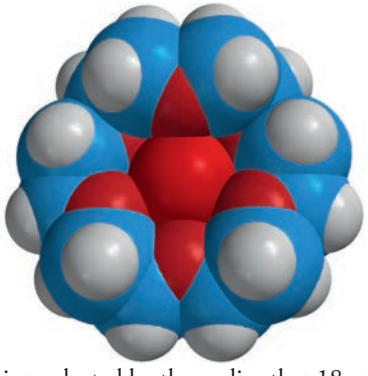
15.84 Indicate two methods to produce the scent marker of the red fox using a thiol as one of the reactants.



16 Ethers and Epoxides



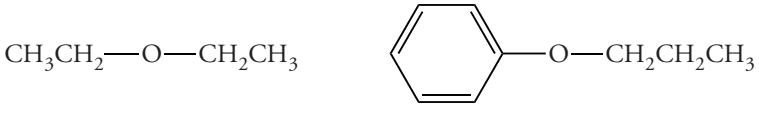
Insect juvenile hormone



K^+ ion solvated by the cyclic ether 18-crown-6

16.1 STRUCTURE OF ETHERS

Ethers contain two alkyl or aryl groups bonded to an oxygen atom. The two alkyl or aryl groups are identical in a **symmetrical ether** and different in an **unsymmetrical ether**.



diethyl ether
(a symmetrical ether)

phenyl propyl ether
(an unsymmetrical ether)

The oxygen atom of an ether is sp^3 hybridized. The C—O—C bond angle of dimethyl ether is 112°, approximately the tetrahedral bond angle (Figure 16.1). Using VSEPR theory, we show the two lone pairs of electrons of the oxygen atom directed to two corners of a tetrahedron. The geometry of the two C—O bonds of ethers allows us to make predictions about their most stable conformations. We can imagine creating an ether by replacing a CH_2 group of an alkane with an oxygen atom. For example, replacing the C-3 methylene group of pentane with an oxygen atom gives diethyl ether. Diethyl ether has an *anti* arrangement of all atoms in its most stable conformation.

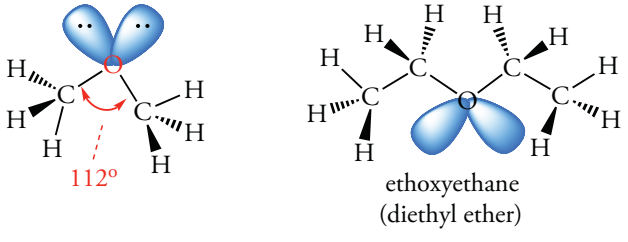
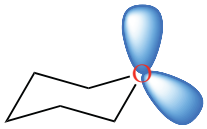


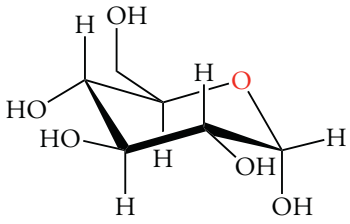
Figure 16.1
Structure of Dimethyl Ether
The oxygen atom of methanol is sp^3 hybridized. The C—O—C bond angle, 112°, is close to the tetrahedral bond angle (109.5). The two sets of lone pair electrons are in sp^3 hybrid orbitals that are directed to two of the corners of a tetrahedron.

A similar situation prevails when we compare conformations of cyclic ethers with those of the corresponding cycloalkanes. For example, tetrahydropyran, the ether analog of cyclohexane, exists in a chair conformation. Following predictions of VSEPR theory, the two oxygen lone pair electrons are shown in positions corresponding to the axial and equatorial C—H bonds of cyclohexane. The conformation of tetrahydropyran is particularly important because many carbohydrates, such as glucose, exist as six-membered tetrahydropyran rings.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00016-4
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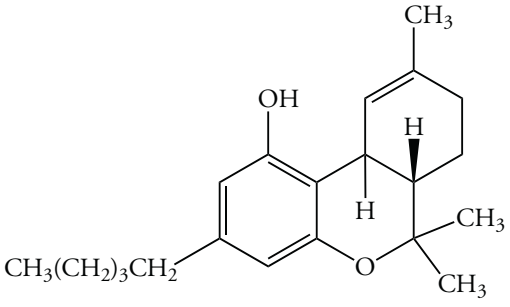
tetrahydropyran



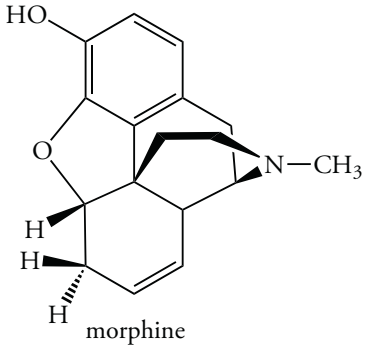
glucose

Figure 16.2 shows examples of naturally occurring, physiologically active cyclic ethers. Tetrahydrocannabinol (THC), the principal active ingredient in marijuana, includes a six-membered ring ether. Morphine contains a five-membered ring ether. Three-membered cyclic ethers (epoxides) are rare in nature. The juvenile hormone of some insects contains a *cis*-substituted epoxide. This hormone controls the rate insect maturation.

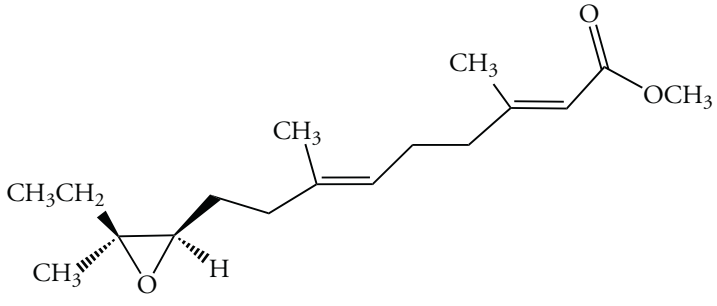
Figure 16.2
Structures of Naturally Occurring Ethers



tetrahydrocannabinol



morphine

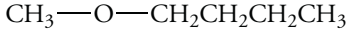


insect juvenile growth hormone

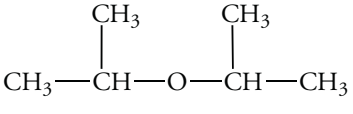
16.2 NOMENCLATURE OF ETHERS

Common Names

Simple ethers are commonly called alkyl alkyl ethers. The name consists of a list of the alkyl (or aryl) groups in alphabetical order followed by the name ether. For example, an unsymmetrical ether with an *n*-butyl group and a methyl group is named *n*-butyl methyl ether. Symmetrical ethers are named by using the prefix di- along with the name of the alkyl group. For example, an ether with two isopropyl groups is called diisopropyl ether.



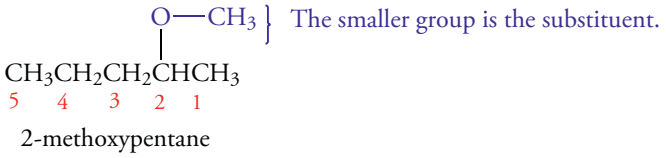
n-butylmethyl ether



diisopropyl ether

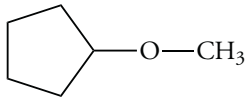
IUPAC Names

According to IUPAC nomenclature, ethers are named *alkoxyalkanes*, where the smaller alkyl group and the oxygen atom constitute an **alkoxy group**. An alkoxy group is treated as a substituent on the larger parent alkane chain. For example, a five-carbon chain (pentane) with an —OCH_3 group at C-2 is named 2-methoxypentane. Figure 16.3 shows other examples of ether nomenclature.

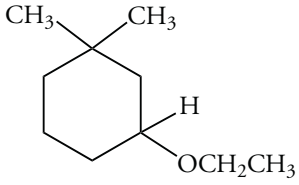


2-methoxypentane

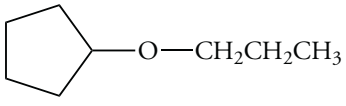
Figure 16.3
IUPAC Names of Ethers



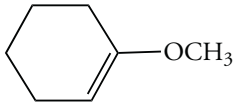
methoxycyclopentane



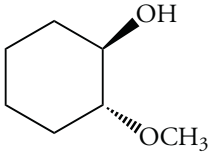
3-ethoxy-1,1-dimethylcyclohexane



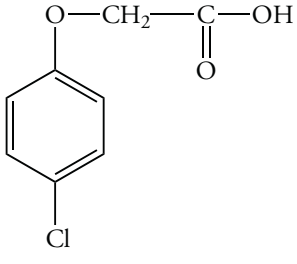
propoxycyclopentane



1-methoxycyclohexene



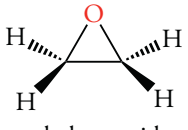
trans-2-methoxycyclohexanol



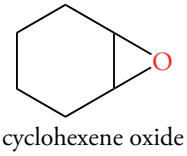
p-chlorophenoxyacetic acid

Cyclic Ethers

Three- through six-membered cyclic ethers have common names. Cyclic ethers with three ring atoms are called epoxides. Since these compounds can be made by oxidizing an alkene, the common name of an epoxide adds *oxide* to the name of the alkene.

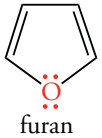


ethylene oxide
(oxirane)

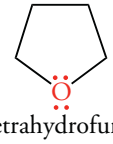


cyclohexene oxide

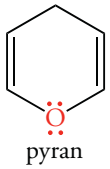
The four-membered ring ethers, called trimethylene oxides, are not common. The five-membered ring ether is called tetrahydrofuran (THF) because of its relationship to the aromatic compound furan. Similarly, tetrahydropyran (THP), a six-membered ring ether, is related to pyran, an unsaturated ether.



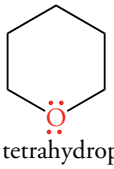
furan



tetrahydrofuran

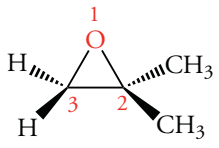


pyran

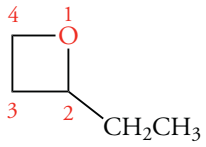


tetrahydropyran

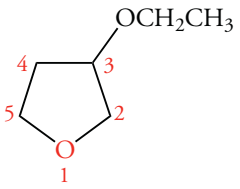
In the IUPAC nomenclature system, the names for cyclic ethers with three-, four-, five-, and six-membered rings are oxirane, oxetane, oxolane, and oxane, respectively. The oxygen atom in each of these rings receives the number 1 in both common names and IUPAC nomenclature. The ring is numbered in the direction that gives the lowest number to the first substituent.



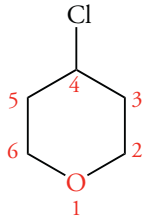
2,2-dimethyloxirane



2-ethyloxetane



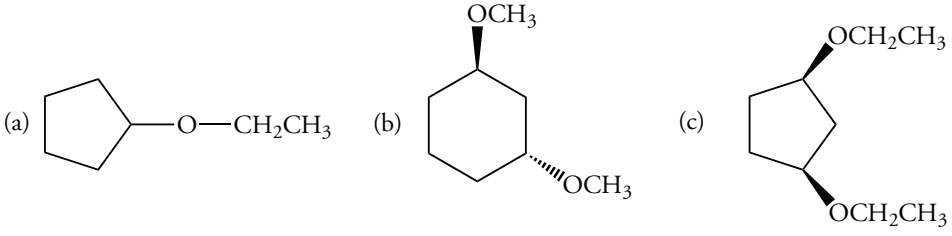
3-ethoxyoxolane



4-chlorooxane

Problem 16. 1

What are the IUPAC names of the following compounds?



Problem 16. 2

Which of the following compounds can exists as pairs of enantiomers?

(a) 2-methoxytetrahydropyran (b) 4-methyltetrahydropyran
(c) 2-ethoxytetrahydrofuran (d) 3-methyltetrahydrofuran

Problem 16. 3

Draw the structure of each of the following compounds.

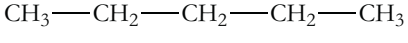
(a) (2*S*,3*R*)-dimethyloxirane (b) (*Z*)-1-methoxy-1-butene
(d) 2-ethoxyoxane (c) *trans*-1,4-dimethoxycyclohexane

16.3 PHYSICAL PROPERTIES OF ETHERS

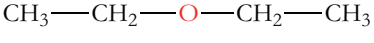
Diethyl ether—often called ethyl ether or just "ether"—was used as a general anesthetic as early as 1842. Administered as a vapor, it acts as a depressant on the central nervous system, causing unconsciousness. However, its high flammability and volatility present hazards in the operating room. Ethers such as ethyl vinyl ether, divinyl ether, and methyl propyl ether have also seen use as anesthetics. All the low molecular weight ethers are potentially explosive when mixed with oxygen.

Dipole Moments and Boiling Points

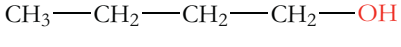
Ethers have two polar C—O bonds and are more polar than alkanes, but less polar than alcohols. Ethers do not have an O—H bond, so they cannot serve as hydrogen bond donors. Therefore, ether molecules do not hydrogen bond to each other, and their boiling points are very close to those of alkanes of similar molecular weight.



pentane (0.1 D)
bp 35 °C



diethyl ether (1.2 D)
bp 35 °C



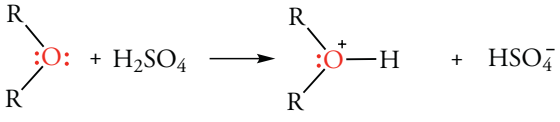
1-butanol (1.7 D)
bp 117 °C

Solubility in Water

Because ethers are polar, they are more soluble in water than alkanes of similar molecular weight. The slight solubility of ethers in water results from hydrogen bonds between the hydrogen atoms of water molecules and the lone pair electrons of the oxygen atom of ether molecules. For example, tetrahydrofuran is miscible in water, and the solubility of diethyl ether is about 10 g per 100 mL of water. The difference in the solubility of cyclic and acyclic ethers reflects the effect of restricted conformational motion in cyclic ethers compared to acyclic ethers. In diethyl ether, the flexible chain of atoms sweeps out a volume that prevents hydrogen bonding between the ether oxygen atom and the hydrogen atoms of water. In tetrahydrofuran, however, the carbon atoms are tied back, and the lone pair electrons of the oxygen atom are available to form hydrogen bonds with water.

The solubility of diethyl ether in water is much higher than that of pentane, but the solubilities of ethers and alkanes approach one another as their molecular weights increase. The ether functional group contributes less to the overall properties of high molecular weight molecules, which resemble alkanes in their solubility.

Ethers are very soluble in concentrated solutions of acids such as sulfuric acid. Their increased solubility results from protonation of the ether oxygen to give an oxonium ion.



oxonium ion

Ethers as Solvents

Ethers such as diethyl ether dissolve a wide range of polar and nonpolar organic compounds. Nonpolar compounds are generally more soluble in diethyl ether than alcohols because ethers do not have a hydrogen bonding network that must be broken up to dissolve the solute. Because diethyl ether has a moderate dipole moment, polar substances dissolve readily in it.

Ethers are aprotic. Thus, basic substances, such as Grignard reagents, can be prepared in ether and tetrahydrofuran. These ethers solvate the magnesium ion, which is coordinated to the lone pair electrons of the ether (Figure 16.4).

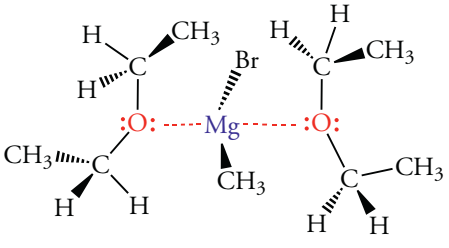
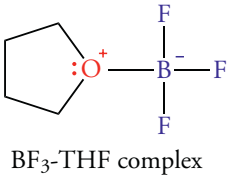
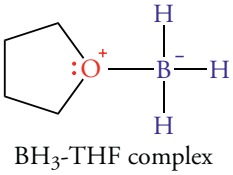


Figure 16.4
Solvation of a Grignard Reagent by Diethyl Ether

The lone pair electrons of an ether also stabilize electron deficient species such as BF_3 and borane (BH_3). For example, the borane-THF complex is used in the hydroboration of alkenes (Section 15.8).



BF_3-THF complex



BH_3-THF complex

Polyethers

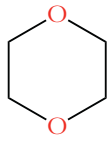
Ethers with more than ether bond readily dissolve polar compounds and hydrogen bond donors. Examples of such solvent include 1,2-dimethoxy methane (glyme), diglyme, and the cyclic ether 1,4-dioxane.

$CH_3—O—CH_2CH_2—O—CH_3$

glyme

$CH_3—O—CH_2CH_2—O—CH_2CH_2—O—CH_3$

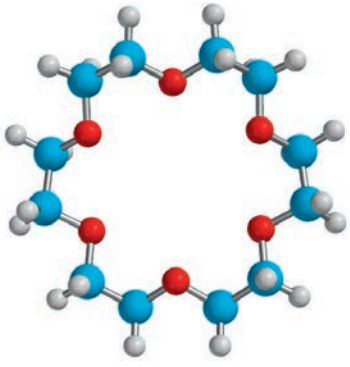
diglyme



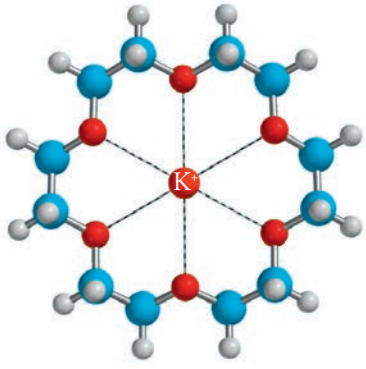
1,4-dioxane

Cations, represented as M^{n+}, are solvated by several water molecules in aqueous solution. Cyclic polyethers can similarly solvate cations and increase the solubility of ionic compounds in nonpolar organic solvents. These compounds, called **crown ethers**, are named *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. The complex is called a *chelate*. The 18-crown-6 ether chelates the potassium ion in a cavity within the ring (Figure 16.5).

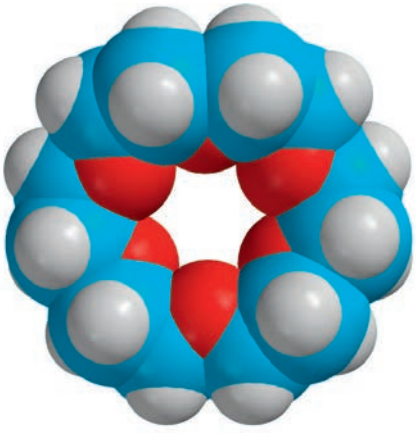
Figure 16.5
Structure of 19-Crown-6



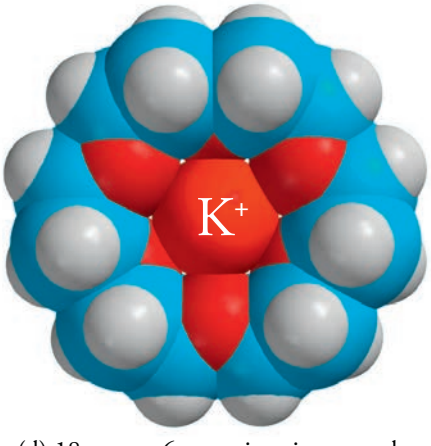
(a) 18-crown-6



(b) 18-crown-6 potassium ion complex



(c) 18-crown-6



(d) 18-crown-6 potassium ion complex

The chelating characteristics of crown ethers depend on the match between the size of the cavity and the ionic radius of the ion. The internal cavity of 18-crown-6 is between 260 and 310 pm, close to the ionic radius of the potassium ion, about 270 pm. Thus, not only does the potassium ion fit within the cavity, but all the oxygen atoms of the crown ether lie close enough to the potassium ion to effectively complex it. Because of this chelation, the solubilities of inorganic salts such as KCN and $KMnO_4$ increase. The separation of the cation from the anion leaves the anion unsolvated and greatly increases its nucleophilicity.

Problem 16. 4
Explain why both glyme and 1,4-dioxane are miscible with water.

Problem 16. 5
15-Crown-5 efficiently complexes a sodium ion. Compare the relative size of the cavity of this crown ether with 18-crown-6. Explain why this cavity can solvate the sodium ion.

Sample Solution

The smaller ring of the 15-crown-5 has a smaller cavity than the 18-crown-6. Sodium has a smaller ionic radius than potassium. We know that potassium ion fits in the cavity of 18-crown-6. Thus, the smaller ring of 15-crown-5 and the smaller sodium ion can form a complex.

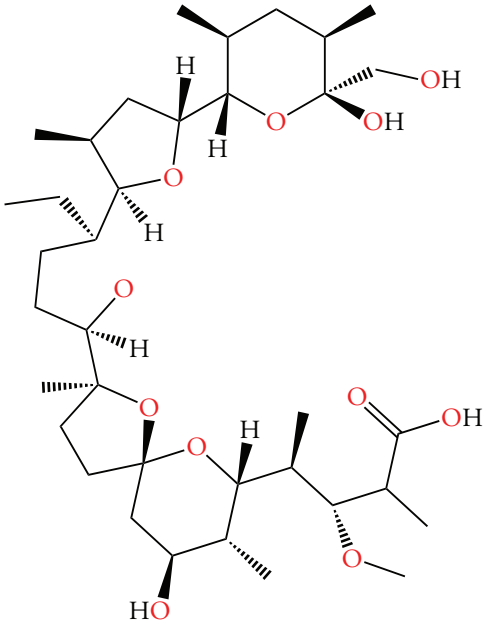
16.4 POLYETHER ANTIBIOTICS

Several cyclic and acyclic polyethers act as antibiotics by transporting ions across biological membranes. These ethers are called **ionophores** (ion carriers). They disrupt the electrolyte balance between the interior and exterior of cells that is necessary for normal maintenance of the cell.

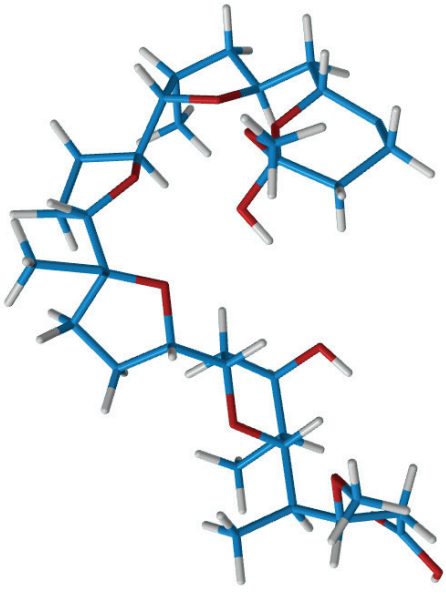
The cyclic ether antibiotic nonactin (Figure 16.6) selectively transports potassium out of bacterial cells. This compound, which contains four five-membered ring ethers, linked by ester units, binds potassium about 10 times better than it binds sodium. Because cells must maintain a higher internal concentration of potassium ions than of sodium ions, the selective removal of potassium ions kills bacteria.

Monensin (Figure 16.6) is a conformationally flexible acyclic polyether that can form complexes with sodium ions. The complex transports sodium ions into cells. The increase in the concentration of sodium ions within the cell's structure increases the osmotic pressure. Water follows the sodium and the consequent cell membrane rupture kills the cell. Farmers add monensin to poultry feed to kill intestinal parasites.

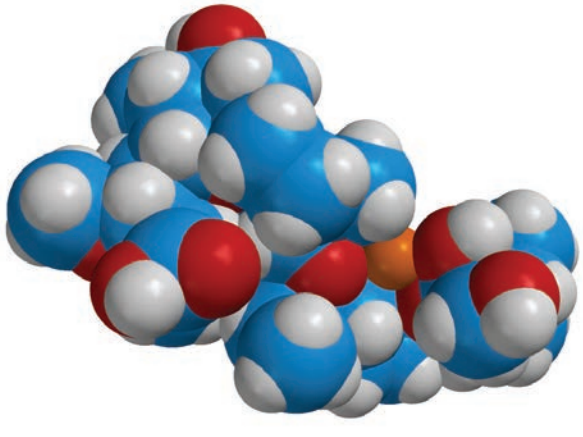
Figure 16.6
Cation Solvation by Polyethers
Cyclic polyethers such as nonactin and monensin coordinate with alkali metal ions. The selectivity of the ether for one metal ion over another depends on the geometry of the polyether and the location of the ether oxygen atoms.



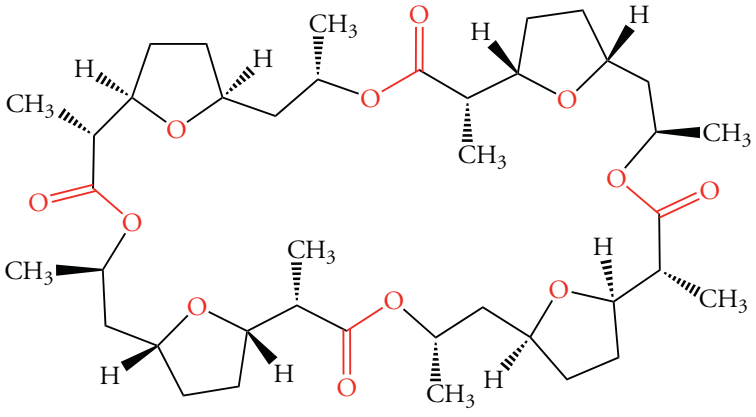
(a) monensin



(b) monensin, molecular model of crystal structure



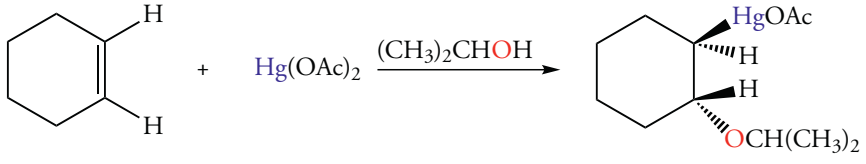
(b) monensin, molecular model of sodium complex



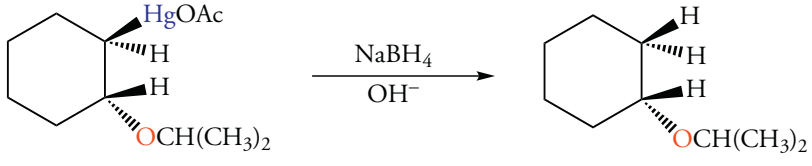
nonactin

16.5 SYNTHESIS OF ETHERS: ALKOXYMERCURATION–DEMERCURATION OF ALKENES

In Chapter 15, we saw that we can convert an alkene to an alcohol by oxymercuration–demercuration. If we perform oxymercuration–demercuration of an alkene in an alcohol as the solvent, the product is an ether. In this reaction, the alcohol, rather than water, acts as the nucleophile. This process, called **alkoxymercuration**, occurs by a mechanism analogous to oxymercuration. First, electrophilic addition of $Hg(OAc)_2$ to the carbon–carbon double bond forms a mercurinium ion intermediate, which is subsequently attacked by the nucleophilic oxygen atom of the alcohol.



The reaction of alkoxymercurated adduct with sodium borohydride in slightly basic solution results in demercuration and formation of the ether product. The regiospecificity of the addition follows Markovnikov's rule.



Problem 16. 6

Write the structure of the product of a reaction of 3,3-dimethyl-l-butene with mercuric acetate in ethanol as solvent.

Problem 16. 7

Select the reagents required to prepare each of the following compounds using the alkoxymercuration-demercuration method.

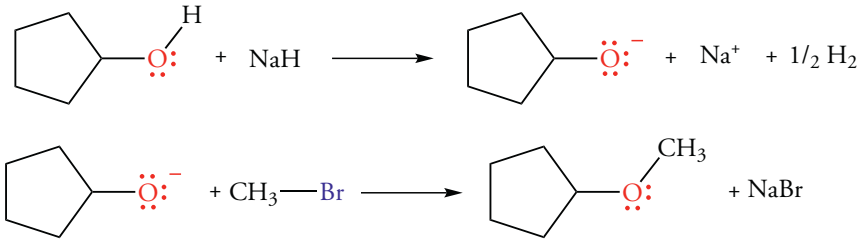
(a) ethoxycyclohexane (b) 1-propoxybutane (c) dicyclohexyl ether

Problem 16. 8

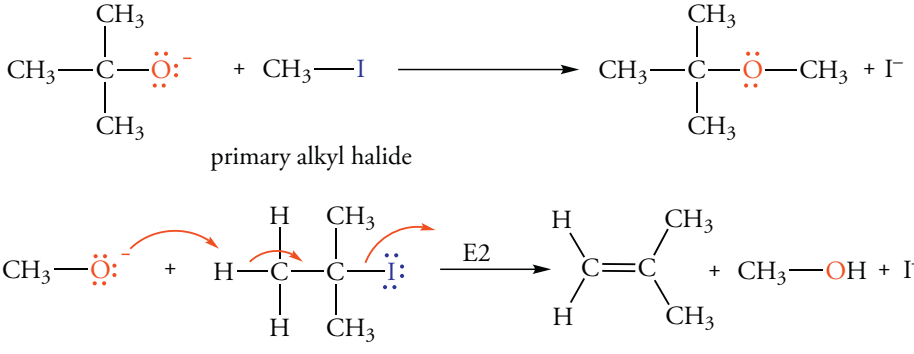
Reaction of 5-hexen-1-ol with mercuric acetate followed by demercuration gives an ether that is isomeric with the unsaturated alcohol. The compound is formed by an intramolecular alkoxymercuration reaction. Draw the structure of the product.

16.6 THE WILLIAMSON ETHER SYNTHESIS

The Williamson ether synthesis is the most widely used method to produce ethers. It occurs by an S_N2 reaction in which a metal alkoxide displaces a halide ion from an alkyl halide. The alkoxide ion is prepared by the reaction of an alcohol with a strong base such as sodium hydride.

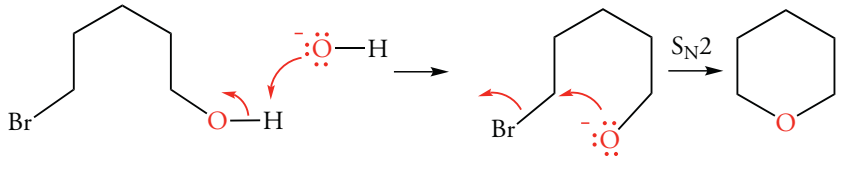


The Williamson synthesis gives the best yields with methyl or primary halides because the reaction occurs by an S_N2 displacement in which a halide ion is the leaving group. The yield is lower for secondary alkyl halides because they also react with the alkoxide ion in a competing elimination reaction. The Williamson synthesis cannot be used with tertiary alkyl halides because they undergo elimination reactions instead of participating in S_N2 reactions. Thus, to make an unsymmetrical ether with a primary and a tertiary alkyl group, a primary alkyl halide and a tertiary alkoxide ion are the best reagents. For example, *tert*-butyl methyl ether can be prepared by the reaction of sodium *tert*-butoxide with methyl iodide, but not by the reaction of sodium methoxide with 2-iodo-2-methylpropane.

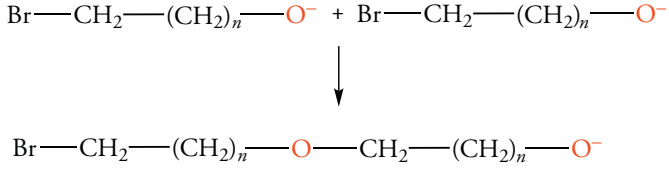


Formation of Cyclic Ethers

Cyclic ethers can be prepared by the intramolecular S_N2 reaction of a halogen-substituted alcohol such as a bromo alcohol. Proton transfer to a base such as sodium hydroxide gives a bromo alkoxide. If the solution is dilute, the alkoxide acts as a nucleophile, and an intramolecular reaction displaces a bromide ion. This process is shown below for 5-bromo-1-penten-1-ol.



In more concentrated solutions, an intermolecular Williamson reaction occurs to give a bromo alkoxy ether. Continued reactions of this type yield long-chain ethers.



The intramolecular reaction is favored in dilute solution because it is first order. The competing intermolecular reaction is second order, and the rate of the reaction decreases as the square of the concentration. Thus, in a dilute solution of the bromoalkoxide, the rate of the intermolecular reaction decreases more rapidly than the rate of the intramolecular reaction.

Rates of Cyclization Reactions

The rates of cyclization of bromo alkoxides as a function of the number of atoms forming the ring (including the oxygen atom) stand in an order that at first glance may appear illogical.

Rates of cyclization and ring size: 3 > 5 > 6 > 4 > 7 > 8

For all these reactions, the same number and types of bonds are being formed and broken. However, the energy change will not be the same for all compounds. We recall that because of angle strain, three- and four-membered rings are less stable than the larger five-, six-, seven-, and eight-membered rings. The same angle strain should affect the energy barrier for the formation of the small ether rings. Because the energy barrier is higher, the rate of reaction is expected to be smaller. The total strain energies of cyclopropane and cyclobutane are approximately equal. In contrast, the strain energies of the five-, six-, seven-, and eight-membered rings are quite small. To the extent that ring strain similarly affects the rate of cyclization, we expect the rates to approximately stand in the following order.

Predicted rates based on strain energy: 3 = 4 > 5 = 6 = 7 = 8

However, this order does not consider an entropy factor. What is the probability that the two reacting centers will approach each other as the length of the chain increases? The degree of freedom and the number of conformations of the chain increase with the number of atoms in the chain. To form a conformation suitable for an intramolecular reaction, the flexibility of the chain must be restricted. With a small number of atoms, the two reacting centers lie close to each other, and we say that the reaction is entropically favored. With an increased number of atoms, the probability of a cyclization reaction decreases. The order of the rates of reaction based only on the probability of cyclization is

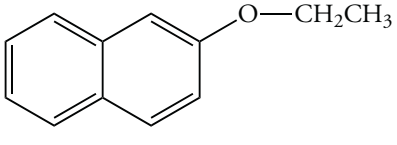
Predicted rates based on probability: 3 > 4 > 5 > 6 > 7 > 8

Now we can interpret the observed order of reactivity. Three-membered rings form rapidly because the contribution of entropy to reaching the transition state is sufficiently favorable to overcome the unfavorable enthalpy of activation associated with ring strain. However, the rate of formation of a four-membered ring is considerably slower because the ring strain is similar to that of a three-membered ring but the probability of the reacting sites being in a conformation suitable for reaction is smaller. Thus, the rate of formation of four-membered rings falls below that of the essentially strain-free five- and six-membered rings.

The five-membered ring, somewhat more strained than the six-membered ring, forms at the faster rate as a result of the probability factor. For larger rings, which have relatively small ring strain, the rate of cyclization is controlled by the entropy factor and decreases as the number of atoms in the ring being formed increases.

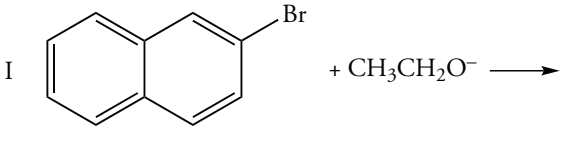
Problem 16. 9

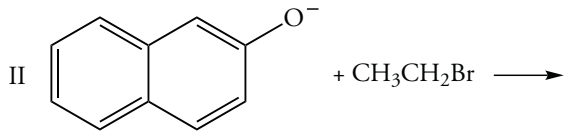
2-Ethoxynaphthalene, known by its trade name Nerolin II, is used in perfumery for its odor of orange blossoms. Propose a synthesis of this compound using the Williamson method.



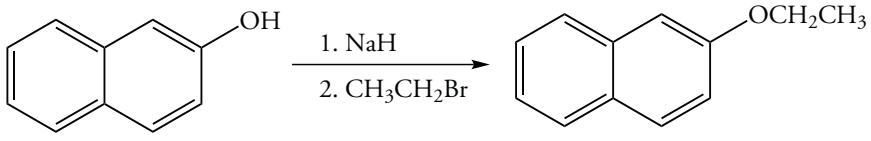
Sample Solution

The ether can be synthesized by the following two combinations of reagents.





The first combination will not give the ether product because S_N2 reactions cannot occur by back-side displacement of halogen atoms at sp^2-hybridized carbon atoms. However, the reaction of the conjugate base of the hydroxyl group at the 2 position of naphthalene with bromoethane occurs readily because bromoethane is an unhindered primary alkyl halide. The nucleophilic oxygen atom of the naphthalene compound is generated by reaction with sodium hydride.

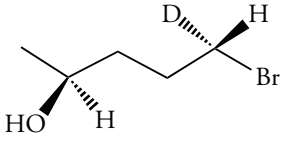


Problem 16. 10

Propose a synthesis of each of the following compounds using the Williamson ether synthesis.
(a) phenyl propyl ether (b) benzyl *tert*-butyl ether (c) 1,4-dimethoxybutane

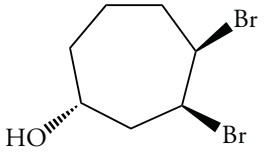
Problem 16. 11

What is the configuration at each chiral center of the following bromo alcohol. Draw the structure of the tetrahydrofuran formed by an intramolecular Williamson ether synthesis or this compound and assign its configuration.



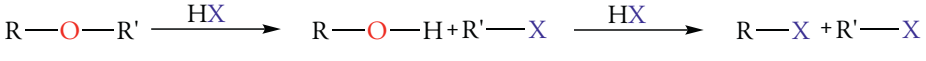
Problem 16. 12

Draw the structures of two possible bicyclic ethers that could result from the intramolecular displacement of bromide by the alkoxide derived from the following dibromo alcohol. Which compound should predominate?

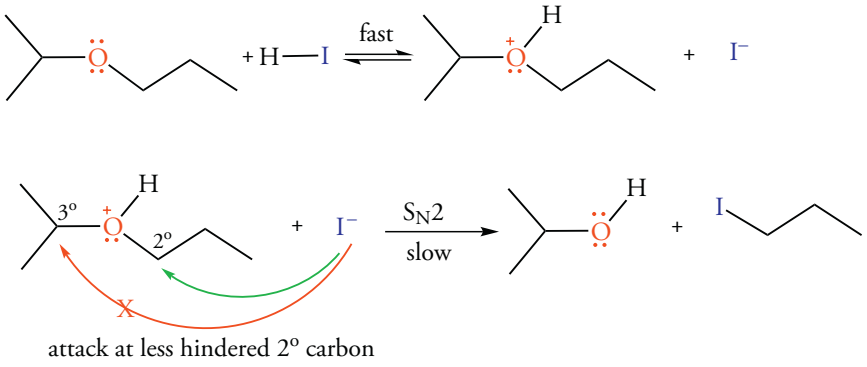


16.7 REACTIONS OF ETHERS

Ethers are very stable compounds that react with few common reagents. They do not react with bases, but do react with strong acids whose conjugate bases are good nucleophiles. For example, ethers react with HI (or with HBr) with cleavage of the carbon–oxygen bond to produce alkyl iodides (or bromides).



The cleavage reaction does not occur with a halide salt. A proton from the halogen acid must protonate the oxygen atom, providing an alcohol as the leaving group. We recall a similar reaction in which alcohols are converted to alkyl halides by way of an S_N2 reaction in which halide ions displace water from a protonated alcohol (Section 9.14). In general, the less substituted alkyl halide forms in this S_N2 reaction. The halide ion attacks the less hindered carbon atom, and the oxygen atom of the displaced alkoxy group remains bonded to the more substituted carbon atom.

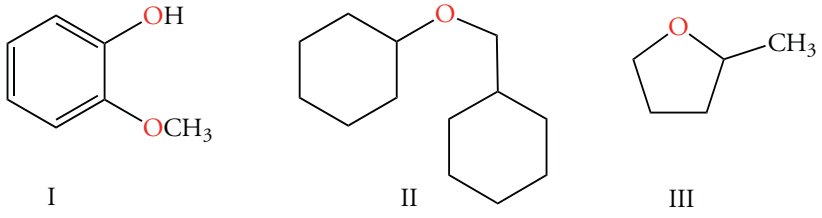


If excess HI is used, a subsequent reaction of the alcohol gives a second mole of an alkyl halide. Both alkyl groups of the ether are eventually converted into alkyl halides.

The cleavage of ethers to produce alkyl halides and alcohols can be used to break complex molecules into simpler units to determine their structures. The identity of the cleavage products reveals the structure of the original ether since the two alkyl groups of the products were originally bonded to an oxygen atom. Note that a cyclic ether would yield a single dihalogen compound.

Problem 16. 13

Based on the mechanism of ether cleavage, write the products of the reaction of HI with each of the following compounds.



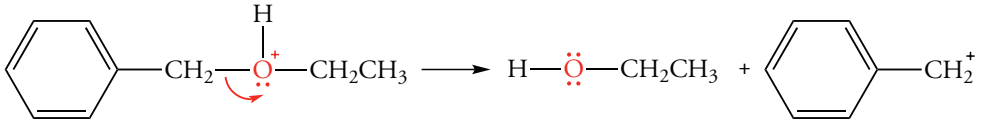
I II III

Problem 16. 14

Allylic and benzylic ethers are not cleaved by an S_N2 process. Suggest an alternate mechanism for the acid-catalyzed cleavage of benzyl ethyl ether.

Sample Solution

A benzyl carbon–oxygen bond of the conjugate acid of benzyl ethyl ether can cleave in an S_N1 reaction. The leaving group is ethanol, and the resulting benzyl carbocation is resonance stabilized.

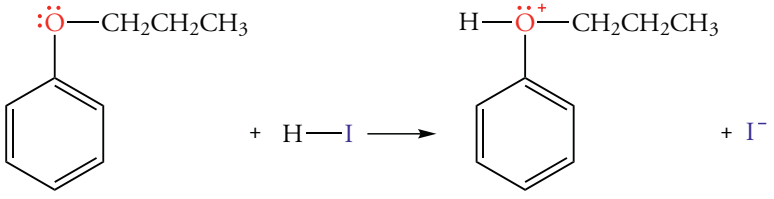


Problem 16. 15

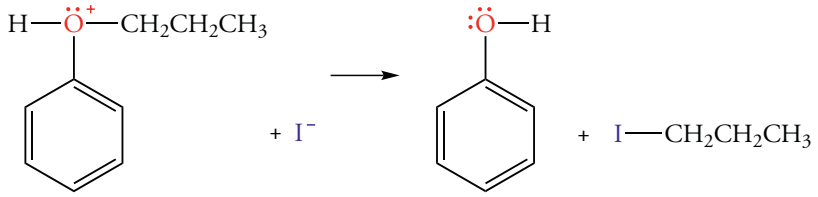
Based on the mechanism of ether cleavage, write the products of the reaction of HI with phenyl propyl ether.

Sample Solution

First, the strong acid protonates the ether oxygen atom to give an oxonium ion.



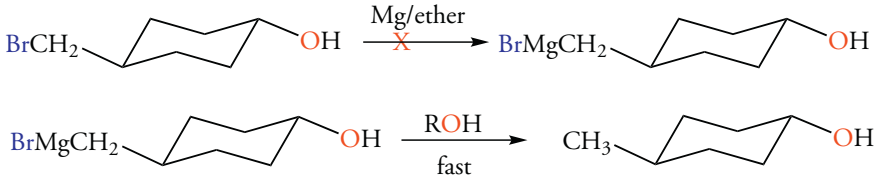
Subsequent nucleophilic attack by the iodide ion can occur only at the methylene carbon atom of the propyl group bearing the oxygen atom. An S_N2 reaction at the carbon atom of the benzene ring that bears the oxygen atom is not possible. The phenol produced also will not react further with HI for the same reason.



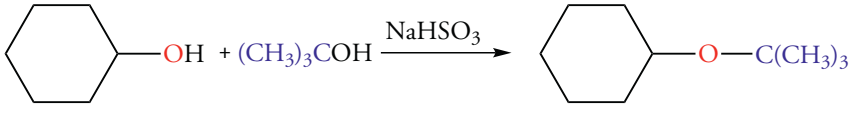
16.8 ETHERS AS PROTECTING GROUPS

Synthetic transformations at one functional group in a molecule that contains two or more functional groups are often complicated by competing reactions at the other reactive sites. However, a functional group can often be converted into an unreactive form called a protecting group. The protected functional group can subsequently be converted back to the original functional group after other synthetic goals are achieved. A protecting group is selected that is both easy to form and easy to remove at the end of the synthesis. Both reactions should occur in high yield.

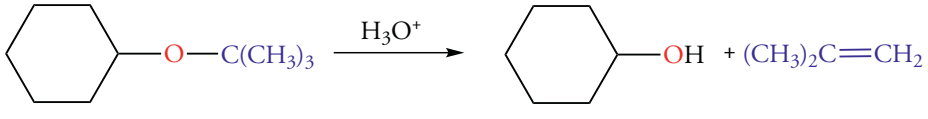
Consider the possibility of forming a Grignard reagent of *trans*-4-(bromo-methyl)cyclohexanol followed by reaction with deuterium oxide to produce a deuterated methyl compound. The synthesis would fail because the hydroxyl group would react immediately with the Grignard reagent. To get around this problem, we first convert the hydroxyl group to an ether. Then, after the formation of the Grignard and subsequent deuteration, the ether could be cleaved to reform the alcohol.



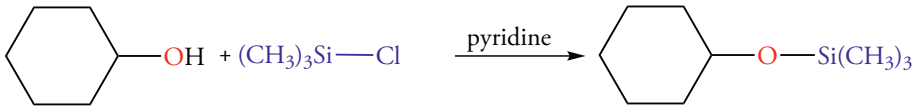
The formation of mixed ethers directly from two alcohols usually gives a mixture of three products. However, it is possible to form mixed ethers in which one alkyl group is tertiary and the other is primary or secondary (Section 16.4). We carry out this acid-catalyzed reaction, converting the tertiary alcohol to a tertiary carbocation, which then reacts with the other alcohol. For example, we can protect the hydroxyl group of cyclohexanol with a *tert*-butyl group.



The protecting group is removed by treating the ether with dilute aqueous acid. The acid protonates the ether to give an oxonium ion that dissociates by an S_N1 reaction to give a *tert*-butyl carbocation and cyclohexanol. Cyclohexanol is the leaving group in this reaction. The *tert*-butyl carbocation then gives 2-methylpropene by an El process. Because 2-methylpropene is a gas, it escapes from the solution, pulling the reaction to completion. The desired alcohol remains in the solvent.



Other alternatives to protecting hydroxyl groups are available that avoid the acidic conditions that could interfere with other functional groups in a molecule. Hydroxyl groups react with trialkylchlorosilanes to give silyl ethers in a reaction analogous to the Williamson ether synthesis. The reaction is carried out with one equivalent of pyridine, which reacts with the HCl by-product to give pyridinium hydrochloride.

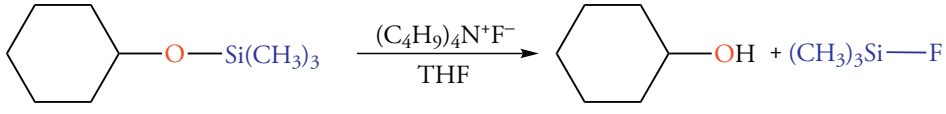


chlorotrimethylsilane (a trimethylsilyl ether)

The Si—Cl bond is so reactive that chloride ion is displaced by the alcohol directly. That is, in contrast to the Williamson synthesis, the alcohol need not be converted to an alkoxide.

The silyl ether forms by an S_N2 reaction at a tertiary center. This reaction can occur at a tertiary silicon center because the C —Si bond length is 195 pm, compared to the 154 pm of a C—C bond length. The alkyl groups bonded to the tertiary silicon atom are farther away from each other than alkyl groups bonded to a tertiary carbon atom. Therefore, they do not present as much steric interference to the approach of a nucleophile as the alkyl groups in the analogous carbon compound, *tert*-butyl chloride.

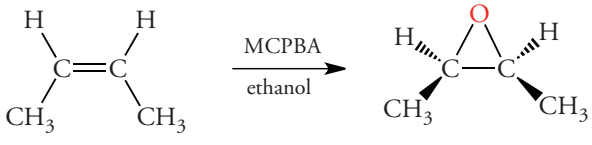
Silyl ethers are less reactive than ethers to both acid and base, and therefore they are stable under most reaction conditions. In practice, *tert*-butyldimethylsilyl (TBDMS) ethers are prepared rather than trimethylsilyl (TMS) ethers because they are more stable. However, either trialkylsilyl group is easily removed by reaction with fluoride ion, provided in the form of the salt tetrabutylammonium fluoride. This cleavage reaction is highly regioselective because the fluoride ion has no effect on most other functional groups.



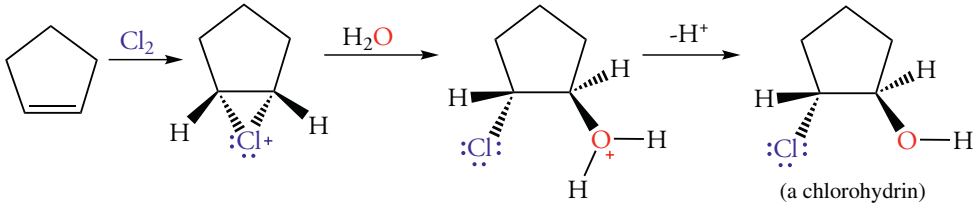
(a trimethylsilyl ether)

16.9 SYNTHESIS OF EPOXIDES

We recall that epoxides can be synthesized by oxidizing an alkene (Section 9.8). The possible oxidizing agents are peroxyacetic acid (CH_3CO_3H), *m*-chloroperoxy-benzoic acid (MCPBA). The epoxidation of alkenes with peroxy acids is stereospecific. The stereochemistry of the groups in the alkene remains: *cis* groups in the alkene remain *cis* in the epoxide, and *trans* groups in the alkene remain *trans* in the epoxide

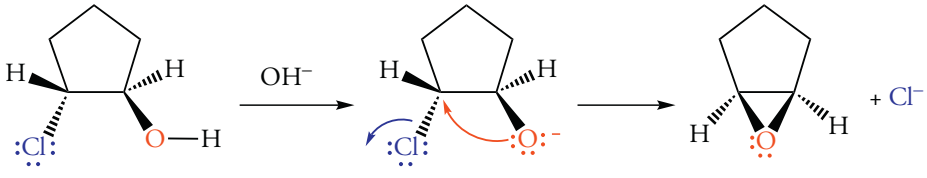


A second method of synthesizing epoxides is an *intramolecular* variation of the Williamson ether synthesis. First, a halohydrin forms in the reaction of an alkene with an aqueous solution of a halogen. For example, chlorine gives a cyclic chloronium ion, which then reacts with water as the nucleophile to give the chlorohydrin.



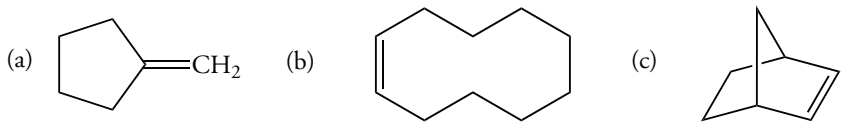
(a chlorohydrin)

The chlorohydrin is treated with a base, producing an alkoxide ion that displaces a chloride ion from the adjacent carbon atom to form the epoxide ring.



Problem 16.16

Draw the structure of the epoxide formed in the reaction of each of the following compounds with MMPP in ethanol.



Problem 16.17

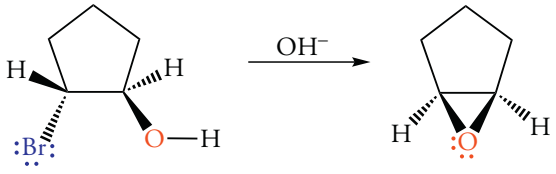
Write the halohydrin product of the electrophilic addition of bromine in water to *cis*-2-butene. What is the stereochemistry of the epoxide formed from this bromohydrin?

Problem 16.18

(1*R*,2*R*)-2-Bromocyclopentanol reacts with sodium hydroxide to form an optically inactive product with the molecular formula C_5H_8O. However, the isomeric 1*S*,2*R* compound is significantly less reactive and forms elimination and substitution products. Explain why.

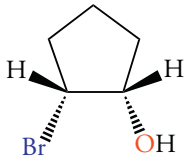
Sample Solution

In the 1*R*,2*R* isomer, the nucleophilic alkoxide ion, derived from loss of a proton from the hydroxyl group, and the bromine atom, which can leave as a bromide ion, are *trans* to each other. An intramolecular Williamson reaction gives an epoxide.



1*R*,2*R*

The 1*S*,2*R* diastereomer cannot react to form an epoxide because the alkoxide ion and the bromine are *cis* to each other. Only E2 and S_N2 reactions typical of a secondary halide can occur.



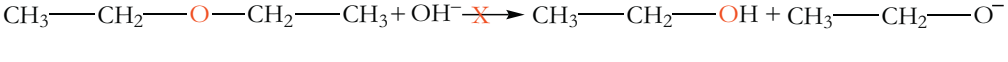
1*S*,2*R*

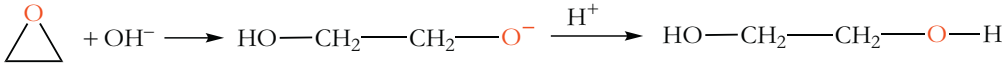
16.10 REACTIONS OF EPOXIDES

Epoxides undergo ring-opening reactions and are more reactive than acyclic and larger cyclic ethers because the three-membered ring has considerable ring strain. When epoxides undergo ring-opening reactions by cleavage of a C—O bond, the products have normal tetrahedral bond angles, so they are not strained. As a result, the energy barrier for cleavage of a C—O bond of an epoxide is smaller than for other ethers, and the rate of cleavage of epoxides is more rapid

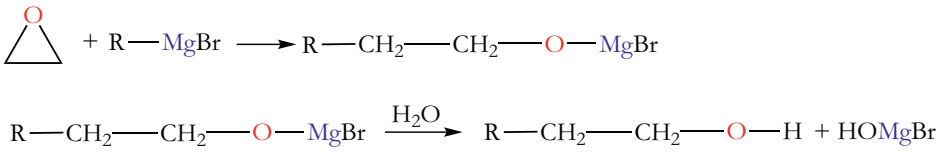
Ring Opening by Nucleophiles

Ethers do not generally react with nucleophiles to displace an alkoxide ion. However, epoxides arc so strained that the C—O bond of the ring is cleaved even by nucleophiles such as OH^-, SH^-, or NH_3 or the related organic species RO^-, RS^-, and RNH_2. For example, hydroxide ion displaces an alkoxide of an epoxide. The alkoxide is not released, as are typical leaving groups of S_N2 reactions, because the ether is cyclic.





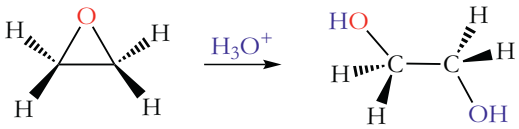
A mechanistically related reaction occurs when epoxides react with Grignard reagents to produce alcohols. The carbon skeleton contains two more carbon atoms than the starting alkyl halide. The sequence of reactions is shown below.



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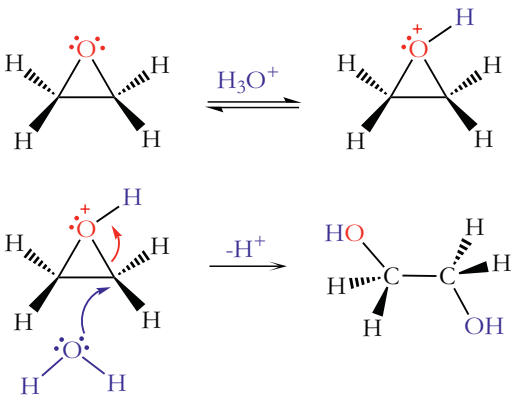
Acid-Catalyzed Ring Opening

Epoxides react very readily with nucleophiles in acid-catalyzed reactions. For example, ethylene oxide reacts in dilute aqueous HCl to form ethylene glycol.



1,2-ethanediol
(ethylene glycol)

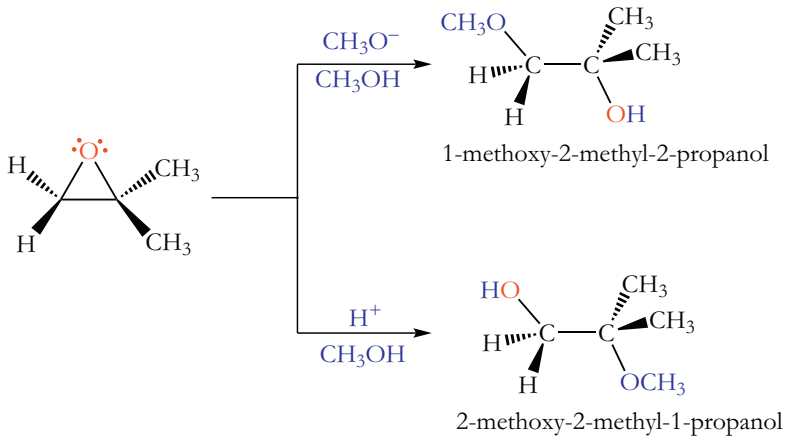
In this acid-catalyzed ring opening of epoxides, water acts as the nucleophile and the protonated oxygen atom of the epoxide is the "leaving group." In general, acid catalysis allows the use of a weak nucleophile in epoxide ring cleavages because a better leaving group is generated at the carbon undergoing nucleophilic attack.



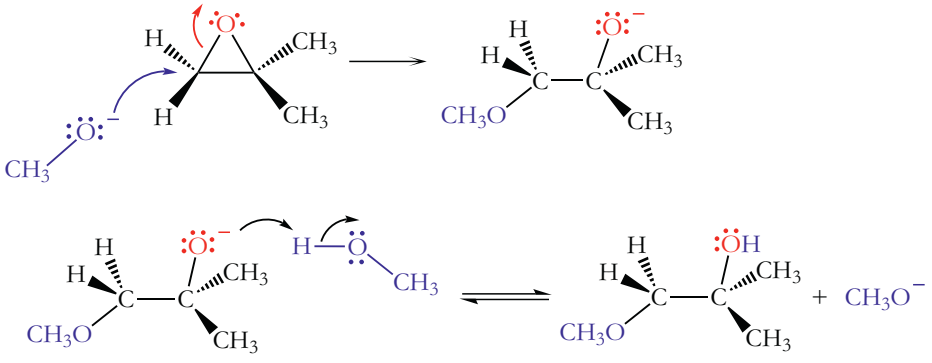
Regioselectivity of Ring Opening

Ring-opening reactions of symmetrical epoxides yield the same products under acidic and basic conditions. However, ring-opening reactions of unsymmetrical epoxides could yield two isomeric products. Under basic conditions, the reaction is regioselective, and the major product results from attack of the nucleophile at the less substituted carbon atom. In the acid-catalyzed reaction, the regioselectivity is different. The major product results from attack of the nucleophile at the more substituted carbon atom. These generalizations are illustrated by comparing the reaction of 2,2-dimethyloxirane with methoxide ion to the acid-catalyzed reaction with methanol (Figure 16.7).

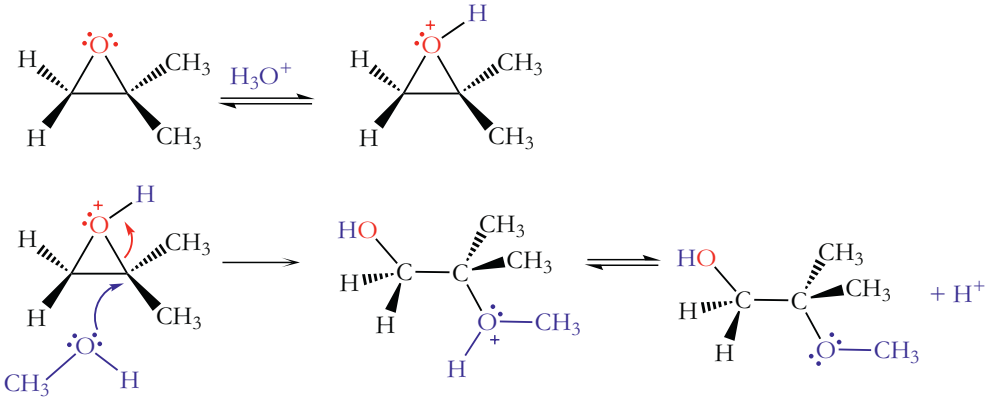
Figure 16.7
Regioselectivity of Epoxide Ring Opening



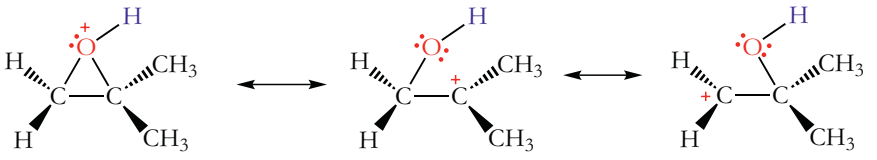
The regioselectivity of epoxide ring opening by CH_3O^- in methanol is controlled by the same features as the S_N2 displacement reactions we considered in Chapter 10. The nucleophilic methoxide anion regioselectively attacks the least hindered carbon atom. That is, it attacks the primary rather than the tertiary carbon atom of 2,2-dimethyloxirane in the rate-determining step. This intermediate alkoxide then abstracts a proton from the solvent in a rapid second step that regenerates the methoxide base.



The regioselectivity is different for the reaction of the same epoxide with methanol in acid. The first step is a rapid reversible protonation of the epoxide. The epoxide then reacts with the nucleophile methanol in the rate-determining step. Subsequently, the protonated product reversibly transfers a proton to the solvent.



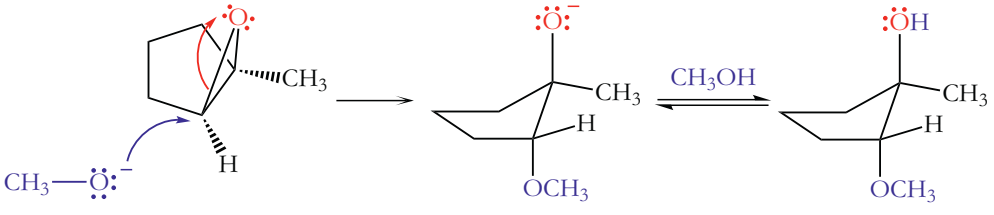
The mechanism for the acid-catalyzed ring opening differs from the base-catalyzed reaction in one important way that explains why the nucleophile now attacks the more hindered carbon atom. The structure of the protonated substrate that reacts with the nucleophile in the rate-determining step can exist in three resonance forms.



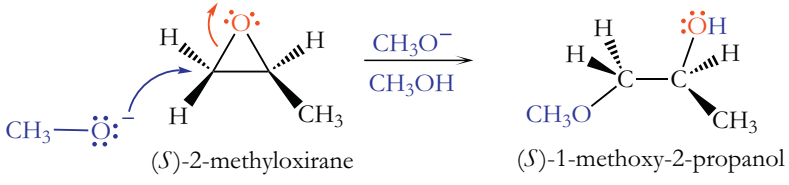
Because a positive charge is more stable on the tertiary carbon atom than on the primary carbon atom, the tertiary carbocation resonance form is a more important contributor to the resonance hybrid than the primary carbocation. This uneven charge distribution accounts for the difference in the energy barriers for the formation of the two possible isomeric products. Nucleophilic attack at the carbon atom with the greater positive charge is favored. That is, it has the lower energy barrier. This stabilization of charge overrides the effect of steric hindrance, which disfavors attack at the tertiary center.

Stereochemistry of Ring Opening

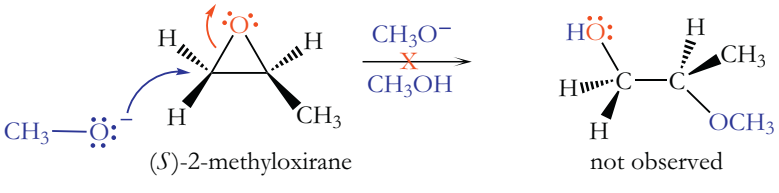
The ring-opening reactions of epoxides can occur at the center at which the nucleophile attacks or the center that retains the carbon–oxygen bond. The stereochemistry of the reaction under basic conditions or acid-catalyzed conditions can be determined by using geometric or optical isomers. For example, the ring opening of 1-methyl-cyclopentene epoxide with methoxide ion in methanol produces the *trans* isomer, indicating that the nucleophilic methoxide ion attacks from the back of the epoxide ring and the ring oxygen atom leaves from the opposite side. Thus, inversion occurs at the site of nucleophilic attack. The configuration of the other carbon atom of the epoxide is unaffected because it does not participate in the reaction. Its bond to oxygen remains intact.



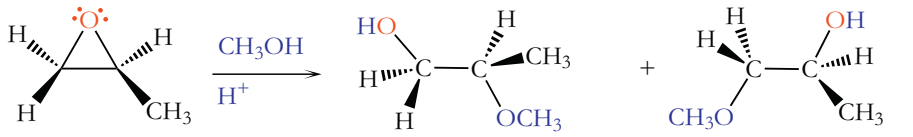
Considerably more information is provided by the reaction of optically active substrates such as (*S*)-2-methyloxirane. The reaction of this substrate could be less regioselective than the reaction of 2,2-dimethyloxirane because there is a smaller difference between the steric environments of the two possible sites for reaction. The sites are primary and secondary in 2-methyloxirane, compared to primary and tertiary in 2,2-dimethyloxirane. However, the reaction is stereospecific. Nucleophilic attack occurs at the less substituted site and gives (*S*)-1-methoxy-2- propanol.



This regioselectivity is the result of the substantial difference in the rates of S_N2 reactions of primary and secondary substrates (Section 10.3). The reaction is stereospecific, and the configuration of the stereogenic center remains because the secondary carbon atom does not participate in the reaction. Its carbon–oxygen bond remains intact in the process.



The reaction of (*S*)-2-methyloxirane with methanol in the acid-catalyzed reaction is somewhat less regioselective. However, both products result from stereospecific reactions. The major product is (*R*)-2-methoxy-l-propanol. The minor product, 1-methoxy-2-propanol, has the *S* configuration.



(*R*)-2-methoxy-1-propanol (major product)

(*S*)-1-methoxy-2-propanol (minor product)

The decreased regioselectivity of the reaction of (*S*)-2-methyloxirane compared to 2,2-dimethyloxirane results from the opposing effects of charge stabilization and steric hindrance. There is a smaller difference in the charge stabilization of a secondary and a primary carbocation compared to the difference between a tertiary and primary carbocation. As a result, the role of steric hindrance becomes more important in (*S*)-2-methyloxirane, and some product results from attack at the primary center.

As established in the reaction of methoxide ion at the primary center, the reaction of methanol at the primary center occurs to give a product with retention of configuration at the secondary center. The C—O bond at C-2 is unaffected in the reaction. More importantly, this acid-catalyzed reaction provides information about the stereochemistry of the nucleophile's site of attack. Inversion of configuration occurs, as is usually observed for S_N2 reactions.

Problem 16. 19

Predict the product of each of the following reactions.

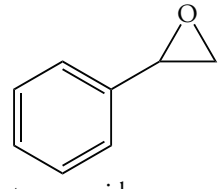
(a) sodium cyanide and ethylene oxide

(b) (*R*)-2-methyloxirane and the ethyl Grignard reagent

(c) propynyl sodium in liquid NH_3 and 2,2-dimethyloxirane

Problem 16. 20

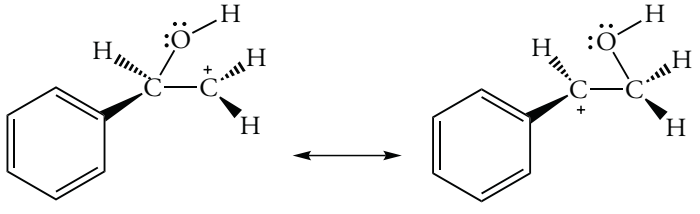
Predict the product of the reaction of styrene oxide (phenyloxirane) in an acid-catalyzed reaction with methanol.



styrene oxide

Sample Solution

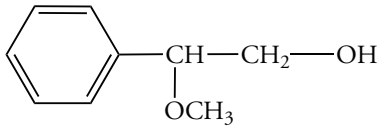
Protonation of the oxirane ring gives an oxonium ion that has two resonance forms. One is a primary carbocation, the other is resonance-stabilized benzyl carbocation.



primary carbocation

benzyl carbocation

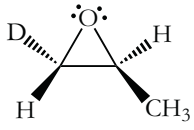
The benzyl carbocation form contributes more to the resonance hybrid than the primary carbocation form. The attack of the nucleophilic methanol occurs at the benzylic center to give 2-methoxy-2-phenyl-1-ethanol.



2-methoxy-2-phenyl-ethanol

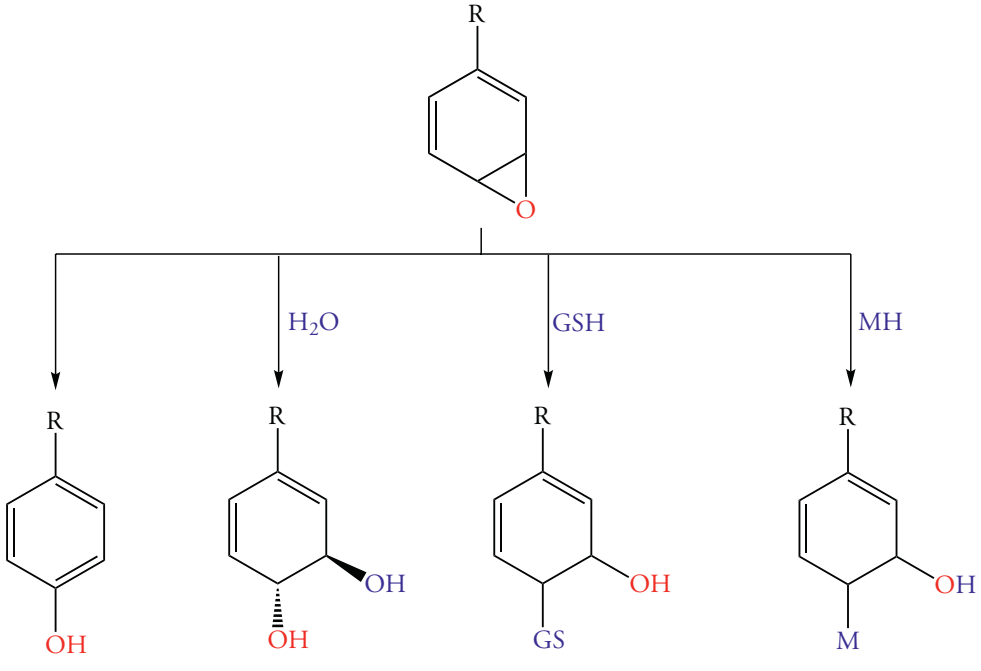
Problem 16. 21

Assign the configuration of both stereogenic centers of the following epoxide. Draw two possible products that could form in the reaction of the epoxide with methanol in an acid-catalyzed reaction. Assign the configuration at any stereogenic centers in both products.



Biochemical Reactions of Epoxides

In earlier chapters, we saw that epoxides are produced biologically as oxidation products of alkenes and aromatic compounds. These epoxides are formed in the liver by cytochrome P450, and they undergo ring-opening reactions with different substances. If the epoxide reacts with a biological macromolecule, the result is potentially devastating. When epoxides are made from aromatic compounds, the products are called arene oxides. These molecules can undergo four kinds of reactions, as shown below.



1. rearrangement
2. hydrolysis
3. reaction with glutathione
4. reaction with macromolecules

Reaction 1. The rearrangement of an arene oxide gives a water-soluble phenol that is easily eliminated from the body. Hence, this pathway does not lead to the accumulation of toxic by-products.

Reaction 2. Ring opening of the arene oxide by water gives a *trans* diol by an S_N2 process. The diol is water soluble and is also easily eliminated from the body.

Reaction 3. Glutathione contains a nucleophilic sulfhydryl group that reacts with toxic metabolites. Glutathione (GSH) reacts with arene oxides in a ring-opening reaction. Because the product contains many polar functional groups, it is water soluble and can be excreted. Figure 16.8 shows the structure of glutathione.

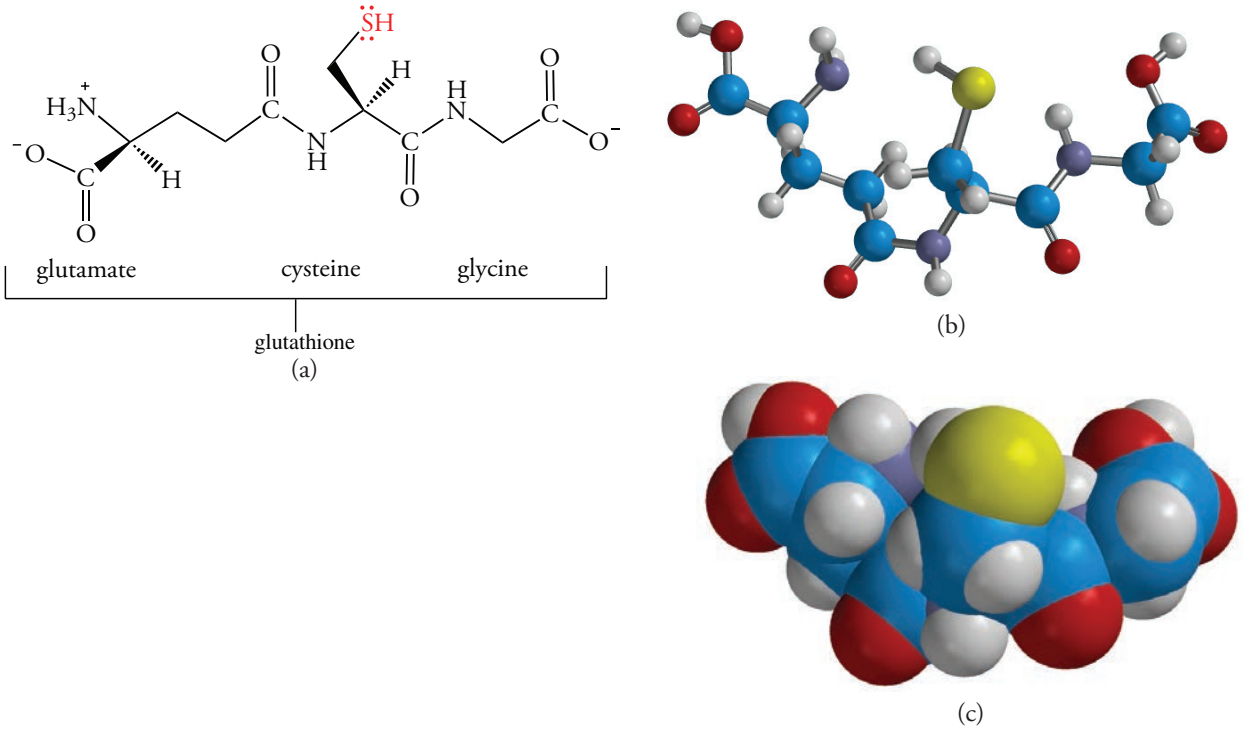
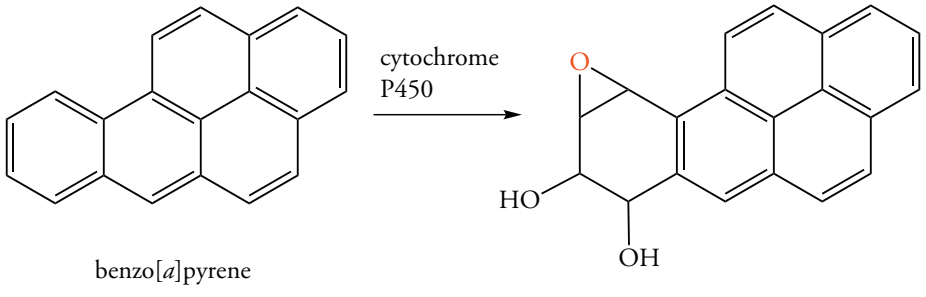
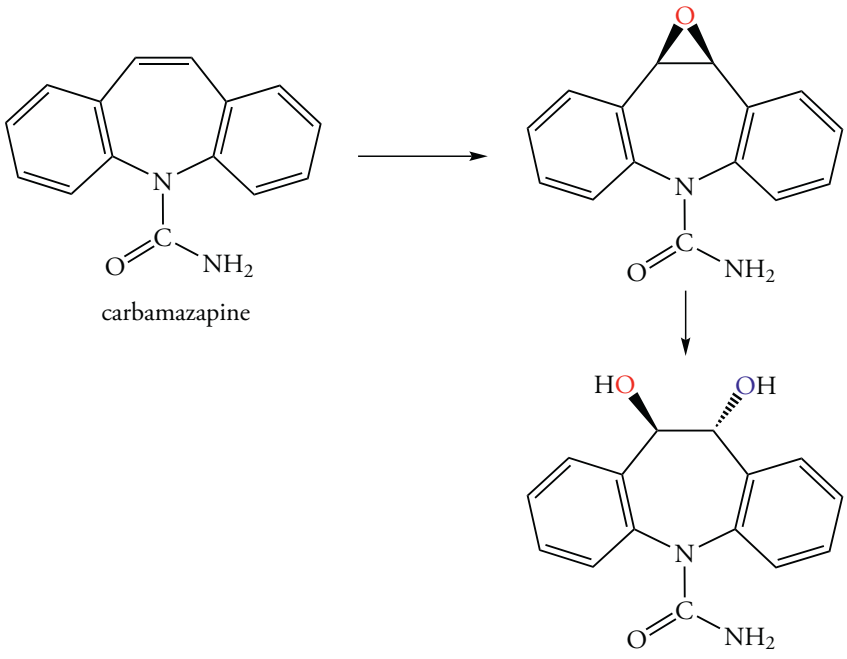


Figure 16.8
Structure of Glutathione
(a) Bond-line structure of glutathione at pH 7. (b) Ball-and-stick structure. (c) Space-filling structure.

Arene oxides react with nucleophilic functional groups present in most macromolecules (represented by MH in the equation) including enzymes, RNA, and DNA. These reactions can cause significant alterations in biological functions. A particularly dangerous arene oxide is the epoxide of benzo[*a*]pyrene, a potent carcinogen that reacts with amino groups in DNA. Benzo[*a*]pyrene is a combustion product found in tobacco smoke. It is also found on the surface of meats that have been grilled at high temperature.



The epoxide metabolites of alkenes tend to be more stable than arene oxides. They undergo ring opening with water to give diols. One example of this type of reaction is the ring opening of the epoxide of the anticonvulsant drug carbamazepine.

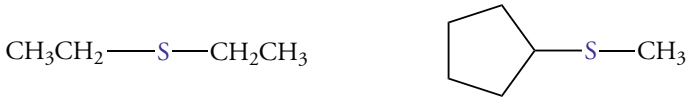


carbamazapine

It is not easy to predict whether an epoxide will react with water or glutathione and be nontoxic, or whether it will react harmfully with macromolecules. However, it appears that relatively stable epoxides tend to undergo ring opening by water or glutathione. Unfortunately, epoxides that have sterically hindered oxirane rings, benzo[*a*]pyrene, for example, tend to react with nucleophilic groups of macromolecules.

16.11 SULFIDES

Sulfides are the sulfur analogs of ethers, R—S—R′. The common names are derived in the same way as ethers. That is, they are called alkyl alkyl sulfides. Sulfides are named according to IUPAC nomenclature as alkylthioalkanes, where the smaller alkyl group and the sulfur atom constitute an alkylthio group. An alkylthio group is treated as a substituent on the larger parent alkane chain. For example, a five-carbon chain (pentane) with an —SCH_3 group at the C-2 atom is named 2-(methylthio)pentane.



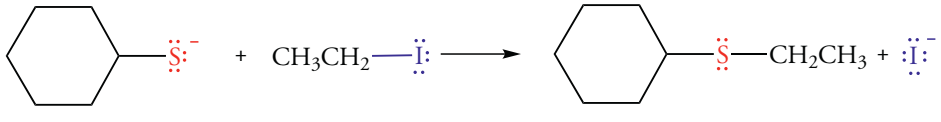
1-(ethylthio)butane
(butyl ethyl sulfide)

methylthiocyclopentane
(cyclopentyl methyl sulfide)

The cyclic sulfide analogs of ethers are named using "*thi*" in place of "*ox*." Thus, the three-, four-, five-, and six-membered sulfides are thiirane, thietane, thiolane, and thiane, respectively.

Synthesis of Sulfides

Sulfides may be prepared by a method analogous to the Williamson ether synthesis. The nucleophile is a thiolate anion rather than an alkoxide. Thiolate ions, RS^-, are better nucleophiles than alkoxides because sulfur is more polarizable than oxygen. Thus, thiolate ions displace halide ions from alkyl halides by an S_N2 reaction to give good yields of sulfides.



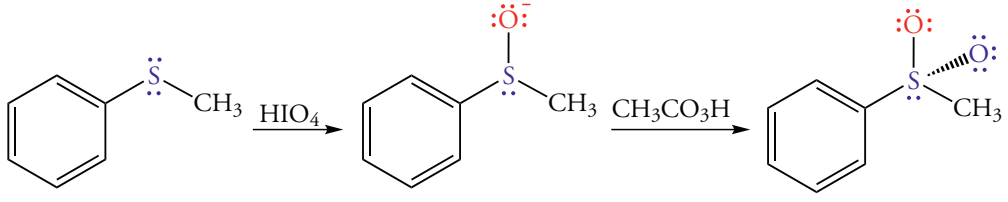
There are two important differences between reactions to form ethers and those that form sulfides.

1. Because thiolates are better nucleophiles and weaker bases than alkoxides, elimination reactions do not compete much with substitution reactions. Even secondary alkyl halides can be used to form sulfides.
2. Second, because thiols are more acidic (pK_a = 8) than alcohols (pK_a = 16), they are quantitatively converted to thiolates by sodium hydroxide.

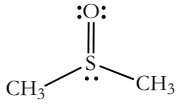
Therefore, it is not necessary to prepare the thiolate in a separate reaction with a strong base, as is required in the reaction of alcohols with sodium hydride. Sulfides are usually prepared by adding the alkyl halide to a basic alcoholic solution of the thiol.

Oxidation of Sulfides

Sulfides are easily oxidized by hydrogen peroxide at room temperature to form sulfoxides. Continued oxidation to form sulfones occurs with excess reagent, but usually requires a peroxy acid such as peroxyacetic acid. Sodium periodate ($NaIO_4$) oxidizes sulfides to sulfoxides, but not to sulfones.



Dimethyl sulfoxide (DMSO) has a high dielectric constant and is an excellent aprotic solvent for nucleophilic substitution reactions. DMSO readily penetrates the skin, and any compound dissolved in DMSO is carried with it across the skin. Hence, great caution is required when this compound is used as a solvent.



dimethyl sulfoxide

Problem 16. 22

Write the product of the base-catalyzed reaction of CH_3CH_2SH and ethyloxirane. Explain why only a catalytic amount of base is required.

16.12 SPECTROSCOPY OF ETHERS, THIOLS, AND SULFIDES

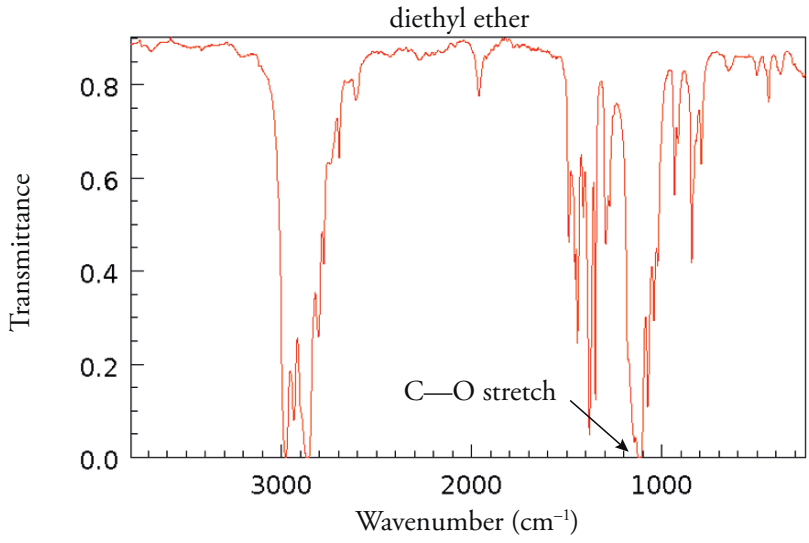
Infrared Spectroscopy of Ethers

Both alcohols and ethers have an intense C—O stretching vibration of alcohols occurs in the 1050–1200 cm^{-1} region. However, because so many other absorptions occur in this region, a strong peak in this region does not necessarily imply that the unknown compound contains a C—O bond. On the other hand, the absence of a strong absorption in the region indicates the absence of a C—O bond (Figure 16.9).

The stretching vibration of the weaker C—S bond appears in the 590–700 cm^{-1} region. This absorption is very weak because the C—S bond is essentially nonpolar. Therefore, the identification of a thiol by the C— S bond is quite tenuous. For the reasons just stated for alcohols and thiols, it is not possible to identify either an ether by the C—O stretching vibration or a thioether by the C—S vibration.

The O—H stretching vibration of an alcohol occurs at 3600 cm^{-1} if the sample is observed at low pressures in the gas phase. However, in the liquid phase or even a relatively dilute solution, there is extensive hydrogen bonding and the absorption occurs in the 3200–3400 cm^{-1} region. The band is very broad because of the variety of hydrogen-bonded species present, but it is a positive identification of an O—H bond.

Figure 16.9
Infrared Spectroscopy of Ethers
The IR spectrum of diethyl ether has a characteristic C—O bond stretching frequency at about 1100 cm^{-1}.



The S—H stretching vibration of a thiol occurs in the 2550–2600 cm^{-1} region. This lower wavenumber position compared to the O—H stretching vibration is the result of the weaker S—H bond. The absorption of the S—H bond is much less intense than that of the O—H bond because the S—H bond is less polar. The S—H absorption is not broad because S—H does not form hydrogen bonds.

Proton NMR Spectroscopy

The chemical shift of the hydrogen atom of the hydroxyl group varies depending on its concentration and the solvent used to obtain the spectrum. In pure ethanol, the O—H resonance occurs at 5.3 δ. In a dilute solution of ethanol in CCl_4, in which there is decreased hydrogen bonding, the resonance occurs in the 2–3 δ region. Regardless of the concentration, the resonance is usually unsplit because the hydrogen atoms exchange too rapidly to be observed as discrete atoms coupled to specific atoms (Figure 16.10).

The O—H resonance can be confirmed by an exchange reaction using D_2O. A drop of D_2O is added to the sample of the alcohol in a solvent such as CCl_4. The O—H group of the alcohol is converted to an O—D group. The other product, HOD, floats to the top of the solvent. A subsequent NMR spectrum obtained from the CCl_4 solution no longer has the resonance of the O—H group of the alcohol, but the remainder of the spectrum is unchanged.

The chemical shift of the hydrogen atom of the S—H group varies slightly with concentration and the solvent used to obtain the spectrum. However, the effect is less pronounced than that of the O—H group. The chemical shift range is 1–2 δ. The S—H resonance can be confirmed by an exchange reaction using D_2O. After adding a drop of D_2O the S—H group of the thiol is converted to an S—D group, which is not observed in the hydrogen NMR spectrum. The remainder of the spectrum is unchanged.

Hydrogen atoms on the α-carbon atoms of primary and secondary alcohols as well as the related ethers have chemical shifts in the 3.0–4.1 δ region. The deshielding effect of the electronegative oxygen atom falls off with distance, as shown by the following examples.

$CH_3—CH_2—OH$ (1.15 δ, 3.59 δ)

$CH_3—CH_2—CH_2—OH$ (0.93 δ, 1.53 δ, 3.49 δ)

Hydrogen atoms on the α-carbon atoms of primary and secondary thiols as well as the related thioethers have chemical shifts in the 2.5 δ region. The deshielding effect of the sulfur atom falls off with distance, as shown by the following examples.

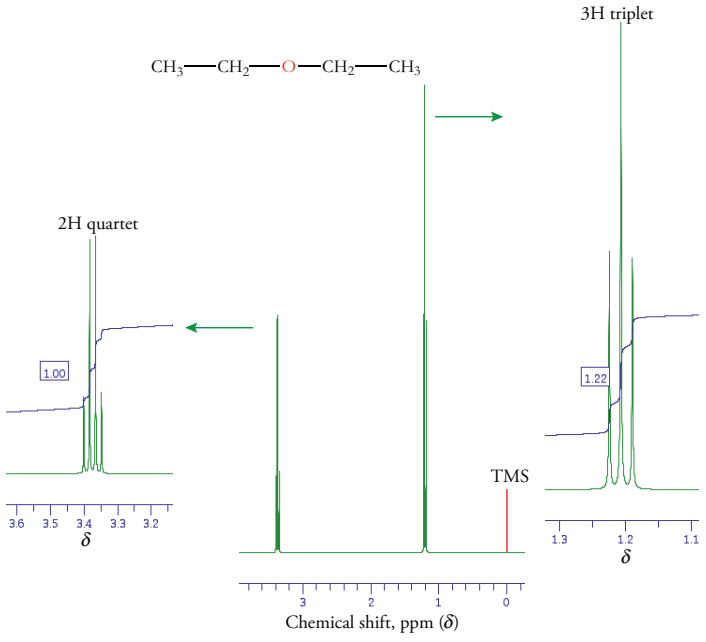
$CH_3—CH_2—SH$ (1.25 δ, 2.44 δ)

$CH_3—CH_2—CH_2—SH$ (1.02 δ, 1.57 δ, 2.49 δ)

$CH_3—CH_2—O—CH_2—CH_3$ (1.18 δ, 3.37 δ)

$CH_3—CH_2—S—CH_2—CH_3$ (1.25 δ, 2.49 δ)

Figure 16.10
NMR Spectrum of Diethyl Ether



C-13 NMR Spectroscopy

The α-carbon atoms of alcohols and ethers are deshielded by the oxygen atom. The effect on the chemical shift of β carbons is small, as shown by the following examples.

$CH_3—CH_2—CH_2—CH_2—OH$
14.8 δ 20.3 δ 36.2 δ 62.6 δ

$CH_3—CH_2—O—CH_2—CH_3$
17.1 δ 67.4 δ

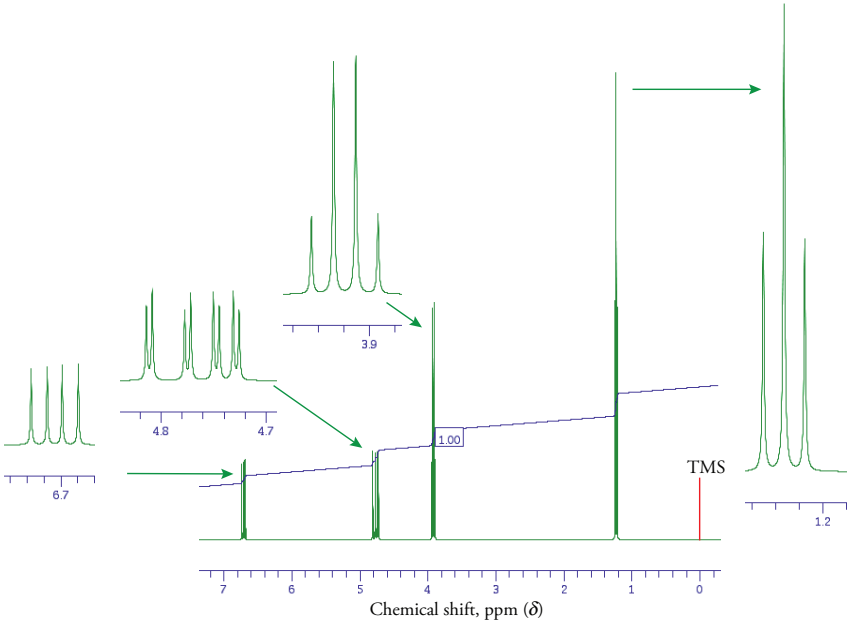
The α-carbon atoms of thiols and thioethers are only slightly deshielded by the sulfur atom.

$CH_3—CH_2—CH_2—CH_2—SH$
24.6 δ

$CH_3—CH_2—O—CH_2—CH_3$
25.5 δ

Problem 16. 23

Deduce the structure of a compound with molecular formula $C_4H_{10}O$ having the following proton NMR spectrum.



Problem 16. 24

Deduce the structure of isomeric compounds having the molecular formula $C_4H_{10}O$ based on the following carbon NMR spectra. The multiplicities are given in parentheses.

(a) 10.0 ppm (quartet), 27.7 ppm (quartet), 37.0 ppm (triplet), 69.2 ppm (doublet)
(b) 18.9 ppm (quartet), 30.8 ppm (doublet), 69.4 ppm (triplet)
(c) 31.7 ppm (quartet), 68.9 ppm (singlet)

EXERCISES

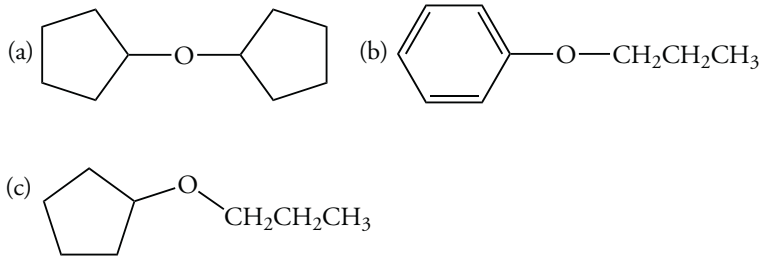
Ether Isomers

16.1 Draw the structures of the isomeric ethers with the following characteristics.
(a) molecular formula $C_4H_{10}O$
(b) a methyl ether with molecular formula $C_5H_{12}O$
(c) a saturated ether with the molecular formula C_3H_6O

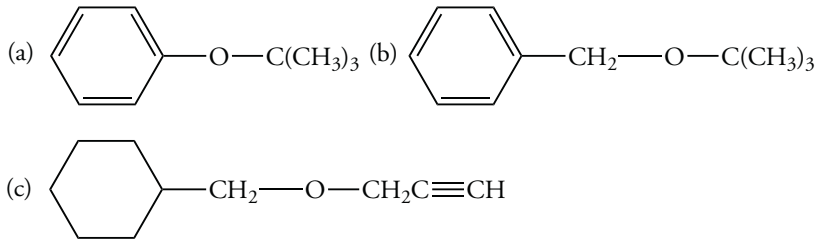
16.2 Draw the structures of the following ethers.
(a) oxane and two methyl oxolane
(b) 2-methoxypropene
(c) *cis*-2,3-dimethyloxetane

Ether Nomenclature

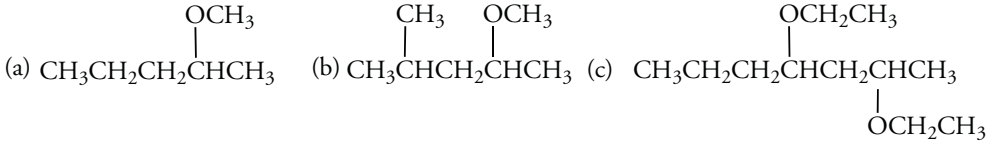
16.3 Give the common name of each of the following compounds.



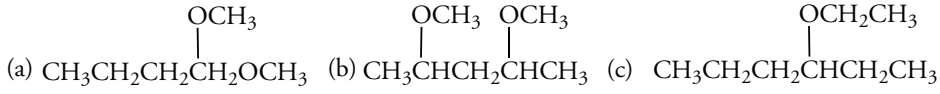
16.4 Give the common name of each of the following compounds.



16.5 Assign the IUPAC name of each of the following compounds.



16.6 Assign the IUPAC name of each of the following compounds.



16.7 Draw the structure of each of the following general anesthetics.
(a) 1,1,1,3,3,3-hexafluoroisopropyl methyl ether (isoindoklon)
(b) 2-chloro-1,1,2-trifluoro-1-(difluoromethoxy)ethane (enflurane)

16.8 What is the common name of each of the following anesthetics?
(a) $CH_2{=}CH{-}O{-}CH{=}CH_2$
(b) $CF_3CHCl{-}O{-}CHF_2$

16.9 Draw the structure of each of the following compounds.
(a) *trans*-4-methoxycyclohexanol
(b) 3-ethoxy-1,1-dimethylcyclohexane
(c) 12-crown-4

16.10 Draw the structure of each of the following compounds.
(a) 3-methoxyoxolane
(b) *trans*-2-chloro-l-methoxycyclobutane
(c) *cis*-2-ethoxy-3-methyloxirane
(d) 15-crown-5

Properties of Ethers

16.11 Explain why 1,4-dioxane is more soluble in water (it is miscible) than diethyl ether.

16.12 Explain why *p*-ethylphenol is more soluble in water than ethoxybenzene.

16.13 The boiling points of dipropyl ether and diisopropyl ether are 91 and 68 °C, respectively. Explain why the boiling points of these isomeric ethers differ.

16.14 The boiling points of 1-ethoxypropane and 1,2-dimethoxyethane are 64 and 83 °C, respectively. Explain why.

16.15 Explain why dipropyl ether is soluble in concentrated sulfuric acid, whereas heptane is insoluble.

16.16 Explain why aluminum trichloride dissolves in tetrahydropyran, releasing heat.

16.17 Explain why some potassium compounds dissolve in 18-crown-6, but the related rubidium compounds do not.

16.18 Some sodium compounds dissolve in 15-crown-5. Would the related lithium compounds be more or less likely to be soluble in 18-crown-6 or 12-crown-4?

16.19 Draw the stable conformation of 1,4-dioxane.

16.20 Explain why the most stable chair conformation of 1,3-dioxan-5-ol has an axial hydroxyl group, but the most stable chair conformation of 5-methoxy-1,3-dioxane has an equatorial methoxy group.

Synthesis of Ethers

16.21 Write a mechanism for the formation of 1,4-dioxane from ethylene glycol catalyzed by sulfuric acid.

16.22 Write a mechanism for the formation of 2,2-dimethyloxolane from 4-methyl-1,4-pentanediol and sulfuric acid. Which of the two oxygen atoms remains in the ether?

16.23 Reaction of 1-hexene with mercuric acetate in methanol as solvent followed by reduction of the intermediate product with sodium borohydride yields 2-methoxyhexane. What is the structure of the intermediate product? How is it formed?

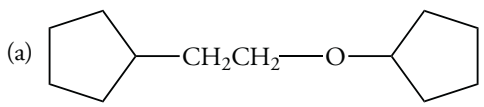
16.24 Reaction of 4-penten-l-ol with mercuric acetate followed by reduction with sodium borohydride yields 2-methyl-oxolane. Write the structure of the intermediate and explain the formation of this ether.

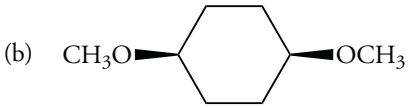
16.25 Reaction of 5-chloro-2-pentanol with sodium hydride yields 2-methyloxolane. Write the structure of the intermediate and explain the formation of this ether.

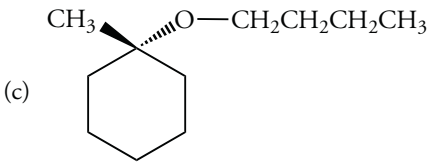
16.26 Treatment of 3,4-dibromo-l-butanol with sodium hydroxide yields a cyclic ether. What is the structure of the ether? What alternate ether could form and why doesn't it?

16.27 Which of the following compounds can be synthesized in good yield using the Williamson method? Explain why the method would fail for the remaining compounds.
(a) ethyl cyclopentyl ether (b) 1-methyl-l-methoxycyclohexane (c) *tert*-butyl cyclohexyl ether
(d) di-*sec*-butyl ether (e) 2-methyl-3-phenoxyhexane

16.28 Determine the best choice of reactants to synthesize each of the following ethers using the Williamson method.







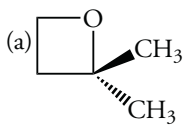
16.29 (*R*)-2-Octanol reacts with sodium hydride followed by treatment with iodoethane to give 2-ethoxyoctane. Based on the mechanism of this reaction, what is the configuration of the product?

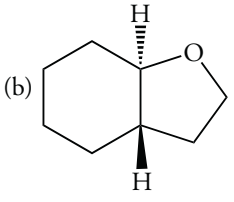
16.30 (*R*)-2-Octanol with *p*-toluenesulfonyl chloride to give a tosylate. Subsequent reaction of the tosylate in ethanol gives 2-ethoxyoctane. Based on the mechanism of these reactions, what is the configuration of the tosylate.

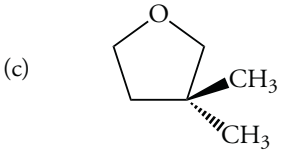
16.31 The following compound reacts with sodium hydroxide to produce 1,4-dioxane. Write the sequence of reactions leading to this product.

$$Cl—CH_2CH_2—O—CH_2CH_2—Cl$$

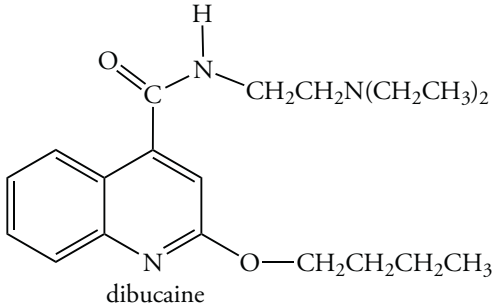
16.32 Determine the best choice of reactants to synthesize each of the following ethers using the Williamson method.





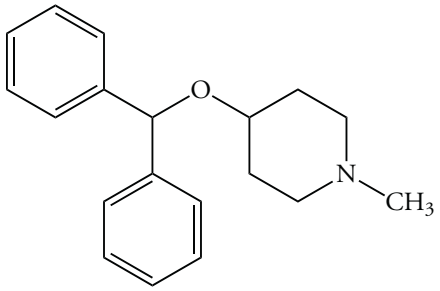


16.33 Determine the best choice of reactants to synthesize each of the following ethers using the Williamson method.



dibucaine

16.34 What reactants might he used to produce the antihistamine diphenylpyraline using the Williamson synthesis? What difficulties might he encountered?



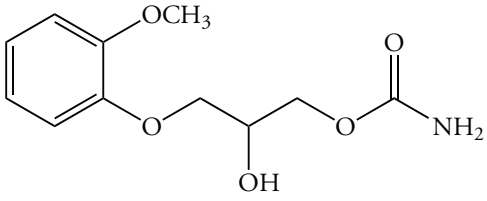
diphenylpyraline

16.51 Write the product of reaction of cyclopentene oxide with aqueous base.

16.52 The reaction of methyllithium with an epoxide followed by neutralization gives an alcohol. Write the product of the reaction of cyclohexene oxide with methyl lithium, showing the structure in its most stable conformation.

16.53 Write the structure of the amino alcohol formed in the reaction of (2*S*,3*R*)-2,3-dimethyloxirane with aqueous ammonia. Explain why this compound forms in preference to a diol. Assign the stereochemistry of each chiral center in the product.

16.54 Epoxide rings can be cleaved by phenoxides. Propose a synthesis of the muscle relaxant methocarbamol using this fact.



methocarbamol

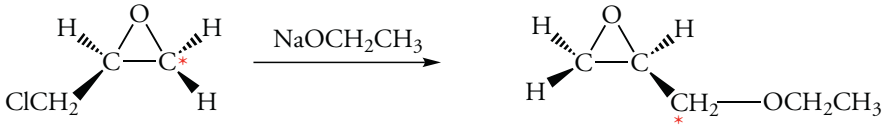
16.55 A mixture of 2,2-dimethyloxirane and ethanethiol is treated with sodium hydroxide. Write the structure of the expected product.

16.56 Epoxide rings can he cleaved by metal hydrides, which serve as a source of hydride ion. Write the product of the reaction of l-methylcyclohexene oxide and $LiAlD_4$.

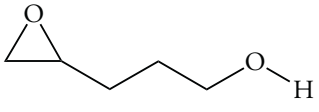
16.57 The reaction of (2*S*,3*R*)-2,3-dimethyloxirane with aqueous acid gives a mixture of enantiomers. Explain why a mixture is obtained. What are the configurations of all stereogenic centers of both isomers?

16.58 The reaction of (2*R*,3*R*)-2,3-dimethyloxirane with aqueous acid gives a single optically inactive product. Explain the origin of this product. What are the configurations of all stereogenic centers of the product?

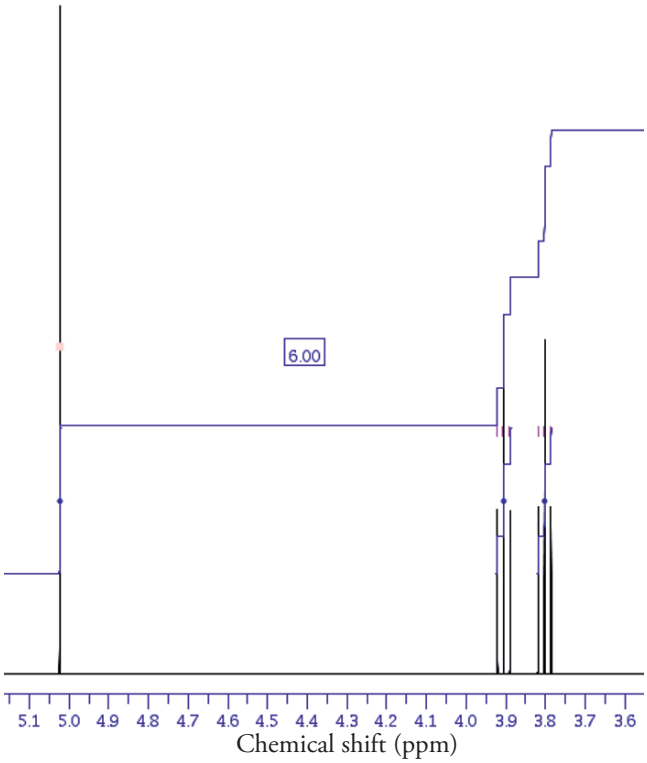
16.59 Sodium ethoxide in ethanol reacts with 1-(chloromethyl)oxirane containing a ^{14}C label at the position shown by the asterisk. Write a two-step mechanism that explains why the label is at the indicated position in the product.



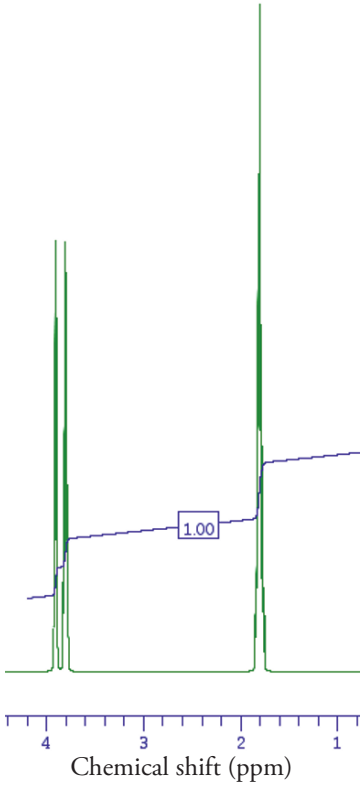
16.60 The following compound isomerizes in aqueous NaOH to give a tetrahydropyran. What is the structure of the product? Write a mechanism for its formation.



16.61 Deduce the structure of a compound with the molecular formula $C_4H_6Cl_2O$ based on the following proton NMR spectrum.

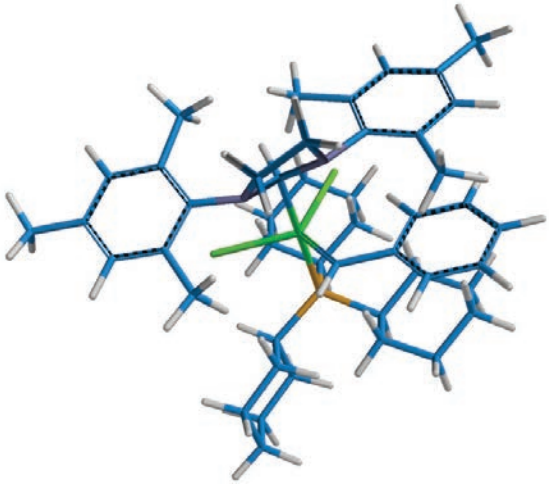


16.62 Deduce the structure of a compound with the molecular formula C_4H_8O based on the following proton NMR spectrum plus the information that the ^{13}C NMR spectrum has two peaks whose chemical shifts are 30 and 45 ppm.



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17 Organometallic Chemistry of Transition Metal Elements And Introduction to Retrosynthesis



In this chapter, we introduce the chemistry of organic compounds that contain transition metals elements. The chemistry of organometallic compounds lies at the interface of inorganic chemistry and organic chemistry. As a prelude to this discussion, we will briefly introduce some basic principles and nomenclature. Then, we will be able to describe the tremendous versatility of organometallic compounds of transition metal elements in organic synthesis. We will focus upon a small number of organometallic reactions and emphasize the basic principles that reach far beyond these reactions.

In the last part of this chapter, we will discuss an approach to the synthesis of complex organic compounds known as retrosynthesis. This is a method of "thinking backwards" in which we dissect the compound we wish to synthesize into smaller pieces that will provide the building blocks for the synthetic procedure.

17.1 BRIEF OVERVIEW OF TRANSITION METAL COMPLEXES

Transition Metal Complexes

Many compounds bind to transition metals. These compounds—which can be negatively charged ions such as hydride or a halide, or a neutral compound such as ammonia—are called **ligands** (Latin, *ligare*, to tie). A **coordination complex** consists of a metal atom or ion that is covalently bonded to one or more ligands. In the formation of a coordination complex, the metal ion acts as a Lewis acid and the ligands act as Lewis bases. A coordination complex in solution is in equilibrium with its component metal atom (or ion) and its ligands.

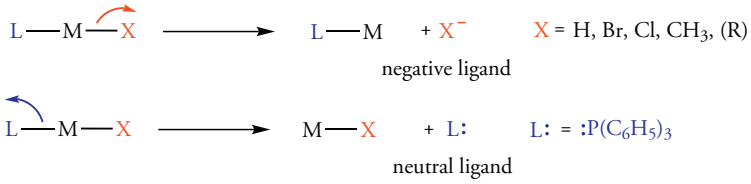
The number of ligands that form coordinate covalent bonds in a transition metal complex is called the **coordination number** of the complex. The most common coordination numbers are 2, 4, and 6. The metal atom (or ion) and its bonded ligands constitute the **coordination sphere** of the complex.

The ligands in a coordination complex donate an electron pair to the metal. A covalent bond in which one of the bonding groups contributes both bonding electrons to the metal is called a **coordinate covalent bond**. Of course, all electrons are identical, and once a coordinate covalent bond has formed, it is equivalent to any other covalent bond. If the ligand is a hydride or halide ion, for example, it donates a pair of electrons to the metal. In these cases, the ligand has a formal charge of –1. The metal-ligand bond is a σ bond. We will represent these bonds in the usual way in Lewis structures with a "stick" (—). If a metal is bound to an alkyl group such as CH_3—, the formal charge on the carbon atom is also –1.

When a transition metal becomes covalently bonded to ligands, its charge is delocalized across its ligands. For that reason, we do not refer to the central metal ion in a complex as having a "charge"; instead, we refer to it as being in a certain *oxidation state*.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00017-6
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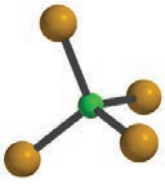
We noted earlier that a ligand can be a neutral molecule. A common ligand in organometallic chemistry is triphenylphosphine, $:P(C_6H_5)_3$. It forms a coordinate covalent bond with a transition metal in a Lewis acid–base reaction. To decide whether a ligand is neutral or negative, we can imagine breaking the metal–ligand bond in either of two ways, shown below.



Geometry of Transition Metal Complexes

A ligand forms a coordinate covalent bond to a metal by contributing an electron pair to a vacant hybrid orbital of the metal. We recall that VSEPR theory tells us the relation between molecular geometry and orbital hybridization. This is how we proceeded when we described carbon atoms as sp, sp^2, or sp^3 hybridized. Thus, if a transition metal in a coordination complex has a coordination number of 2, and if the complex is linear, the central atom is sp hybridized. For example, $Ag[NH_3]_2^+$, whose coordination number is 2, has vacant s and p orbitals available for bonding. The silver atom is sp hybridized. Its oxidation state is +1.

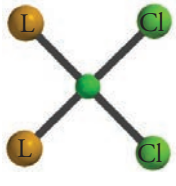
Coordination complexes of palladium are catalysts in many of the reactions we will discuss in this chapter. Palladium metal, Pd(0), has a $[Kr]4d^{10}$ electron configuration. Thus, the 4d energy level is full and the 5s and 5p orbitals of Pd(0) are vacant. Coordination complexes of Pd(0) that have four ligands have tetrahedral geometry in which the ligands are linked by sp^3 hybrid orbitals.



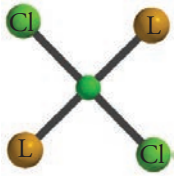
Pd(0) bound to four ligands. The geometry of the complex is tetrahedral, and the metal atom is sp^3 hybridized.

Pd(II) has a $[Kr]4d^8$ electron configuration. It has square planar geometry in which Pd(II) is dsp^2 hybridized. This configuration places the electron pairs in the coordinate covalent bonds, and therefore the ligands, as far apart as possible. For example, a $Pd(L_2)Cl_2$ is a square planar complex.

Square planar complexes of $Pd(II)L_2Cl_2$, Pd(II) is dsp^2 hybridized.

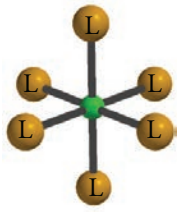


$Pd(II)L_2Cl_2$
cis isomer



$Pd(II)L_2Cl_2$
trans isomer

Some coordination complexes of palladium and other metals have six ligands. Although more than one type of geometry is possible, the most common geometry is a complex in which the metal sits at the corners of an octahedron. This geometry minimizes steric repulsion. The bonding in an octahedral complex is d^2sp^3.

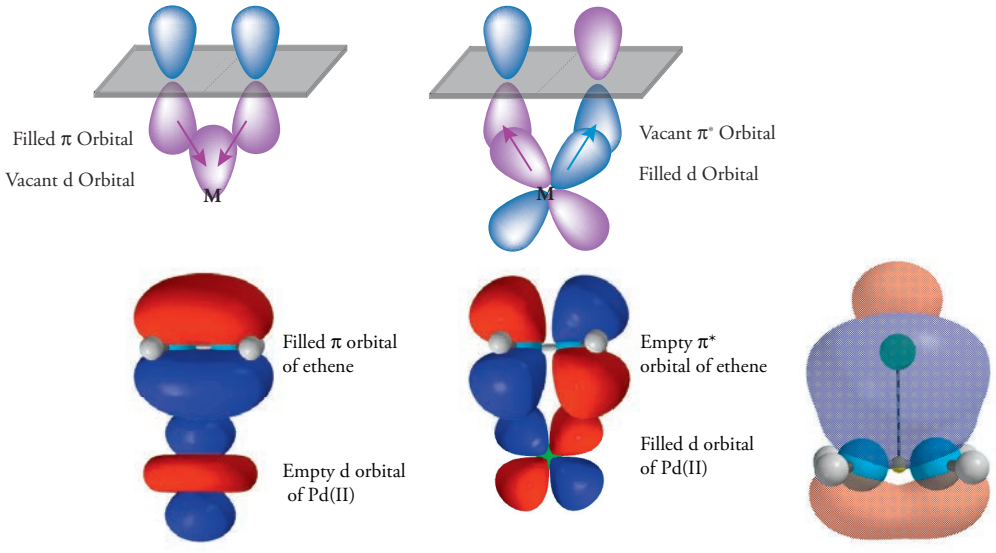


Octahedral PdL_6 complex
Pd is d^2sp^3 hybridized.

Formation of π Complexes

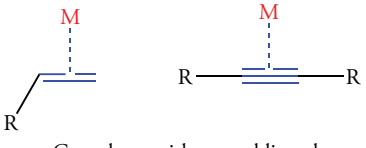
Alkenyl, alkynyl, and aryl groups can form π complexes to transition metals. The π electrons in these ligands interact with the metal by overlap of the π electrons of the unsaturated group with a vacant d orbital of the transition metal. Consider the interaction of an alkene with Pd(II). We have seen that Pd(II) has a $[Kr]4d^8$ electron configuration. The π bond of an alkene donates electrons to the metal by overlap of its filled π orbital with a vacant 4d orbital on Pd(II). *At the same time*, a filled 3d orbital donates electrons to the vacant π*, antibonding orbital of the alkene. The result of this interaction is a *π complex* (Figure 17.1).

Figure 17.1 Schematic View of Bonding In a π Complex of an Alkene With a Transition Metal



(a) (b) (c) Net result of the orbital interactions in (a) and (b)

We will draw the Lewis structure of a π complex as a dashed line between the metal and an alkene or alkyne, as shown below.



π Complexes with neutral ligands.
The transition metal has a vacant d orbtal,
the π bond is the electron donor.

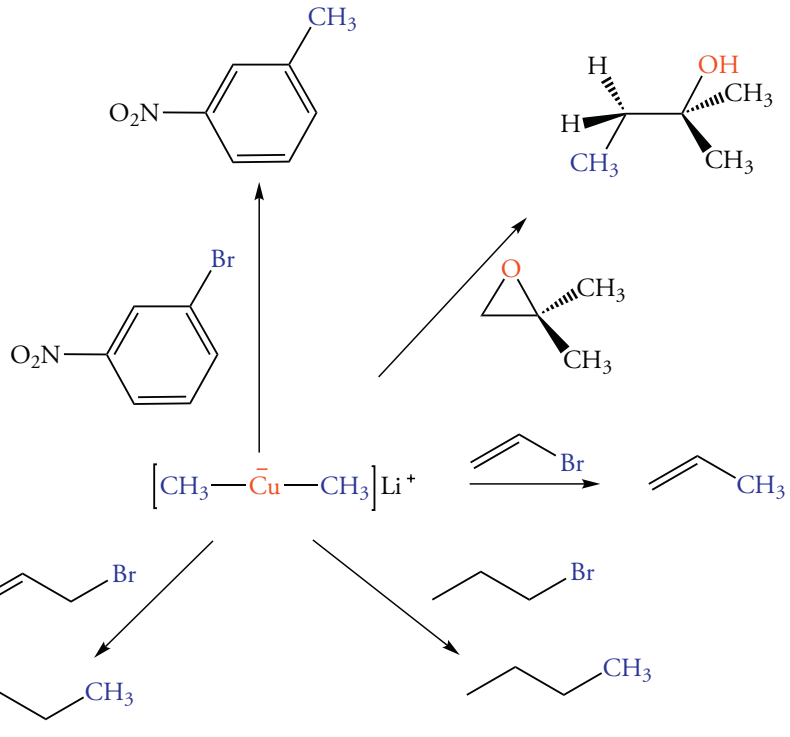
With this brief introduction in place, we will begin our discussion of the organometallic chemistry of transition metal elements.

17.2 THE GILMAN REAGENT

Overview of Gilman Reagents

A **Gilman reagent** (also known as the Corey–House reagent) is an organometallic compound that contains both copper and lithium. It has the general formula R_2CuLi, where the R group is derived from an alkyl halide. Gilman reagents undergo a wide variety of substitution reactions in which the R group of the reagent acts as a nucleophile that replaces a halogen in an alkyl, alkenyl, or aryl halide (Figure 17.2). The reaction of a Gilman reagent with an alkyl halide, an alkenyl halide, or an aryl halide to give a new carbon–carbon bond is called **cross-coupling**.

Figure 17.2 Coupling Reactions of the Gilman Reagent



Preparation of Gilman Reagents

The preparation of a Gilman reagent from an alkyl halide is a two-step process. First, lithium reacts with haloalkanes to give organolithium reagents (Section 9.8). For example, methyl bromide reacts with lithium to give methyl lithium.

$$CH_3—Br + 2\,Li \longrightarrow CH_3—Li + LiBr$$

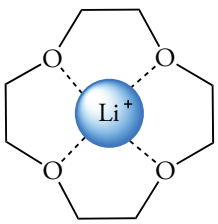
methyl lithium

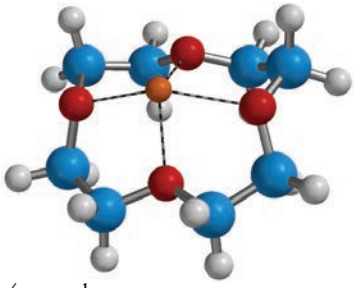
In the second step, the alkyllithium compound reacts with copper(I) iodide in an ether solvent to give a lithium dialkylcuprate. This is a **Gilman reagent**. For example, methyllithium reacts with CuI to give lithium dimethylcuprate. Dimethylcuprate is a linear complex that has a net charge of –1. Cu(I) has a $[Kr]3d^{10}$ electron configuration. The Gilman reagent is a "soft" nucleophile because the negative charge is delocalized over both carbon atoms and the electrons in the filled 3d orbital of large copper ion are highly polarizable. In contrast, methyl lithium is a "hard" nucleophile because the negative charge is highly concentrated on carbon.

$$2\,CH_3—Li + CuI \longrightarrow [CH_3—\bar{C}u—CH_3]\,Li^+ + LiI$$

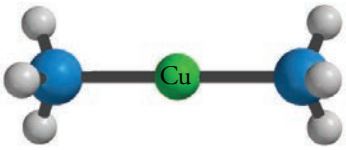
alkyl lithium — lithium dimethylcuprate (a Gilman reagent)

In Section 16.3, we saw that cyclic ethers called crown ethers form complexes with cations. The crown ether called 12-crown-4 specifically binds lithium. The name 12-crown-4 tells us three things: first, the compound is a cyclic ether; second, the ether contains 12 atoms; third, that there are four oxygen atoms in the ring that are linked by ethylene bridges. In the presence 12-crown-4, dimethylcuprate exists as a linear complex. However, the lithium ion is important because the reaction does not occur if lithium is sequestered by the crown ether.





Lithium 12-crown-4 complex



dimethylcuprate

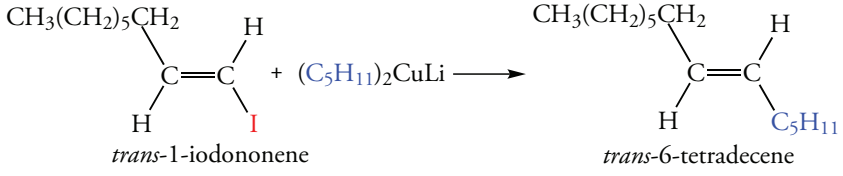
Reactions of Gilman Reagents

Gilman reagents react with haloalkanes to form a new carbon–carbon bond between two alkyl groups. In this reaction, one of the alkyl groups of the Gilman reagent replaces a halogen from a haloalkane to give a "coupled" product.

$$\left[(CH_3)_2Cu^-\right]Li^+ + CH_3(CH_2)_6CH_2I \longrightarrow CH_3(CH_2)_6CH_3$$

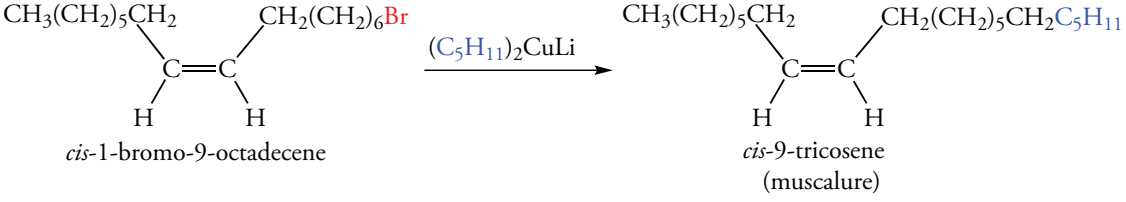
1-iodooctane — nonane

A Gilman reagent couples with alkyl halides, alkenyl halides (vinyl halides), and aryl halides.



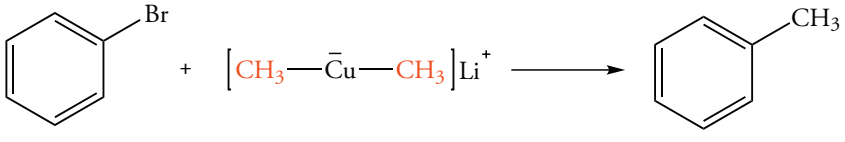
trans-1-iodononene — *trans*-6-tetradecene

The Gilman reagent has been used in the industrial synthesis of muscalure, the sex attractant of the common house-fly. Muscalure is added to fly bait that also contains an insecticide. When the fly eats the bait, the attraction is fatal.

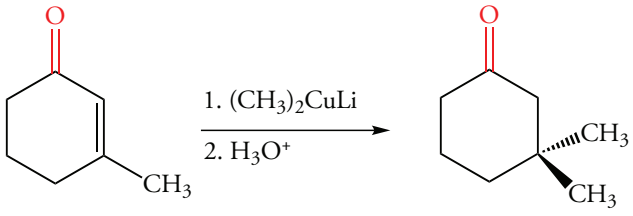


cis-1-bromo-9-octadecene — *cis*-9-tricosene (muscalure)

The Gilman reagents also undergo coupling reactions with aryl halides. For example, bromobenzene reacts with lithium dimethylcuprate to give toluene.

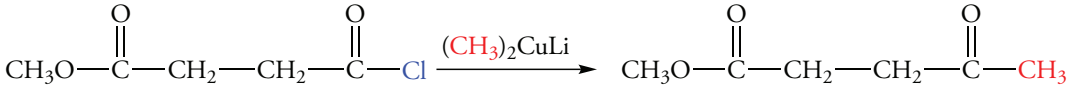


When we discuss α,β-unsaturated carbonyl compounds in Chapter 21, we will find that Gilman reagents selectively add to the β-carbon, in contrast to Grignard reagents, which add to the carbonyl group. Here is a preview:

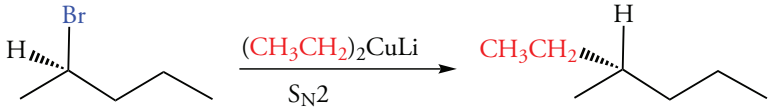


3,3-dimethylcyclohexanone

Acid chloride derivatives of carboxylic acids react with many nucleophiles. The reaction of Grignard reagents with acid chlorides is not a useful synthetic procedure because the reaction is difficult to control. However, Gilman reagents react with acid chlorides to give ketones. The Gilman reagent does not react with esters because they are less susceptible to nucleophilic acyl substitution than acid chlorides.



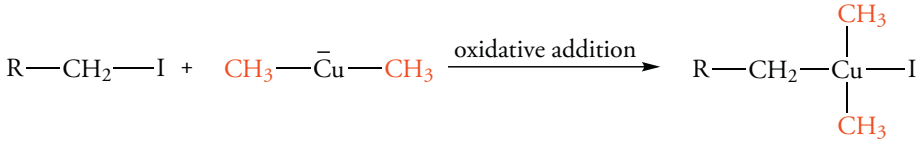
The mechanism of the Gilman reaction depends upon the structure of the cuprate, the structure of the substrate, the halide leaving group, and the solvent. Some reactions of Gilman reagents occur by an S_N2 mechanism. For example, chiral alkyl bromides react with Gilman reagents to give products with inversion of stereochemistry. However, alkyl iodides react by a different mechanism and yield racemic products.



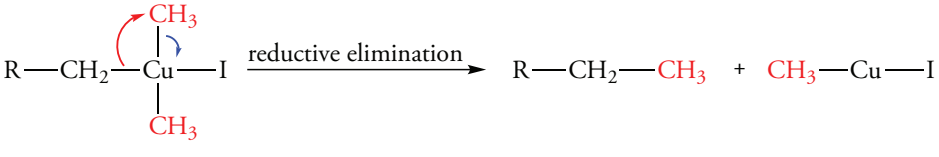
Oxidative Addition and Reductive Elimination in the Gilman Reaction

Some reactions of the Gilman reagent with an alkyl halide occur in two steps, not by an S_N2 mechanism. A two-step sequence occurs when a dialkyl cuprate reacts with an alkyl iodide.

1. *Oxidative addition*. In an oxidative addition reaction, the oxidation state of the transition metal, copper(I) in a Gilman reagent, changes to copper(III).

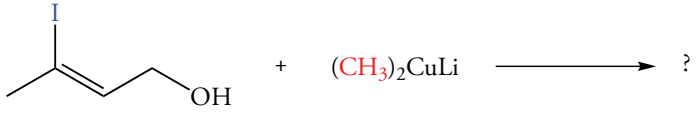


2. *Reductive elimination.* The second step of the reaction is reductive elimination. In this step, the initial adduct rearranges to give a new carbon–carbon bond.



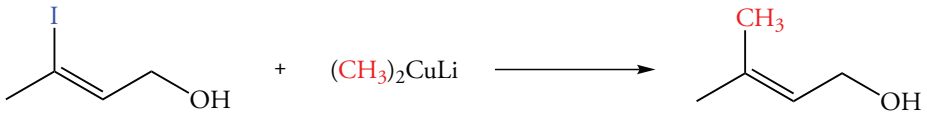
Problem 17.1

What is the product of the following reaction?



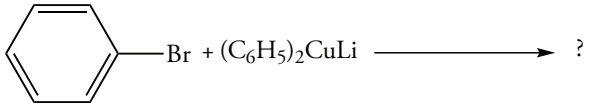
Sample Solution

The above reaction is an example of coupling reaction of a Gilman dialkylcuprate and a vinyl halide. The reaction replaces iodide with a methyl group. A Grignard reagent could not be used without first protecting the alcohol group,



Problem 17.2

What is the product of the following reaction?



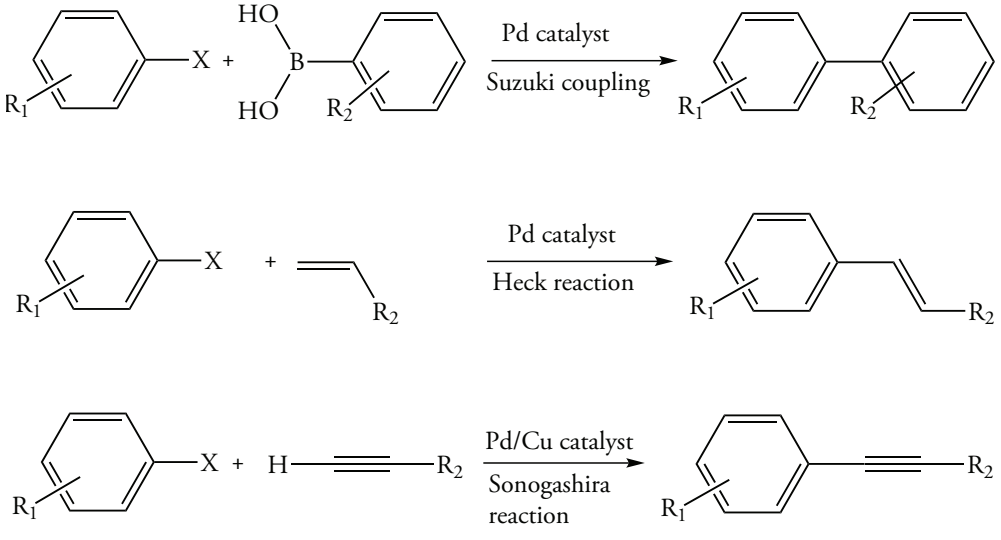
17.3 OVERVIEW OF PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

Organopalladium complexes catalyze cross-coupling reactions between aryl groups, between aryl halides and alkenes, and between aryl halides and alkynes. We will consider three reactions of this type.

1. The Suzuki reaction couples an aryl group and an alkenyl group (Section 17.4).
2. The Heck reaction couples aryl halides and alkenes (Section 17.5).
3. The Sonogashira reaction couples an aryl group and a terminal alkyne (Section 17.6).

Figure 17.3 shows the net reaction for each type of coupling. The catalytic cycle for each of these reactions has an oxidative addition step in which the substrate adds to the transition metal complex and a reductive elimination step in which the coupling reaction occurs. The reductive elimination step also regenerates the catalyst.

Figure 17.3 Cross-Coupling Reactions of Organopalladium Complexes



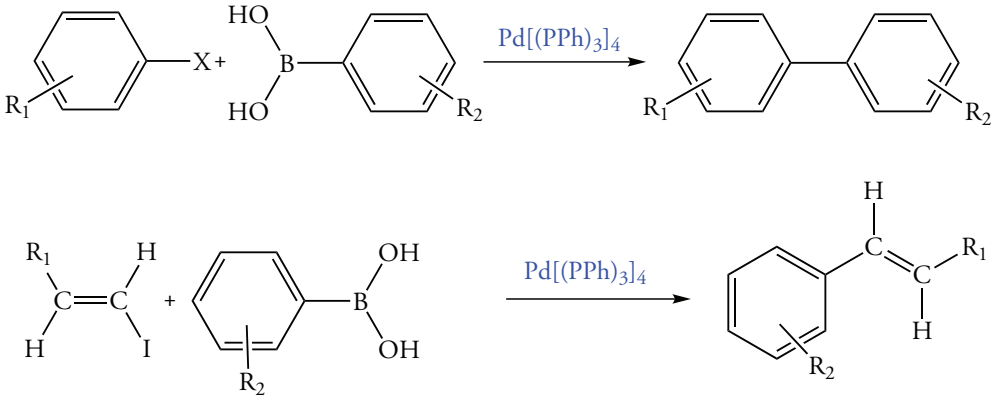
The palladium catalysts for these reactions can have many different ligands, and each variation in ligands confers new properties on the catalyst. In our discussions of these reactions, we will focus on the broad outlines of the catalytic mechanisms. These reactions are widely used both in basic research and in the chemical industry, especially in the synthesis of pharmaceuticals.

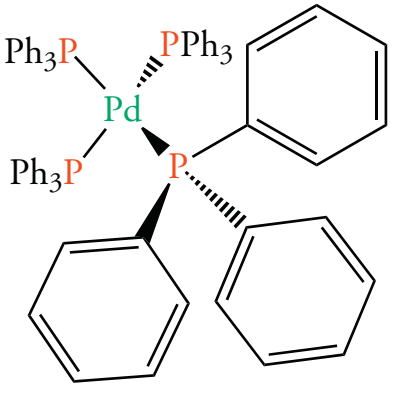
17.4 THE SUZUKI COUPLING REACTION

The Suzuki coupling reaction, also called the Suzuki–Miyaura reaction, couples an aryl, or vinyl halide to an aryl or vinyl boronic acid in which the *Suzuki catalyst*—a palladium catalyst with four triphenylphosphine ligands—plays the central bond forming role.

The Suzuki catalyst has the rather forbidding name tetrakis(triphenylphosphine)palladium(0). This looks a bit less complex when we write its condensed formula: $Pd[P(C_6H_5)_3]_4$. Since "Ph" is a common abbreviation for the phenyl group, C_6H_5, we can condense the formula even more as $Pd(PPh_3)_4$. The palladium atom sits at the center of a tetrahedron and has an oxidation number of zero (Figure 17.4). The phosphorus atom of the triphenylphosphine donates an electron pair to a vacant 4d orbital of Pd(0) without altering its oxidation state.

Suzuki coupling reactions





Suzuki catalyst
(Ph = C_6H_5)

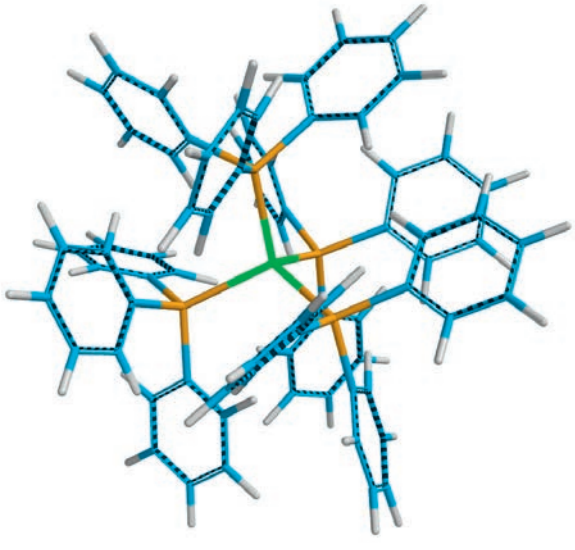
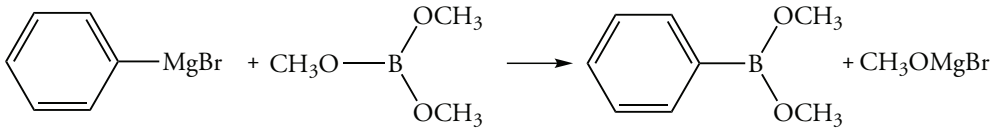


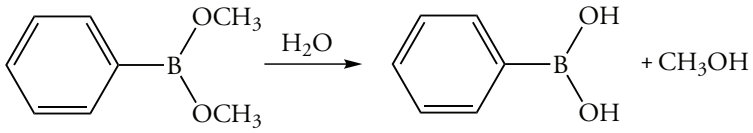
Figure 17.4 Structure of the Suzuki Catalyst
The palladium, Pd(0), atom of the catalyst is at the center of a tetrahedron. A triphenylphosphine group (PPh_3) is at each corner of the tetrahedron.

Preparation of Aryl Boronic Acids

Many methods have been developed for synthesizing alkenyl and aryl boronic acids. For example, an aryl Grignard reagent reacts with trimethoxyborane, $B(OCH_3)_3$, which is commercially available, to give a dimethoxyaryl borane, $ArB(OCH_3)_2$. Hydrolysis of the borane gives the aryl boronic acid, as shown below.



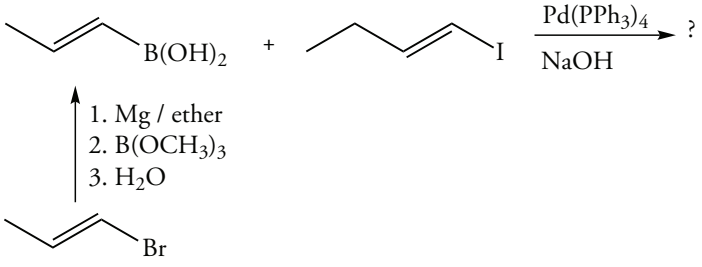
trimethoxyborane dimethoxyphenylborane



phenylboronic acid

Problem 17.3

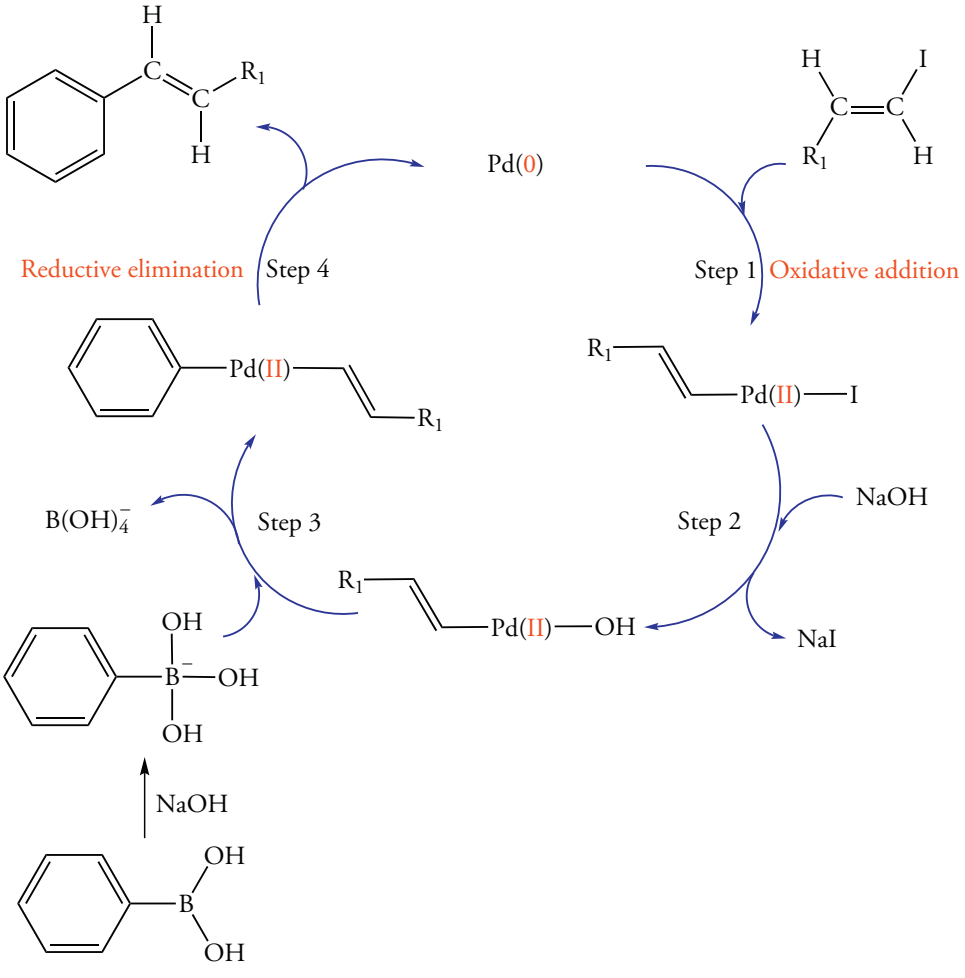
What is the product of the following reaction?



The Catalytic Cycle in the Suzuki Coupling Reaction

Since the palladium catalyst plays the crucial bond making and bond breaking reaction in the Suzuki coupling reaction, we will consider the catalytic cycle from the point of view of the catalyst (Figure 17.5).

Figure 17.5 Catalytic Cycle of the Suzuki Coupling Reaction
Step 1. The vinyl halide adds to the catalyst in an oxidative addition step.
Step 2. Hydroxide displaces iodide.
Step 3. The base that is present in the reaction medium activates the boronic acid. The aryl group of the borate anion then adds to the catalyst.
Step 4. Cross-coupling of the aryl and vinyl groups occurs in a reductive elimination step. The palladium atom of the catalyst returns to its original oxidation state, Pd(0), and the cycle continues. The ligands have been eliminated from the diagram for clarity.



17.5 THE HECK REACTION

The Heck reaction uses a palladium catalyst reaction to couple aryl halides and alkenes. The product of the reaction is a conjugated aryl alkene. The catalytic cycle, which is somewhat more complicated than the Suzuki reaction cycle, can be divided into a half dozen steps (Figure 17.6).

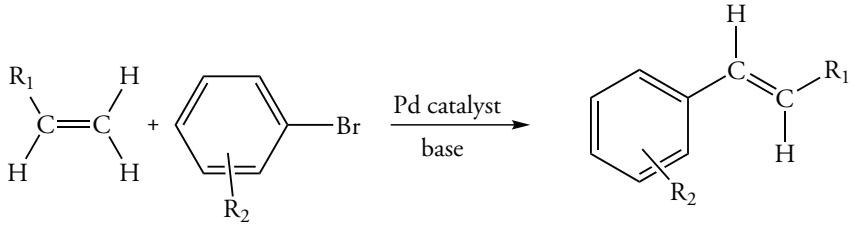
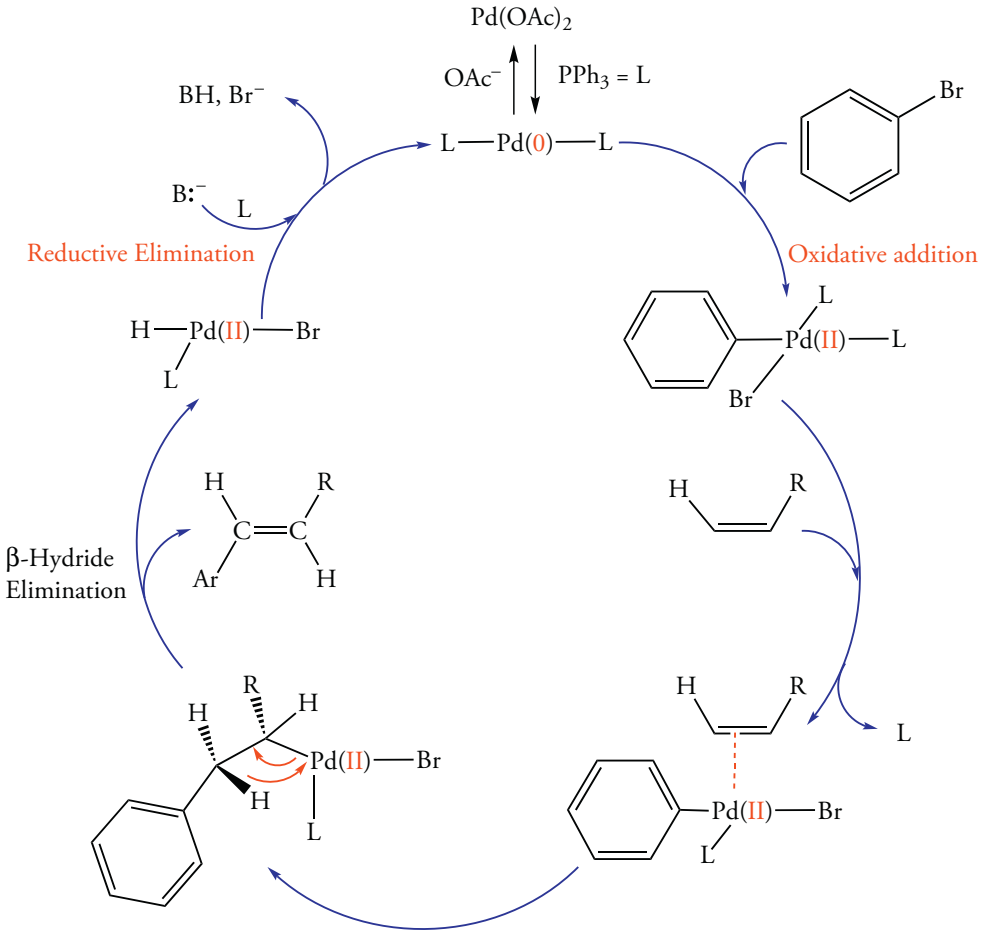
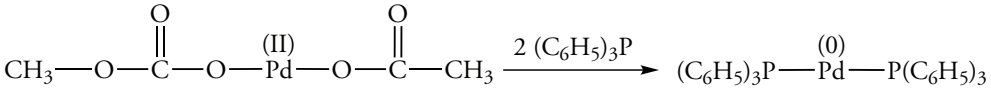


Figure 17.6 Catalytic Cycle of the Heck Reaction

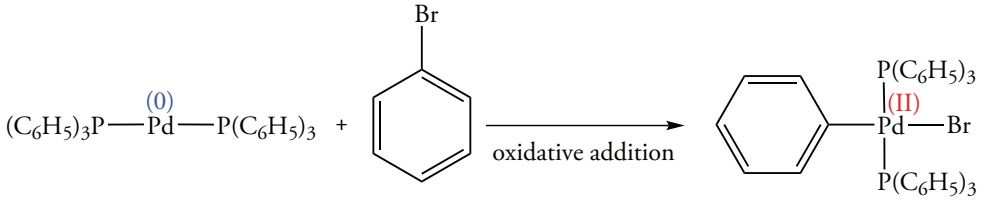


The Catalytic Steps in the Heck Reaction

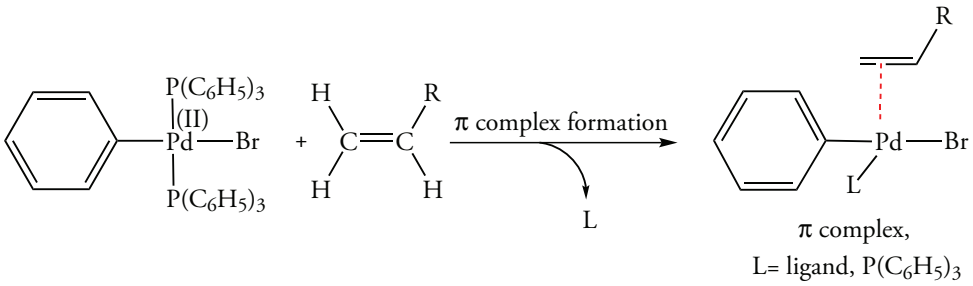
We will begin, as in the Suzuki coupling reaction, with the Pd(0) catalyst. In the Heck reaction, the catalyst forms in the reaction mixture from palladium(II) acetate in the presence of triphenylphosphine.



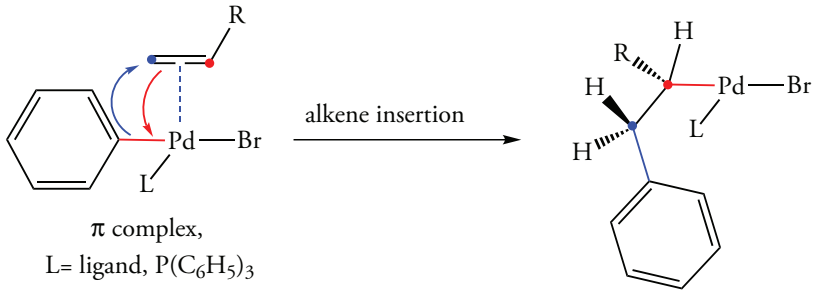
Step 1. Oxidative addition of the aryl halide, bromobenzene in this example, to the Pd(0) catalyst occurs when palladium(II) inserts into the C—Br bond of bromobenzene.



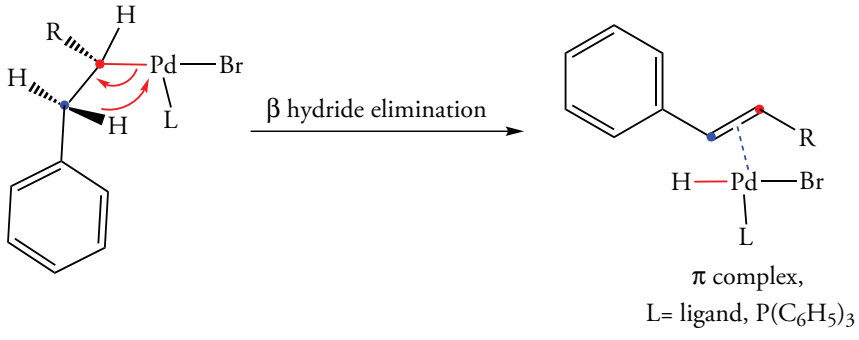
Step 2. The vinyl halide then forms a π complex with Pd(II) which has a [Kr]4d^8 electron configuration.



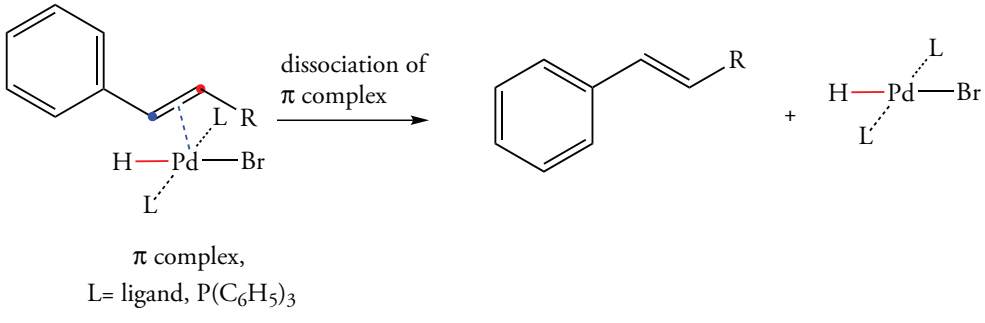
Step 3. The alkene inserts into the palladium–carbon bond. This step generates the carbon skeleton of the product, but the alkene has not formed yet.



Step 4. The product from step 3 undergoes β-*hydride elimination*. This is an *intramolecular* process. This step generates a π bond and forms a new Pd—H bond. It also simultaneously gives a new π complex of the product with the catalyst.

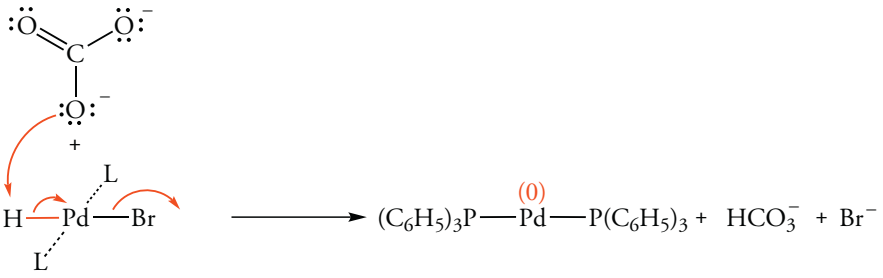


Step 5. Dissociation of the π complex releases the product.



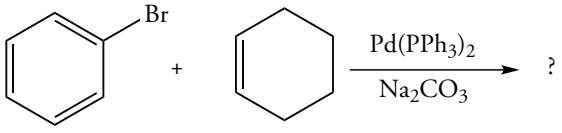
We have shown the product in this reaction as a *trans* alkene. One of the great advantages of the Heck reaction is that it is highly selective for *trans* products.

Step 6. Reductive elimination. Sodium carbonate is present in the reaction mixture in stoichiometric amounts. Carbonate reacts with the palladium–hydrogen bond, and bromide is released. At the end of step 6, the catalyst is regenerated as Pd(0), and the reaction cycle starts again. Base is required in the reductive elimination step.



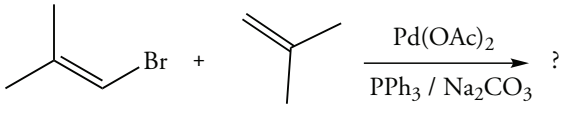
Problem 17.4

What is the product of the following reaction?



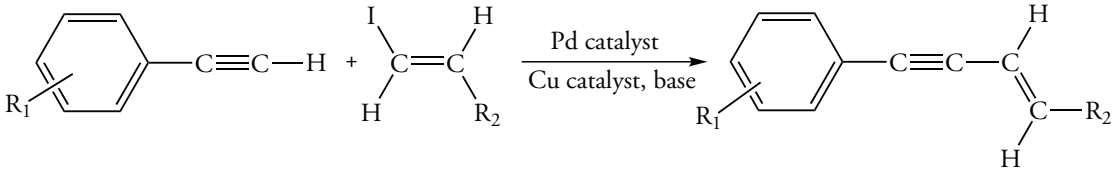
Problem 17.5

What is the product of the following reaction?



17.6 THE SONOGASHIRA REACTION

The Sonogashira reaction couples the sp-hybridized carbon of a terminal alkyne to aryl and alkenyl halides. The reaction requires a palladium catalyst and a catalytic amount of CuI. The reaction is carried out in an amine solvent.



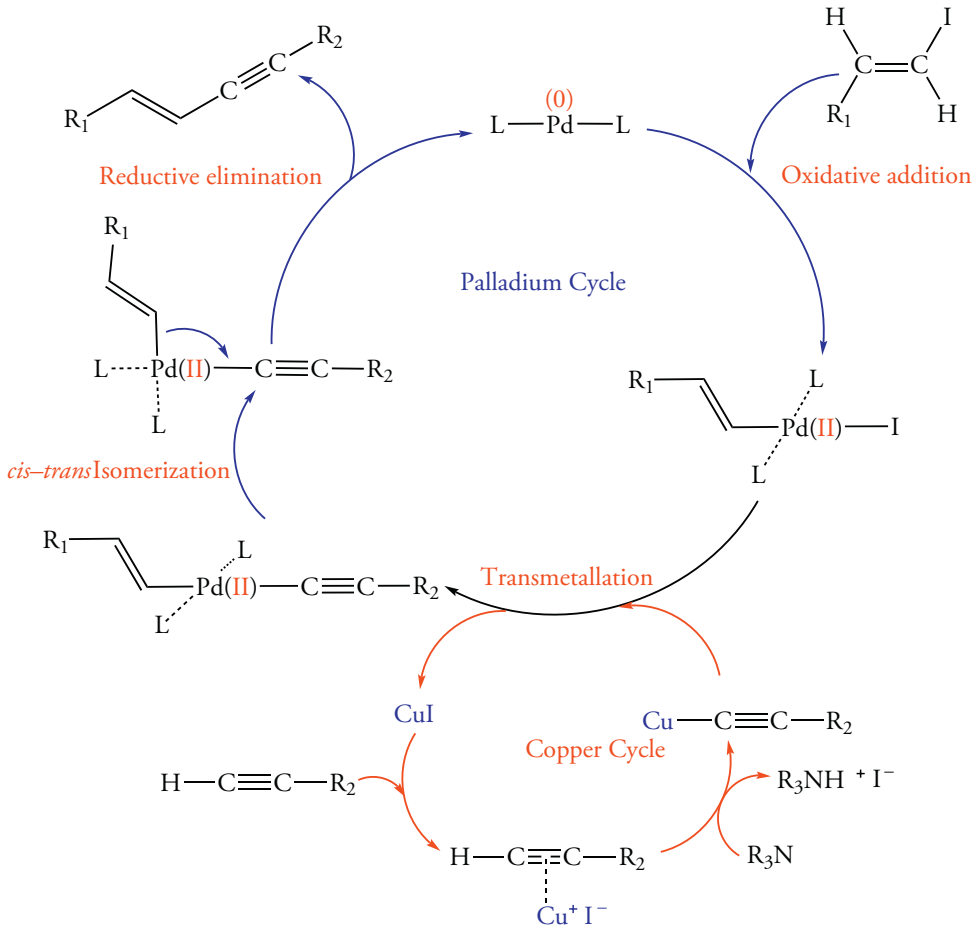
The Catalytic Cycles in the Sonogashira Reaction

Since the Sonogashira reaction has two catalysts, each catalyst has its own catalytic cycle, one for the palladium catalyst, the other for the copper catalyst (Figure 17.7).

The Palladium Cycle

1. The palladium cycle begins with a Pd(0) catalyst, which undergoes oxidative addition of the aryl or alkenyl halide that is to be coupled to the alkyne. This is the slow, rate-limiting step of the reaction.
2. In the second step, the palladium cycle and the copper cycle intersect, and a *transmetallation* reaction occurs.
3. The palladium catalyst undergoes a *cis–trans* isomerization.
4. The final step of the cycle is reductive elimination of the coupled product. The Pd(0) catalyst is regenerated in this step.

Figure 17.7 Catalytic Cycle of the Sonogashira Reaction
The Sonosaghira reaction couples aryl and alkenyl halides with terminal alkenes. A Pd(0) catalyst, a copper(I) catalyst, and an amine base, which is the solvent, are required for the reaction.

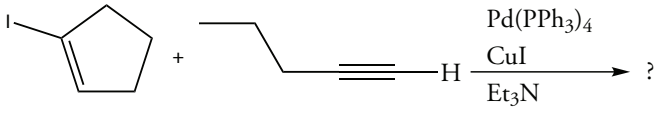


The Copper Cycle

1. The copper cycle begins with the formation of a π complex between Cu(I) and a terminal alkyne.
2. The π complex then reacts with the amine to give a copper(I)–alkyne adduct.
3. The copper(I)-alkyne adduct undergoes a transmetallation reaction in which the alkyne group becomes bonded in a Pd(II) complex. The alkyne group is initially *trans* to the species to which it will be coupled.

The next series of steps then continues as part of the palladium cycle described above.

Problem 17.6
What is the product of the following reaction?

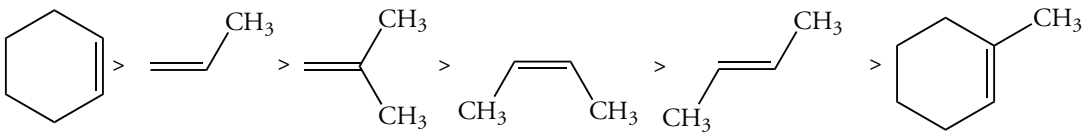


17.7 THE WILKINSON CATALYST: HOMOGENEOUS CATALYTIC HYDROGENATION

In Section 5.9, we saw that alkenes can be converted to alkanes by catalytic hydrogenation by a variety of catalysts, such as palladium and platinum. These are heterogeneous catalysts. We also noted that homogeneous catalytic hydrogenation can be carried out by Wilkinson's catalyst, $Ru[(PPh_3)_3Cl$. We now return to that subject to discuss the reaction mechanism. We will find that hydrogenation by Wilkinson's catalyst occurs in a catalytic cycle that is strikingly similar to the catalytic cycles of the reactions we have discussed thus far in this chapter. The transition metal in the Wilkinson catalyst, however, is ruthenium, not palladium.

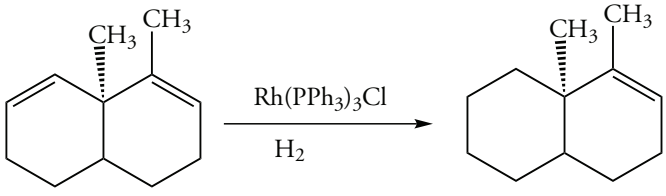
Relative Reactivities of Alkenes in Wilkinson Homogenous Hydrogenation

The Wilkinson catalyst is a complex of rhodium(I) and triphenylphosphine. It is prepared by refluxing rhodium(III) chloride with excess triphenylphosphine in ethanol. The initial product, $Rh(PPh_3)_3Cl$, loses a molecule of triphenylphosphine at the beginning of the catalytic cycle (Figure 17.8).



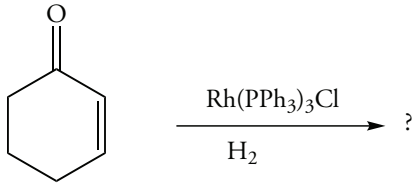
Relative rates of hydrogenation by Wilkinson's catalyst

Thus, reduction reactions with the Wilkinson catalyst are regioselective. For example, the disubstituted double bond in the compound shown below is reduced, but the trisubstituted one is not.



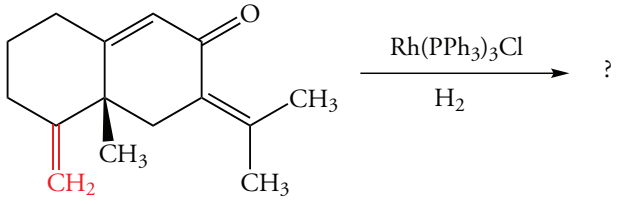
Problem 17.7

What is the product of the following reaction?



Problem 17.8

What is the product of the following reaction?



Sample Solution

There are three alkenyl groups in the above structure. The least sterically hindered one is the exocyclic methylene group. Hydrogenation occurs from the least sterically hindered "bottom face" of the ring system to give the product shown below.

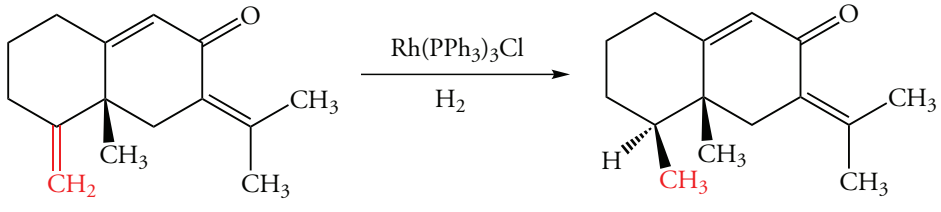
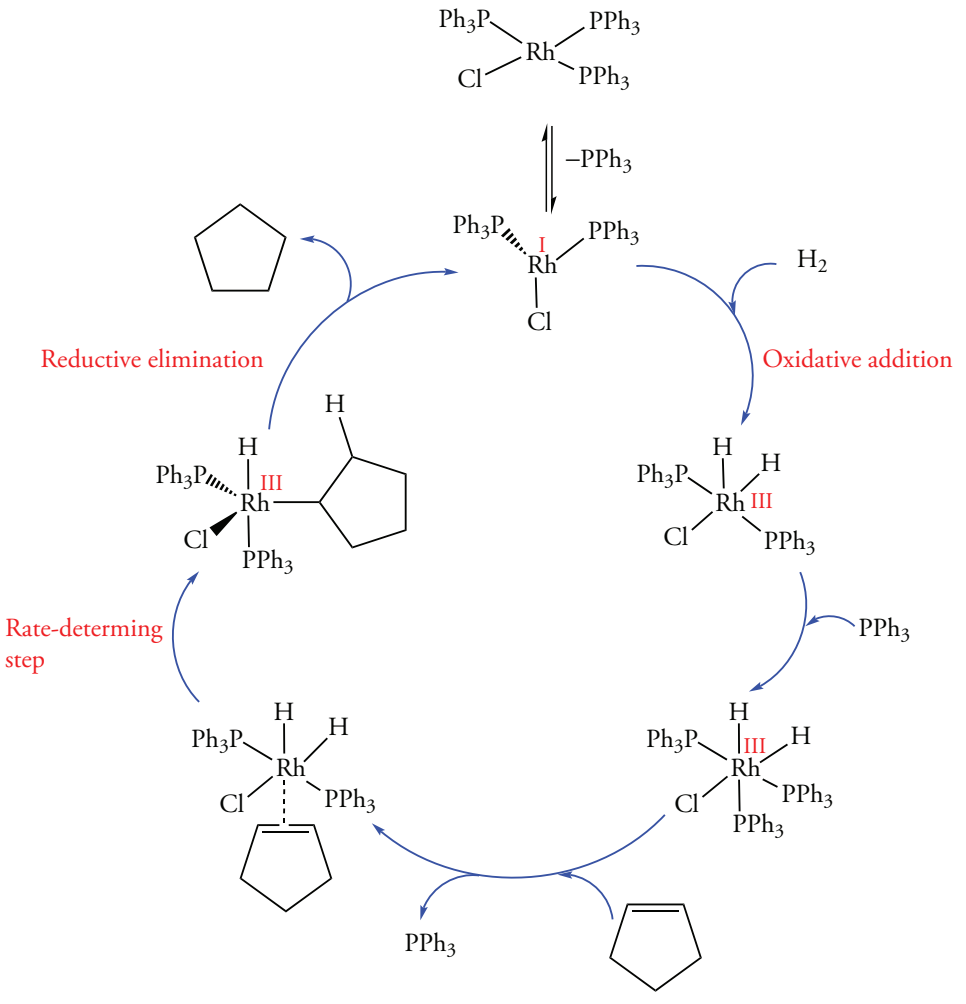


Figure 17.8 Catalytic Cycle of the Wilkinson Catalyst

Wilkinson's catalyst carries out homogenous hydrogenation of alkenes. The initial rhodium(I) complex undergoes oxidation addition of hydrogen to give a rhodium(III) species. After a ligand exchange step, the alkene forms a π complex with the catalyst. The slow, rate-determining step of the reaction is addition of the first hydrogen atom to the double bond of the substrate. Reductive elimination releases the product and regenerates the catalyst in its +1 oxidation state.



17.8 ASYMMETRIC HYDROGENATION WITH CHIRAL RUTHENIUM CATALYSTS

A major goal of synthetic organic chemistry is the synthesis of chiral products from achiral reactants. Many methods of chiral synthesis are now available. One of these builds directly upon a variation of Wilkinson's catalyst that we have just discussed.

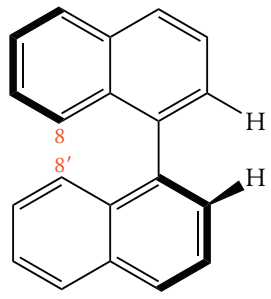
Chiral Binaphthyl Compounds

Chiral synthesis requires a chiral catalyst, and transition metal catalysts have been developed that have chiral ligands. These ligands differ markedly from the chiral substances we discussed in Chapter 8. One important class of chiral catalysts is based on derivatives of a dimer of naphthalene that are bonded from C-1 to C-1, that is 1,1′-dinaphthyl. 1,1′-dinaphthyl cannot be planar because the hydrogens at C-8 and C-8′ repel each other sterically. This steric hindrance blocks rotation around the 1′1′ carbon–carbon bond. The isomer that cannot rotate in a clockwise direction is designated *R*, its nonsuperimposable mirror image is designated *S*. It cannot rotate in a counterclockwise direction. Stereoisomers that arise from hindered rotation about single bonds are called atropisomers (Greek, *a*, not + *tropos*, turn.) These stereoisomers have either a right-handed helical or left-handed helical configuration (Figure 17.9).

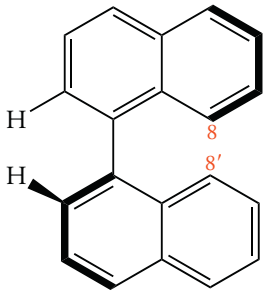
1,1′-Binaphthyl is one of many atropisomers possible for binaphthyl systems. Two important examples are the 2,2′-diol called BINOL and the 2,2′-diphenylphosphine derivative called BINAP. When chiral ligands are used, chiral synthesis becomes possible. That is, an achiral reactant can be stereospecifically converted to a chiral product.

Figure 17.9 1,1′-Binaphthyl, a Chiral Ligand

Stereoisomers that result from restricted rotation around single bonds are atropisomers. (*S*)-1,1′-binaphthyl is an example of an atropisomer. The space-filling model is identical to the ball-and-stick model, but it shows the three-dimensional structure more clearly. The naphthyl groups cannot rotate around each other. Therefore, two nonsuperimposable, mirror-image isomers exist.

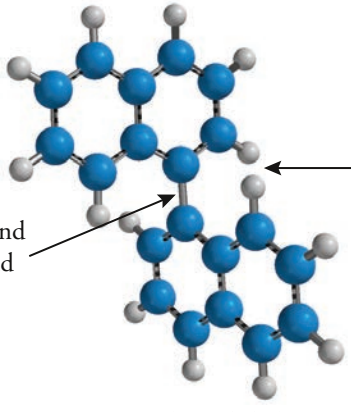


(*S*)-1,1′-binaphthyl



(*R*)-1,1′-binaphthyl

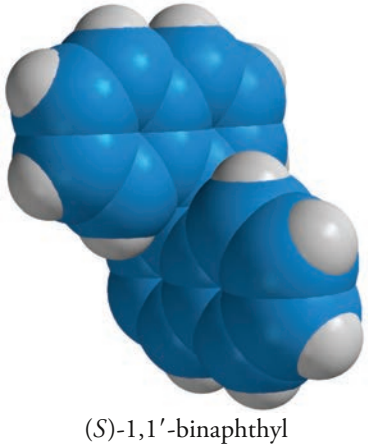
mirror plane



Steric hindrance between hydrogens at C-8 and C-8′.

Restricted rotation around 1-1′ carbon-carbon bond

(*S*)-1,1′-binaphthyl

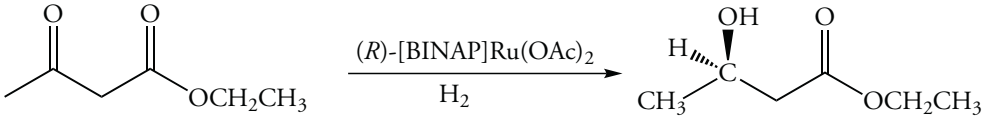


(*S*)-1,1′-binaphthyl

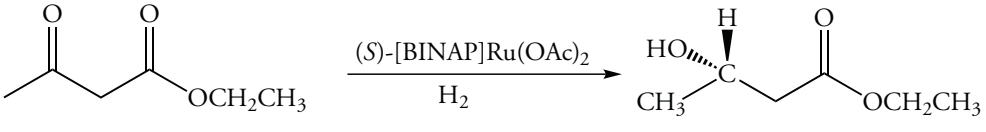
Noyori Asymmetric Reduction of Ketones

In Section 15.9, we saw that sodium borohydride and lithium aluminum hydride reduce ketones to alcohols. The reactions are regiospecific, but they are not stereospecific. However, the Noyori asymmetric hydrogenation of ketones uses chiral ruthenium catalysts for the stereospecific hydrogenation of ketones. Ryoji Noyori shared the Nobel Prize in Chemistry in 2001 with William S. Knowles for the study of asymmetric hydrogenation.

For example, the ruthenium complex with *R*-BINAP leads exclusively to the R isomer when hydrogen adds to the *si* face of the keto group. That is, hydrogen adds from the bottom face to give the *R* isomer. The ruthenium complex with *S*-BINAP leads exclusively to the *S* isomer. That is, hydrogen adds to the *re* face of the keto group to give the *S* isomer. Thus, the prochiral faces of the keto group are *diastereotopic* in the presence of the chiral catalyst (Section 8.12).

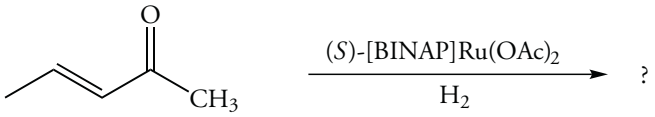


R isomer



S isomer

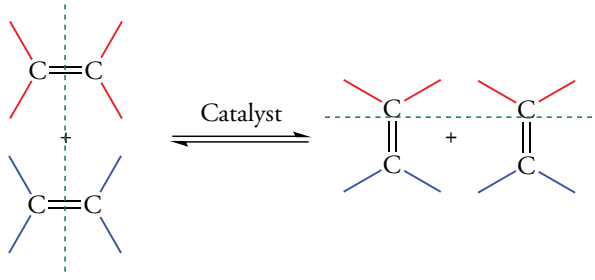
Problem 17.9
What is the product of the following reaction?



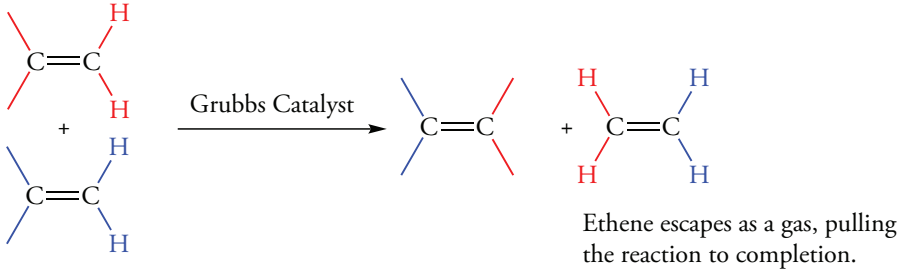
17.9 THE GRUBBS REACTION: A METATHESIS REACTION FOR ALKENE SYNTHESIS

The Grubbs Metathesis Reaction

The Grubbs reaction exchanges the groups attached to the double bond of alkenes. The two alkenes exchange partners to give two new products in which neither one is oxidized or reduced. This process is a metathesis reaction.

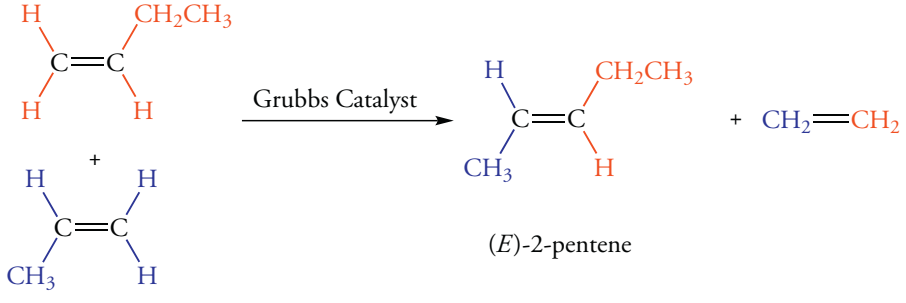


Most of the time both reactants for the Grubbs reaction are terminal alkenes. When two terminal alkenes react, they exchange methylene groups. Thus, one of the products is ethene, which escapes from the solution as a gas, converting a reversible process to one that is effectively irreversible.



Ethene escapes as a gas, pulling the reaction to completion.

For example, the reaction of 1-butene with 1-propene gives (*E*)-2-heptene and ethene.



(*E*)-2-pentene

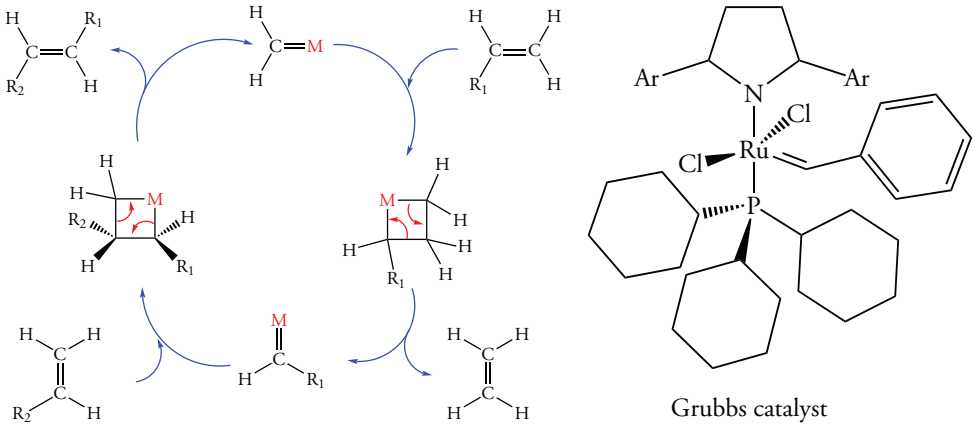
The Grubbs Catalyst

The Grubbs catalyst is an organoruthenium complex (Figure 17.10). The Grubbs reaction can be used in myriad ways with alkenes that contain many functional groups. It is one of the most important and widely used reactions in synthetic organic chemistry.

Americans Robert H. Grubbs and Richard R. Schrock and Frenchman Yves Chauvin shared the 2005 Nobel Prize in Chemistry for this reaction; a synthetic and mechanistic tour de force.

Figure 17.10 The Grubbs Catalyst

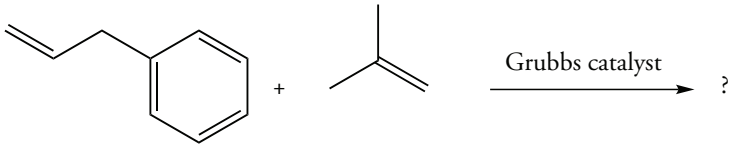
The Grubbs catalyst is an organoruthenium complex. The π bond between carbon and ruthenium is the center at which the catalytic reaction occurs.



For example, the ruthenium complex with *R*-BINAP leads exclusively to the *R* isomer when hydrogen adds to the *si* face of the keto group. That is, hydrogen adds from the bottom face to give the *R* isomer. The ruthenium complex with *S*-BINAP leads exclusively to the *S* isomer. That is, hydrogen adds to the *re* face of the keto group to give the *S* isomer. Thus, the prochiral faces of the keto group are *diastereotopic* in the presence of the chiral catalyst (Section 8.12).

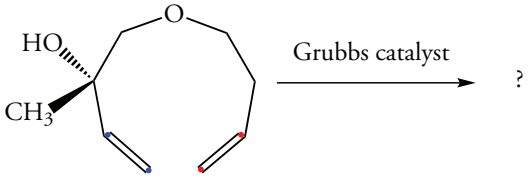
Problem 17.10

What is the product of the following reaction?



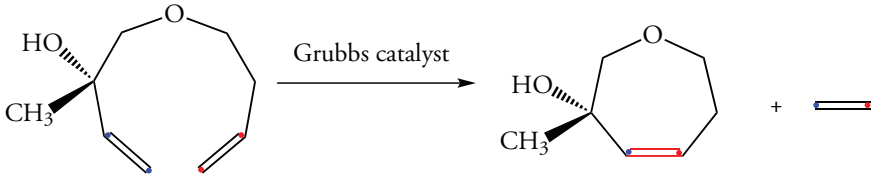
Problem 17.11

What is the product of the following reaction?



Sample Solution

The above reactant contains two terminal alkenyl groups. They can assume a conformation that brings them together in a Grubbs metathesis reaction. One of the products is a seven-membered ring; the other is ethene.



The Chauvin Mechanism for the Grubbs Reaction

Figure 17.11 shows a schematic diagram of the catalytic cycle for the Grubbs reaction. This catalytic cycle is called the **Chauvin mechanism**. Both *E* and *Z* alkenes can form in the reaction, but the major product is the more stable *E* isomer.

The reaction produces ethene, which escapes as a gas, pulling the reaction to completion. Thus, the driving force for the reaction is primarily entropic. We recall that four-membered rings are highly strained (Section 4.6), and relief of steric strain is in the four-membered rings between catalyst and substrate also helps to pull the reaction to completion.

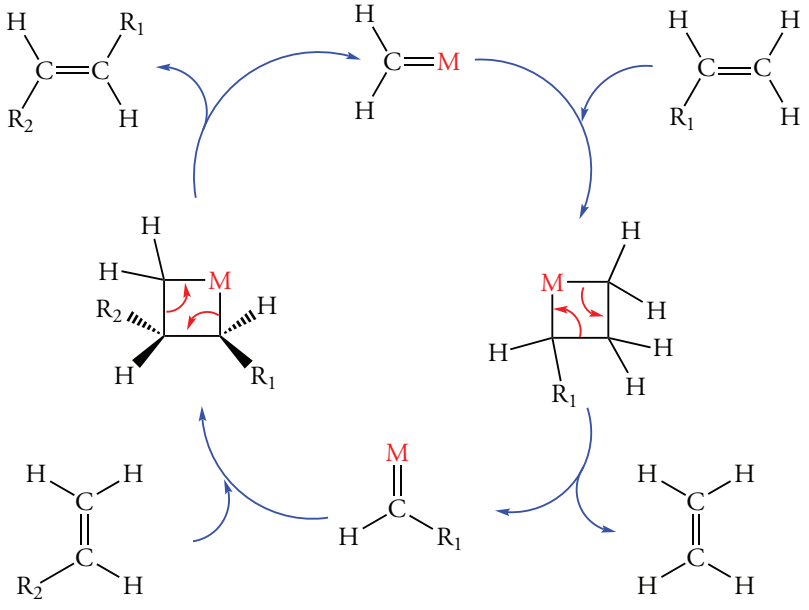
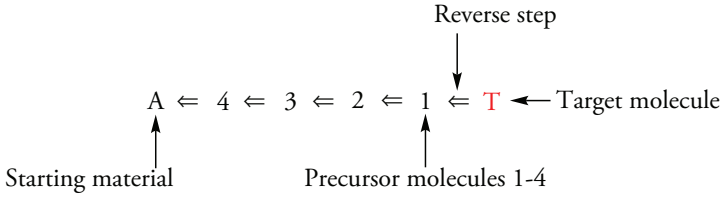


Figure 17.11 The Chauvin Grubbs Mechanism for the Grubbs Metathesis Reaction
The ligands of the Grubbs catalyst are omitted from the mechanism for clarity, and the ruthenium atom has been replaced with a generic transition metal, M. The catalytic cycle for the Grubbs reaction with two terminal alkenes generates ethene in each catalytic cycle. Ethene escapes as a gas, pulling the reaction to completion.

17.9 INTRODUCTION TO RETROSYNTHESIS: THINKING BACKWARDS

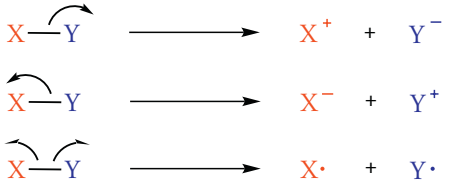
The Terminology of Retrosynthesis

The design of a series of steps leading from simple, readily available starting materials to a more complex product that contains new functional groups and carbon–carbon bonds requires careful thought. One way to imagine a complex synthetic procedure is to go backward from the desired end-product to the initial reactants. This mode of thinking backward is called **retrosynthesis**. Consider the following synthetic scheme, viewed from right to left. The molecules leading to the **target molecule**, **T**, are called **precursor molecules**. In this scheme, there are four precursor molecules. Each double arrow pointing to the left is a **reverse step**.



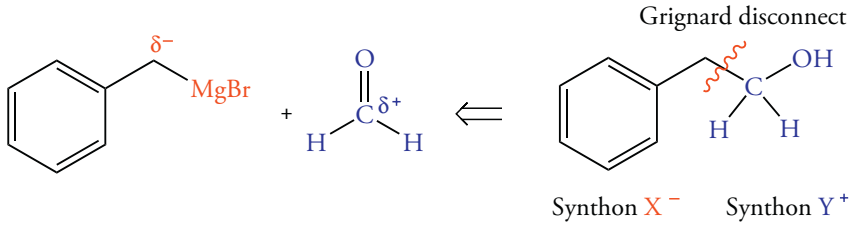
Retrosynthetic Scheme I

Each precursor molecule is also a target molecule. In terms of structural complexity, then, A < 4 < 3 < 2 < 1 < T. In each reverse step, we imagine how a bond can break to give two fragments; this is called a bond **disconnection**. Disconnection for any bond X—Y can occur in three ways, as shown below.

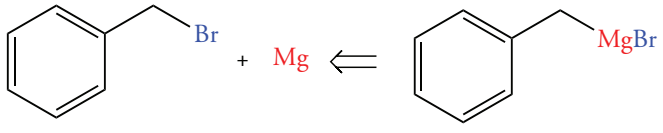


Types of Bond Disconnection

The idealized fragments of a hypothetical bond dissociation are called **synthons**. In many cases, a synthon is not a stable compound. To have synthetic value, a synthon must correspond to an actual molecule called a **synthetic equivalent** that can be used in a synthetic reaction. For example, X^- is a nucleophile and Y^+ is an electrophile. Neither X^- nor Y^+ are actual compounds; however, they imply that a nucleophile and an electrophile have the potential to react when we package them in real molecules so that they can form a bond in a target molecule. For example, we know that a Grignard reagent acts as a nucleophile, and that it adds to an electrophilic carbonyl carbon of an aldehyde to give a primary alcohol (Section 15.6). The Grignard reagent and aldehyde are thus the synthetic equivalents of the synthons X^- and Y^+.



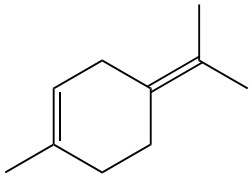
We have discussed many reactions that convert one functional group to another. In the terminology of retrosynthesis, such a reaction is called a **functional group interconversion** (**FGI**). The synthesis of a Grignard reagent from an benzyl bromide is an example.



Functional group interconversion

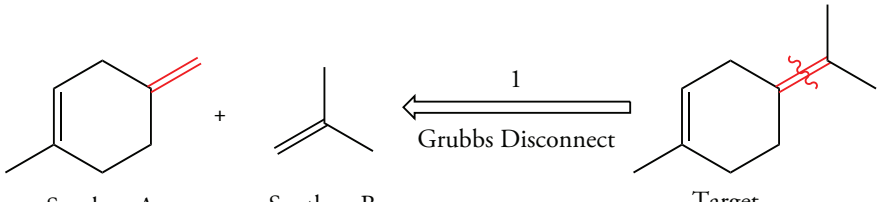
Synthesis of Terpinolene: A Retrosynthetic Analysis

Terpinolene is a food additive that has an odor of lime or citrus fruits. We would like to know how to synthesize terpinolene from readily available, inexpensive precursors, and we will approach its synthesis by a retrosynthetic analysis.

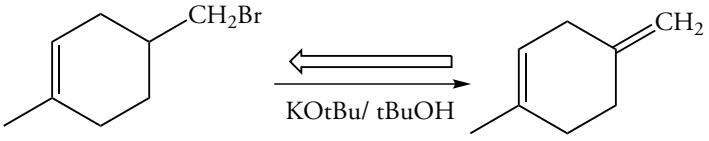


Terpinolene
(1-methyl-4-isopropylidene-cyclohexene)

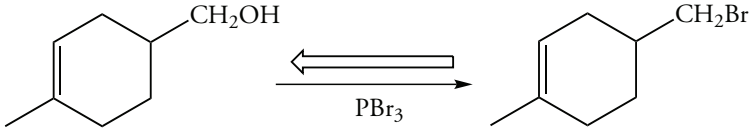
The first thing we notice is that the target molecule has an isopropylidene unit. This certainly looks like a candidate for a Grubbs disconnect.



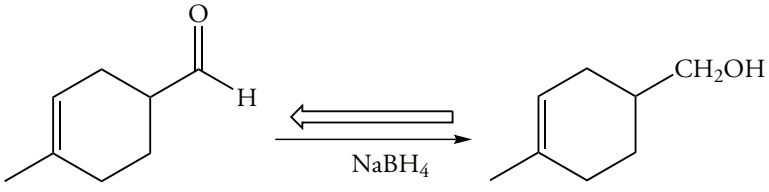
In retrosynthetic step 1, we have taken some liberty with the process by noticing that a Grubbs metathesis reaction will give us the target molecule, and it would be extremely unrealistic to propose a disconnect that gives one fragment a charge of –2 and the other a charge of +2. Synthon B is 2-methylpropene, a readily available starting material. What about Synthon A, 1-methyl-4-methylidenecyclohexene? A series of functional group transformations will be required to produce Synthon A. We know an E2 reaction converts a haloalkane to an alkene. Thus, the precursor to the methylidene group would be a primary bromide. It would react by an E2 reaction to give an alkene.



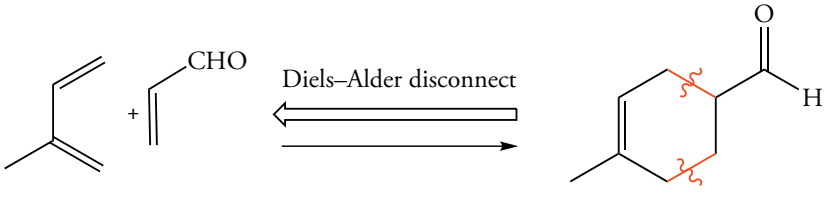
We know that we can synthesize an alkyl bromide from an alcohol with PBr_3.



We can convert an aldehyde to an alcohol with $NABH_4$.



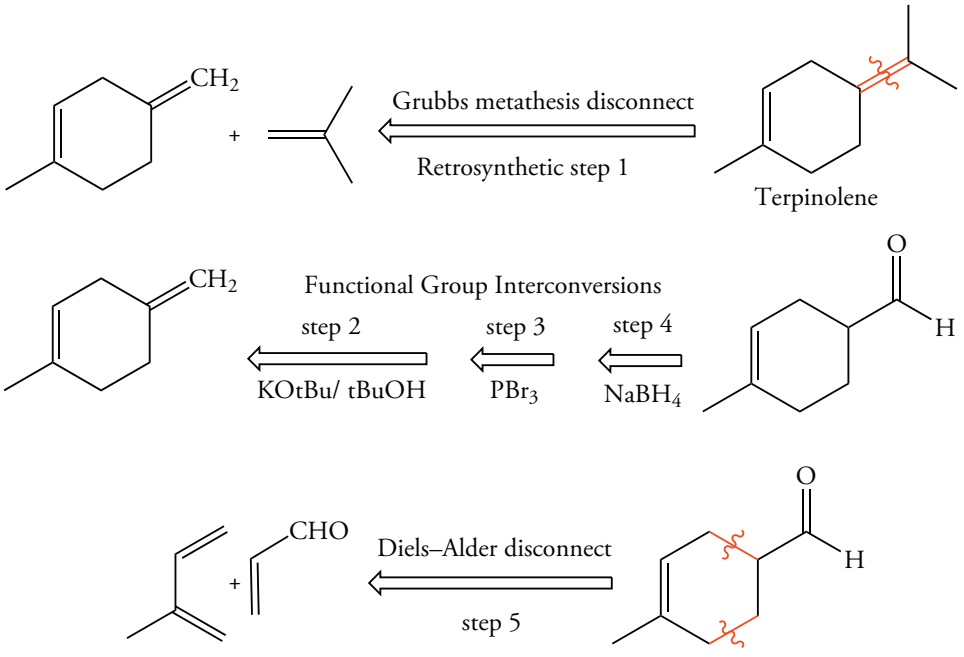
The last functional group interconversion gives us the six-membered ring we need. The next step in our retrosynthetic scheme is a Diels–Alder disconnect.



Performing these reactions in reverse order will yield terpinolene (Figure 17.12).

Figure 17.12 Retrosynthetic Scheme for the Synthesis of Terpinolene

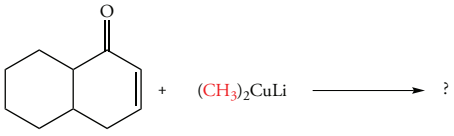
The synthesis would proceed in reverse order, that is, from retrosynthetic step 5 to retrosynthetic step 1. First, a Diels–Alder reaction yields the six-membered ring with the methyl group and the aldehyde side chain in the correct positions to give terpinolene. We see in the Grubbs disconnect how to convert 1-methyl-4-methylidene-cyclohexene into terpinolene. We need a methylidene group at C-4 of the six-membered ring to have the reactants we need for the Grubbs metathesis reaction. We can convert the aldehyde group to a methylidene group by a series of functional group conversions.



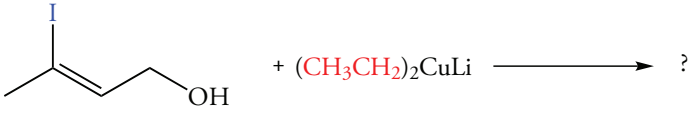
EXERCISES

Gilman Reagent

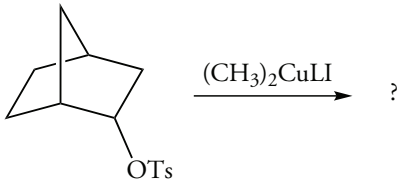
17.1 What is the product of the following reaction?



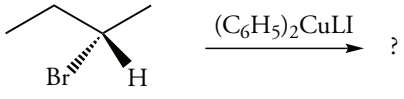
17.2 What is the product of the following reaction?



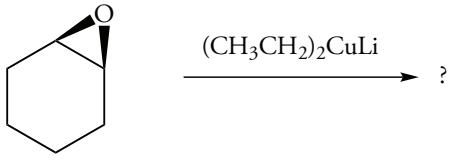
17.3 What is the product of the following reaction?



17.4 What is the product of the following reaction?

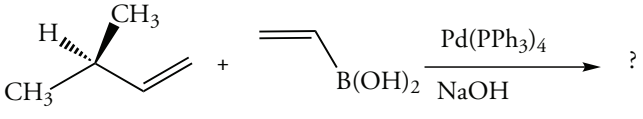


17.5 What is the product of the following reaction?

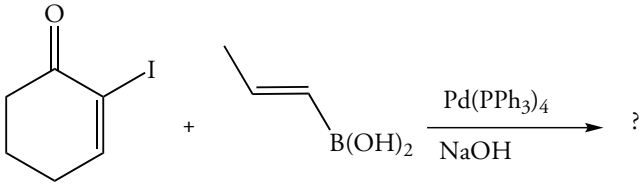


Suzuki Coupling

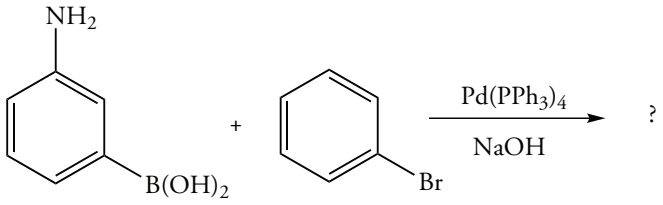
17.6 What is the product of the following reaction?



17.7 What is the product of the following reaction?

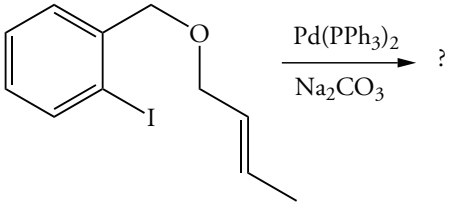


17.8 What is the product of the following reaction?

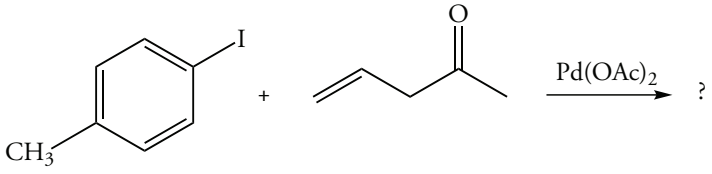


The Heck Reaction

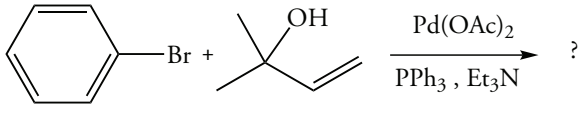
17.9 What is the product of the following reaction?



17.10 What is the product of the following reaction?

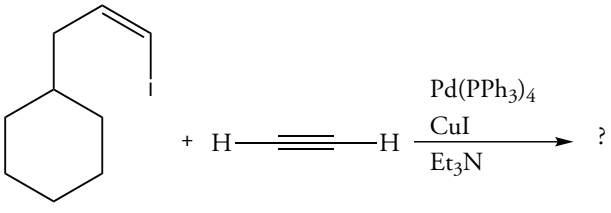


17.11 What is the product of the following reaction?



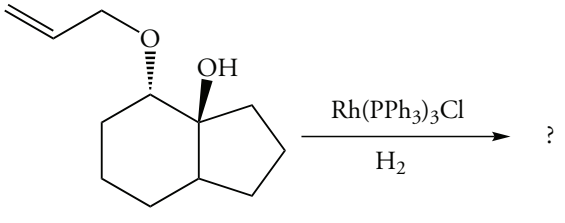
Sonogashira Coupling

17.12 What is the product of the following reaction?

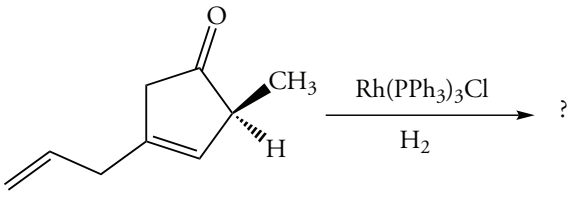


Wilkinson's Catalyst

17.13 What is the product of the following reaction?

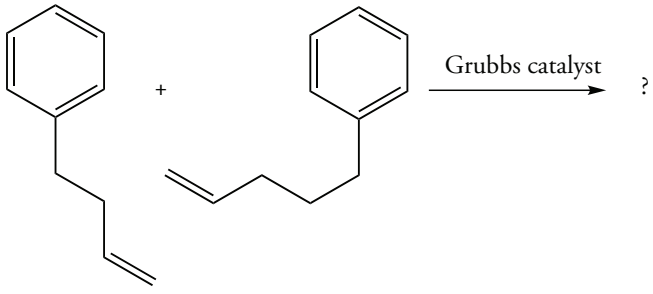


17.14 What is the product of the following reaction?

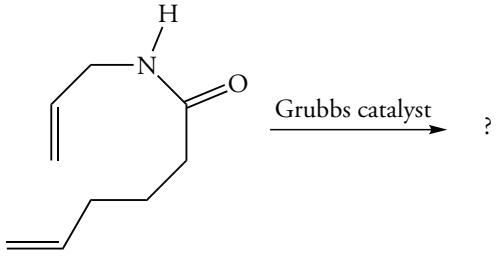


Grubbs Alkene Metathesis

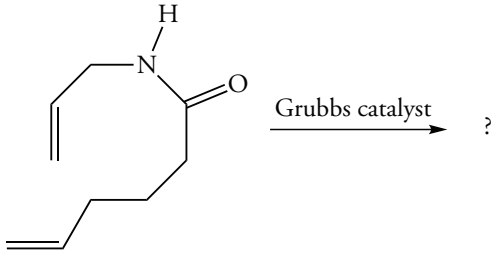
17.15 What is the product of the following reaction?



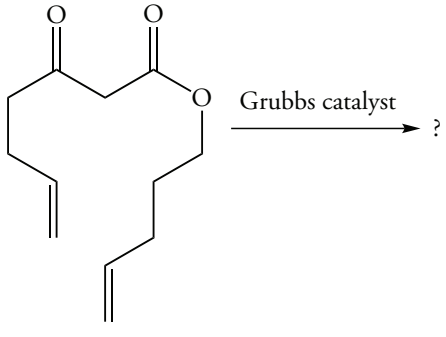
17.16 What is the product of the following reaction?



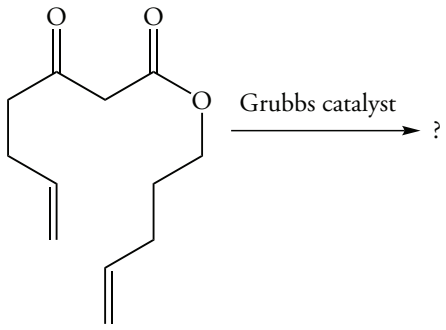
17.17 What is the product of the following reaction?



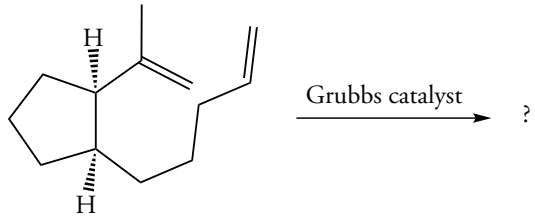
17.18 What is the product of the following reaction?



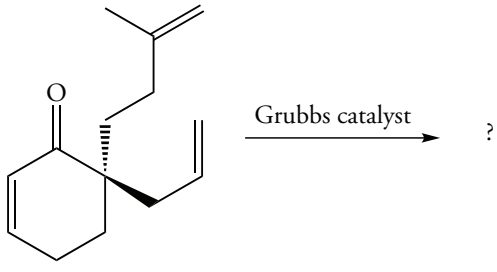
17.19 What is the product of the following reaction?



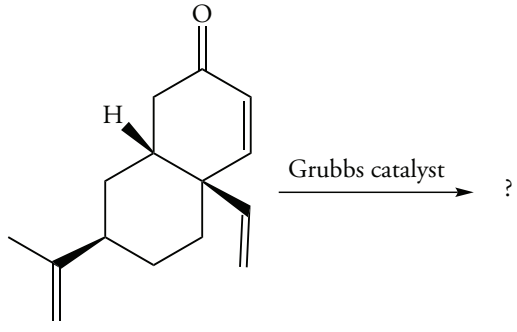
17.20 What is the product of the following reaction?



17.21 What is the product of the following reaction?

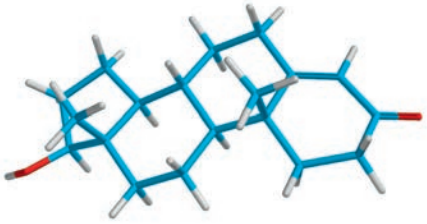


17.22 What is the product of the following reaction?

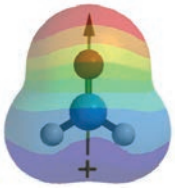


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18 Aldehydes and Ketones



Testosterone

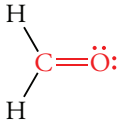


Formaldehyde

In this chapter, we begin to study the reactions functional groups that contain a carbonyl group (C=O). The simplest of these is formaldehyde; a model that shows the dipole and electron distribution is shown on the left. The high polarity of the carbonyl group dominates the chemistry of carbonyl compounds. Functional groups that contain a carbonyl group include aldehydes, ketones, carboxylic acids, and their derivatives, and many classes of cellular molecules. These compounds have some common chemistry, but there are many variations. We will discuss carbonyl compounds in Chapters 18–22.

18.1 THE CARBONYL GROUP

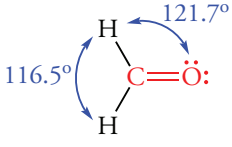
A carbonyl group consists of a double bond linking a carbonyl carbon atom and a carbonyl oxygen atom. The carbonyl oxygen atom shares two of its six valence electrons with the carbonyl carbon atom. Its remaining four valence electrons remain as two sets of electron lone pairs. The carbonyl carbon atom shares two of its four valence electrons with the carbonyl oxygen atom, and its remaining two electrons form two single bonds to other atoms. Formaldehyde (CH_2O) is the simplest compound with a carbonyl group.



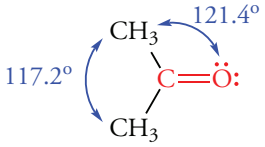
Formaldehyde, the carbonyl group, is shown in red.

The carbonyl carbon atom, which is sp^2 hybridized, contributes one electron to each of the three hybrid orbitals, forming three σ bonds. Formaldehyde has two σ bonds to hydrogen atoms and one σ bond to the carbonyl oxygen atom. These coplanar bonds lie at approximately 120° to each other. The fourth electron of the carbonyl carbon atom occupies a 2p orbital perpendicular to the plane of the three sp^2 hybrid orbitals. The carbonyl oxygen atom, also sp^2 hybridized, contributes one of its six valence electrons to the sp^2 hybrid orbital that forms a σ bond with the carbonyl carbon atom. Four valence electrons remain as two sets of nonbonded electron pairs in the other two sp^2 hybrid orbitals. They lie in the same plane approximately 120° to each other and to the carbon—oxygen bond (Figure 18.1). The last valence electron occupies a 2p orbital perpendicular to the plane of the sp^2 hybrid orbitals. The 2p orbitals of the carbon and oxygen atoms overlap to form a π bond.

The three atoms or groups of atoms bonded to the carbonyl carbon of an aldehyde or a ketone are not equivalent, but the bond angles around the carbonyl carbon atom in aldehydes and ketones come close to the idealized 120° bond angles of an sp^2-hybridized carbon atom, as shown for formaldehyde and acetone.



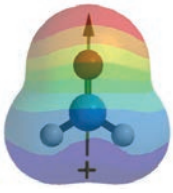
formaldehyde



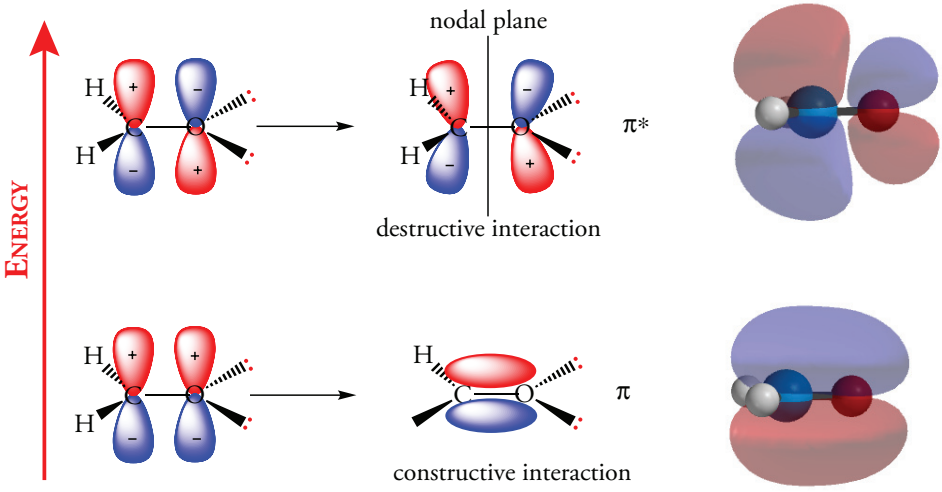
acetone

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00018-8
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Figure 18.1
Structure of Formaldehyde
The carbonyl carbon and oxygen atoms of formaldehyde are sp^2-hybridized. The H—C—H bond angle is close to 120°. The two sets of lone pair electrons are in sp^2 hybrid orbitals that are in the same plane as the hydrogen atoms.



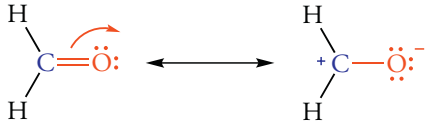
Formaldehyde



Bonding and Antibonding Molecular Orbitals of Formaldehyde

The carbon–oxygen bond length in aldehydes and ketones is approximately 122 pm, smaller than the carbon–oxygen bond length of 141 pm in alcohols. This decrease in bond length is similar to the decrease from a carbon–carbon single bond to a carbon–carbon double bond. It reflects the contribution of the π bond, which brings the bonded atoms closer together.

Because oxygen is more electronegative than carbon, the oxygen atom attracts the electrons in the carbon–oxygen double bond, making the carbonyl bond polar. The carbonyl group is also resonance stabilized, as shown by the charged contributing structure **2**.



1 **2**

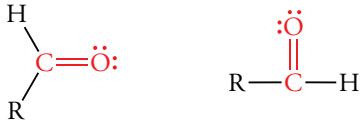
Contributing structure **1** is more important because each atom has a Lewis octet, and there is no formal charge on either atom. However, the contribution of polar structure **2** significantly affects the physical properties of the carbonyl group. For example, the dipole moment of propanal is significantly larger than that of 1-butene, a compound with an otherwise similar structure.

$CH_3—CH_2—CH=CH_2$	$CH_3—CH_2—CH=O$
1-butene (0.2 D)	propanal (2.5 D)

The polar resonance forms of carbonyl compounds also help us explain the chemical properties of aldehydes and ketones. We shall see that the carbonyl carbon atom is electrophilic and the carbonyl oxygen atom is nucleophilic.

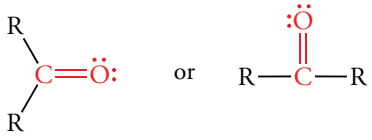
Carbonyl Compounds

When a carbonyl carbon atom is bonded to at least one hydrogen atom, the resulting compound is an aldehyde. The aldehyde with the simplest structure is formaldehyde, in which the carbonyl carbon atom is bonded to two hydrogen atoms. The carbonyl group is bonded to one hydrogen atom and either an alkyl group (R) or an aromatic group (Ar) in other aldehydes. Although the bond angles around the carbonyl carbon atom are approximately 120°, structures are often written with a linear arrangement of carbon atoms.



general formulas for an aldehyde

When a carbonyl carbon atom is bonded to two other carbon atoms, the compound is a ketone. The bonded groups may be any combination of alkyl or aromatic groups. A ketone has 120° bond angles at the carbonyl carbon atom, but structures are often written with a linear arrangement of carbon atoms.



general formulas for a ketone

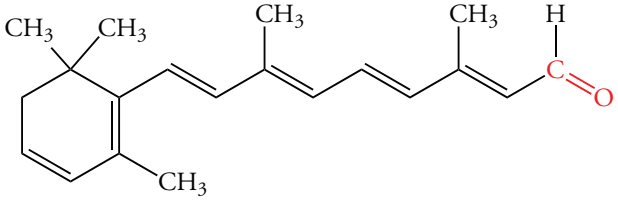
An aldehyde can be written with the condensed formula RCHO or ArCHO, where the symbol CHO indicates that both hydrogen and oxygen atoms are bonded to the carbonyl carbon atom. A ketone has the condensed formula RCOR. In this condensed formula, the symbol CO represents the carbonyl group, and the two R groups flanking the CO group are bonded to the carbonyl carbon atom.

Naturally Occurring Aldehydes and Ketones

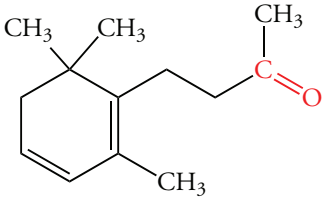
The carbonyl group is the most common functional group in oxygen-containing organic compounds isolated from biological sources. One of two suffixes in common names may indicate the presence of a carbonyl group in a molecule. If the carbonyl compound is an aldehyde, we use the suffix *-al*. If the carbonyl compound is a ketone, we use the suffix *-one*. For example, retinal is an aldehyde required for vision. The first part of the name indicates that this compound is present in the retina, and the suffix tells us that it is an aldehyde. Another example of a common name is α-ionone, a fragrant ketone responsible for the scent of irises that is used in perfumes.

Carbonyl groups are present in some steroids. For example, the synthetic steroids norethindrone, an oral contraceptive, and methandrostenolone, an anabolic steroid, both contain a carbonyl group (Figure 18.2).

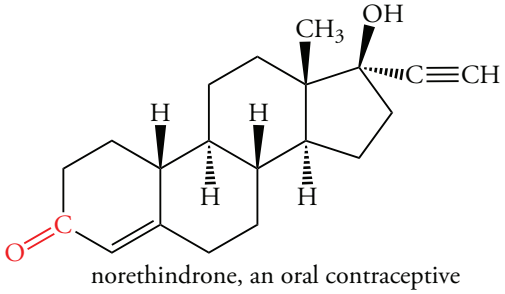
Figure 18.2
Structures of Naturally Occurring Aldehydes and Ketones



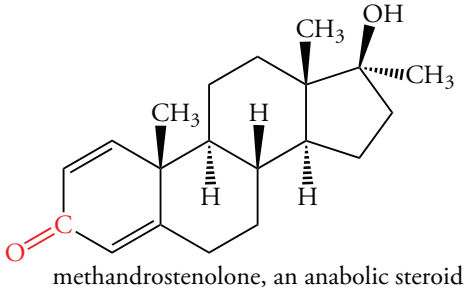
retinal



α-ionone



norethindrone, an oral contraceptive

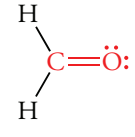


methandrostenolone, an anabolic steroid

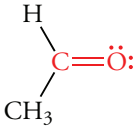
18.2 NOMENCLATURE OF ALDEHYDES AND KETONES

Common Names of Aldehydes

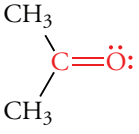
Aldehydes and ketones with low molecular weights are often referred to by their common names. We will discuss the origin of these names—they are derived from the common names of acids—in Chapter 19.



formaldehyde

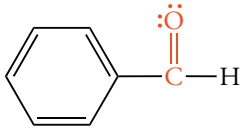


acetaldehyde

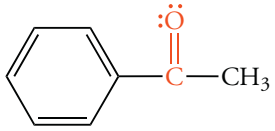


acetone

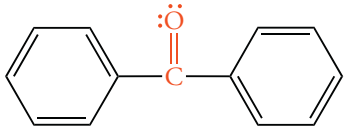
The common names of some aromatic aldehydes and ketones include the following.



benzaldehyde



acetophenone



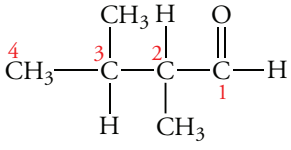
benzophenone

IUPAC Names of Aldehydes

The IUPAC rules for naming aldehydes are similar to those outlined for alcohols.

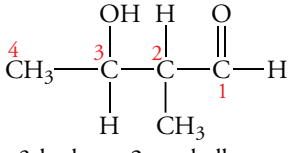
1. Name the longest continuous carbon chain that contains the carbonyl carbon atom as the parent chain. Replace the final *-e* of the parent hydrocarbon by the ending *-al*.

2. Number the parent chain to make the carbonyl carbon atom C-1. The number 1 is not required because the position of the carbonyl carbon atom must be at the end of the chain. Determine the name of each substituent and the number of the carbon atom to which it is attached. Add this information to the parent name as a prefix.



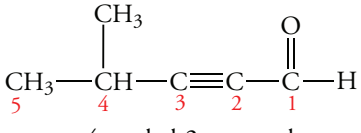
This is 2,3-dimethylbutanal, *not* 2,3-dimethyl-1-butanal.

3. The aldehyde functional group has a higher priority than alkyl, halogen, hydroxyl, and alkoxy groups. If any of these groups is present, indicate their names and positions as prefixes to the name of the parent aldehyde.



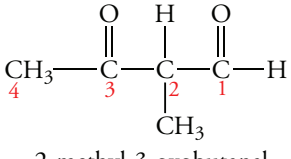
3-hydroxy-2-methylbutanal

4. The aldehyde functional group has a higher priority than double or triple bonds. When the parent chain contains a double or a triple bond, replace the final *-e* of the name of the parent alkene or alkyne with the suffix *-al*. Indicate the position of the multiple bond with a prefix.



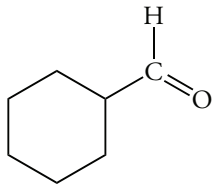
4-methyl-2-pentynal

5. If an aldehyde or a ketone contains other groups with a higher priority, such as carboxylic acids, give the carbonyl group the prefix *-oxo*. Use a number to indicate the position of the *oxo* group. The priority order is carboxylic acid > aldehyde > ketone.

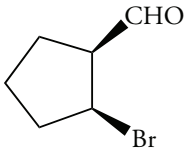


2-methyl-3-oxobutanal

6. If an aldehyde group is attached to a ring, use the suffix *-carbaldehyde*.



cyclohexanecarbaldehyde



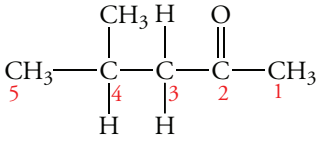
cis-2-bromocyclopentanecarbaldehyde

IUPAC Names of Ketones

The IUPAC rules for naming ketones are similar to those used for aldehydes. However, because the carbonyl group in a ketone is not on a terminal carbon atom, we use a number to indicate its position.

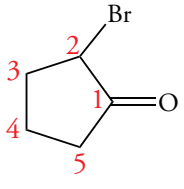
1. Name the longest continuous carbon chain that contains the carbonyl carbon atom as the parent chain. Replace the final *-e* of the parent hydrocarbon with the ending *-one*.

2. Number the carbon chain so that the carbonyl carbon atom has the lower number. Use this number as a prefix to the parent name. Give the name and location of substituents as a prefix to the parent name.

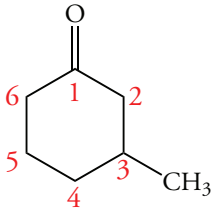


This is 4-methyl-2-pentanone,
not 2-methyl-4-pentanone.

3. Name cyclic ketones as cycloalkanones. The carbonyl carbon is C-1 . Number the ring in the direction that gives the lower number to the first substituent encountered.



2-bromocyclopentanone

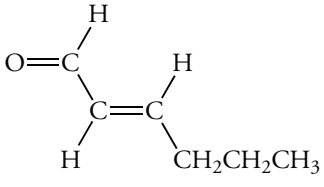


3-methylcyclohexanone

4. Halogen, hydroxyl, alkoxy groups, and multiple bonds have lower priorities than the ketone groups. These substituted ketones are named using the same method described for aldehydes.

Problem 18. 1

What is the IUPAC name for the following compound, which is an alarm pheromone in some species of ants.



Sample Solution

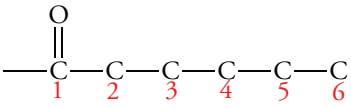
The aldehyde carbon atom on the left of the structure is C-1. The double bond is therefore located at C-2, and the name, disregarding stereochemistry, is 2-hexenal. The higher priority groups bonded to the unsaturated carbon atoms—the CHO and propyl groups—are in an *E* arrangement. The IUPAC name is (*E*)-2-hexenal.

Problem 18. 2

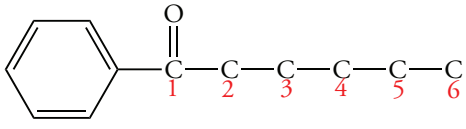
The IUPAC name for capillin, a drug used against skin fungi, is 1-phenyl-2,4-hexadiyn-1-one. Draw its structure.

Sample Solution

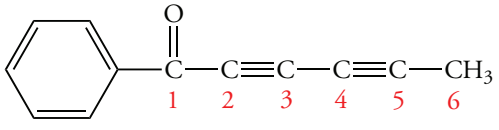
When we dissect the name, we see that it has the suffix -1-one and the stem name hexa, indicating that the parent chain is a ketone containing six carbon atoms. We write the carbon skeleton and number the chain. Place the carbonyl oxygen atom on C-1.



The name has the prefix 1-phenyl. Therefore, we add a phenyl group at C-1. Note that the presence of the phenyl group makes the compound a ketone. A carbonyl carbon atom at the end of a chain would otherwise be an aldehyde.



The name "diyn" tells us that there are two triple bonds; they are located at C-2 and C-4. Fill in the requisite hydrogen atoms.



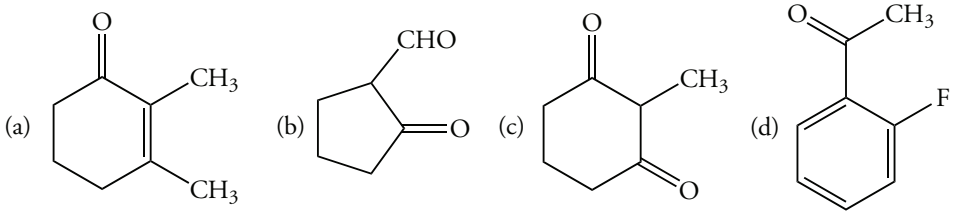
Problem 18. 3

Draw the structure of each of the following compounds.

(a) 2-methylcyclohexanecarbaldehyde (b) 1,3-dipheny1-1,3-propanedione
(c) *cis*-2,3-dibromocyclohexanone (d) 5-methyl-4-hexenal
(e) 1-hydroxy-3-pentanone (f) 7-fluoro-7-methyl-4-octen-2-one

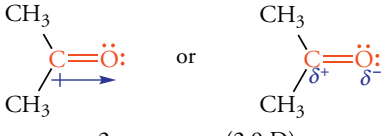
Problem 18. 4

Assign the IUPAC name to each of the following structures.



18.3 PHYSICAL PROPERTIES OF ALDEHYDES AND KETONES

Because oxygen is more electronegative than carbon, it pulls the electrons in the carbonyl bond toward it, making the carbonyl group polar. (The contributing charged structure of the resonance hybrid we described earlier predicts this property.) An arrow in which the arrowhead represents the negative end of the dipole indicates the polarity of the carbonyl group. We also represent the positive and negative ends of the carbonyl bond by the symbols δ^+ and δ^-, where the lowercase Greek letter delta means "partial charge."



2-propanone (2.9 D)
(acetone)

The dipole moment of acetone, a typical ketone, is 2.9 D. In contrast, the dipole moment of 2-methylpropane is 0.1 D. The high polarity of the carbonyl group reflects the contribution of the charged structure to the resonance hybrid. The physical properties of aldehydes and ketones reflect the polarity of the carbonyl group (Figure 18.3).

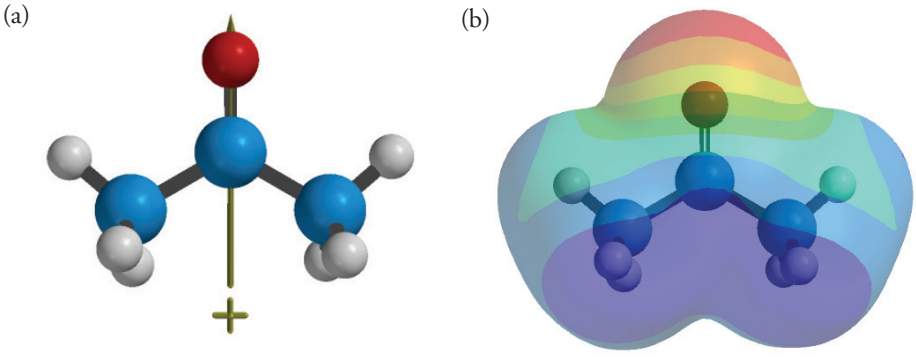


Figure 18.3
Electron Density Map of Acetone
(a) The carbonyl bond is highly polar. The oxygen atom, shown in red, has a large, partial negative charge; the carbonyl carbon has a partial positive charge, as do the two carbons that are α to the carbonyl group. (b) Electrostatic potential map. Regions shown in red have a partial negative charge; regions shown in blue have a partial positive charge.

Boiling Points of Aldehydes and Ketones

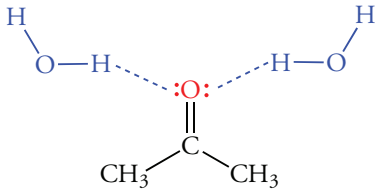
Aldehydes and ketones have boiling points distinctly different from those of alkanes or alcohols of similar molecular weight (Table 18.1). Aldehydes and ketones have higher boiling points than alkanes because of dipole–dipole intermolecular forces of the carbonyl group. Alcohols have higher boiling points than aldehydes and ketones of similar molecular weight. Thus, the dipole–dipole attractive forces of carbonyl compounds are weaker than hydrogen-bonding interactions between alcohol molecules. As the molecular weights of the carbonyl compounds increase, their dipole–dipole attractive forces become less important compared to London forces of the hydrocarbon skeleton. As a result, the physical properties of aldehydes and ketones become more like those of hydrocarbons as the chain length increases. Although the boiling point differences become smaller, the order of boiling points remains alcohol > carbonyl compound > alkane.

Table 18.1
Effect of Functional Groups on Boiling Points

Compound	*Formula*	*Molecular Weight*	*Boiling Point (°C)*
Ethane	CH_3CH_3	30	–89
Methanol	CH_3OH	32	64.6
Methanal	CH_3CHO	30	–21
Propane	$CH_3CH_2CH_3$	44	–42
Ethanol	CH_3CH_2OH	46	78.3
Ethanal	CH_3CH_2CHO	44	20
Butane	$CH_3CH_2CH_2CH_3$	58	–1
1-Propanol	$CH_3CH_2CH_2OH$	60	97.1
Propanal	CH_3CH_2CHO	58	48.8
Methylpropane	$CH_3CH(CH_3)_2$	58	–12
2-Propanol	$CH_3CH(OH)CH_3$	60	82.5
Propanone	CH_3COCH_3	58	56.1

Solubility of Aldehydes and Ketones in Water

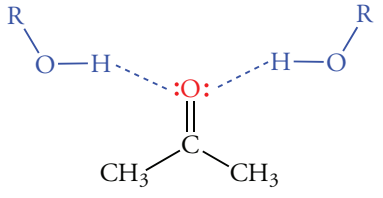
Aldehydes and ketones cannot form hydrogen bonds with one another because they cannot function as hydrogen bond donors. However, because the carbonyl oxygen atom has lone pair electrons that can act as hydrogen bond acceptors, carbonyl groups can form hydrogen bonds with water. As a result, the lower molecular weight compounds formaldehyde, acetaldehyde, and acetone dissolve in water in all proportions. However, the solubility of carbonyl compounds in water decreases as the chain length increases, and their solubilities become more like those of hydrocarbons.



The lone pair electrons of the carbonyl group act as hydrogen bond acceptors.

Acetone and 2-Butanone as Solvents

Both acetone and 2-butanone (known in industry as methyl ethyl ketone (MEK) are excellent solvents for a variety of organic compounds. These polar solvents dissolve polar solutes because "like dissolves like." Acetone is especially effective in dissolving protic solutes such as alcohols and carboxylic acids because the carbonyl group acts as a hydrogen bond acceptor for these compounds.



The lone pair electrons of the carbonyl group act as hydrogen bond acceptors. Hence, acetone is an excellent solvent for alcohols.

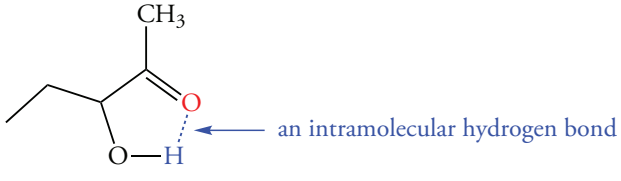
Acetone is an aprotic solvent (Section 10.3) because it does not have hydrogen atoms that can form hydrogen bonds to nucleophiles. The electron pairs of the carbonyl oxygen atom can solvate cations, but not anions. Consequently, anions have greater nucleophilicity in acetone than in protic solvents such as ethanol.

Problem 18. 5

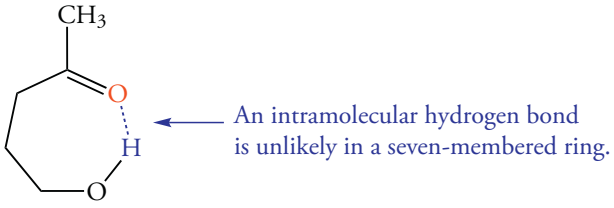
The boiling points of 3-hydroxy-2-pentanone and 5-hydroxy-2-pentanone are 147 and 210 °C, respectively. Suggest a reason for this difference.

Sample Solution

Intermolecular hydrogen bonding decreases the escaping tendency of molecules from the liquid phase and increases the boiling point. In both compounds, the hydroxyl group can form intermolecular hydrogen bonds not only to hydroxyl groups but also to the carbonyl oxygen atoms. In 3-hydroxy-2-pentanone, the proximity of the hydroxyl hydrogen atom to the carbonyl oxygen atom allows formation of an intramolecular hydrogen bond in a five-membered ring.



As a consequence, the extent of intermolecular hydrogen bonding is decreased. Decreased intermolecular hydrogen bonding allows molecules to escape more readily and lowers the boiling point. The probability of an intramolecular hydrogen bond in 5-hydroxy-2-pentanone is far less than in 3-hydroxyl-2-pentanone because a seven-membered ring would be required.

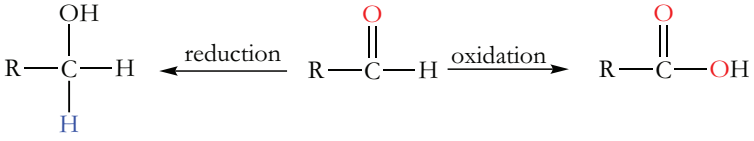


Problem 18. 6

Draw two conformations of 2-methylacetophenone that have the carbonyl group conjugated with the aromatic ring. Which is the more stable?

18.4 OXIDATION–REDUCTION REACTIONS OF CARBONYL COMPOUNDS

The carbonyl group of an aldehyde is in an oxidation state between that of an alcohol and a carboxylic acid. Thus, the carbonyl group of an aldehyde can be reduced to an alcohol or oxidized to a carboxylic acid. The carbonyl group of a ketone can be reduced to an alcohol, but cannot be easily oxidized.

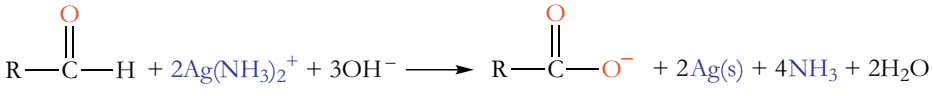


Oxidation of Aldehydes

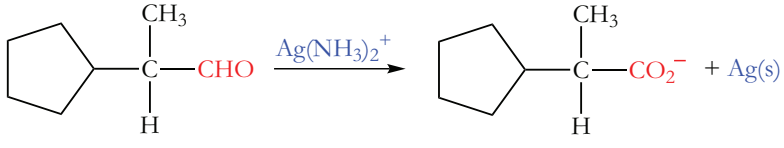
In Chapter 15, we saw that primary alcohols are oxidized to aldehydes, which are then easily oxidized to acids. Under the same conditions, secondary alcohols are oxidized to ketones, but no further. This difference in reactivity distinguishes primary from secondary alcohols.

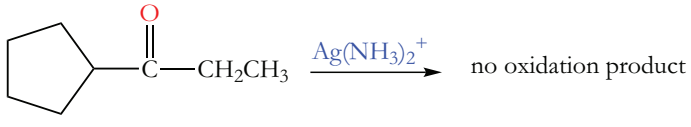
In a similar way, we can use oxidation to distinguish aldehydes from ketones. Aldehydes are easily oxidized. They react with several mild oxidizing reagents, including Tollens reagent, Benedict's solution, and Fehling's solution. Each of these reagents converts aldehydes to carboxylic acids. None of them oxidize ketones. These reagents therefore provide a qualitative way of distinguishing aldehydes from ketones.

Tollens reagent is a basic solution of a silver ammonia complex ion. When an aldehyde is added to a test tube containing Tollens reagent, the aldehyde is oxidized and deposits metallic silver as a mirror on the wall of the test tube.

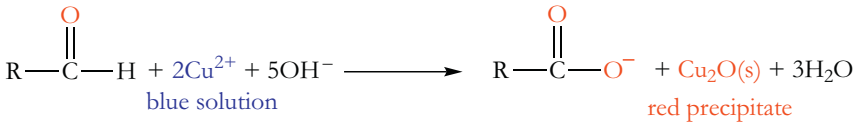


Adding Tollens reagent to each of the following isomeric carbonyl compounds gives a clear result that distinguishes between the two isomers.

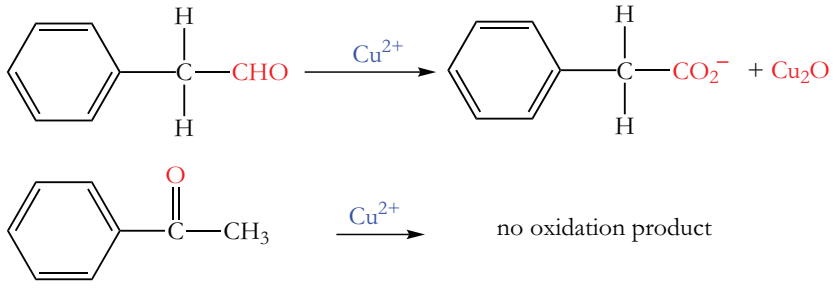




Benedict's solution contains cupric ion (Cu^{2+}) as a complex ion in a basic solution; like Tollens reagent, it converts aldehydes to carboxylic acids. In this reaction, Cu^{2+} is reduced to Cu^{+}, which forms as a brick-red precipitate, Cu_2O. Benedict's solution has the characteristic blue color of Cu^{2+}, which fades as the red precipitate of Cu_2O forms. Benedict's solution is basic, and in a basic solution, a carboxylic acid is converted to its conjugate base, that is, a carboxylate anion.

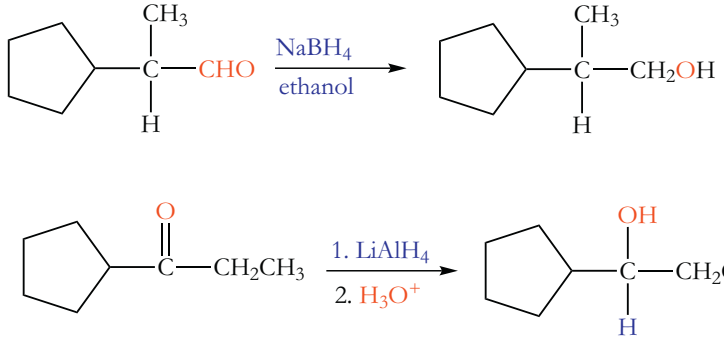


Fehling's solution, which contains Cu^{2+} as a different complex ion in a basic solution, also oxidizes aldehydes but not ketones. Either of the reagents can be used to distinguish between compounds such as the following isomeric aldehyde and ketone.

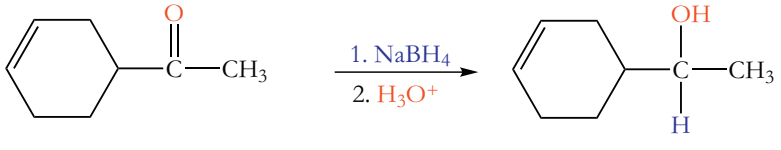


Reduction of Aldehydes and Ketones to Alcohols

In Chapter 5, we saw that hydrogen gas can reduce carbon–carbon double bonds in the presence of a nickel, palladium, or platinum catalyst. In Chapter 15, we learned that hydrogen gas can reduce aldehydes and ketones to alcohols in the presence of Raney nickel. However, this type of reduction requires more severe conditions than those required to reduce alkenes. We also learned that both lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) reduce carbonyl groups, but that neither reagent reduces carbon–carbon double nor triple bonds.

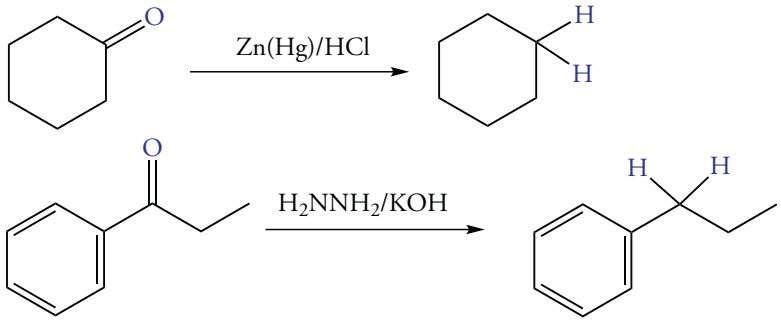


Because neither lithium aluminum hydride nor sodium borohydride reacts with alkenes or alkynes, these reagents selectively reduce a carbonyl group in compounds with carbon–carbon multiple bonds.



Reduction of a Carbonyl Group to a Methylene Group

We first introduced the reduction of a carbonyl group to a methylene group in Section 13.3 as a method of converting the ketone product of a Friedel–Crafts acylation to an alkyl group that could not be produced by direct Friedel–Crafts alkylation. The carbonyl group of either an aldehyde or a ketone can be reduced directly to a methylene group by a Clemmensen reduction, which are zinc amalgam (Zn/Hg) and HCl. A carbonyl group can also be converted to a methylene group by the Wolff–Kishner reduction, using hydrazine (NH_2NH_2) and base in a solvent with a high-boiling point solvent such as diethylene glycol, $(HOCH_2CH_2)_2O$. Neither reagent reduces the carbonyl group of carboxylic acids or esters.

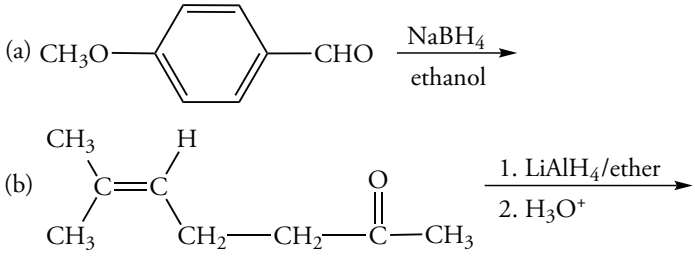


Problem 18. 7

Can the isomeric carbonyl-containing compounds of molecular formula C_4H_8O be distinguished by Tollens reagent?

Problem 18. 8

Draw the structure of the product of each of the following reactions.



Problem 18. 9

Devise a synthesis of each of the following compounds starting from the Friedel–Crafts acylation of benzene.

(a) 1-phenyl-1-butanol (b) 1-phenylbutane (c) 2-phenyl-2-pentanol

Sample Solution

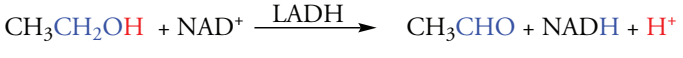
The additional four carbon atoms required to synthesize 1-phenyl-1-butanol and 1-phenylbutane can be provided by a Friedel–Crafts reaction of benzene and a four-carbon acid chloride. This product, 1-phenyl-1-butanone, has a carbonyl group that can be reduced to provide products (a) and (b). Reduction of 1-phenyl-1-butanone with a metal hydride such as $NaBH_4$ gives 1-phenyl-1-butanol. Reduction of 1-phenyl-1-butanone using either Clemmensen or Wolff–Kishner conditions gives 1-phenylbutane.

Compound (c) is a tertiary alcohol that can be prepared by the addition of a Grignard reagent to a ketone. Three combinations of ketones and Grignard reagents can be used. One is 1-phenyl-1-butanone and methylmagnesium bromide.

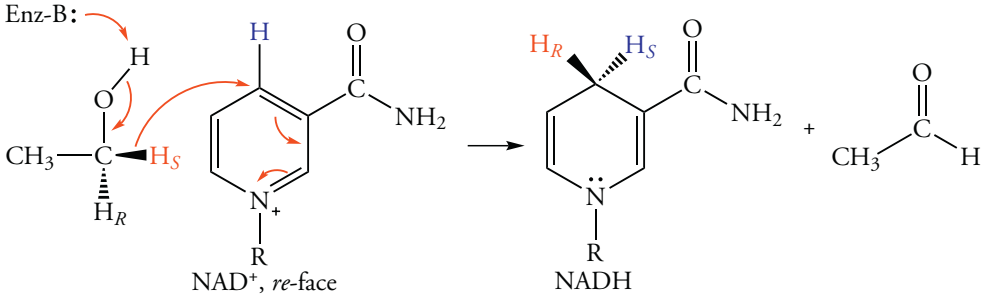
NAD-Dependent Oxidation of Ethanol

The oxidation of an alcohol to a carbonyl group is a common metabolic reaction. The reverse reaction, reduction of a carbonyl compound to an alcohol, is also common. In fact, the two related reactions often occur by the same mechanism, with the direction of the reaction controlled by needs of the cell. The two reactions transfer a hydride ion either to or from carbon atoms bonded to the oxygen atom in the substrate to a carbon atom of a coenzyme.

In human liver cells, the enzyme alcohol dehydrogenase (LADH) catalyzes the oxidation of ethanol to yield acetaldehyde. In this reaction, the coenzyme nicotinamide adenine dinucleotide, NAD^+, is converted to its reduced form, NADH.



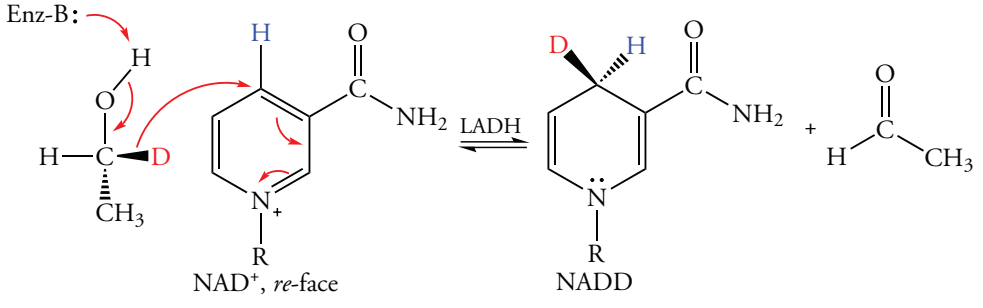
The oxidized and reduced forms of the coenzyme are drawn using a shorthand in which the R group attached to the heterocyclic ring represents a part of the molecule that does not directly participate in its reactions. The oxidation or reduction of the coenzyme occurs within the six-membered pyridine ring. The pyridinium ion ring system of NAD^+ is prochiral. The enzyme stereospecifically transfers a hydride ion from ethanol to the *re*-face and gives a product, NADH, that is also prochiral.



When ethanol is oxidized, a hydride ion is transferred from C-1 of ethanol to C-4 of the pyridinium ring. In the reverse reaction, acetaldehyde is reduced by transfer of a hydride ion from C-4 of NADH to the carbonyl carbon atom. The hydrogen atoms at C-1 of ethanol are also prochiral. Thus, the chiral enzyme active site can distinguish these enantiotopic hydrogen atoms. The two hydrogen atoms at C-4 of NADH are not equivalent because replacing one of them with deuterium yields two different stereoisomers. However, when the planar pyridinium ring system is bound to the enzyme active site, only one face of the ring can be attacked: in the chiral environment, the prochiral faces of the ring system and the prochiral hydrogens of ethanol are *diastereotopic*.

The stereochemistry of the oxidation of ethanol and the reduction of acetaldehyde has been determined using deuterium-labeled reactants. Reaction of 1-deutero-ethanol with NAD^+ occurs to give NADH-4-*d* with the *R* configuration at the C-4 ring atom. Therefore, the hydride ion was transferred to the *re* face.

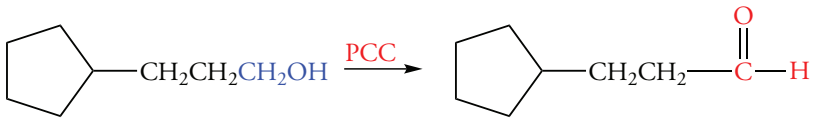
In the reverse reaction, the reduction acetaldehyde by (*R*)-NADH-4-*d*. Only the deuterium is transferred yielding (*R*)-1-[^{2}H]-ethanol even though cleaving a C—D bond requires more energy than cleaving a C—H bond. We conclude that the arrangement of the reactants within the reactive site of the enzyme places the deuterium in a position to be transferred to the carbonyl carbon atom. The plane of NAD^+ and the plane of acetaldehyde are arranged so that the two *re* faces are next to each other. As a consequence, the deuterium is stereospecifically transferred.



18.5 SYNTHESIS OF CARBONYL COMPOUNDS: A REVIEW

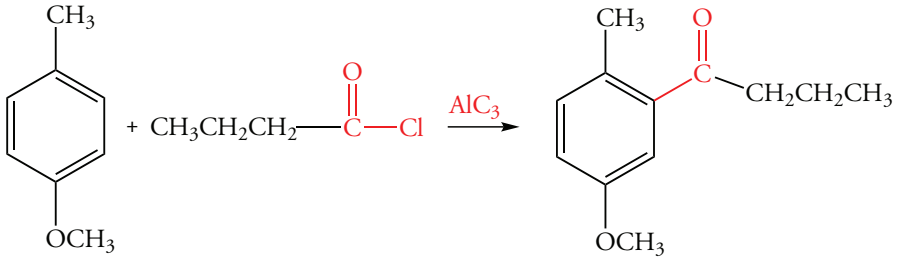
Oxidation of Alcohols

Alcohols provide the most common starting materials for the synthesis of carbonyl compounds. Because alcohols can be prepared by a variety of synthetic methods, they are very important synthetic intermediates. Oxidation of alcohols yields carbonyl compounds. Primary alcohols yield aldehydes; secondary alcohols yield ketones. However, we recall that the oxidation of primary alcohols is complicated because aldehydes are easily oxidized to carboxylic acids. Thus, PCC, which does not oxidize aldehydes, is the reagent of choice for the oxidation of primary alcohols. Secondary alcohols can be oxidized by either PCC or the Jones reagent (Section 16.4).

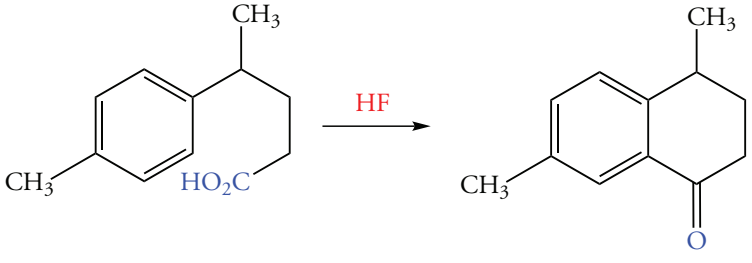


Friedel–Crafts Acylation

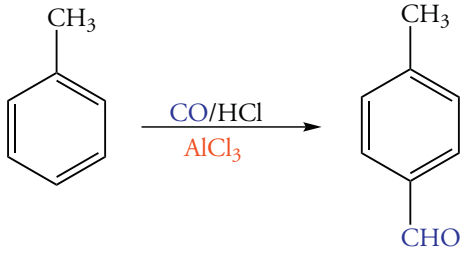
Both alkyl aryl ketones and diaryl ketones can be synthesized using the Friedel–Crafts reaction. However, the method is limited. Aromatic compounds that have strongly deactivating groups, such as NO_2, or carbonyl groups, such as aldehydes, ketones, acids, and esters, do not react.



The intramolecular acylation of an aromatic compound can be accomplished using a carboxylic acid rather than the acid halide. The reaction requires HF to produce the intermediate acyl cation (Section 13.2).

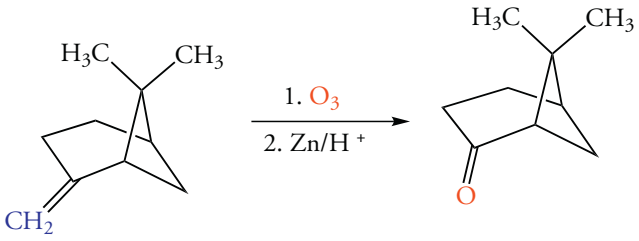


Aldehydes cannot be synthesized by the Friedel–Crafts reaction using methanoyl chloride (formyl chloride) because it is an unstable compound. However, a gaseous mixture of carbon monoxide and hydrogen chloride reacts like formyl chloride. The formylation of an aromatic compound using this gaseous mixture and aluminum trichloride is called the **Gatterman–Koch** synthesis. Like the Friedel–Crafts reaction, this method is limited to activated aromatic compounds.



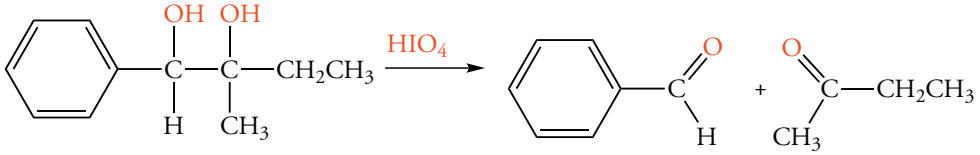
Ozonolysis of Alkenes

Ozonolysis followed by reductive workup gives a mixture of aldehydes and ketones whose structures depend on the groups bonded to the sp^2-hybridized carbon atoms. Thus, as a synthetic method, the process is limited by the requirement of having the appropriate alkene. This reaction also "wastes" part of the starting material because usually only one of the cleavage products is desired and the two carbonyl compounds must be separated. Nevertheless, the method proves useful in specific cases, such as the oxidative cleavage of α-pinene. In this case, the methanal by-product is a gas that escapes from solution and does not contaminate the bicyclic ketone product.

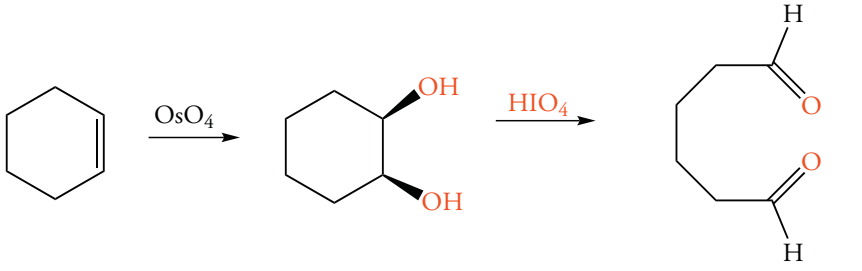


Oxidative Cleavage of Vicinal Diols

For the same reasons as described for the ozonolysis of alkenes, the oxidative cleavage of vicinal diols by periodate is limited as a synthetic method. The vicinal diol is seldom directly available, and it must be prepared from an alkene. We also recall that the hydroxyl groups must be located in a *cis* configuration, or the molecule must have sufficient conformational freedom to bring the two hydroxyl groups into a gauche conformation. The vicinal diol is prepared from an alkene by oxidation with osmium tetroxide.



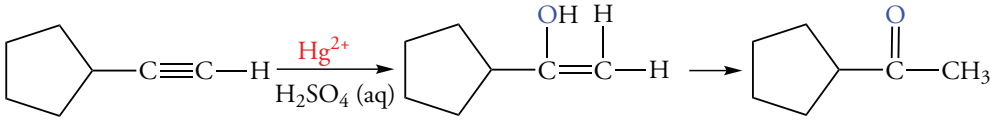
2-methyl-1-phenyl-1,2-butanediol benzaldehyde 2-butanone



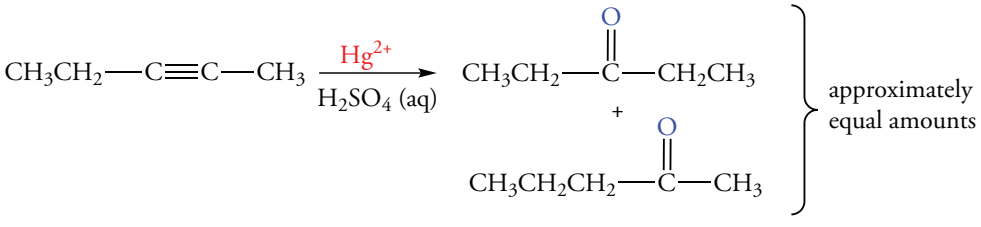
cis-1,2-cyclohexanediol 6-oxohexanal

Hydration of Alkynes

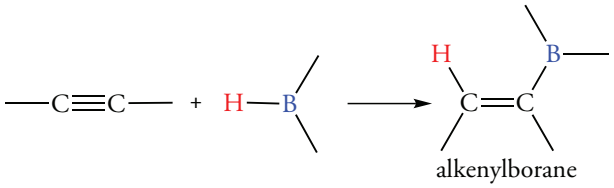
The hydration of alkynes to yield ketones is generally useful only for terminal alkynes. For example, ethynylcyclopentane reacts with water in aqueous sulfuric acid and mercuric ion to give an enol, which quickly isomerizes to a methyl ketone.

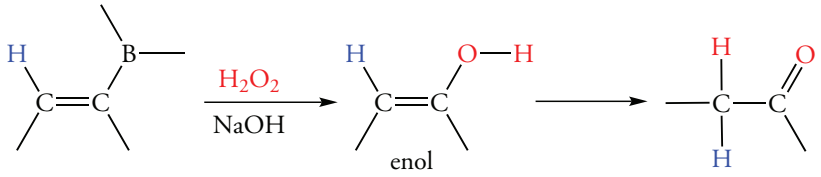


For internal alkynes, regioselectivity seldom occurs. The Markovnikov addition of water to internal alkynes gives a mixture of ketone products that have to be separated.

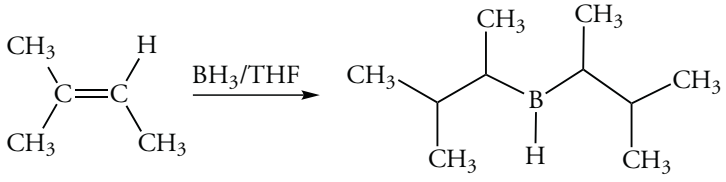


We recall that alkenes react regiospecifically with borane to give an alkylborane, the anti-Markovnikov product. Subsequent oxidation of the alkylborane ultimately yields an alcohol that corresponds to anti-Markovnikov addition of water. Borane and substituted boranes also react with alkynes. The resulting alkenylborane is subsequently oxidized to give an enol, which quickly rearranges to give a carbonyl compound.



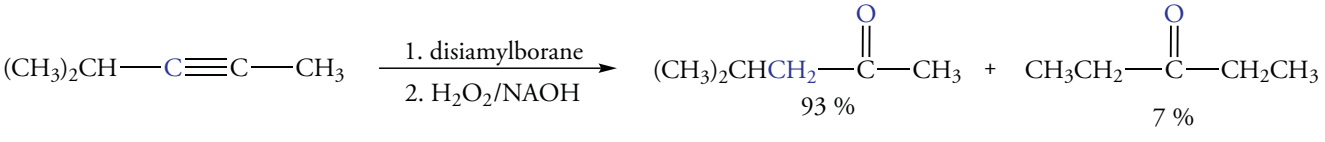


Terminal alkynes undergo regiospecific hydroboration in which boron is bonded to the less hindered carbon atom. Subsequent oxidation and isomerization therefore yield an aldehyde. In contrast, a terminal alkyne reacts with mercury(II) acetate to give a methyl ketone. The hydroboration reaction actually requires a substituted, hindered borane rather than diborane itself. With diborane, the alkenylborane can react with a second equivalent of diborane. Di(1,2-dimethylpropyl)borane—also called di(*sec*-isoamyl)borane and abbreviated disiamylborane—is prepared by adding borane to 2-methyl-2-butene.



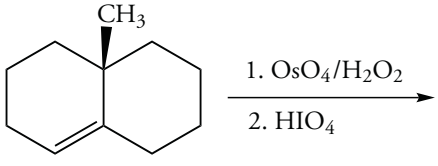
Diborane adds two equivalents of the alkene because the resulting substituted borane is sterically hindered, and does not easily add to another equivalent of an alkene. However, disiamylborane is sufficiently reactive to add to an alkyne. The resulting alkenyl borane is too sterically hindered to react with a second equivalent of disiamylborane.

Disiamylborane is very regioselective and adds to terminal alkynes to give aldehydes after the oxidation step. Furthermore, the reagent is quite regioselective in the hydroboration of unsymmetrical internal alkynes. The boron atom of the reagent adds to the less hindered carbon atom of the alkyne. Upon oxidation, a hydroxyl group replaces the boron atom, and after rearrangement of the enol, a carbonyl group forms. Thus, the carbonyl oxygen atom ends up at the position originally occupied by boron.



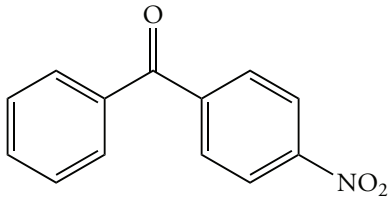
Problem 18.10

Draw the structures of the compounds formed in each step of the following reaction sequence, showing the stereochemistry of each.



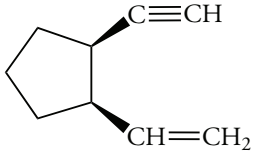
Problem 18.11

Outline a synthesis of the following compound using starting materials that contain no more than seven carbon atoms.



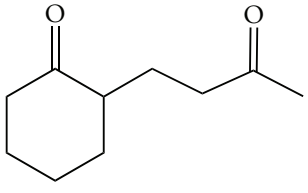
Problem 18.12

Draw the structure of the product formed from reaction of the following compound with disiamylborane followed by oxidation with basic hydrogen peroxide.



Problem 18.13

A hydrocarbon with the molecular formula $C_{10}H_{16}$ reacts with ozone followed by a reductive workup to give the following compound. What is the structure of the hydrocarbon?



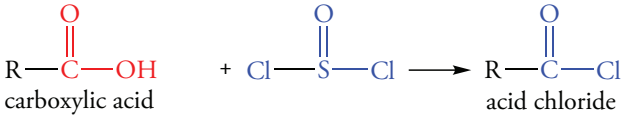
18.6 SYNTHESIS OF CARBONYL COMPOUNDS: A PREVIEW

In this section, we consider the synthesis of carbonyl compounds using functional groups whose chemistry will be examined in detail only in later chapters. We will preview some of the reactions of acid chlorides, carboxylic acids, esters, and nitriles that yield carbonyl compounds.

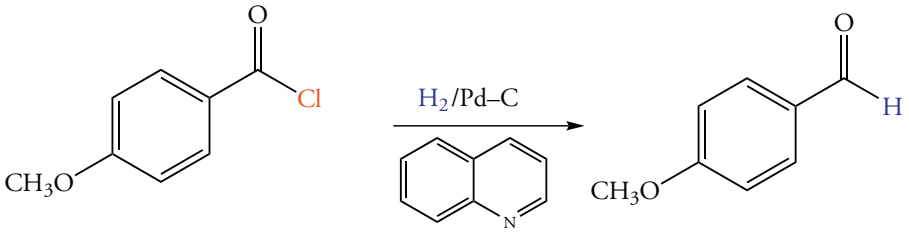


Reduction of Acid Chlorides

Acid chlorides are extremely reactive compounds that are usually prepared for the single purpose of reacting them with another compound. They are prepared by the reaction of a carboxylic acid with thionyl chloride. The stoichiometry is the same as for the conversion of an alcohol to an alkyl halide using thionyl chloride (Section 15.3).



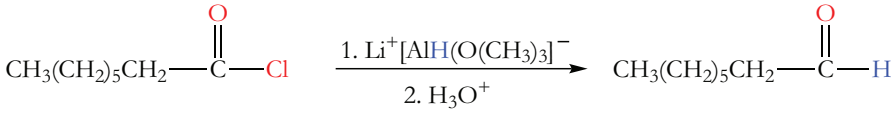
Acid chlorides can be reduced to aldehydes either by catalytic hydrogenation or by reaction with a metal hydride. In both cases, the reagent and the reaction conditions are selected to avoid the further reduction of the aldehyde. The conversion of an acid chloride to an aldehyde can be carried out by the Rosenmund reduction, which uses hydrogen gas and a modified palladium catalyst. The palladium catalyst is altered to prevent further reduction of the aldehyde. To prepare the catalyst, the palladium is treated with quinoline, an aromatic heterocyclic amine, and is heated with sulfur.



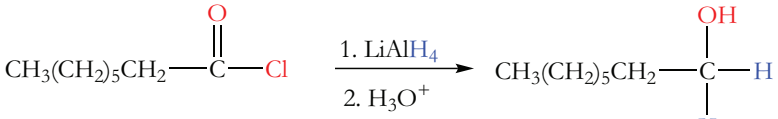
Acid chlorides can also be converted to aldehydes with lithium tri(*tert*-butoxy)aluminum hydride. The reagent is prepared by reacting lithium aluminum hydride with three equivalents of *tert*-butyl alcohol.

$$LiAlH_4 + 3(CH_3)_3COH \longrightarrow Li^+[AlH(O(CH_3)_3]^- + 3H_2$$

The electron-withdrawing *tert*-butoxy groups decrease the reactivity of the Al—H bond. As a result, lithium tri(*tert*-butoxy)aluminum hydride displaces a chloride ion from an acyl chloride, but will not reduce the carbonyl group of the aldehyde. By contrast, lithium aluminum hydride reduces acyl chlorides to primary alcohols.



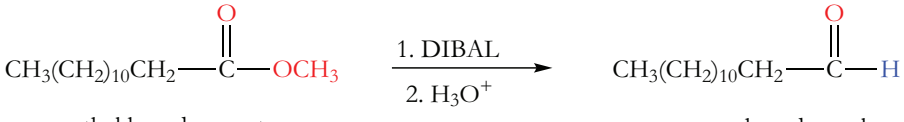
octanoyl chloride octanal



octanoyl chloride 1-octanol

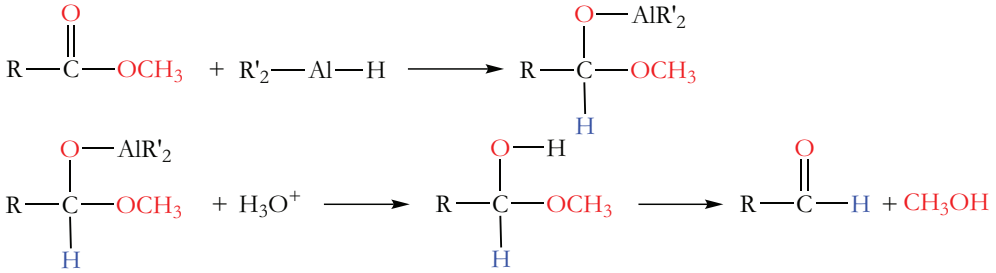
Reduction of Esters

The reduction of an ester either by lithium aluminum hydride or by catalytic hydrogenation at high temperatures under a high pressure of hydrogen yields a primary alcohol. Any aldehyde intermediate that forms is much more easily reduced than the ester. Diisobutylaluminum hydride, $[(CH_3)_2CHCH_2)]_2AlH$, is less reactive than lithium aluminum hydride. At –78 °C in toluene, the reagent, known as DIBAL, reduces esters to aldehydes.



methyl hexadecanoate hexadecanal

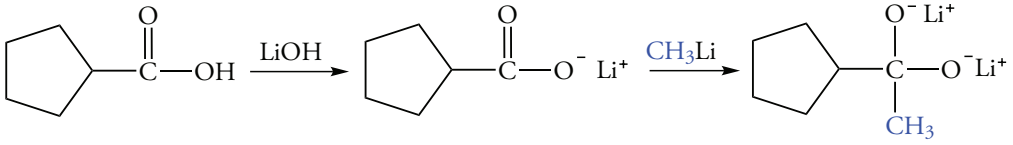
The aldehyde forms in two steps. First, addition of aluminum to the carbonyl oxygen atom and hydrogen to the carbonyl carbon atom forms an aluminate. Subsequent hydrolysis yields a hemiacetal, which decomposes to give the aldehyde. The hemiacetal is not converted to an aldehyde in the presence of DIBAL, so it is not reduced to an alcohol.



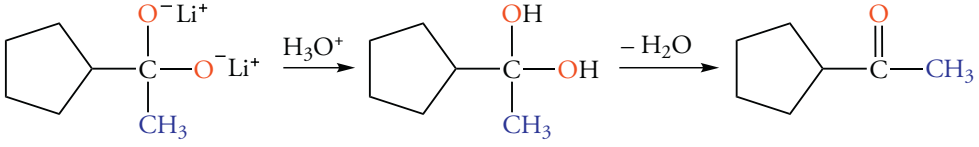
a hemiacetal

Reactions of Acid Derivatives with Organometallic Reagents

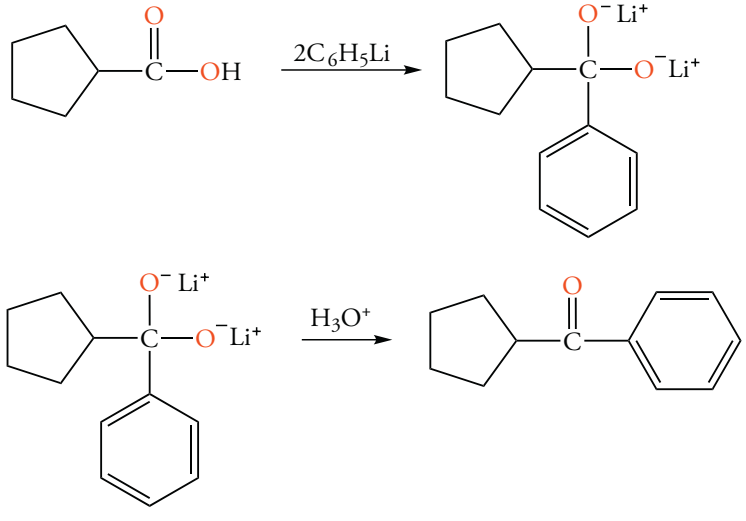
We recall that Grignard reagents add to aldehydes and ketones to give alcohols. We will also learn that Grignard reagents add to the carbonyl group of esters (Chapter 20). Organolithium compounds are more reactive than Grignard reagents, and they add to carbonyl groups. In fact, they are so reactive that they add to carboxylate anions even though the negative charge of a carboxylate anion makes its carbonyl carbon atom far less electrophilic than other carbonyl carbon atoms. For example, adding an organolithium reagent such as methyllithium to a carboxylate anion gives a dianion.



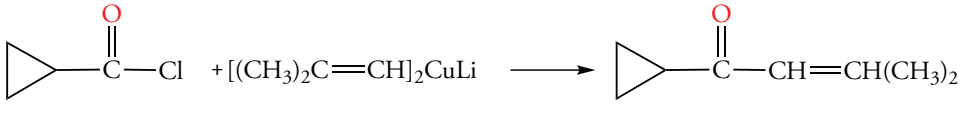
The dianion is treated with aqueous acid, yielding an unstable geminal diol. As we will learn in the next chapter, geminal diols spontaneously eliminate water to give carbonyl compounds. Thus, adding an organolithium reagent to a carboxylate anion gives a ketone in which the groups bonded to the carbonyl carbon atom are derived from both the carbonyl carbon atom and the organolithium reagent.



When the organolithium reagent is inexpensive, as in the case of phenyllithium, it is customary to add two equivalents of the reagent directly to the carboxylic acid. The first equivalent reacts with the carboxylic acid to form the lithium carboxylate salt. The second equivalent reacts with the carbonyl carbon atom of the carboxylate ion.

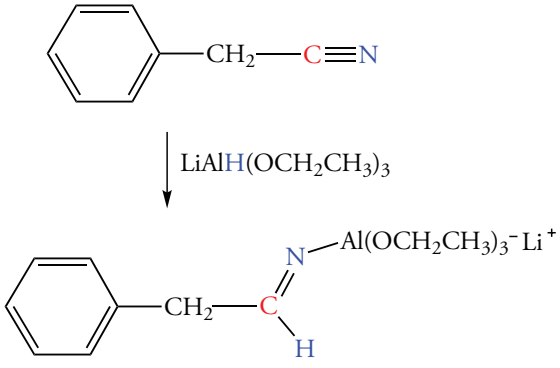


The carbonyl group of an acid chloride reacts with a nucleophilic carbanion of the Gilman reagent (Section 7.8), lithium dialkyl copper. This reagent reacts with acid chlorides and aldehydes, but only very slowly with ketones. Esters of carboxylic acids do not react at all. Thus, another synthesis of ketones using a carbonyl compound and an organometallic reagent has been developed using acid chlorides and the Gilman reagent. The resulting ketone product does not react further with agent under the reaction conditions.

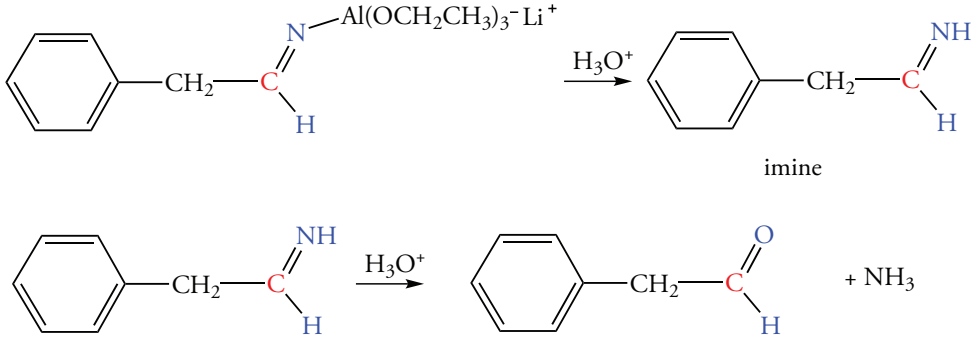


Synthesis of Carbonyl Compounds From Nitriles

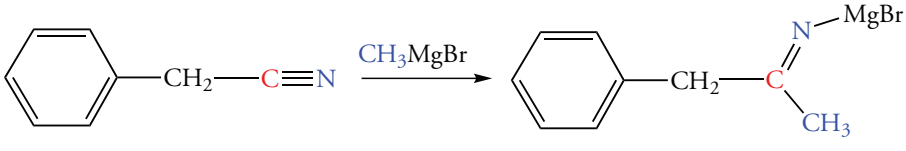
Nitriles can be reduced to amines by either catalytic hydrogenation or lithium aluminum hydride. However, the modified hydride reagent lithium triethoxyaluminum hydride adds to the bond only once to give an imine anion derivative.



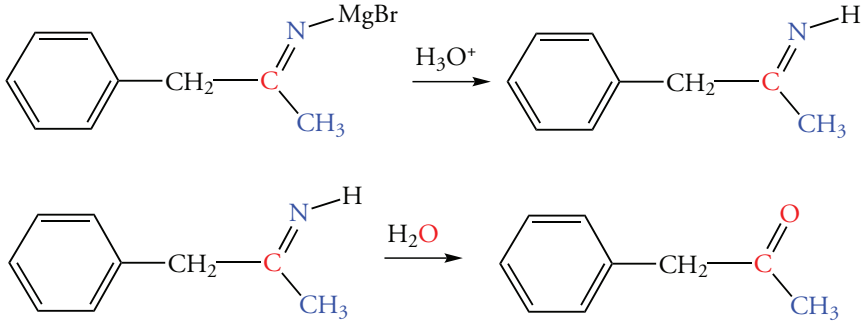
Treating the aluminum anion with aqueous acid yields an imine that is rapidly converted to an aldehyde. We will discuss the relative stabilities of imines and carbonyl groups in the next chapter.



Grignard reagents add to the triple bond of a nitrile to give an imine anion complexed with magnesium. The intermediate imine anion has a double bond, which might add a second equivalent of the Grignard reagent. However, this addition reaction does not occur under the reaction conditions.

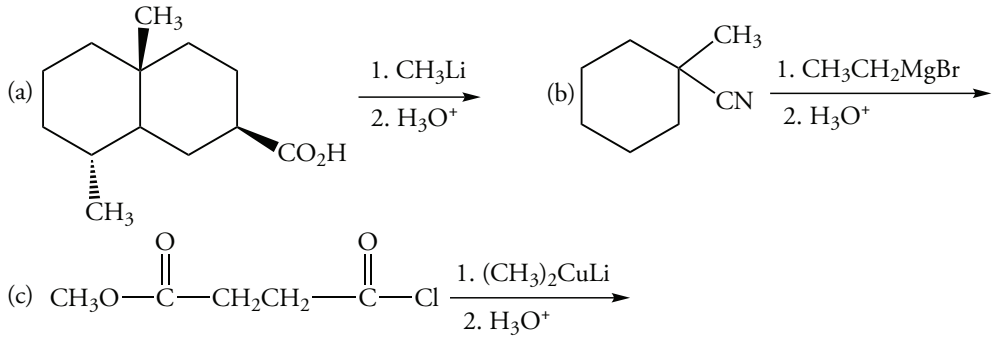


Treating the magnesium salt of the imine with aqueous acid rapidly gives the more stable ketone.



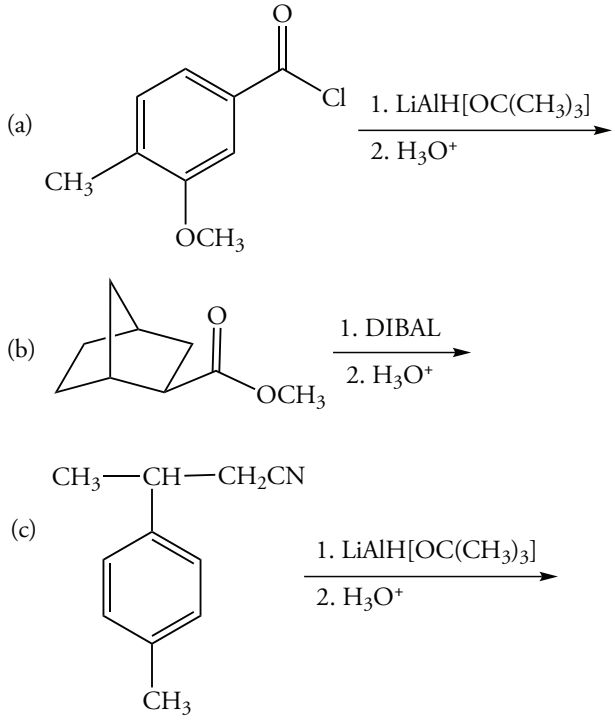
Problem 18. 14

Draw the structure of the product of each of the following reactions.



Problem 18. 15

Draw the structure of the product of each of the following reactions.



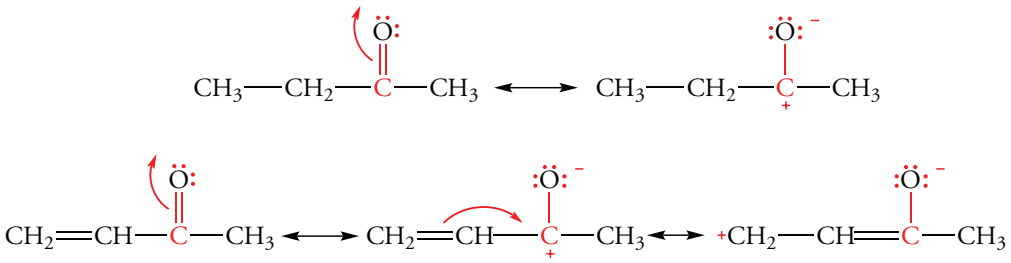
18.7 SPECTROSCOPY OF ALDEHYDES AND KETONES

Infrared Spectroscopy

The C=O stretching absorption is one of the most important and characteristic absorptions because it varies predictably as a result of differences in structure. The absorption, which is extremely intense, occurs in the vicinity of 1700 cm^{-1}. Because the C=O bond is stronger than the C=C bond, the carbonyl absorption occurs at higher wavenumber.

Simple ketones absorb at 1710–1715 cm^{-1}; simple aldehydes absorb at 1720–1725 cm^{-1}. Aldehydes also have a characteristic absorption near 2710 cm^{-1} for the aldehyde C—H bond. Cyclohexanones have carbonyl absorptions at the same position as simple acyclic ketones. However, decreased ring size results in shifts to higher wavenumber. Cyclopentanone, cyclobutanone, and cyclopropanone absorb at 1745, 1780, and 1850 cm^{-1}, respectively.

Compounds with carbon–carbon double bonds or aromatic rings in conjugation with the carbonyl group have absorptions at lower wavenumber than unconjugated carbonyl compounds. For example, the carbonyl absorptions of 3-buten-2-one and acetophenone occur at 1670 and 1685 cm^{-1}, respectively, whereas the carbonyl absorption of 2-butanone occurs at 1715 cm^{-1}. The decreased energy required to stretch the carbonyl group in a conjugated compound reflects the increased importance of contributing dipolar resonance structures. The carbonyl group of a conjugated compound has more single bond character illustrated by a second contributing dipolar resonance form of 3-buten-2-one compared to 2-butanone (Figure 18.4).



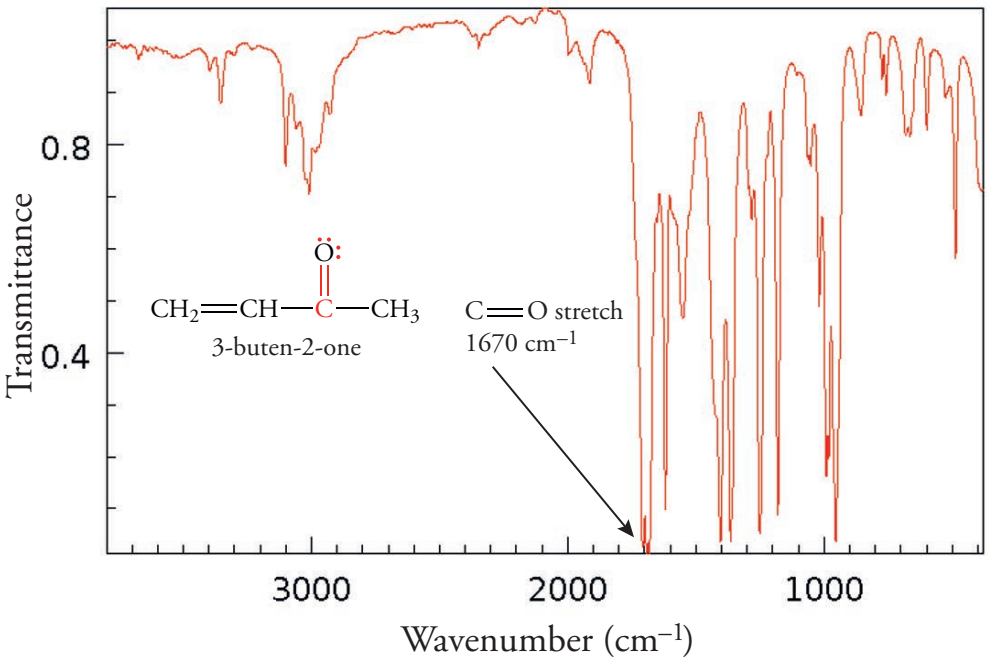


Figure 18.4
IR Spectrum of 3-buten-2-one
The carbonyl stretching frequency occurs at 1670 cm^{-1}.

Proton NMR Spectroscopy

In both aldehydes and ketones, the protons on the carbon atoms adjacent to the carbonyl carbon atom—the α-protons— have NMR absorptions in the 2.0-2.5 δ region depending on the degree of substitution of the α carbon atom. The absorption of the aldehyde hydrogen atom occurs in the 9.5–10 δ region. This strong deshielding effect is a consequence of the contribution of π electrons of the carbonyl group as well as the inductive effect of the carbonyl oxygen atom. The NMR absorptions of ethanal, propanone, and 2-butanone illustrate typical data obtained for aldehydes and ketones are shown below. Figure 18.5 shows the proton NMR spectrum of 2-butanone.

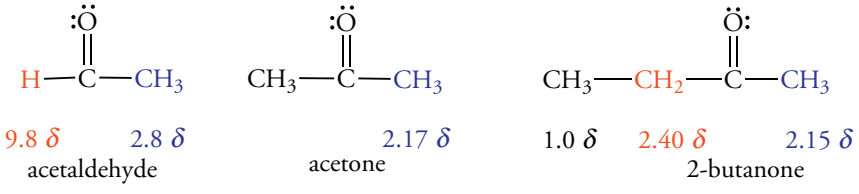
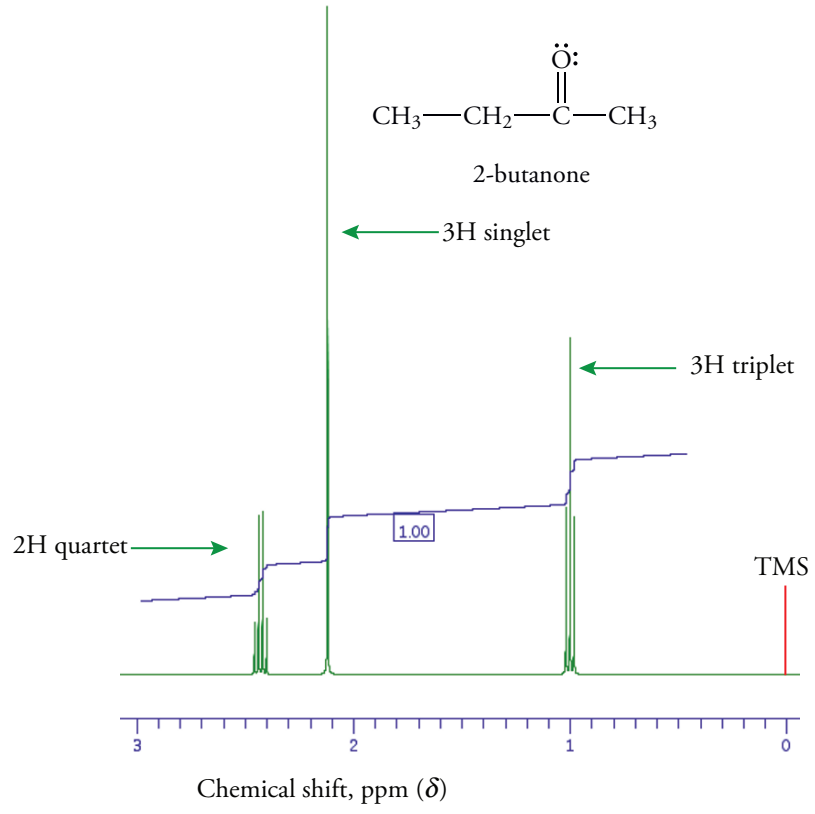


Figure 18.5
Proton NMR Spectrum of
2-Butanone

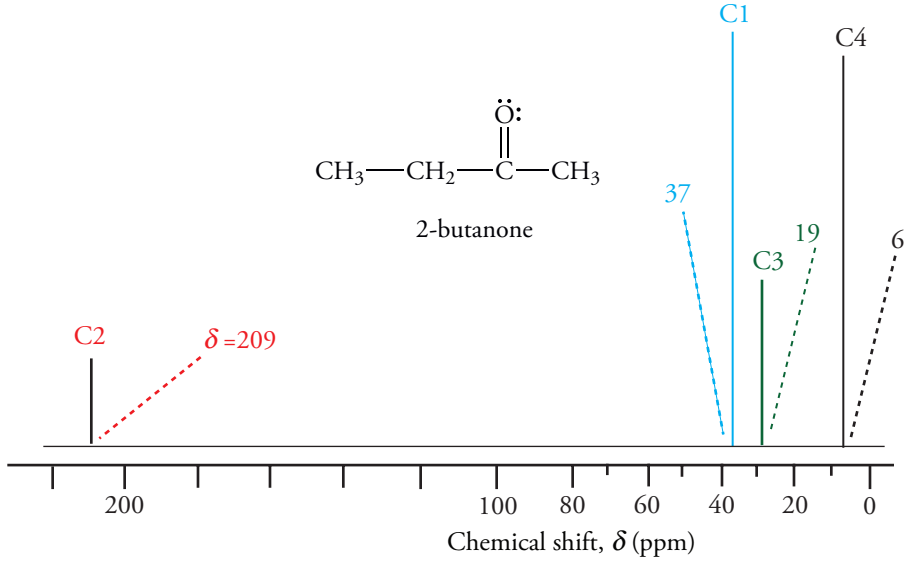


C-13 NMR Spectroscopy

The absorption of the α carbon atom of aldehydes and ketones occurs in the 30–50 δ region with the usual effects of increased substitution resulting in absorptions at lower field. Other carbon atoms with a variety of functional groups in the proximity also absorb in this region. Therefore, absorptions in this region cannot be used to unambiguously assign the structure of a carbonyl compound.

The most characteristic absorption of aldehydes and ketones is due to the carbonyl carbon atom itself and occurs in the 190–220 δ range. This very low field position is due to both the effect of π electrons and the inductive effect of the electronegative oxygen atom. The absorption of the carbonyl carbon atom of an aldehyde is a doublet as a result of coupling with the aldehyde hydrogen atom but a singlet in ketones, which have no hydrogen atoms bonded directly to the carbonyl carbon atom. As we noted earlier (Section 14.8), the intensity of carbon-13 NMR resonances is not directly proportional to the number of carbon atoms. In the case of carbonyl carbon atoms, the absorption is very weak (Figure 18.6).

Figure 18.6
C-13 NMR Spectrum of
2-Butanone



Problem 18. 16

How could IR spectroscopy be used to distinguish between the isomers of each of the following pairs?

(a) 2-methylcyclopentanone and 2-ethylcyclobutanone
(b) 3-cyclohexenone and 2-cyclohexenone
(c) 4-methylbenzaldehyde and 4-methoxybenzaldehyde
(d) 2-methylcyclohexanone and cyclohexanecarbaldehyde

Problem 18. 17

Suggest a reason for the observation that the IR absorption of the carbonyl group of a ketone is at lower wavenumber than that of the carbonyl group of an aldehyde.

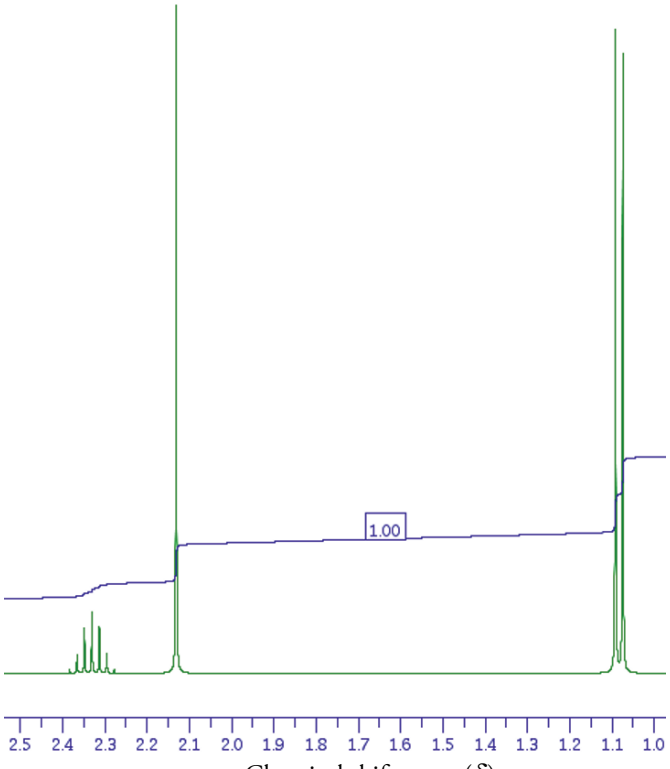
Problem 18. 18

Deduce the structure of isomeric compounds having the molecular formula C_4H_8O based on the following C-13 NMR data.

(a) 7.6 ppm, 28.8 ppm, 36.4 ppm, 206.3 ppm
(b) 13.3 ppm, 15.7 ppm, 45.7 ppm, 201.6 ppm

Problem 18. 20

Deduce the structure of a compound with the molecular formula $C_5H_{10}O$ based on the following proton NMR spectrum.



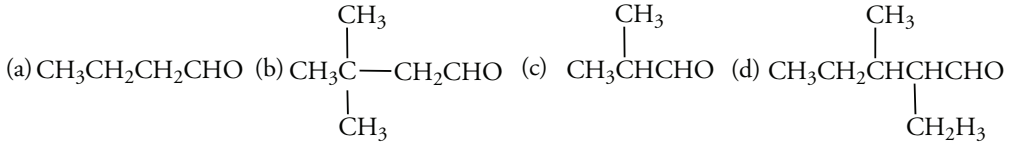
EXERCISES

Nomenclature of Aldehydes and Ketones

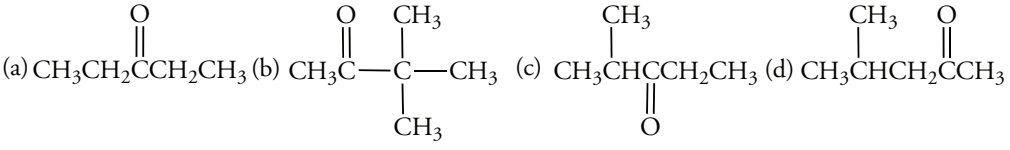
18.1 Write the structure for each of the following compounds.
(a) 2-methylbutanal (b) 3-ethylpentanal (c) 2-bromopentanal
(d) 3,4-dimethyloctanal (e) 1-bromocyclobutanecarbaldehyde

18.2 Write the structure of each of the following compounds.
(a) 3-bromo-2-pentanone (b) 2,4-dimethyl-3-pentanone (c) 4-methyl-2-pentanone
(d) 3,4-dimethyl-2-pentanone (e) 2-methyl-1,3-cyclohexanedione

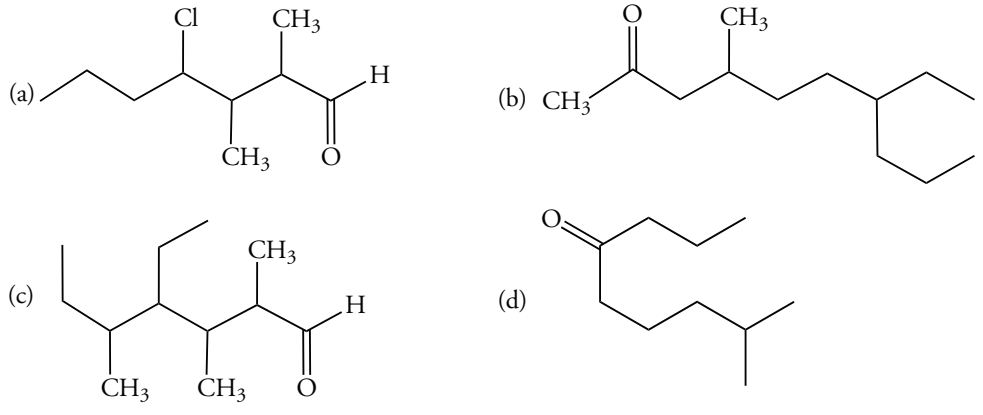
18.3 Give the IUPAC name of each of the following compounds.



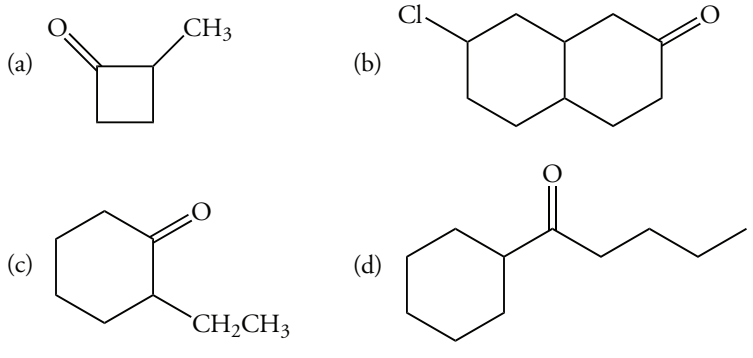
18.4 Give the IUPAC name of each of the following compounds.



18.5 Give the IUPAC name of each of the following compounds.



18.6 Give the IUPAC name of each of the following compounds.



18.7 Many aldehydes and ketones are better known by their common names. Draw the structural formula of each of the following carbonyl compounds. Their common names are given within parentheses.

(a) 2,2-dimethylpropanal (pivaldehyde)
(b) 2-hydroxy-1,2-dipheny1-1-ethanone (benzoin)
(c) 2-propenal (acrolein)
(d) 4-methyl-3-penten-2-one (mesityl oxide)
(e) 5,5-dimethy1-1,3-cyclohexanedione (dimedone)

18.8 Draw the structural formula of each of the following carbonyl compounds. The common name of each compound is given within parentheses.

(a) 3,3-dimethyl-2-butanone (pinacolone)
(b) 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol)
(c) (*E*)-2-butenal (crotonaldehyde)
(d) 1,3-dipheny1-2-buten-l-one (dypnone)
(e) 2,3-butanedione (biacetyl)

Properties of Aldehydes and Ketones

18.9 The H—C—H bond angle of formaldehyde is 116.5°. The H—C—C bond angle of acetaldehyde is 118.2°. Explain this difference.

18.10 The C=C bond length in alkenes and the C=O bond length in aldehydes are 134 and 123 ppm, respectively. Explain this difference.

18.11 The dipole moments of acetone and isopropyl alcohol are 2.7 and 1.7 D, respectively. Explain this difference.

18.12 The dipole moments of propanal and propenal are 2.52 and 3.12 D, respectively. Consider the resonance forms of these compounds and explain the difference in their dipole moments.

18.13 The boiling points of butanal and 2-methylpropanal are 75 and 61 °C, respectively. Explain this difference.

18.14 The boiling points of 2-heptanone, 3-heptanone, and 4-heptanone are 151, 147, and 144 °C, respectively. What is responsible for this trend?

18.15 The boiling points of 2-hydroxy- and 3-hydroxybenzaldehydes are 197 and 240 °C, respectively. Suggest a reason for this difference.

18.16 The boiling points of 2-hydroxy- and 3-hydroxyacetophenones are 218 and 296 °C, respectively. Suggest a reason for this difference.

18.17 The solubilities of butanal and 1-butanol in water are 7 and 9 g/100 mL, respectively. Explain this difference.

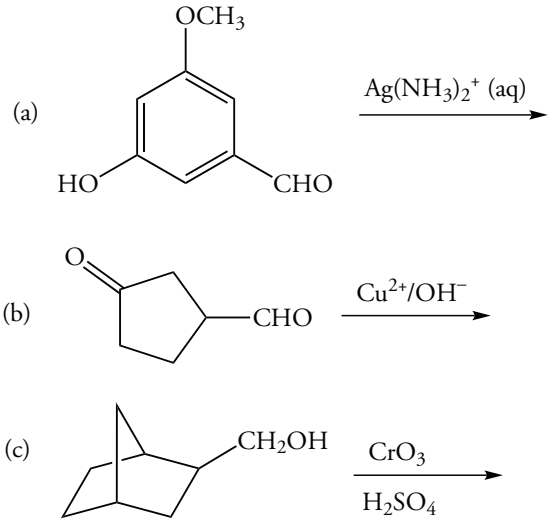
18.18 The solubilities of butanal and 2-methylpropanal in water are 7 and 11 g/100 mL, respectively. Explain this difference.

Oxidation and Reduction of Carbonyl Compounds

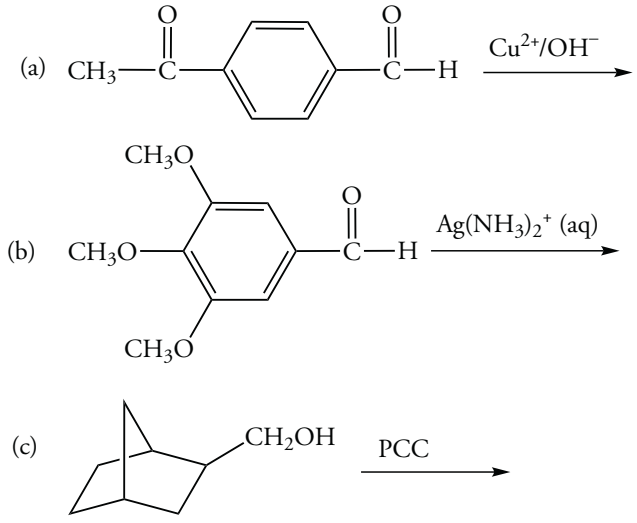
18.19 What is observed when an aldehyde reacts with Benedict's solution? What is observed when an aldehyde reacts with Tollens reagent?

18.20 What class of compounds results from the reduction of ketones with sodium borohydride? What class of compounds results from the reduction of aldehydes by lithium aluminum hydride?

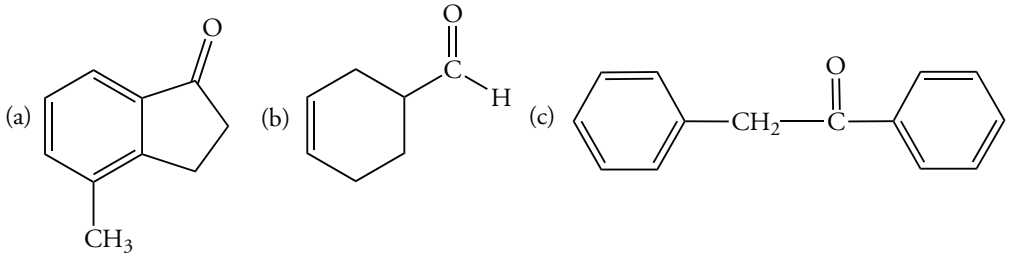
18.21 Draw the structure of the product of each of the following reactions.



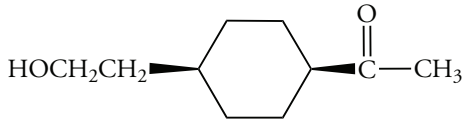
18.22 Determine the best choice of reactants to synthesize each of the following ethers using the Williamson method.

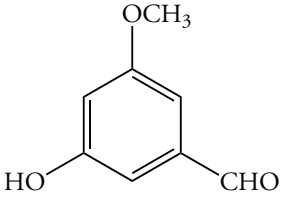


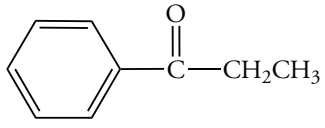
18.23 What is the product when each of the following reacts with lithium aluminum hydride?



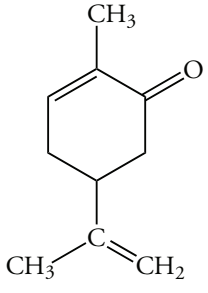
18.24 What is the product when each of the following reacts with sodium borohydride?

(a) 

(b) 

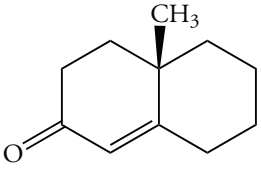
(c) 

18.25 Explain why the reduction of carvone by lithium aluminum hydride yields two products.

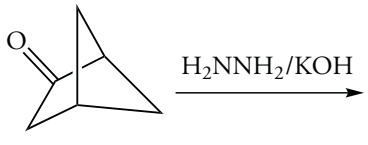


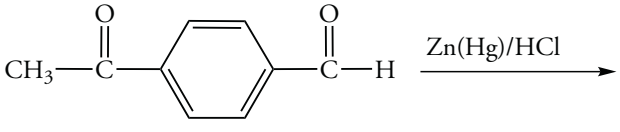
carvone

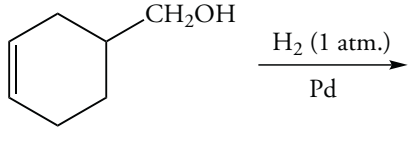
18.26 Explain why the reduction of the following compound by sodium borohydride yields two products.



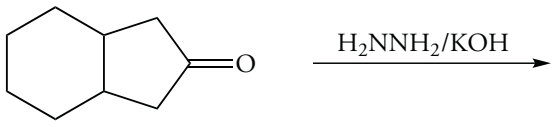
18.27 What is the product of each of the following reactions?

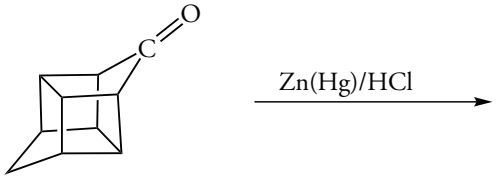
(a) 

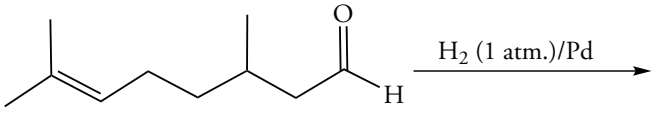
(b) 

(c) 

18.28 What is the product of each of the following reactions?

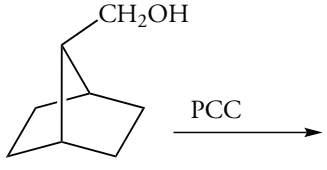
(a) 

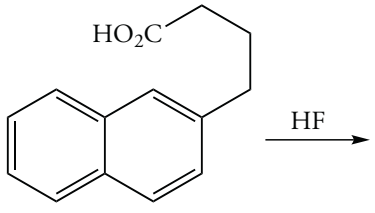
(b) 

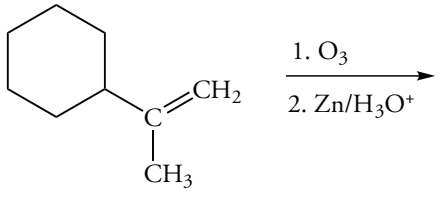
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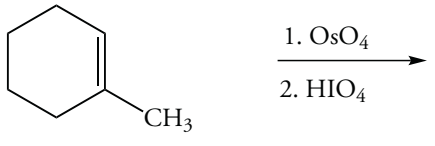
Synthesis of Carbonyl Compounds

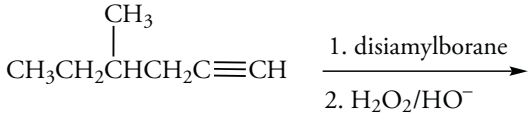
18.29 What is the product of each of the following reactions?

(a) 

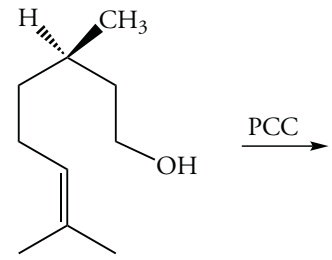
(b) 

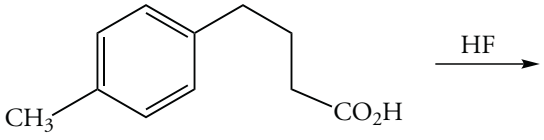
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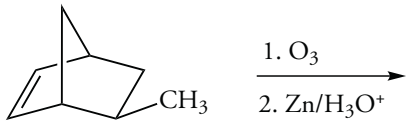
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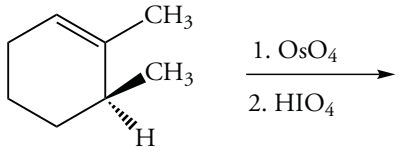
(e) 

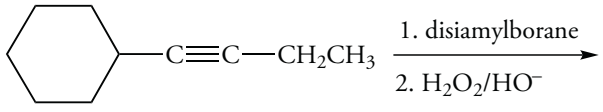
18.30 What is the product of each of the following reactions?

(a) 

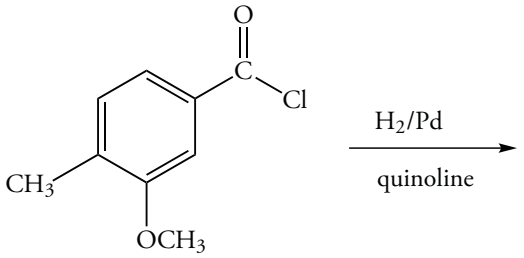
(b) 

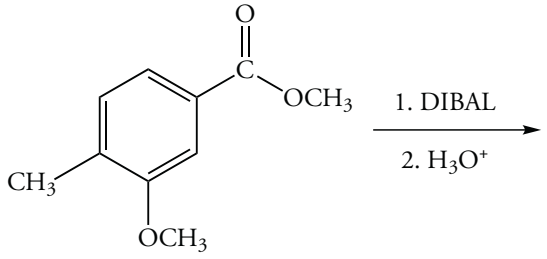
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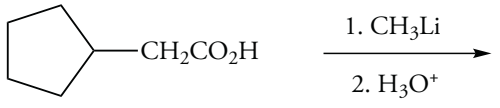
(d) 

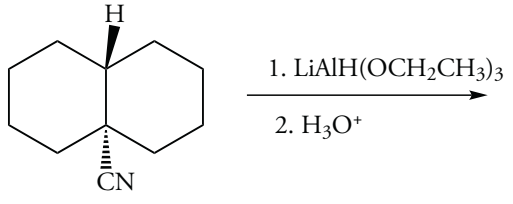
(e) 

18.31 What is the product of each of the following reactions?

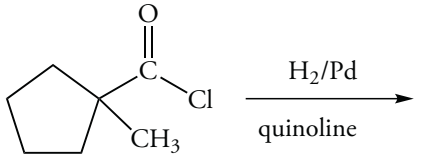
(a) 

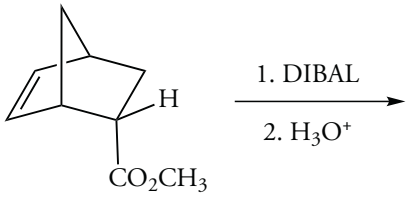
(b) 

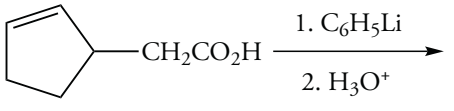
(c) 

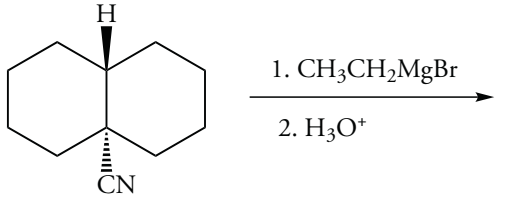
(d) 

18.32 What is the product of each of the following reactions?

(a) 

(b) 

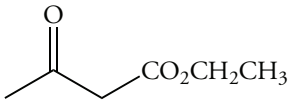
(c) 

(d) 

Biochemical Reductions

18.33 Reduction of 5-chloro-2-pentanone by NADPH in an enzyme-catalyzed reaction yields (*S*)-5-chloro-2-pentanol. From which face does the hydrogenation occur?

18.34 Reduction of the ketone group of the following keto ester occurs stereospecifically at the *re* face using NADH in an enzyme-catalyzed reaction. Draw the structure of the product and assign its configuration.



Spectroscopy of Aldehydes and Ketones

18.35 Explain why the IR absorption of the C=C bond of 1-butene (1642 cm^{-1}) is at higher wavenumber than the C=C bond absorption of 3-buten-2-one (1613 cm^{-1}).

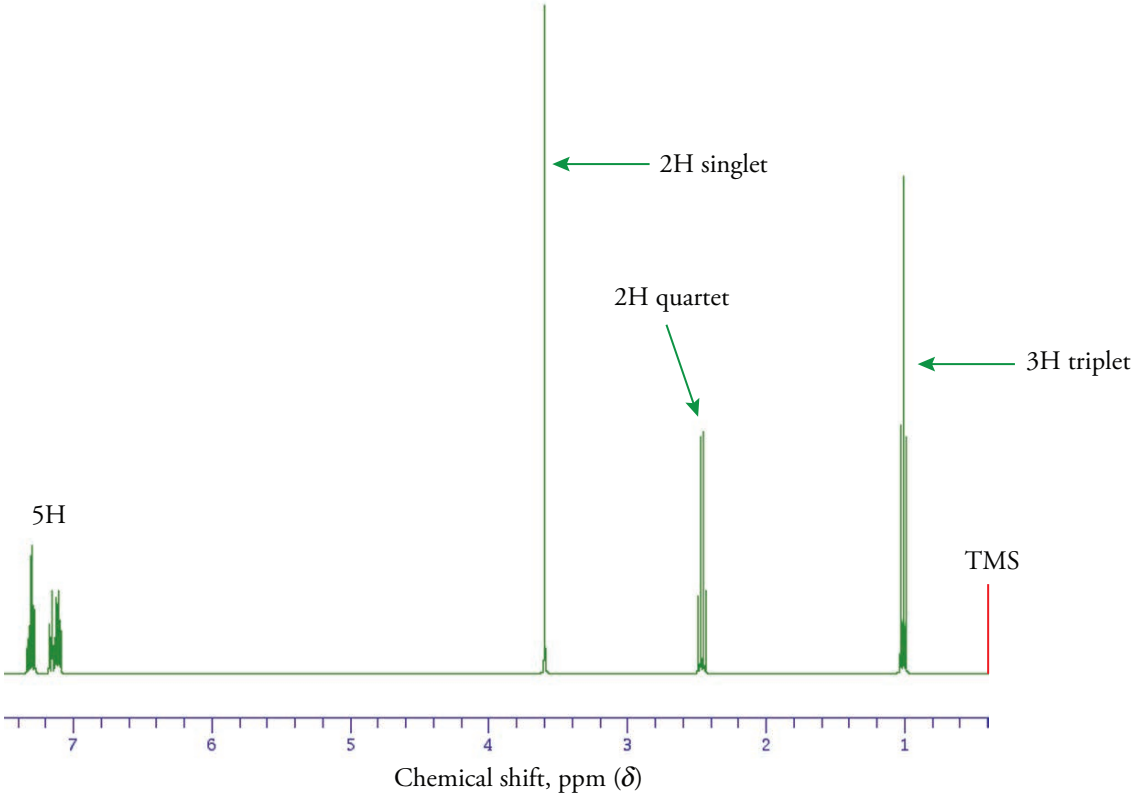
18.36 Explain why the carbonyl stretching absorption of cyclohexanones are shifted approximately 20 cm^{-1} to higher wavenumber when a bromine atom is substituted in the equatorial position at the α carbon atom.

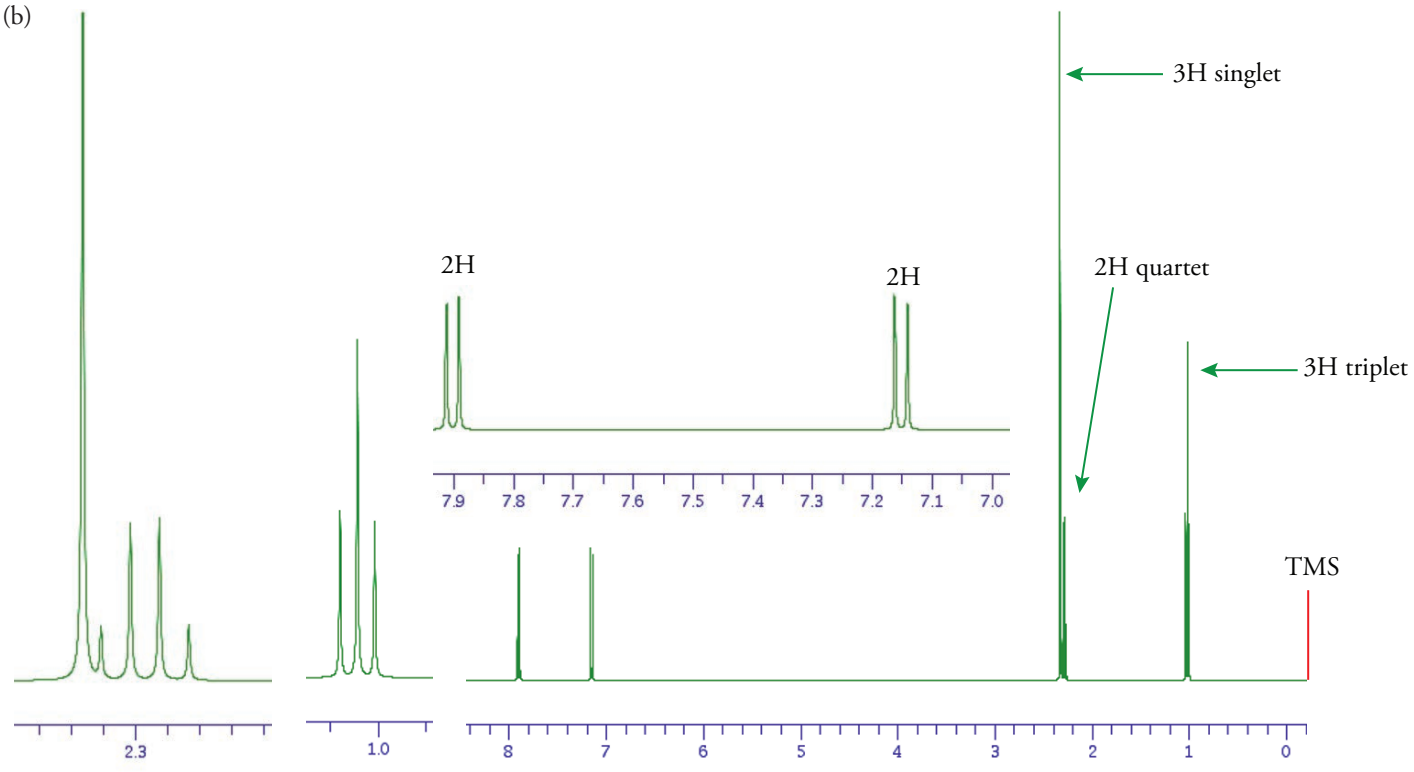
18.37 Based on the following C-13 NMR data, deduce the structures of isomeric compounds having the molecular formula C_4H_8O.
(a) 25.7 ppm, 68.0 ppm
(b) 15.5 ppm, 41.0 ppm, 204.9 ppm
(c) 7.9 ppm, 29.4 ppm, 36.9 ppm, 209.2 ppm
(d) 13.7 ppm, 15.7 ppm, 45.8 ppm, 207.6 ppm

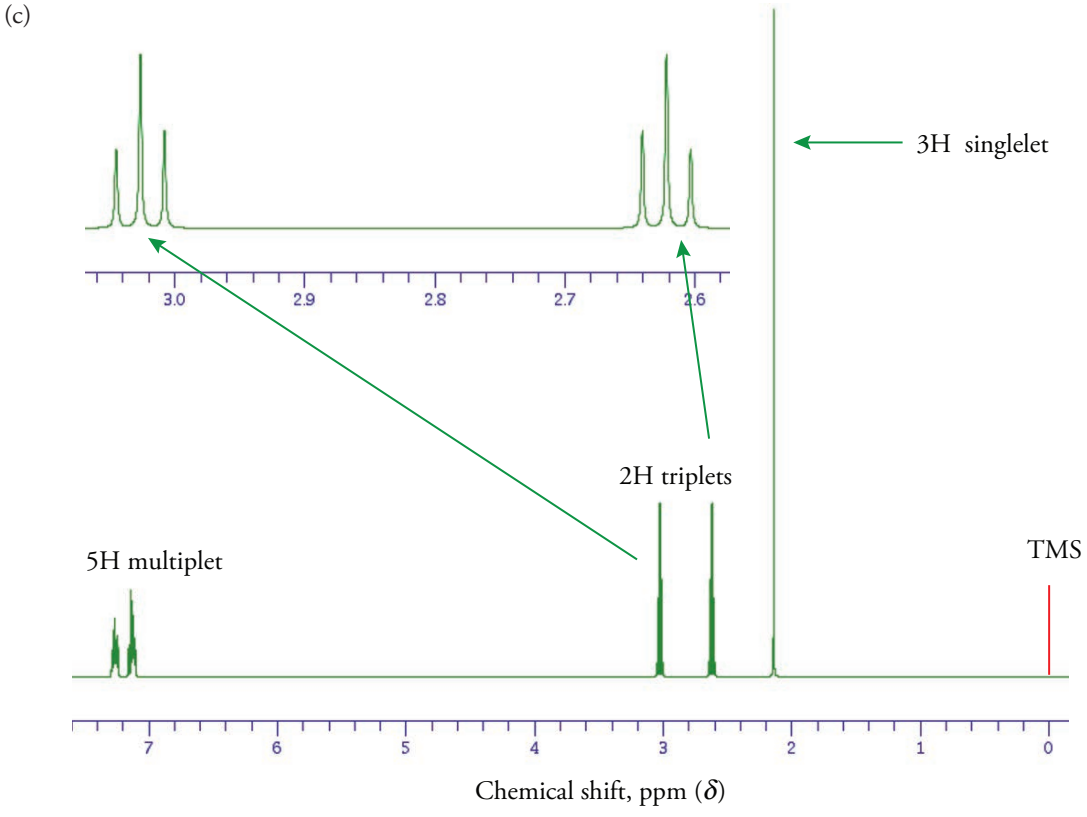
18.38 Based on the following C-13 NMR data, deduce the structures of isomeric ketones having the molecular formula $C_5H_{10}O$.
(a) 18.1 ppm, 27.3 ppm, 41.5 ppm, 211.7 ppm
(b) 13.5 ppm, 18.5 ppm, 29.3 ppm, 45.2 ppm, 206.6 ppm
(c) 7.3 ppm, 35.3 ppm, 209.3 ppm

18.39 Deduce the structure of isomeric ketones having the molecular formula $C_{10}H_{12}O$ based on the following proton NMR spectra.

(a)

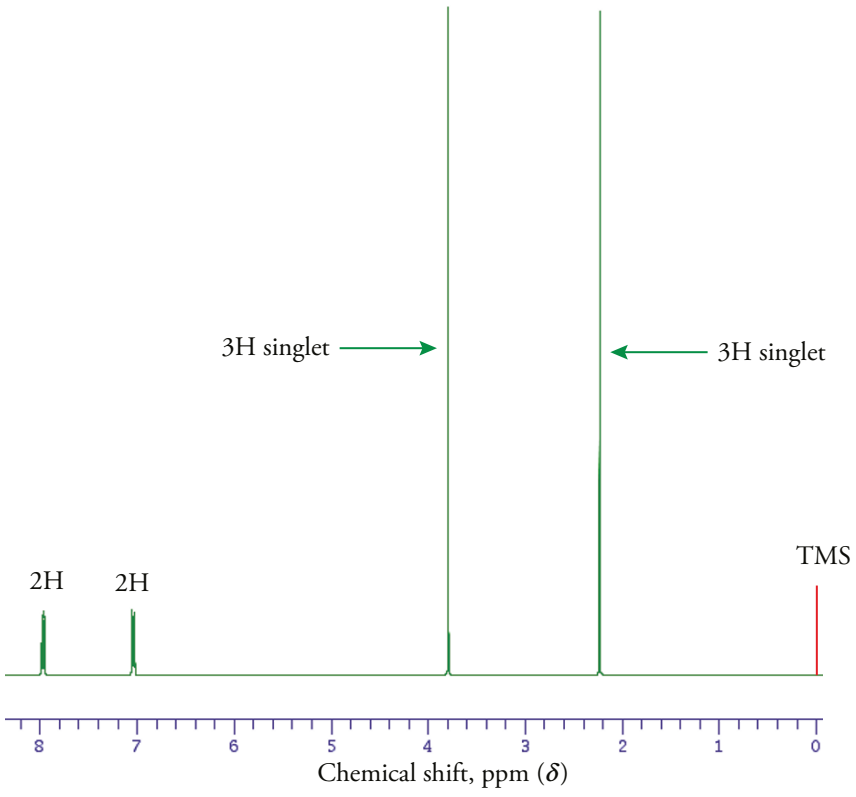



(b)
3H singlet
2H
2H
2H quartet
3H triplet
TMS
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
2.3
1.0
8
7
6
5
4
3
2
1
0
Chemical shift, ppm (δ)

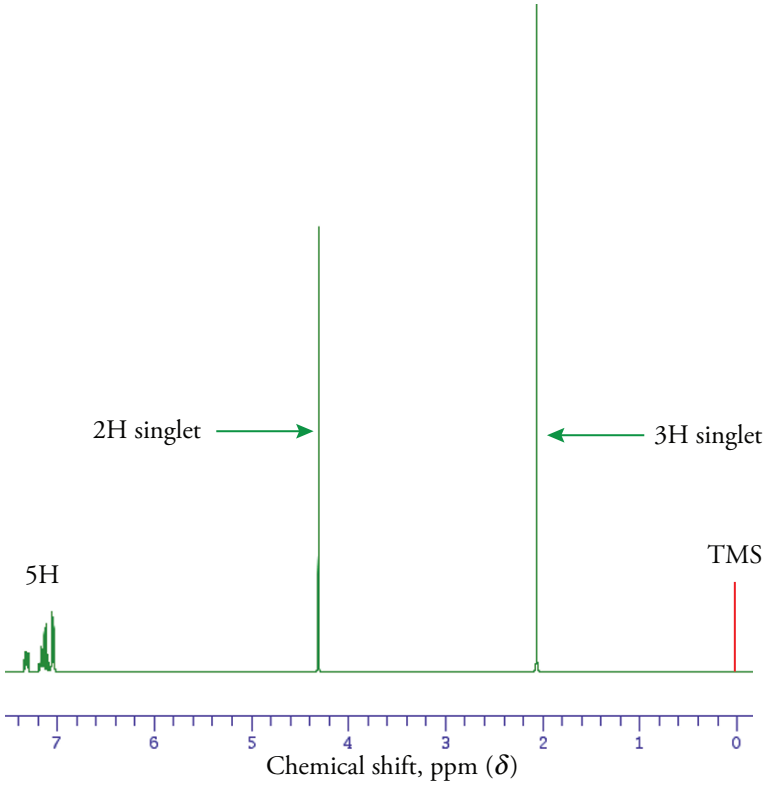

(c)
3H singlelet
3.0
2.9
2.8
2.7
2.6
2H triplets
5H multiplet
TMS
7
6
5
4
3
2
1
0
Chemical shift, ppm (δ)

18.40 Deduce the structure of isomeric ketones having the molecular formula $C_9H_{10}O_2$ based on the following proton NMR spectra.

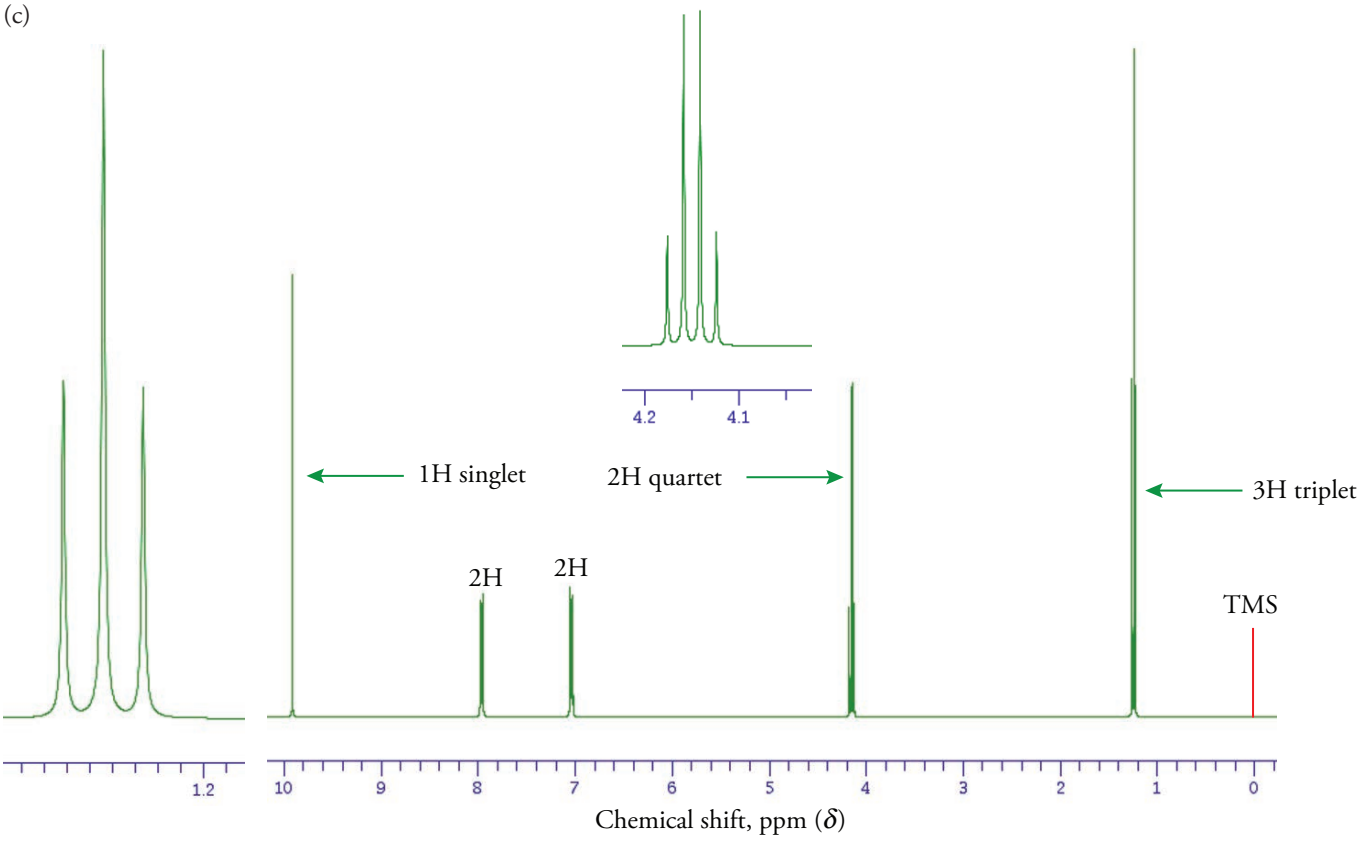
(a)



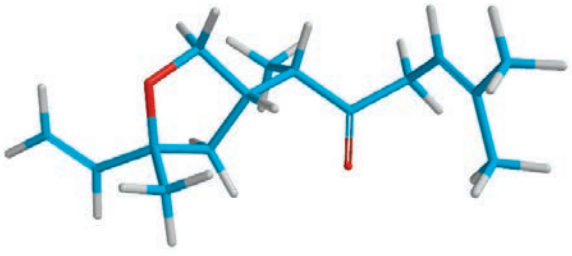
(b)



(c)


4.2
4.1
1H singlet
2H quartet
3H triplet
2H
2H
TMS
1.2
10
9
8
7
6
5
4
3
2
1
0
Chemical shift, ppm (δ)

19 Aldehydes and Ketones: Nucleophilic Addition Reactions

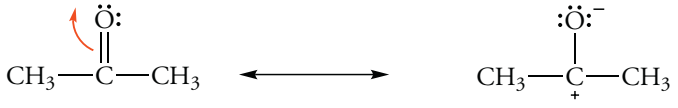


Davanone

In the preceding chapter, we saw that the chemistry of the carbonyl group turns upon its polarity. In this chapter, we examine the differences in stability and reactivity of aldehydes and ketones. Many of the reactions we discuss occur by addition of a nucleophile to the carbonyl carbon and the addition of an electrophile to the carbonyl oxygen. Sometimes these reactions produce a stable, tetrahedral adduct, as we see in the compound shown at the left. In other cases, the tetrahedral adduct undergoes further reaction. Nucleophilic addition to carbonyl groups is a major new class of reaction mechanism.

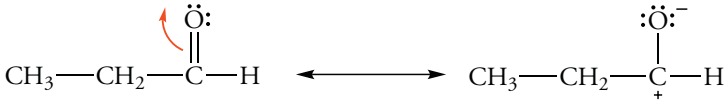
19.1 RELATIVE STABILITIES OF ALDEHYDES AND KETONES

Ketones are more stable than aldehydes. If a reactant is stable, a reaction that destroys its structure is less likely to take place. The carbonyl group of either an aldehyde or a ketone has two resonance forms. In one form, the carbonyl carbon has a positive charge and the carbonyl oxygen atom has a negative charge. We know that alkyl groups stabilize carbocations. Thus, the dipolar resonance form of propanone, in which the carbonyl carbon is bonded to two alkyl groups, is more stable than the dipolar resonance form of propanal, which is bonded to one alkyl group and a hydrogen atom. The dipolar resonance form of a ketone is a secondary oxycarbocation; the dipolar resonance form of an aldehyde is a primary oxycarbocation. The secondary oxycarbocation is more stable. Thus, the carbonyl carbon of aldehydes is more electrophilic than the carbonyl carbon of ketones.



propanone

dipolar resonance structure, secondary oxycarbocation



propanal

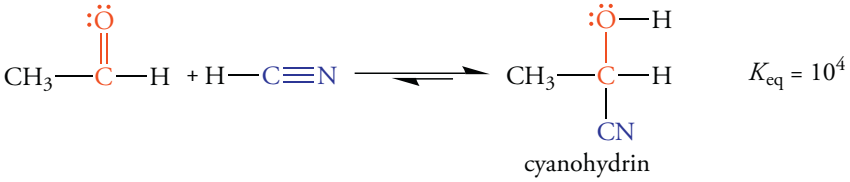
dipolar resonance structure, primary oxycarbocation

The importance of the dipolar resonance forms is reflected in the stabilities of isomeric carbonyl compounds. Propanal is approximately 27 kJ mole^{-1} less stable than propanone. For addition reactions, two isomeric products with different stabilities also form. Therefore, we also have to consider the relative stabilities of the products. Hydrogenation of propanal and propanone gives isomeric alcohols. 1-Propanol is approximately 16 kJ mole^{-1} less stable than 2-propanol. Since the difference in the stabilities of the reactants is *greater* than the difference in the stabilities of the products, the equilibrium constants for the addition reactions of carbonyl compounds depend on more differences in the structure of the carbonyl compound than on the differences in the structure of the addition product. Thus, because ketones are more stable than aldehydes, the addition reactions of ketones are less favorable (have smaller equilibrium constants) than addition reactions of aldehydes.

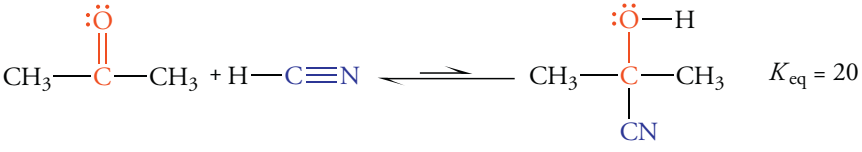
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00019-X
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19.2 FORMATION OF CYANOHYDRINS

Hydrogen cyanide adds to an aldehyde or ketone to give a compound called a **cyanohydrin**. In the product, the nucleophilic cyano group is bonded to the carbonyl carbon and the proton is bonded to the carbonyl oxygen. As we noted above, because ketones are more stable than aldehydes, the addition reactions of ketones are less favorable (have smaller equilibrium constants) than addition reactions of aldehydes. Thus, the equilibrium constant for the addition of HCN is much more favorable for aldehydes than for ketones.



cyanohydrin



Many addition reactions of aldehydes and ketones are reversible. Under acidic conditions, the reaction for ethanal has a favorable equilibrium constant; however, the equilibrium constant for cyanohydrin of propanone is quite unfavorable. Cyanohydrins are stable under acidic conditions.

Under basic conditions, a cyanohydrin readily undergoes elimination to give an aldehyde. Thus, we cannot make a cyanohydrin under basic conditions. Note that the 1,2 elimination reaction of the cyanohydrin is analogous to the β-elimination reactions of haloalkanes to give alkenes that we discussed in Chapters 9 and 10.

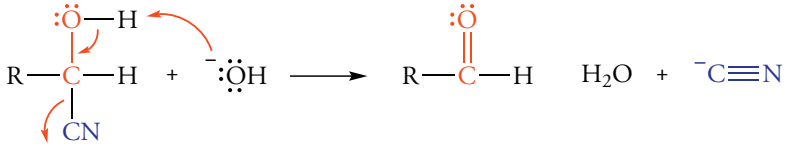


Table 19.1
Equilibrium Constants for Cyanohydrin Formation

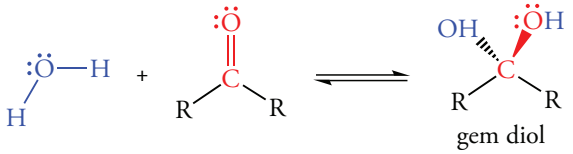
Compound	K_{eq}
Acetaldehyde	10,000
Acetone	20
Benzaldehyde	210
p-Methoxybenzaldehyde	30
Acetophenone	0.8

The equilibrium constants for cyanohydrin formation depend upon three factors (Table 19.1).

1. Carbonyl addition reactions of aldehydes have larger equilibrium constants than addition reactions of ketones.
2. Carbonyl addition reactions have smaller equilibrium constants when groups bonded to the carbonyl carbon atom donate electrons by resonance.
3. Addition reactions are favored by electron withdrawing groups since these groups increase the electrophilicity of the carbonyl carbon.

19.3 HYDRATION OF CARBONYL COMPOUNDS

Aldehydes and ketones react with water to form *gem* diols called *hydrates*. The equilibrium constant for hydrate formation depends on both steric and electronic factors. As in the case of cyanohydrins, the reaction with aldehydes is far more favorable than the reaction with ketones.



gem diol
(a hydrate)

Table 19.2 lists the K_{eq} values for some representative hydration reactions. These equilibrium constants show the same trends found for the addition of HCN to a carbonyl group. Aldehydes with low molecular weights readily form hydrates. Formaldehyde is over 99% hydrated. Its hydrate is called **formalin**, a 37% by weight solution of formaldehyde in water that was used in the past to preserve biological specimens. Other aldehydes are substantially less hydrated. Ketones are normally hydrated less than 1%. The hydrates of aldehydes and ketones usually cannot be isolated and exist only in solution.

Table 19.2
Equilibrium Constants for Hydrate Formation

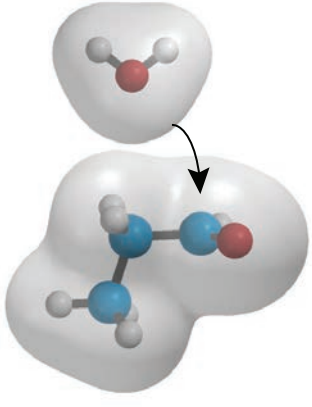
Compound	K_{eq}
Methanal	2.2×10^{3}
Ethanal	1
Chloroacetaldehyde	40
Acetone	1.4×10^{-3}
Benzaldehyde	8×10^{-3}
Acetophenone	6.6×10^{-6}

Steric Effects on Nucleophilic Addition Reactions

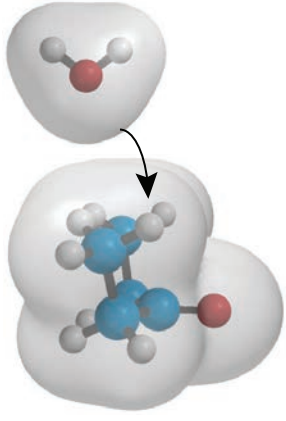
We have already seen that the carbonyl addition reactions of ketones occur less readily than the addition reactions of aldehydes because ketones are more stable. Steric effects are also important. The two groups bonded to sp^2-hybridized carbonyl carbon atom in the product are 120° apart. These groups block the approach of the nucleophile. Since a ketone has two alkyl (or aryl) groups, a ketone is more sterically hindered than an aldehyde having the same alkyl group. Thus, ketones react more slowly than aldehydes (Figure 19.1)

In the product, they are approximately 109° apart. Therefore, there is more crowding in the product than in the reactant. Thus, increasing the size of the groups attached to the carbonyl carbon atom also decreases the equilibrium constant for hydration.

Figure 19.1
Steric Effects on the Equilibrium of Hydration Reactions
The carbonyl group of an aldehyde (a) is less sterically hindered than the carbonyl group of a ketone (b). Therefore, ketones react more slowly than aldehydes in nucleophilic addition reactions. The nucleophile here is water.

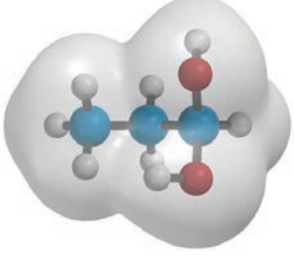


(a) Hydration of an aldehyde

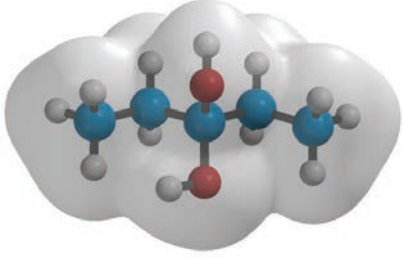


(b) Hydration of a ketone

Figure 19.2
Steric Effects in Hydrates
The hydrate of an aldehyde (a) is less sterically hindered than the hydrate of a ketone (b).



(a) 1,1-propanediol



(b) 3,3-pentanediol

Inductive Effects on Addition Reactions

The equilibrium constants for the addition reactions of acetone and hexafluoroacetone are dramatically different. There is very little difference in the steric effect of a CH_3 and a CF_3 group because the van der Waals radii of hydrogen and fluorine are similar. However, the CH_3 and CF_3 groups have different effects on the stability of the carbonyl group. The CF_3 group withdraws electron density from the carbonyl carbon atom and therefore destabilizes the carbonyl group. The CF_3 group has a much smaller destabilizing effect on the addition product. Therefore, the electron-withdrawing CF_3 group increases the equilibrium constant for the addition reaction (Figure 19.2).

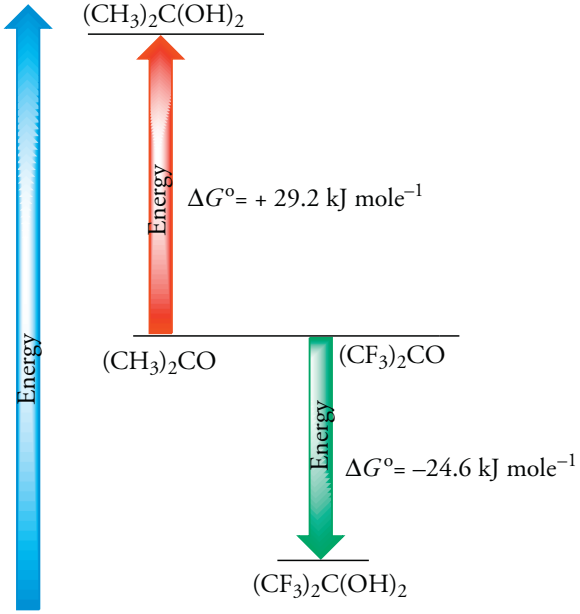


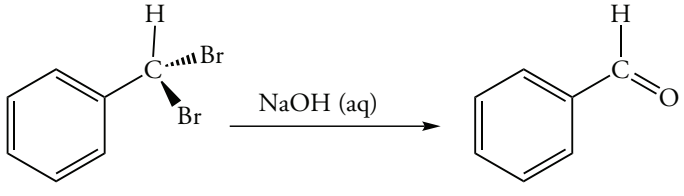
Figure 19.3
Inductive Effects on the Equilibrium of Hydration Reactions
The relative energies of acetone and hexafluoroacetone are arbitrarily set as equal. The free energy of hydration of acetone is positive, whereas the free energy of hydration of hexafluoroacetone is negative.

Problem 19. 1
The equilibrium constants for the formation of cyanohydrins of benzaldehyde and *p*-methoxyacetophenone are approximately 210 and 30, respectively. Does this difference reflect a steric effect, a resonance effect, or an inductive effect?

Problem 19. 2
The equilibrium constant for the hydration of trichloroethanal is 3×10^4. Why is this value so much larger than the equilibrium constant for the hydration of ethanal?

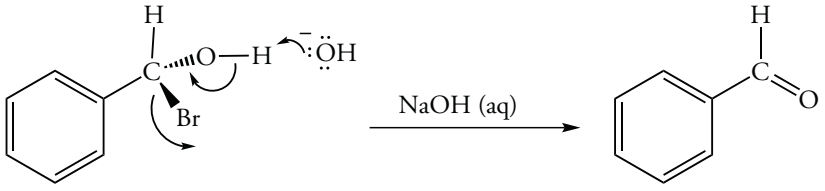
Sample Solution
The combined electron-withdrawing inductive effect of the three chlorine atoms bonded to the carbonyl group destabilized the polar resonance contributor to the resonance hybrid. This provides a much greater driving force for the reaction.

Problem 19. 3
Explain why the S_N2 reaction of (dibromomethyl)benzene with NaOH yields benzaldehyde.



Sample Solution

Displacement of the first bromide ion by hydroxide ion yields a benzyl alcohol with the remaining bromine bonded to the benzyl carbon atom. This compound is the potential addition product of hydrogen bromide with benzaldehyde. We know that K_{eq} is unfavorable for the addition reaction. Thus, the elimination reaction is favored, and the intermediate bromo alcohol formed in the S_N2 reaction of (dibromomethyl)benzene loses HBr to give benzaldehyde (Figure 19.3).

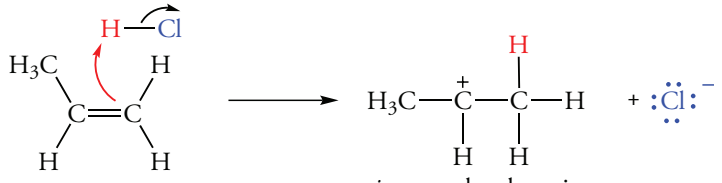


Problem 19. 4

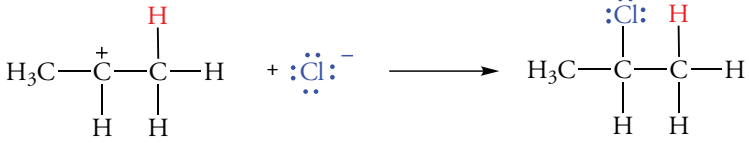
The equilibrium constants for the formation of cyanohydrins of acetaldehyde and acetone are 1×10^4 and 30, respectively. What structural features of the reactants account for the difference between the equilibrium constants?

19.4 MECHANISMS OF ACID- AND BASE-CATALYZED CARBONYL ADDITION REACTIONS

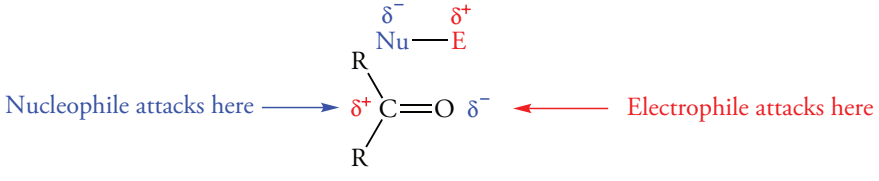
We recall from our discussion of alkenes in Chapter 6 that unsymmetrical reagents such as HCl add to π bonds. In these reactions, the electrophilic proton reacts with the π bond to give an intermediate carbocation whose stability determines the position of electrophilic attack on the double bond. The carbocation intermediate then reacts with a nucleophile to give the addition product.



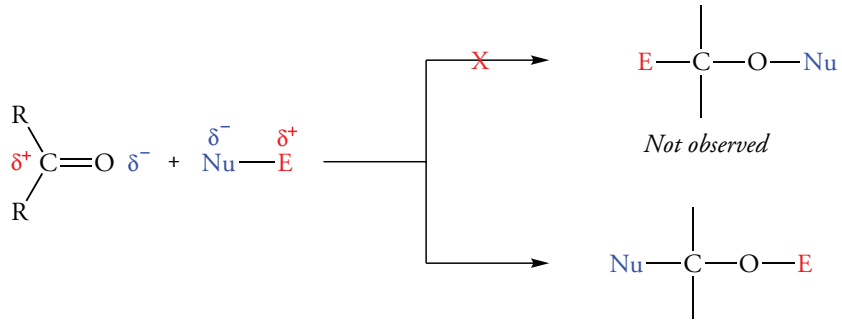
iso-propyl carbocation
(secondary carbocation)



Aldehydes and ketones also contain a π bond. They too react with unsymmetrical reagents to give addition products. The carbonyl bond is polar, and a polar reagent reacts so that the electrophilic part, (E), bonds to the carbonyl oxygen and the nucleophilic part, (Nu), bonds to the carbonyl carbon.



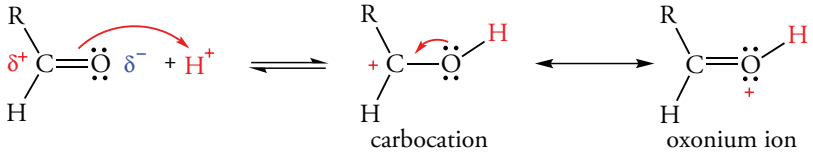
The reaction is regiospecific; only one nucleophilic addition product forms.



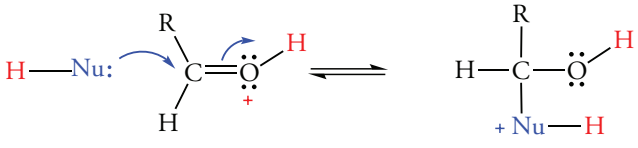
Many reagents that add to carbonyl compounds can be represented by H—Nu. The electrophilic part of the reagent is H^+; the nucleophilic part is Nu^-. (The reagent also may have lone pair electrons, represented H—Nu: .) The addition reaction occurs in several steps. The order of the steps depends on whether acid or base catalyzes the reaction.

Acid-Catalyzed Nucleophilic Addition Reactions

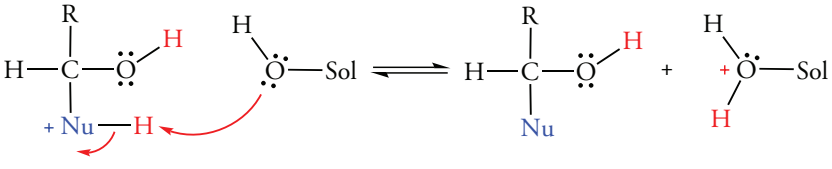
1. A proton (electrophile) reacts with the carbonyl oxygen atom (a Lewis base) to produce a carbocation, which is an oxonium ion in the alternate resonance form.



2. The carbocation, which has a vacant 2p orbital, is a Lewis acid. It reacts with the lone pair electrons of the nucleophile, Nu:, which is a Lewis base.



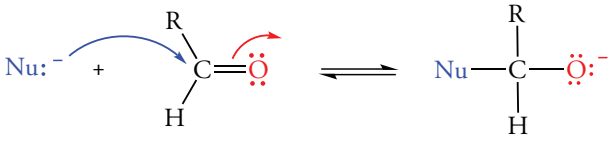
3. An acid–base reaction with a hydroxylic solvent, Sol—O—H, acts as a base and accepts a proton. The protonated solvent is now available for the first step of this acid-catalyzed reaction sequence.



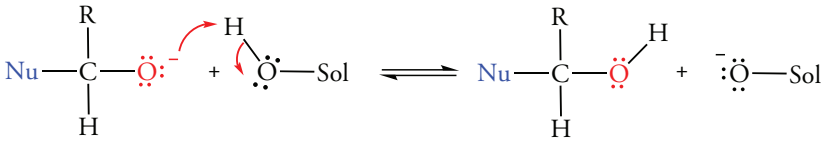
Base-Catalyzed Nucleophilic Addition Reactions

The sequence of steps differs for a base-catalyzed reaction.

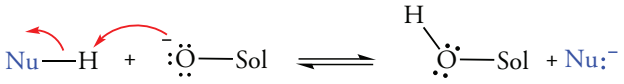
1. The nucleophile, $Nu:^-$, attacks the carbonyl carbon atom, which has a partial positive charge, and is therefore electrophilic. The first product is a tetrahedral intermediate.



2. An acid–base reaction with a hydroxylic solvent, Sol—O—H, protonates the alkoxide ion.



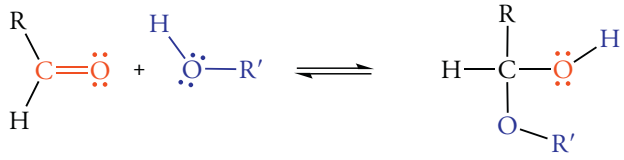
3. The conjugate base of the solvent removes a proton from H—Nu to regenerate Nu:⁻.



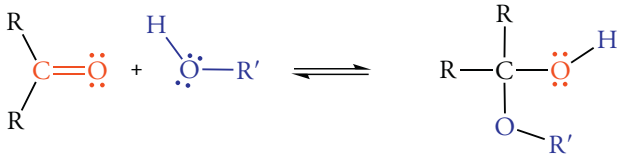
Problem 19. 5
Write the steps for the acid-catalyzed hydration of CH_3CHO in aqueous solution.

19.5 FORMATION OF ACETALS AND KETALS

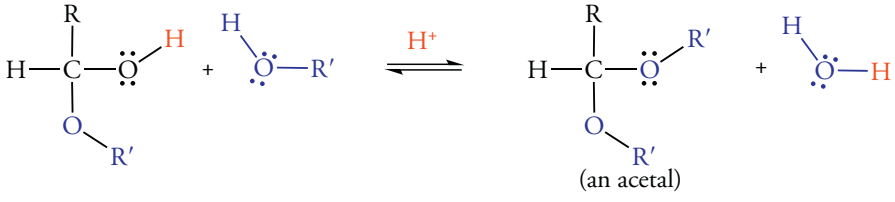
Aldehydes and ketones react with two moles of an alcohol to give products called **acetals** and **ketals**. If one mole of an alcohol reacts with one mole of an aldehyde or ketone, the product is a **hemiacetal** or a **hemiketal**.



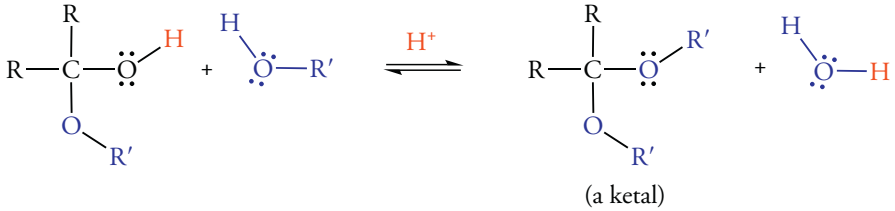
(a hemiacetal)



(a hemiketal)

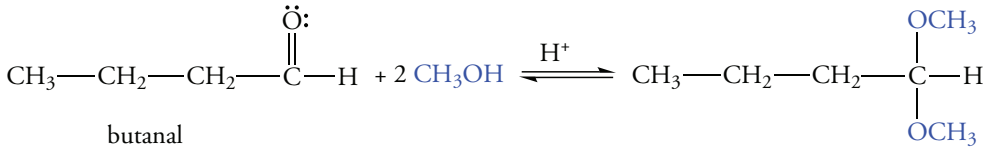


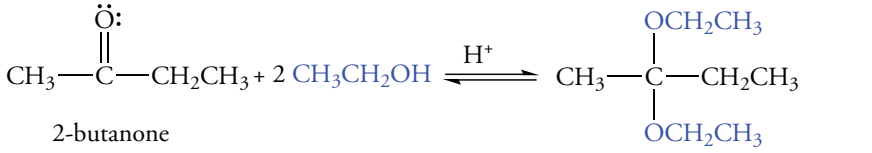
(an acetal)



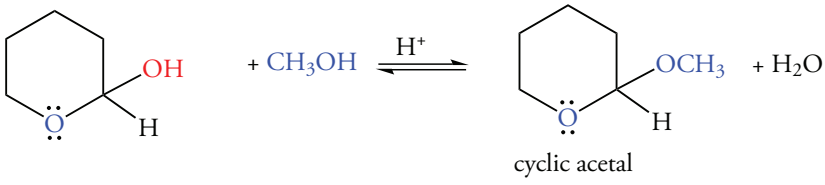
(a ketal)

Both acetals and ketals have two alkoxy groups (—OR′) attached to the same carbon atom. An acetal has a hydrogen atom and an alkyl group attached to the carbon atom, and a ketal has two alkyl groups attached.

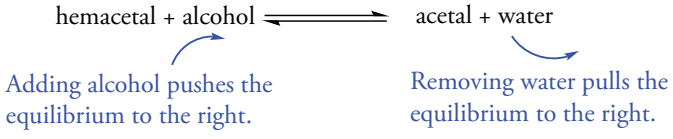




Cyclic hemiacetals and hemiketals also react with alcohols to produce cyclic acetals and cyclic ketals. We will see this reaction again when we consider carbohydrates in Chapter 24.



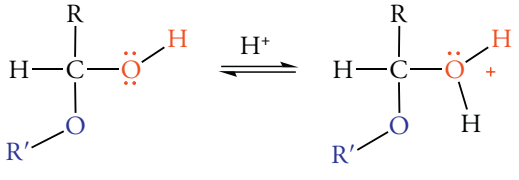
The conversion of a hemiacetal to an acetal and the conversion of a hemiketal to a ketal are reversible in acid solution. Removing the water formed in the reaction or increasing the concentration of alcohol shifts the position of the equilibrium to the right, toward formation of an acetal or ketal.



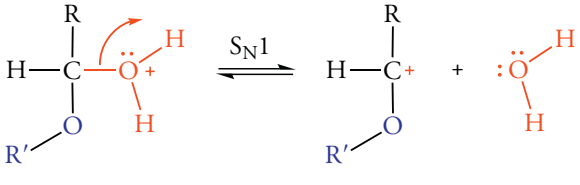
Mechanism of Acetal and Ketal Formation

The conversion of hemiacetals and hemiketals to acetals and ketals occurs in four reversible steps. They occur in rapid succession and parallel many of the reactions of carbocations that we have described previously.

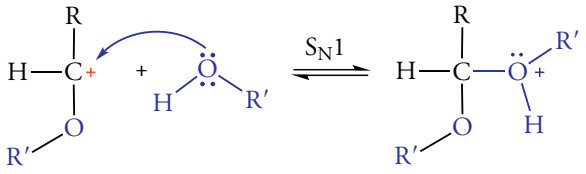
1. The acid protonates the oxygen atom of the hemiacetal hydroxyl group. This step is rapid and reversible.



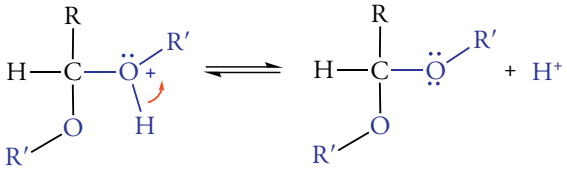
2. Water leaves and a carbocation forms. Step 2 occurs readily for two reasons. First, the OH group is protonated to form water, a far better leaving group than hydroxide ion. Second, the oxygen atom's lone pair electrons resonance stabilize the carbocation formed in this S_N1 reaction.



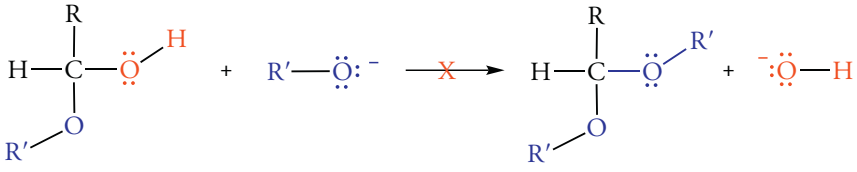
3. The carbocation reacts with the alcohol in another S_N1 reaction to give a protonated acetal.



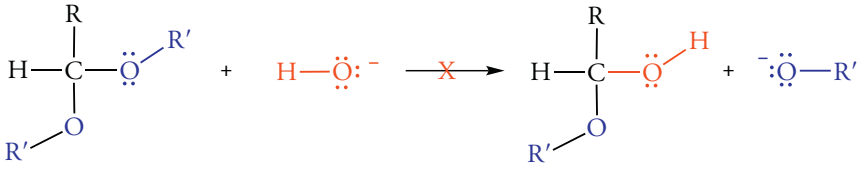
4. The proton bonded to the oxygen atom leaves, giving an acetal. The reaction is acid catalyzed. It starts acetal formation by protonating the hemiacetal, and H^+ is regenerated step 4 when the acetal forms.



Base catalyzes neither acetal formation nor the reverse reaction, called acetal hydrolysis. An S_N2 displacement of hydroxide by alkoxide would be required in the formation of the acetal. However, we know that hydroxide ion is not a good leaving group.

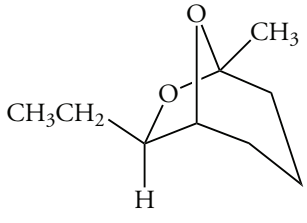


Similarly, the hydrolysis of an acetal by base would require an S_N2 displacement of an alkoxide ion, and this reaction does not occur either.



Problem 19. 6

Identify the functional group of brevicomin, the sex attractant of a species of pine beetle.



brevicomin

Problem 19. 7

Write the structures of the acetal or ketal formed in each of the following pairs of compounds.

(a) cyclopentanone and methanol

(b) 3-pentanone and ethanol

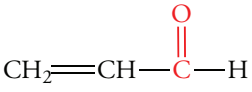
(c) benzaldehyde and 1-propanol

19.6 ACETALS AS PROTECTING GROUPS

Synthetic transformations at one functional group in a molecule containing two or more functional groups are often complicated by competing reactions at the other reactive sites. To eliminate the complications of reactions at undesired sites, we use protecting groups. These convert a functional group to an unreactive form that can be converted back to the original functional group after we achieve other synthetic goals. A protecting group is selected so that it is easy to make and easy to remove at the end of the synthesis. Both reactions should occur in high yield.

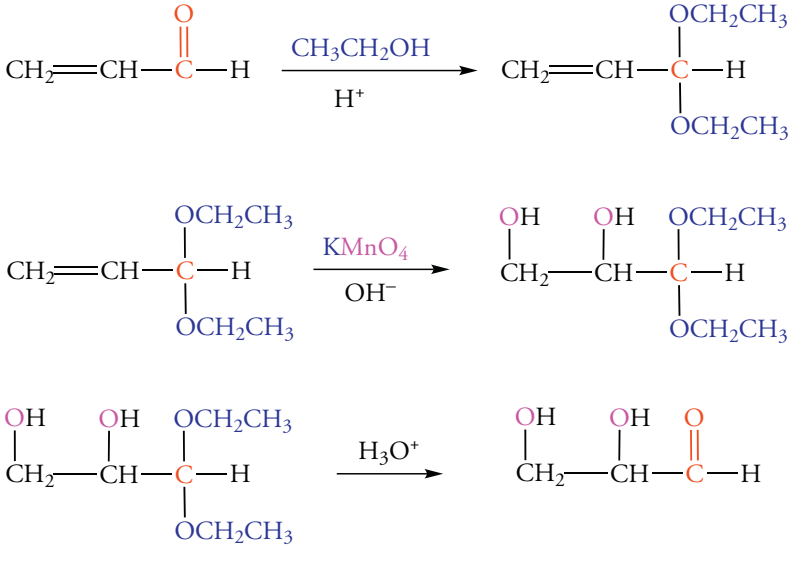
The formation of acetals (or ketals) followed by their hydrolysis at a later stage in a synthetic sequence is a useful technique to protect the carbonyl group. With the exception of acid-catalyzed hydrolysis, acetals are unreactive. We recall that ethers, which resemble acetals, are unreactive toward bases, oxidizing agents, and reducing agents. They are so unreactive; they are used as solvents for the Grignard reagent. Acetals are also unreactive toward the same reagents. Thus, the very reactive aldehyde (or ketone) can be protected, or "masked," to prevent its reaction with reagents required to transform other functional groups in the same molecule. Finally, an acid-catalyzed reaction releases the carbonyl functional group. When we select conditions for the reactions of other functional groups, we must avoid acidic conditions because the acetal will hydrolyze.

An example of acetal protection is the oxidation of an carbon–carbon double bond in the presence of an aldehyde. An acetal can be made protect the aldehyde of propenal when the goal is to oxidize the carbon–carbon double bond using basic potassium permanganate. This reagent would also oxidize an aldehyde group.



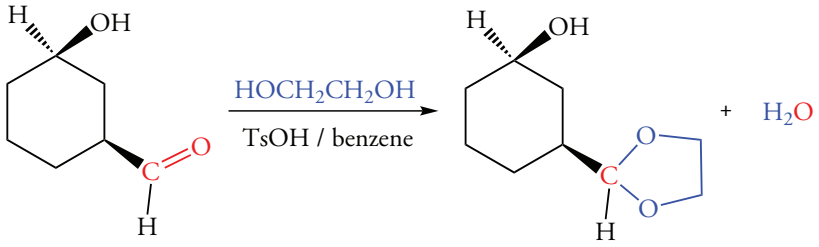
Permanganate will oxidize the double bond and the aldehyde.

The aldehyde group is first protected by converting it to an acetal using an alcohol such as ethanol. Because the dihydroxylation using permanganate occurs under basic conditions, the acetal is stable and the aldehyde remains protected. The acetal hydrolyzed in a final step using a mildly acidic aqueous solution.

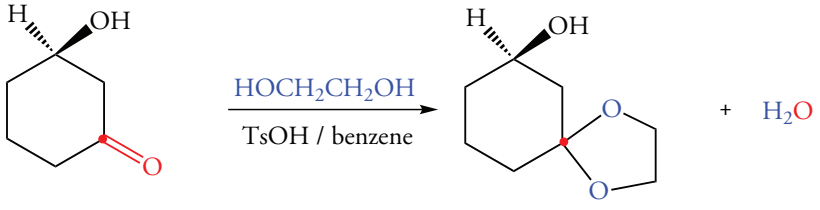


Synthesis of Cyclic Acetals

We noted earlier that the reaction of an aldehyde with an alcohol to give an acetal is not favorable entropically. However, the simple expedient of using a diol to make the acetal eliminates this unfavorable entropy change. The most common alcohol used is for making cyclic acetals 1,2-ethanediol (ethylene glycol). In this reaction, two molecules of reactant yield two molecules of product, and the entropy change is approximately zero. The acid catalyst is *p*-tolunesulfonic acid (TsOH), and benzene is the solvent.

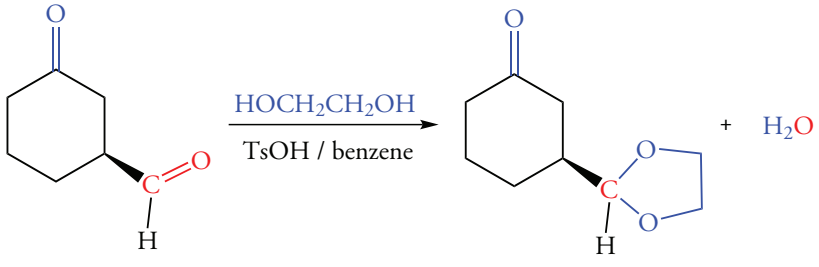


Ketones also react with ethylene glycol to give good yields of ketals. Distillation with toluene or benzene drives the position of the equilibrium toward products. Benzene and toluene co distill with water as a mixture with a constant boiling called an azeotrope.

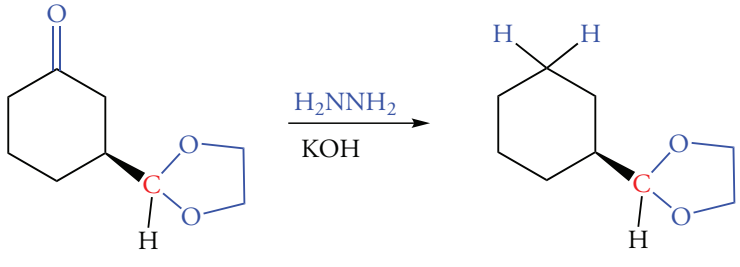


Selective Acetal Synthesis

If there are substantial differences in the equilibrium constants for acetal formation of two carbonyl groups, it may be possible to form one acetal in preference to another. Selective acetal formation occurs in the competition between an aldehyde and a ketone. For example, 3-oxocyclohexanecarbaldehyde reacts with one equivalent of ethylene glycol to give an acetal that protects the aldehyde group.

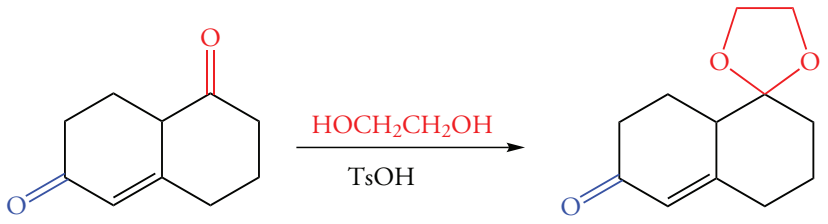


The ability to protect an aldehyde in the presence of a ketone allows chemical reactions of the ketone group without competitive reactions that would occur in the original unprotected compound. For example, the Wolff–Kishner reduction converts the carbonyl group to a methylene group.



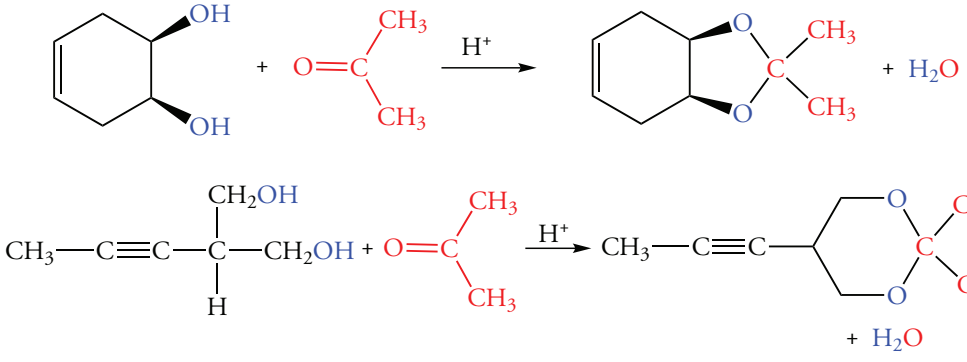
The ketone cannot be reduced selectively by a Clemmensen reduction because it requires HCl. The acid hydrolyzes the acetal, so the aldehyde is no longer protected, and thus both carbonyl groups would be reduced.

Another example of the selective formation of an acetal exploits the difference in stability of a conjugated carbonyl group in an α,β-unsaturated ketone and an unconjugated carbonyl group. Just as a conjugated diene is more stable than an isolated double bond (Section 11.2), a conjugated carbonyl group is more stable than an isolated carbonyl group.

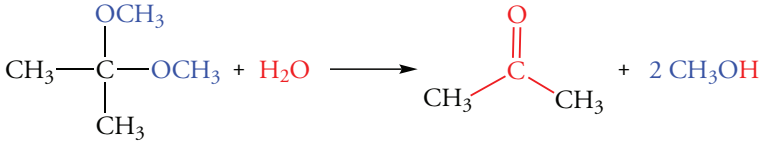


Protection of Alcohols by Acetal Formation

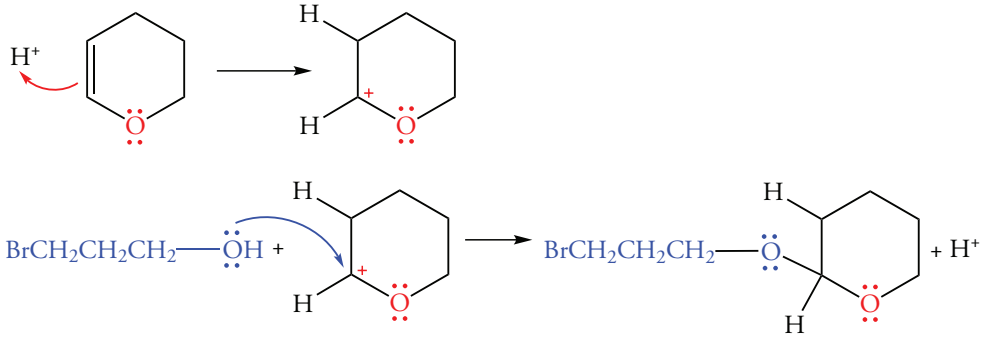
If alcohols can be used to protect carbonyl compounds by formation of an acetal (or ketal), then the same method can protect an alcohol using a carbonyl compound. For example, victual diols can be protected by forming a cyclic five-membered ketal with acetone. Similarly, 1,3-diols react with acetone to form cyclic six-membered ketals.



2,2-Dimethoxypropane drives such reactions to completion. It is an unstable ketal that reacts with the water generated by the reaction of the diol with acetone.



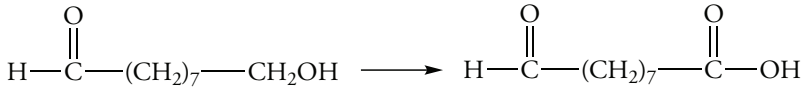
Alcohols that contain only one hydroxyl group can also be protected by forming an acetal. Alcohols react regiospecifically with dihydropyran in an acid-catalyzed addition reaction. The carbocation formed is resonance stabilized by the lone pair electrons of the ring oxygen atom. Subsequent attack of the carbocation by the nucleophilic oxygen atom of the alcohol followed by deprotonation yields an alkoxy-substituted tetrahydropyran known as a THP derivative.



Although the addition of an alcohol to the double bond forms an ether linkage, the THP derivative is not an ether. Two oxygen atoms are bonded to a common carbon atom, making the compound an acetal. The THP derivative is stable unless it is exposed to aqueous acid. Therefore, the original alcohol is protected at the hydroxyl group. The THP derivative is hydrolyzed with dilute acid to regenerate the hydroxyl group.

Problem 19.8

The following reaction cannot be accomplished directly using potassium permanganate as the oxidizing agent. Explain why not and outline a method to obtain the product using appropriate protecting groups.

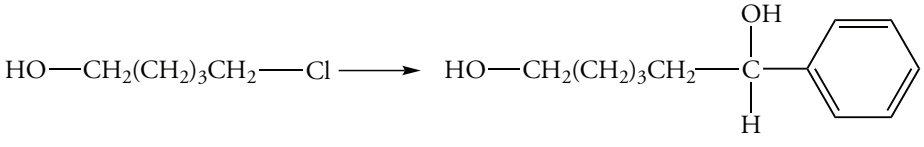


Sample Solution

Aldehydes are oxidized even by mild oxidizing agents. Potassium permanganate is a strong oxidizing agent that will oxidize the hydroxy aldehyde to form a dicarboxylic acid. The aldehyde group must first be protected by forming an acetal. Although alcohols such as methanol or ethanol could be used, the equilibrium constant for formation of a cyclic acetal makes ethylene glycol the reagent of choice. In the subsequent oxidation of the alcohol, the acetal remains intact. In the last step, hydrolysis with dilute acid liberates the free aldehyde group, and the desired product forms.

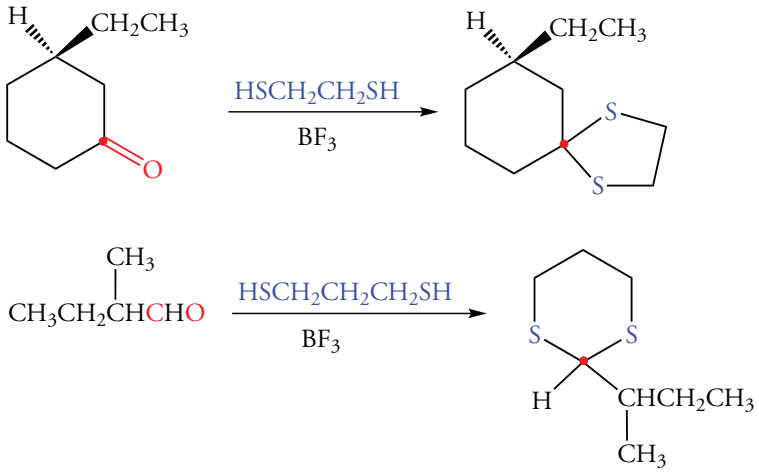
Problem 19.9

The following reaction cannot be accomplished by preparing a Grignard reagent and reacting it with benzaldehyde. Explain why not and outline a method to obtain the product using appropriate protecting groups.

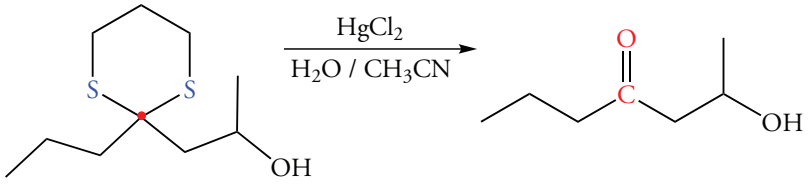


19.7 THIOACETALS AND THIOKETALS

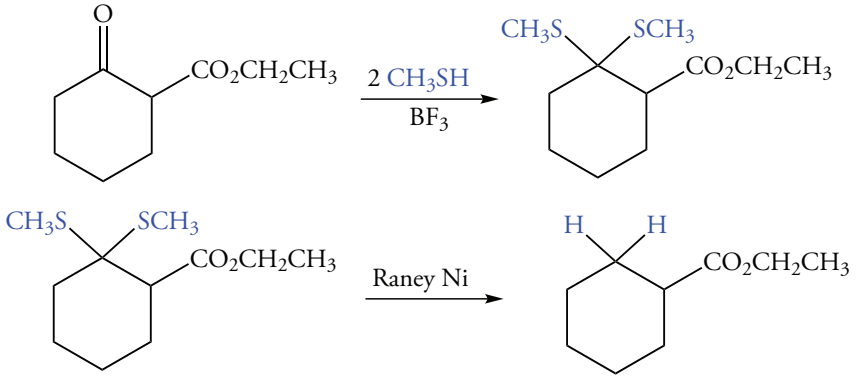
Thiols are the sulfur analogs of alcohols (Section 15.11). The sulfur atom of a thiol is a better nucleophile than the oxygen atom of an alcohol. Thus, thiols react with aldehydes or ketones to form thioacetals or thioketals by a mechanism similar to that described for acetals and ketals. These sulfur derivatives form in high yield because the equilibrium constant for thioacetal formation is much greater than that for acetal formation. We use Lewis acids such as BF_3 or $ZnCl_2$ rather than protic acids to catalyze the formation of the thioacetal. Both 1,2-ethanedithiol and 1,3-propanedithiol are used to form cyclic thioacetals and thioketals.



Like acetals, thioacetals are stable in basic solution. However, thioacetals also survive under the acidic conditions that would hydrolyze an acetal. Thus, they protect a carbonyl group and allow us to react many other functional groups under acidic or basic conditions. Because thioacetals are stable in acid, their hydrolysis requires use of mercuric chloride in aqueous acetonitrile. The formation of an insoluble mercury(II) sulfide provides the driving force for the reaction.



Thioacetals are valuable intermediates for organic synthesis in their own right. For example, thioacetals are desulfurized by Raney nickel to give the corresponding hydrocarbon. This provides another path from an aldehyde or ketone to a methylene group that does not require either strong acid or strong base. Therefore, this method complements the Wolff—Kishner and Clemmensen reductions.



Problem 19.10

Draw the structures of the products of each of the following combination of reagents.

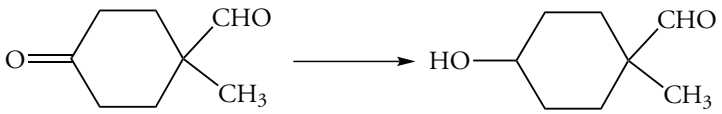
(a) cyclohexanone and methanethiol

(b) 2-butanone and 1,2-ethanedithiol

(c) cyclohexanecarbaldehyde and 2-thioethanol

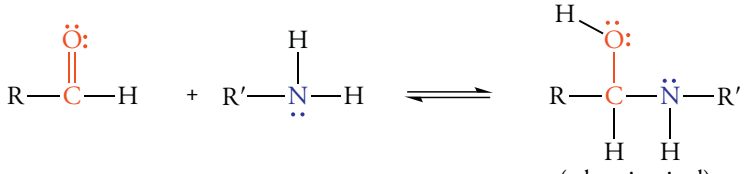
Problem 19.11

Outline the steps required to accomplish the following synthesis using a thioacetal derivative in one of the steps.

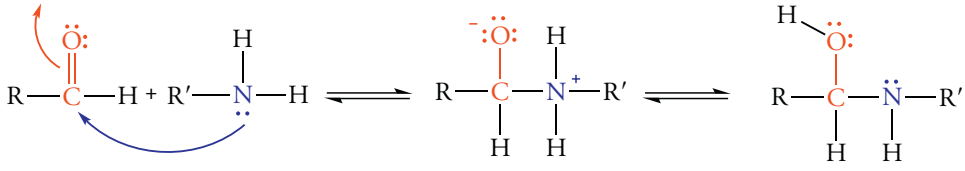


19.8 ADDITION OF NITROGEN COMPOUNDS TO ALDEHYDES AND KETONES

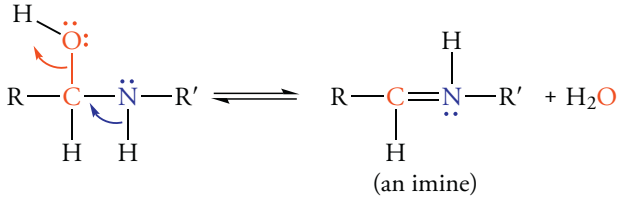
Ammonia and amines of the general formula RNH_2 are nitrogen analogs of water and alcohols. They are more nucleophilic than water and alcohols and react faster with carbonyl groups of aldehydes and ketones. In these reactions, a nitrogen analog of a hemiacetal, called a **hemiaminal**, forms.



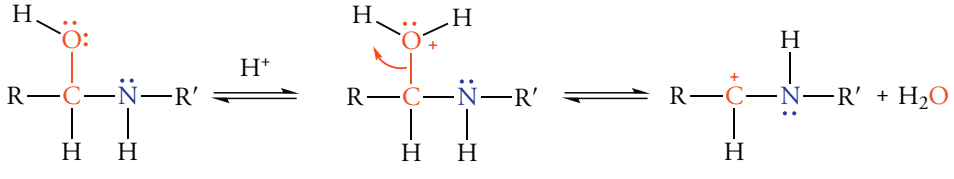
A hemiaminal forms by mechanism that is similar to the mechanism for hemiacetal formation. First, the nucleophilic nitrogen attacks the carbonyl carbon atom to give a tetrahedral adduct with a plus charge on nitrogen and a minus charge on oxygen. The initial product rapidly undergoes an intermolecular proton transfer from the nitrogen to the oxygen.



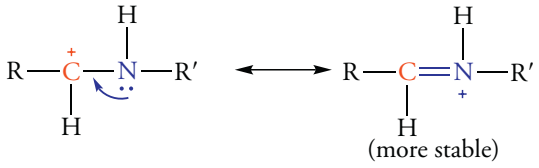
The hemiaminal does not react with a second mole of amine to form the nitrogen analog of an acetal because it readily loses water to form a compound with a carbon–nitrogen double bond, called an **imine**.



The mechanism for this dehydration resembles that of the conversion of an acetal to a carbonyl compound (Section 19.6). Although protonation of the more basic nitrogen atom of the hemiaminal does occur, this reaction leads only to the reverse of the reaction that formed it. However, protonation of the hydroxyl group opens up an alternate reaction pathway, which leads to the imine.



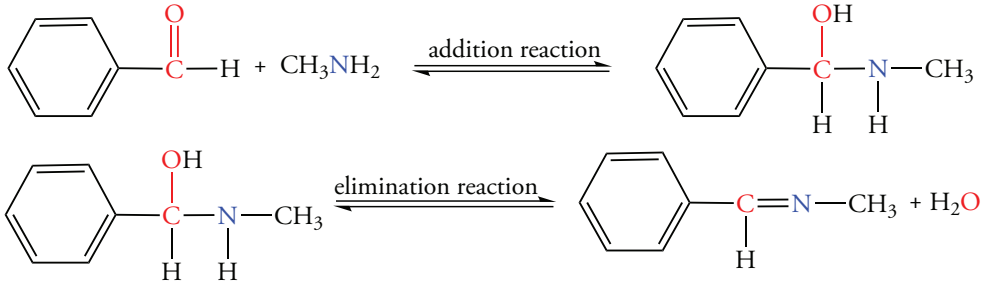
The carbocation formed by loss of water is resonance stabilized by the lone pair elections of nitrogen in the same way that the lone pair electrons of oxygen stabilize the oxocarbocation intermediate in the formation of acetals. However, nitrogen is more effective in stabilizing the carbocation because it is less electronegative than oxygen and is better able to supply electron density by resonance.



resonance forms of an iminium ion

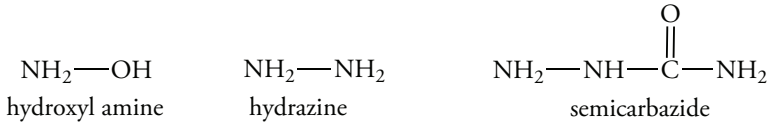
Loss of a proton from the iminium gives the imine product. All of the reactions leading to imine are reversible. Therefore, an imine can hydrolyze to form an amine and a carbonyl compound. Le Chatelier's principle allows us to predict the conditions required to drive the reaction in the given direction. Removing water as it forms favors formation of the imine. Adding excess water favors imine hydrolysis.

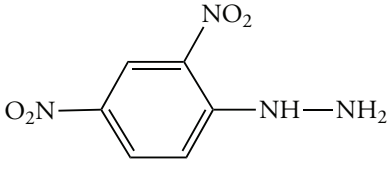
The overall reaction of a carbonyl compound with an amine is an **addition–elimination reaction**. In the addition step, the nitrogen atom bonds to the carbonyl carbon atom and a hydrogen atom bonds to the carbonyl oxygen atom. The addition product then loses a molecule of water in an elimination reaction to give an imine.



Stable Imine Derivatives

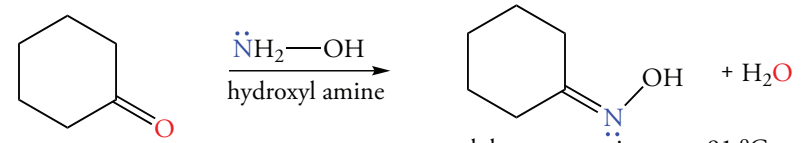
Some compounds in which a nitrogen atom bonds directly to electronegative groups with lone pair electrons form stable mine derivatives. These compounds include hydroxylamine, hydrazine, and substituted amine such as semicarbazide and 2,4-dinitrophenylhydrazine.

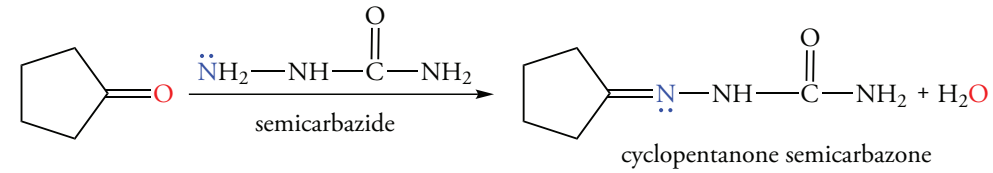


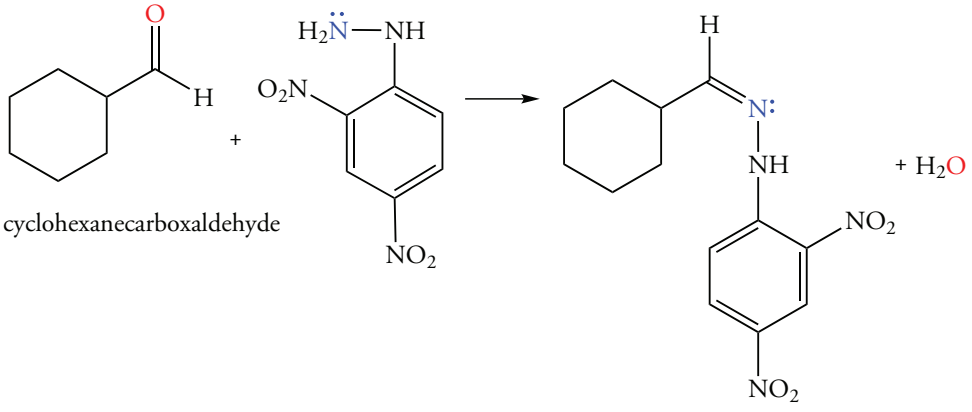


2,4-dinitrophenylhydrazine

Many liquid carbonyl compounds react with these compounds to give solid derivatives. For example, cyclohexanone reacts with hydroxylamine to give a solid oxime.







The reaction of carbonyl compounds with semicarbazide yields semicarbazones. The reaction occurs at only one of the two possible NH_2 groups. The lone-pair electrons of the NH_2 group bonded to the carbonyl are less nucleophilic than those of the other NH_2 group because the carbonyl carbon atom decreases the electron density at that nitrogen atom.

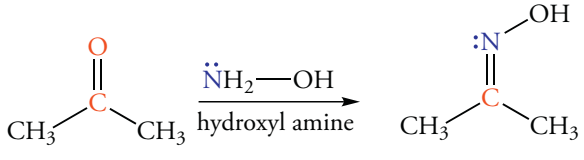
An aldehyde reacts with 2,4-dinitrophenylhydrazine to give a bright, yellow-to-orange crystalline solid called a 2,4-dinitrophenylhydrazone (2,4-DNP).

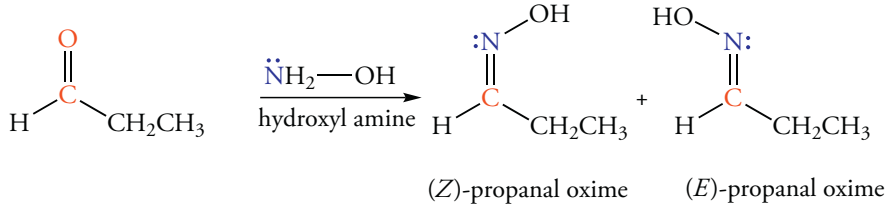
Problem 19.12

Two equivalents of benzaldehyde react with hydrazine to give a compound with molecular formula $C_{14}H_{12\ 2}$. Draw the structure of the compound.

Problem 19.13

Two isomers of propanal exist, but only one of propanone. Consider the hybridization of the nitrogen atom in an oxime and the geometry of the products and explain this observation.



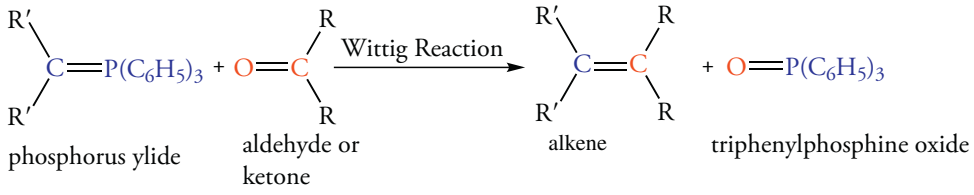


Sample Solution

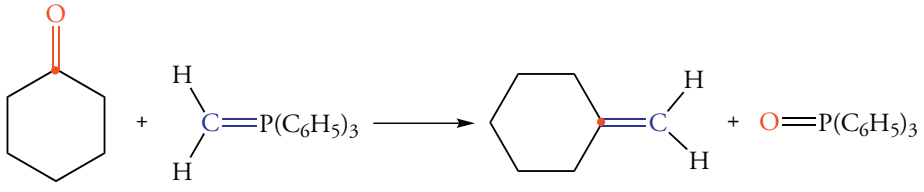
Because the nitrogen atom is sp^2-hybridized, propanol has a C=N—O angle of 120° and, like an alkene, can exist as *cis–trans* isomers. In the case of propanone, the two methyl groups preclude *cis–trans* isomers.

19.9 THE WITTIG REACTION

Carbonyl compounds react with phosphorus compounds called **ylides** to yield alkenes according to the following general equation. This reaction, discovered by Georg Wittig, is called the **Wittig reaction.** It provides a way to synthesize alkenes from carbonyl compounds. The term ylide refers to a molecule in which a contributing structure to a resonance hybrid has positive and negative charges on the bonded atoms, and *both* atoms have a full octet.



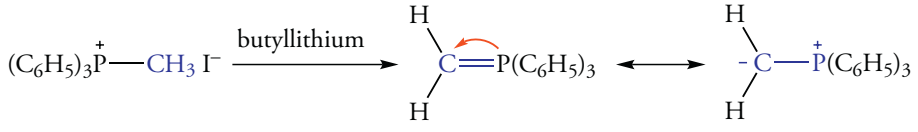
The Wittig reaction is regiospecific. The double bond forms between the carbonyl carbon atom and the carbon atom bonded to the phosphorus atom of the ylide. However, the reaction is not stereospecific. Thus, if geometric isomers are possible, both isomers form. The Wittig reaction is carried out in polar aprotic solvents such as diethyl ether, tetrahydrofuran, or dimethyl sulfoxide. The Wittig reaction can be carried out in the presence of alkene, alkyne, halogen, ether, or ester functional groups.



Preparation of Phosphorus Ylides

Phosphorus ylides are usually obtained from alkyl halides and triphenylphosphine in a two-step sequence. We recall that the nucleophilicity of third-row elements such as sulfur and phosphorus is greater than that of second-row elements because the atoms are more polarizable (Section 10.1). The phosphorus atom of triphenylphosphine is an effective nucleophile. Since it is also a weak base, a competing elimination does not occur, and bimolecular substitution of primary and secondary alkyl halides gives good yields. In the first step, the halide ion of the alkyl halide is displaced in an S_N2 reaction to yield an alkyltriphenylphosphonium salt.

Alkyltriphenylphosphonium salts are stable and can be isolated, crystallized, and stored until needed. In a separate second step, the alkyltriphenylphosphonium salt is deprotonated using a strong base such as sodium hydride or butyllithium. The proton on the carbon atom bonded to phosphorus is weakly acidic because the positively charged phosphorus inductively withdraws electrons. As we noted above, in an ylide, one of the contributing structures has a positive charge on phosphorus and a carbon to which it is bonded has a negative charge.

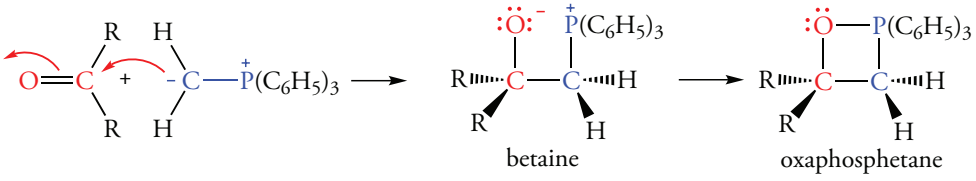


Two resonance forms depict the structure of the ylide. The dipolar resonance form is generally used to show the mechanism of the Wittig reaction. This resonance form has a single bond between the phosphorus and carbon atoms. Although positive and negative charges are located on adjacent atoms, the dipolar form is the major contributor to the ylide structure. The uncharged resonance form has a double bond between the phosphorus and carbon atoms, so the phosphorus atom has

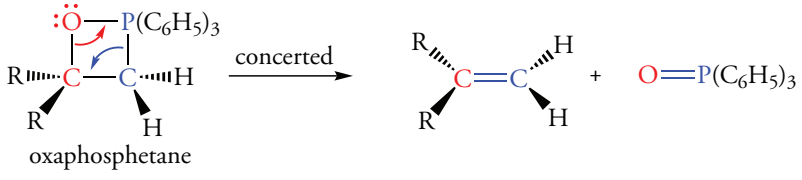
10 electrons in its valence shell. Although expansion of the valence shell occurs for third-row elements by using empty 3d orbitals, the 3d-2p π bond formed between a third-row and a second-row element is weak because of ineffective overlap of atomic orbitals. We recall that a similar argument accounts for the diminished capacity of the halogen atoms to donate electrons in electrophilic aromatic substitution of aromatic rings (Section 13.6). The importance of the dipolar resonance form accounts for the strongly nucleophilic character of the carbon atom of the ylide and its reactivity with a carbonyl carbon atom in the Wittig reaction.

Mechanism of the Wittig Reaction

The first step in the Wittig reaction is nucleophilic attack of the negatively charged carbon atom of the ylide on the carbonyl group to give an adduct called a **betaine** that rapidly converts to an oxaphosphetane. The exact course of the reaction may depend on the type of groups bonded to the carbonyl carbon atom and the type of ylide. Nevertheless, the direction of the addition of the ylide to the carbonyl atoms is the same as for other addition reactions studied in this chapter. The electrophilic carbon atom of the ylide forms a bond to the carbonyl carbon atom and the phosphorus bonds to the oxygen atom.



The intermediate phosphorus compound, either the betaine or the oxaphosphetane, immediately decomposes to yield the alkene and a phosphine oxide. This step is concerted; all bonds break and form simultaneously in the transition state. The driving force for this reaction is the formation of a very strong phosphorus–oxygen bond. (The P—O bond dissociation energy in triphenylphosphine oxide is approximately 550 kJ mole^{-1}.)



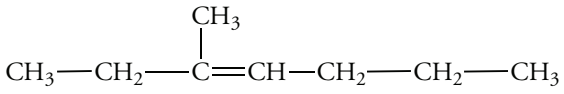
Problem 19.14

What combination of phosphorus ylide and a carbonyl compound could be used to prepare each of the following alkenes?

(a) methylenecyclooctane (b) 2-methyl-2-pentene

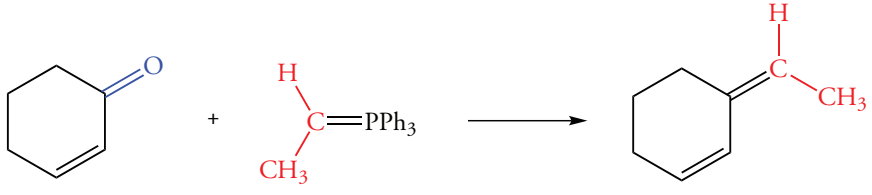
Problem 19.15

Outline two possible syntheses of the following compound. Would you predict any difficulties in obtaining a pure product?

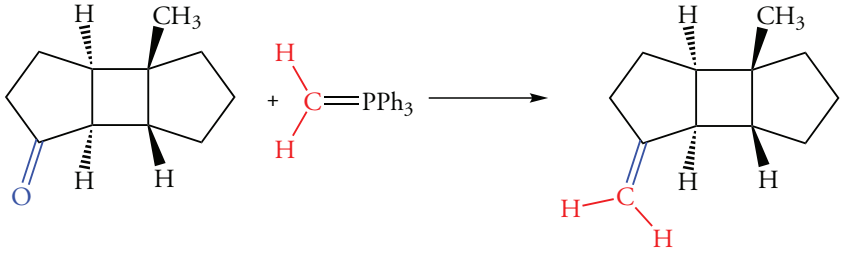


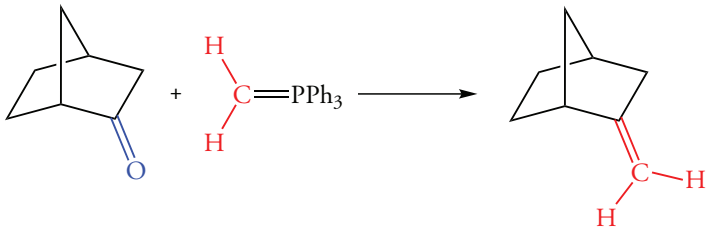
The Wittig Reaction in Organic Synthesis

The Wittig reaction provides a path from aldehydes and ketones to alkenes and, consequently, is a valuable tool in organic synthesis. For example, the Wittig reaction will convert an α,β-unsaturated ketone to a conjugated alkene.



The Wittig reaction can also be used to convert a ketone to a methylene group in a single step.





EXERCISES

Reactivity of Carbonyl Compounds

19.1 Which member of each of the following pairs of compounds reacts faster with sodium borohydride?
(a) cyclopropanone or cyclopentanone
(b) acetophenone or benzaldehyde
(c) acetone or 3,3-dimethyl-2-butanone

19.2 Which member of each of the following pairs of compounds reacts faster with sodium borohydride?
(a) benzaldehyde or acetaldehyde
(b) cyclopentanone or cyclohexanone
(c) *p*-trifluoromethylbenzaldehyde or benzaldehyde

Equilibrium Constants of Hydration Reactions

19.3 The equilibrium constants for the formation of hydrates of acetaldehyde and chloroacetaldehyde are 1 and 37, respectively. Explain whether you expect the equilibrium constant for formation of the hydrate of trichloroacetaldehyde to be greater or less than 37.

19.4 The equilibrium constant for formation of a hydrate of acetone is 1.4×10^{-3}. Explain whether you expect the equilibrium constant for formation of the hydrate of 1,3-dichloroacetone to be greater or less than 1.4×10^{-3}.

19.5 Explain why the methoxy group of *p*-methoxybenzaldehyde decreases the equilibrium constant for hydration relative to benzaldehyde, whereas the methoxy group of *m*-methoxybenzaldehyde increases the equilibrium constant.

19.6 The equilibrium constants for the formation of hydrates of acetone, acetophenone, and benzophenone are 1.4×10^{-3}, 6.6×10^{-6}, and 1.7×10^{-7}, respectively. Explain why the second phenyl group of benzophenone has a much smaller effect on the equilibrium constant than the phenyl group of acetophenone compared to acetone.

19.7 Explain why the equilibrium constant for hydration of cyclopropanone is significantly larger than for hydration of cyclopentanone.

19.8 Considering the role of torsional interactions in determining cycloalkane stability, predict the order of the equilibrium constants for hydration of cyclopentanone and cyclohexanone.

Formation of Cyanohydrins

19.9 Explain why hydrogen cyanide reacts with 2-propanone to give a good yield of an addition product, but 2,2,4,4-tetramethy1-3-pentanone gives a poor yield in the same reaction.

19.10 Explain why the equilibrium constant for formation of a cyanohydrin of cyclohexanone is about 20 times larger than the equilibrium constant for formation of a cyanohydrin of cyclopentanone.

19.11 Explain why the equilibrium constant for formation of a cyanohydrin of butanone is about 40 times larger than the equilibrium constant for the formation of a cyanohydrin of 3,3-dimethylbutanone.

19.12 Explain why the equilibrium constant for formation of a cyanohydrin of *p*-methoxybenzaldehyde ($K_{eq} = 30$) is smaller than the equilibrium constant for benzaldehyde.

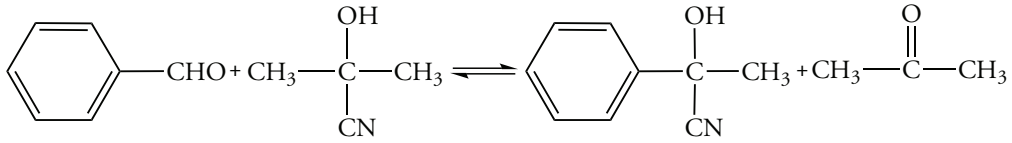
19.13 Is the equilibrium constant for formation of a cyanohydrin of *p*-methylbenzaldehyde larger or smaller than the equilibrium constant for benzaldehyde?

19.14 Is the equilibrium constant for formation of a cyanohydrin of *p*-ethoxybenzaldehyde larger or smaller than the equilibrium constant for *p*-dimethylaminobenzaldehyde?

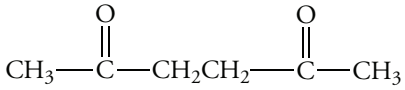
19.15 Explain why the equilibrium constant for formation of a cyanohydrin of 3,3,5-tiimethylcyclohexanone is smaller than the equilibrium constant for cyclohexanone.

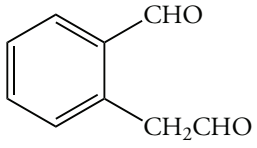
19.16 Two cyanohydrins of 4-*tert*-butyl-butylcyclohexanone exist. Which is the kinetic product? Which is the thermodynamic product?

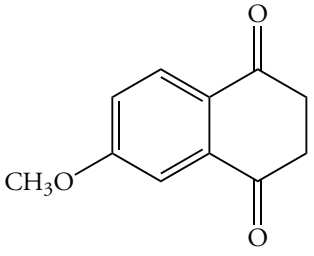
19.17 When benzaldehyde is heated with acetone cyanohydrin and a catalytic amount of base, the following reaction occurs. Explain whether you expect the equilibrium constant to be greater or less than 1.0. Write a mechanism for the reaction.

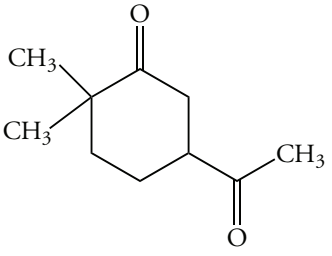


19.18 Write the structure of the product for the reaction of one equivalent of HCN with each of the following compounds.

(a) 

(b) 

(c) 

(d) 

Addition of Alcohols to Carbonyl Compounds

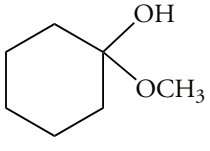
19.19 Identity each of the following as a hemiacetal, hemiketal, acetal, or ketal.

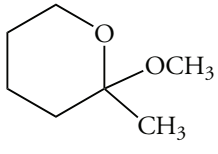
(a) $CH_3CH_2CH(OCH_3)_2$ (b) $CH_3CH_2C(OCH_3)_2CH_3$

(c) $CH_3CHOCH_2CH_3$ with OCH_2CH_3 (d) CH_3CH_2CHOH with OCH_3

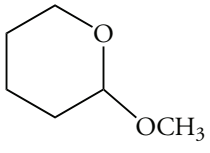
19.20 Identity each of the following as a hemiacetal, hemiketal, acetal, or ketal.

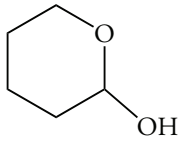
(a) $CH_3CH_2CCH_3$ with OCH_3 and OCH_3 (b) $(CH_3O)_2CHCH_2CH(OCH_3)_2$

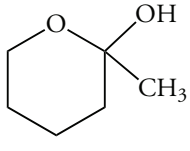
(c) 

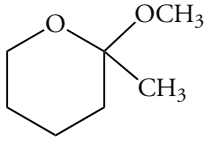
(d) 

19.21 Identity each of the following as a hemiacetal, hemiketal, acetal, or ketal.

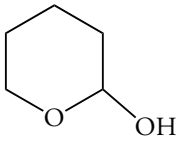
(a) 

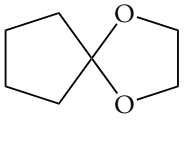
(b) 

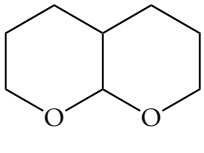
(c) 

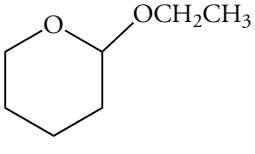
(d) 

19.22 Identity each of the following as a hemiacetal, hemiketal, acetal, or ketal.

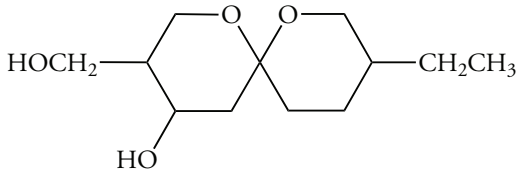
(a) 

(b) 

(c) 

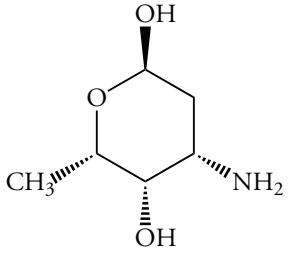
(d) 

19.23 Identify the functional groups in talaromycin A, a substance found in the fungus that grows in poultry litter.



talaromycin A

19.24 Identify the functional groups in daunosamine, a component of Adriamycin, used in cancer chemotherapy.



daunosamine

19.25 Is the equilibrium constant for the following reaction greater than or less than 1.0?

$$CF_3CHO + CH_3CH(OCH_3)_2 \rightleftharpoons CH_3CHO + CF_3CH(OCH_3)_2$$

19.26 Which compound should exist to the larger extent as a hemiacetal, 4-hydroxybutanal or 5-hydroxypentanal?

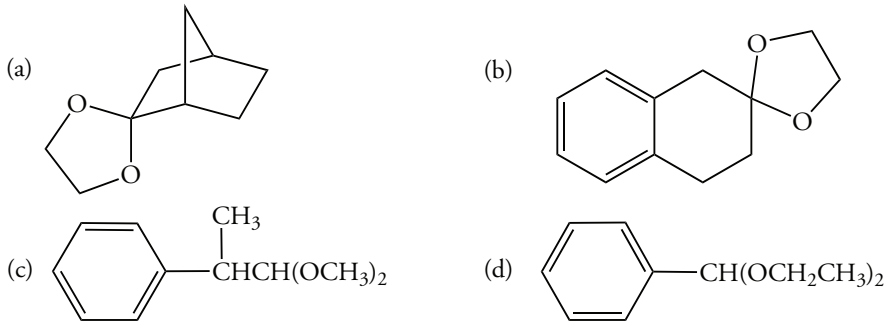
19.27 Benzaldehyde reacts with 1,2-propanediol to give two isomeric acetals. Draw their structures.

19.28 Acetone reacts with 1,2,3-propanetriol to give two isomeric ketals. Draw their structures.

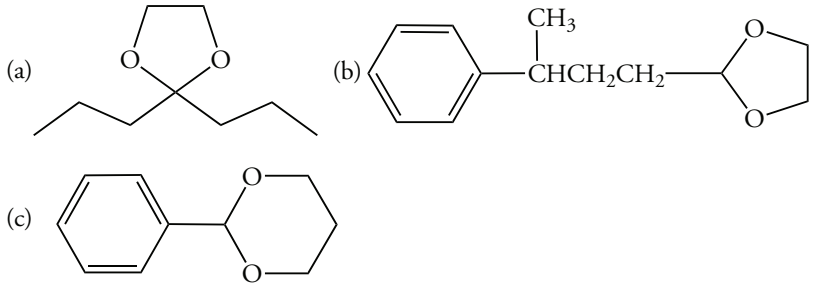
19.29 2-Oxopropanal reacts with excess methanol in an acid-catalyzed reaction to give a compound with molecular formula $C_5H_{10}O_3$. Draw its structure.

19.30 2-Oxopropanal reacts with excess ethylene glycol in an acid-catalyzed reaction to give a compound with molecular formula $C_7H_{12}O_4$. Draw its structure. What is the difference between the product of this reaction and the product in Exercise 19.27?

19.31 What carbonyl compound and alcohol are required to form each of the following compounds?

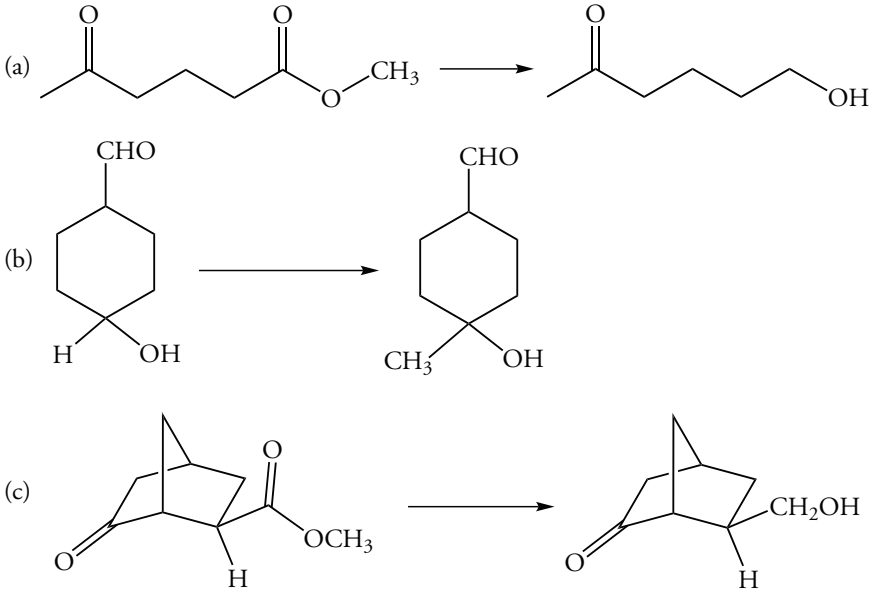


19.32 What carbonyl compound and alcohol are required to form each of the following compounds?

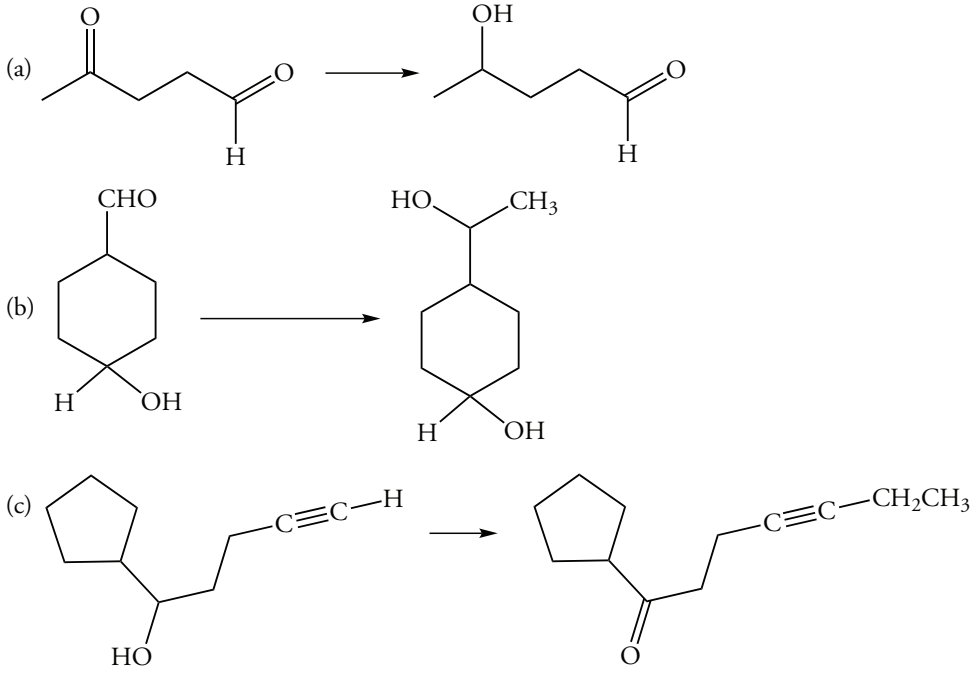


Use of Protecting Groups in Synthesis

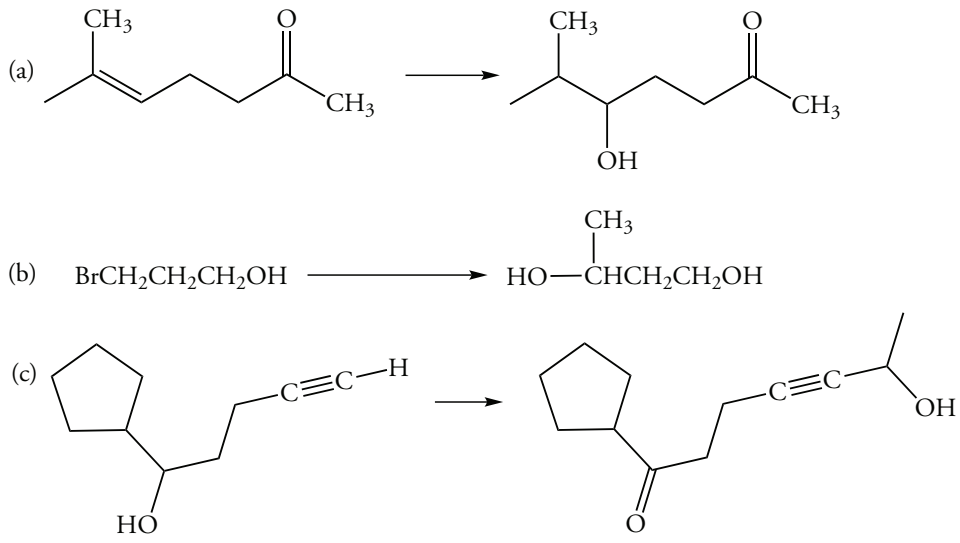
19.33 Outline a series of steps to carry out the following syntheses.



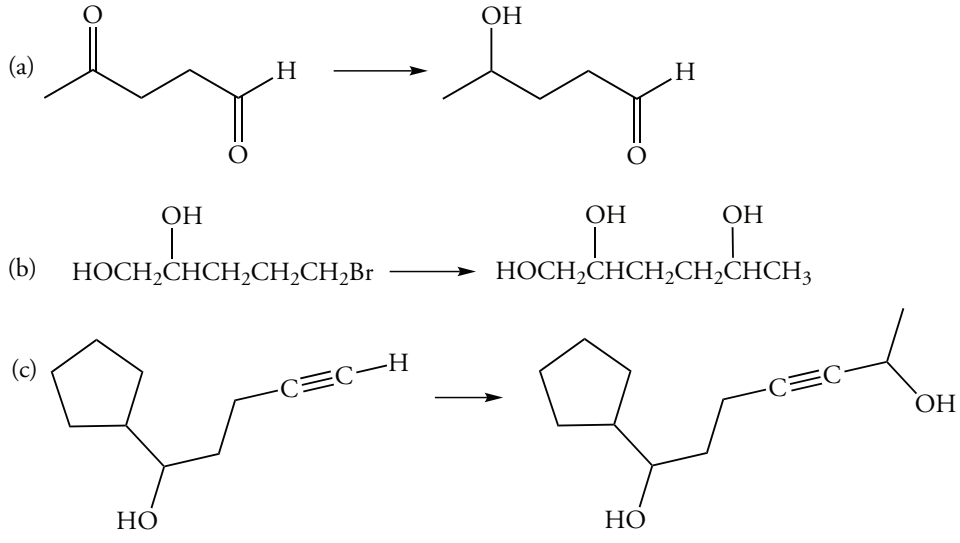
19.34 Outline a series of reactions to carry out the following syntheses.



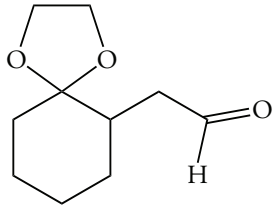
19.35 Outline a series of reactions to carry out the following syntheses.



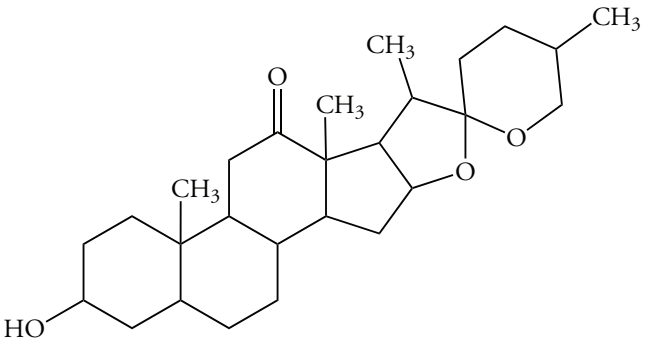
19.36 Outline a series of reactions to carry out the following syntheses.



19.37 Reduction of the following compound by the Wolff–Kishner method gives $C_{10}H_{20}O_2$, but Clemmensen reduction gives C_8H_{16}. Why do the products differ?

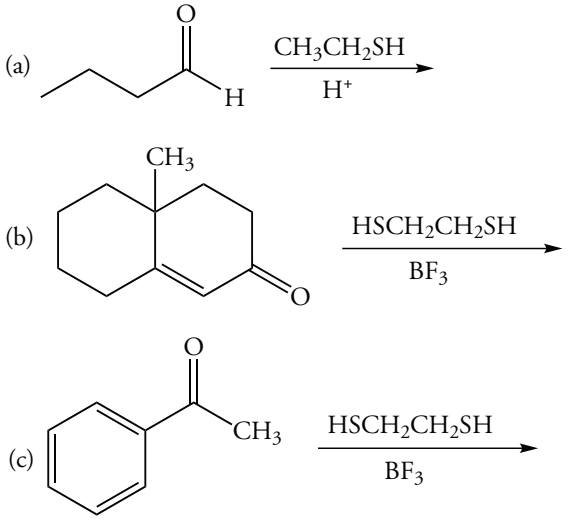


19.38 (a) Draw the structure of the product obtained from the following reactant using Wolff–Kishner conditions. (b) What product would be observed for a Clemmensen reduction?



Thioacetals and Thioketals

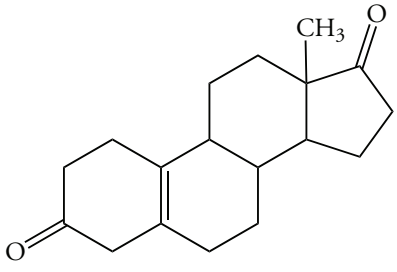
19.39 Draw the structure of the product of each of the following reactions.



19.40 Thiols react with dihydropyran in an acid-catalyzed reaction to form an addition product. Write the mechanism for the reaction and draw the structure of the addition product.

19.41 Aldehydes and ketones react with 2-thioethanol to give cyclic derivatives. Draw the structures of two possible products from the reaction of 4-*tert*-butylcyclohexanone with this reagent.

19.42 Predict the product of the reaction of one equivalent of 1,2-ethanedithiol with the following steroid.

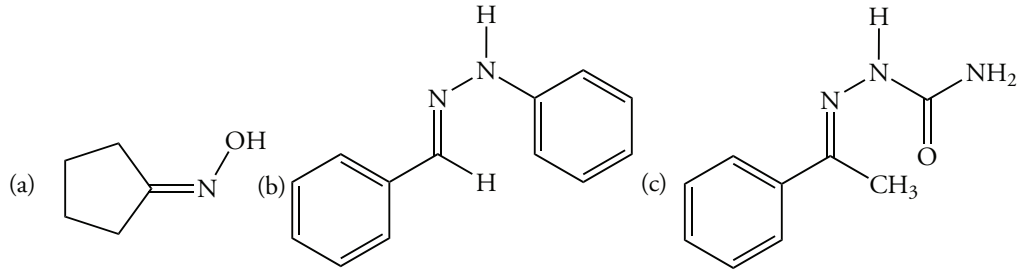


Addition of Nitrogen Compounds

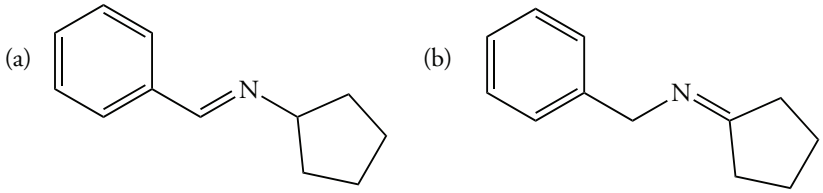
19.43 Write the structure of the product for each of the following combinations of reactants.

(a) ethanal and methylamine
(b) acetone and ethylamine
(c) benzaldehyde and hydrazine
(d) 3-pentanone and hydroxylamine
(e) 1-phenyl-2-propanone and semicarbazide

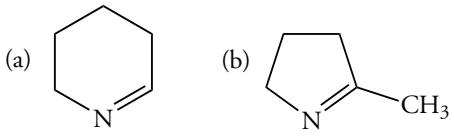
19.44 What reactants are required to form each of the following structures?



19.45 What reactants are required to form each of the following imines?



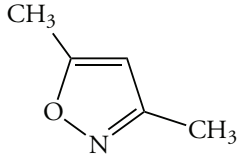
19.46 What reactants are required to form each of the following imines?



19.47 Explain why reaction of cyclohexanone with hydroxylamine yields a single product. However, cyclopentanecarbaldehyde yields two isomeric oximes.

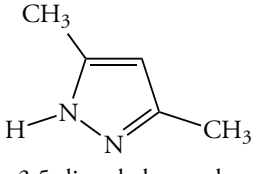
19.48 Draw the structure of the product of reaction of hydrazine with two molar equivalents of benzaldehyde.

19.49 2,4-Pentanedione reacts with hydroxylamine to yield 3,5-dimethylisoxazole. Write a mechanism for the reaction.

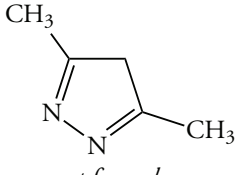


3,5-dimethylisoxazole

19.50 2,4-Pentanedione reacts with hydrazine to yield 3,5-dimethylpyrazole, not an isomeric diimine. Explain why the pyrazole forms.

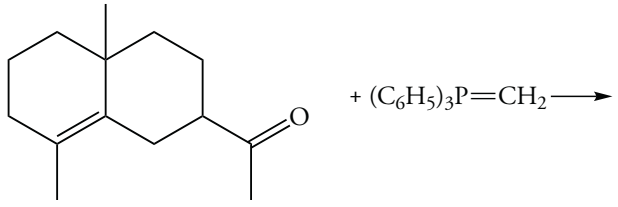


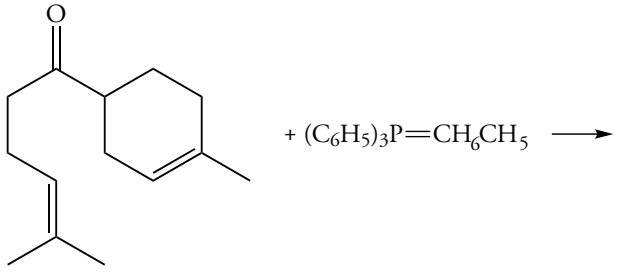
3,5-dimethylpyrazole

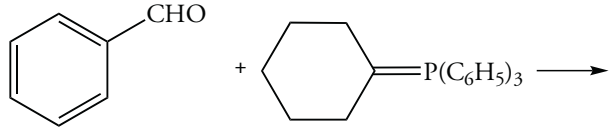


not formed

19.51 Draw the structure of the product of each of the following reactions.

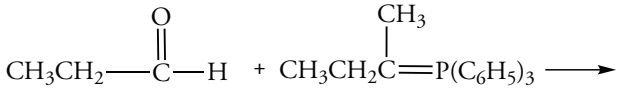
(a) 

(b) 

(c) 

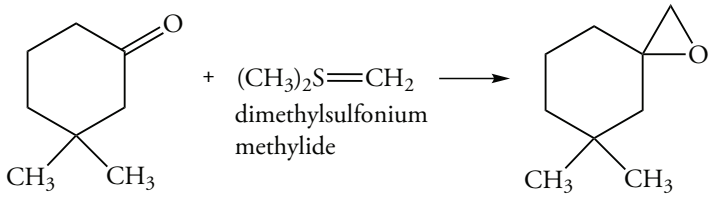
19.52 Outline a synthesis of each of the following compounds using a Wittig reaction.
(a) ethylidenecyclopentane (b) 2-ethyl-1-pentene (c) 4-propyl-3-heptene

19.53 Draw the structures of the two products formed in the following reaction.

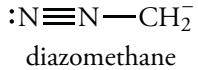


19.54 Draw the structure of the ylide formed by reacting 1-bromo-2-butyne with triphenylphosphine, followed by reaction with sodium ethoxide. Explain why such a relatively weak base is sufficient to generate the ylide.

19.55 Suggest a mechanism for the following reaction of a sulfur ylide with a ketone.



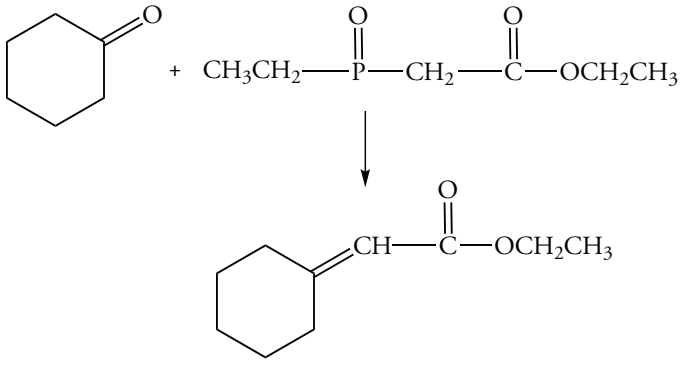
19.56 Acetone reacts with diazomethane to yield 2,2-dimethyloxirane Write a mechanism for this reaction.



diazomethane

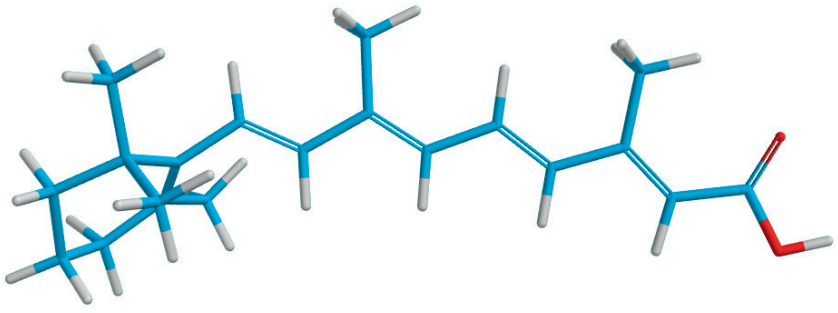
19.57 The reaction of dimethylsulfonium methylide, $(CH_3)_2S{=}CH_2$, with 4-*tert*-butylcyclohexanone can potentially give two isomeric epoxide products. Draw their structures. What factors may control the relative amounts of the two compounds formed?

19.58 Suggest a mechanism for the following reaction of cyclohexanone with triethylphosphonoacetate Draw the structure of the by-product of the reaction.



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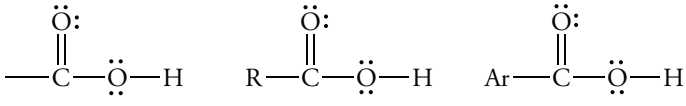
20 Carboxylic Acids



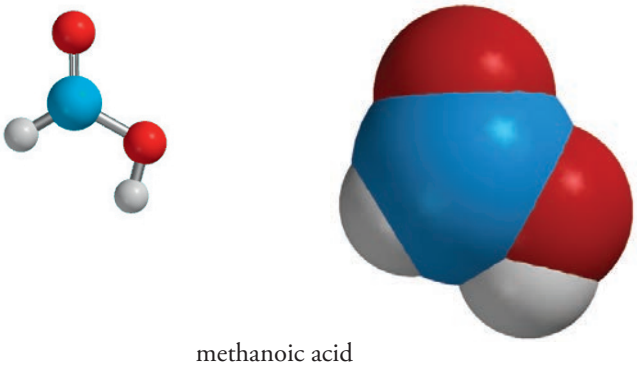
Retinoic Acid

20.1 CARBOXYLIC ACIDS AND ACYL GROUPS

At first sight, a carboxylic acid looks like two functional groups—an alcohol and an aldehyde—that happen to be bonded to the same carbon atom. However, the chemistry of carboxylic acids differs considerably from the functional groups we have described in previous chapters. The simplest carboxylic acid is methanoic acid, more commonly called formic acid. In this chapter, we consider the structure, properties, reactions, and synthesis of carboxylic acids.

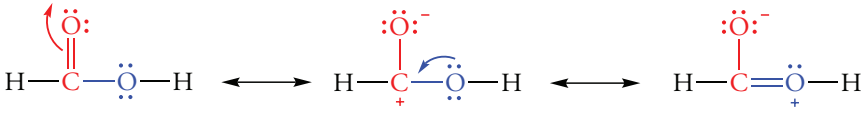


carboxyl group carboxylic acids



methanoic acid

We can write the structure of formic acid as a Lewis structure as a resonance hybrid of three contributing resonance structures as shown below.



1 **2** **3**

1. Lewis structure **1** is the most stable resonance form since both carbon and oxygen have Lewis octets.
2. The dipolar Lewis resonance structure **2** in which the carbonyl carbon atom has a positive charged carbon is less stable than structure **1**.
3. The hydroxyl oxygen atom can donate an electron pair to carbon to give resonance structure **3** in which every atom has a Lewis octet. This stabilizes the C=0 group, and the carbonyl carbon atom is less electrophilic than that of aldehydes or ketones. However, since this contributing structure has a positively charged oxygen atom, it is only a minor contributor to the resonance hybrid.

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The carbonyl carbon atom in a carboxyl group is sp^2 hybridized, and three of its valence electrons form three σ bonds at 120° angles to one another (Figure 20.1). One of the σ bonds is to a hydrogen atom or a carbon atom of an alkyl, aromatic, or heterocyclic group. The other two σ bonds are to oxygen atoms: one to the hydroxyl oxygen atom and the other to the carbonyl oxygen atom. The carbonyl carbon atom also has one electron in a 2p orbital forming a π bond with an electron in a 2p orbital of the carbonyl oxygen atom. The carbon–oxygen double bond of a carboxylic acid is shorter than the carbon–oxygen single bond.

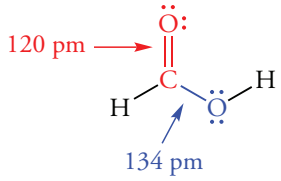
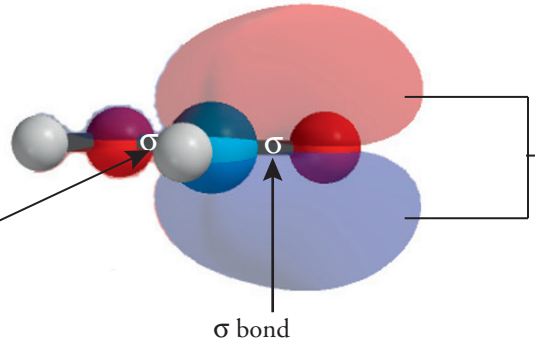


Figure 20.1
Bonding in Carboxylic Acids

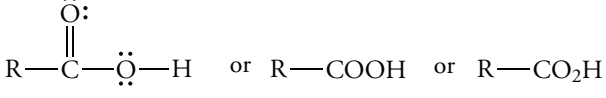


An electron of the sp^2 hybrid orbital of the carbonyl carbon atom and an electron of the sp^3 hybrid orbital of the oxygen atom form a σ bond.

The π bond forms by overlap of the half-filled 2p orbitals of carbon and oxygen.

An electron of the sp^2 hybrid orbital of the carbonyl carbon atom and an electron of the sp^2 hybrid orbital of the oxygen atom form a σ bond.

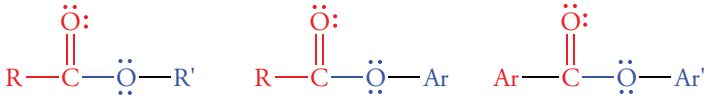
Although the bond angles at the carbonyl carbon atom are all approximately 120°, the carboxyl group is often drawn with vertical and horizontal lines. Two condensed representations of the carboxyl group are often used. The nonbonded electrons are not shown unless they are required to account for the mechanism of a reaction,



equivalent representation of carboxylic acids

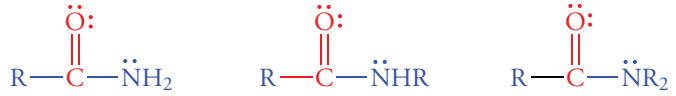
The Acyl Group and Carboxylic Acid Derivatives

The "RCO" unit contained in a carboxylic acid and its derivatives is an **acyl group**. Replacing the OH group of a carboxylic acid by other groups of electronegative atoms gives families of carboxylic acid derivatives. If an alkoxy (—OR) or phenoxy (—OAr) group is bonded to the acyl group, the derivative is an ester.



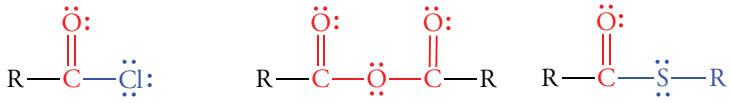
examples of esters (acyl groups shown in red)

If the substituent is linked to the acyl group through a nitrogen atom, the compound is an **amide**. The classification of amides depends on the number of carbon atoms, including the carbonyl carbon group, bonded to the nitrogen atom. Primary, secondary, and tertiary amides are possible.



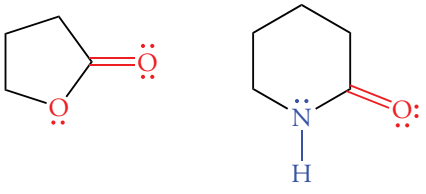
primary amide secondary amide tertiary amide

When the substituent attached to an acyl group is a chlorine atom, the derivative is an **acid chloride**. These compounds, which are highly reactive, do not occur in nature, but they are valuable reagents for the laboratory synthesis of esters and amides. When two acyl groups are bonded to a common oxygen atom, the compound is an **acid anhydride**. These compounds are also employed for laboratory synthesis of esters and amides. When a substituent is linked to an acyl group through a sulfur atom, the derivative is a **thioester**. Thioesters are less reactive than acid chlorides and acid anhydrides, but are sufficiently reactive to participate in many biochemical reactions.

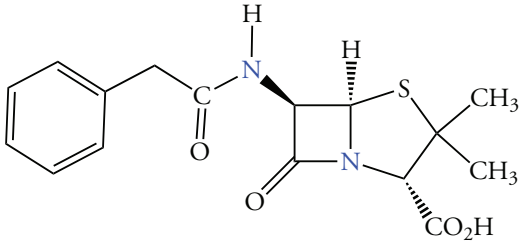


acid chloride acid anhydride thioester

Esters, amides, anhydrides, and thioesters may make up part of a cyclic structure. Cyclic esters are **lactones**. Cyclic amides are **lactams**. Penicillin G contains both a secondary amine and a lactam.



lactone (a cyclic ester) lactam (a cyclic amide)



penicillin G

Problem 20.1

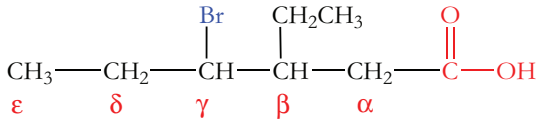
Propose two reasons why the C—O single bond of carboxylic acids (136 pm) is shorter than that of an alcohol (142 pm). Which of the two factors is the more important?

20.2 NOMENCLATURE OF CARBOXYLIC ACIDS

Carboxylic acids are abundant in nature and were among the first organic substances isolated. Because they have been known for so long, many have common names. Table 20.1 gives common and IUPAC names of several carboxylic acids.

Common Names

In common names, the positions of groups attached to the parent chain of a carboxylic acid are designated alpha (α), beta (β), gamma (γ), delta (δ), epsilon (ε), and so forth. The —COOH group itself is not designated by a Greek letter.

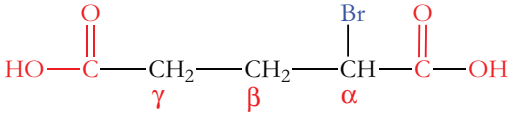


γ-bromo-β-ethylcaproic acid

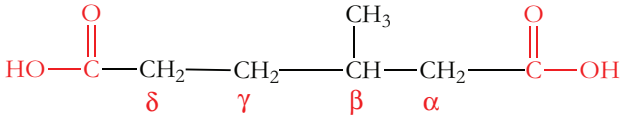
Some unbranched carboxylic acids contain a —COOH group at each end of the chain. The common names of some of these dicarboxylic acids use Greek letters starting with the carbon atom adjacent to the carboxyl group closest to the substituent.

Table 20.1
Nomenclature of Carboxylic Acids

Formula	*Common Name*	*IUPAC Name*
HCO_2H	Formic acid	Methanoic acid
CH_3CO_2H	Acetic acid	Ethanoic acid
$CH_3CH_2CO_2H$	Propionic acid	Propanoic acid
$CH_3(CH_2)_2CO_2H$	Butyric acid	Butanoic acid
$CH_3(CH_2)_3CO_2H$	Valeric acid	Pentanoic acid
$CH_3(CH_2)_4CO_2H$	Caproic acid	Hexanoic acid
$CH_3(CH_2)_6CO_2H$	Caprylic acid	Octanoic acid
$CH_3(CH_2)_{10}CO_2H$	Lauric acid	Dodecanoic acid
$CH_3(CH_2)_{12}CO_2H$	Myristic	Tetradecanoic acid
$CH_3(CH_2)_{14}CO_2H$	Palmitic	Hexadecanoic acid
$CH_3(CH_2)_{16}CO_2H$	Stearic	Octadecanoic acid

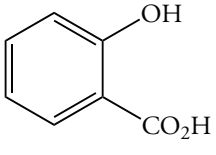


α-bromoglutaric acid

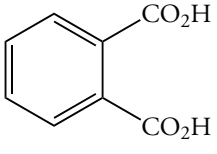


β-methyladipic acid

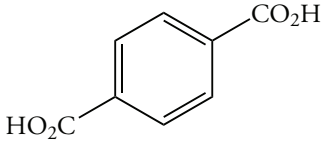
Aromatic acids containing one or more carboxyl groups are often referred to by their common names.



salicylic acid



phthalic acid



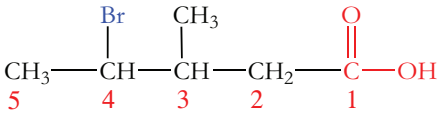
terephthalic acid

IUPAC Names of Carboxylic Acids

Carboxylic acids are named by rules similar to those for naming aldehydes.

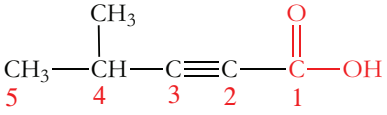
1. Name the longest continuous carbon chain containing the carboxyl carbon atom as the parent chain. Replace the final *-e* of the parent hydrocarbon by the ending *-oic acid*. Table 20.1 gives examples of IUPAC names of unsubstituted carboxylic acids.

2. Number the parent chain by assigning the number 1 to the carboxyl carbon atom. Do *not* add the number "1" to the name to indicate the position of the carboxyl carbon because it must be located at the end of the chain. Add the names and locations of any substituents as prefixes to the parent name.



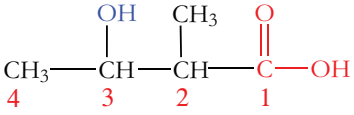
4-bromo-3-methylpentanoic acid

3. The carboxylic acid group has a higher priority than double or triple bonds. To name a carboxylic acid that contains a double or triple bond, replace the final *-e* of the name of the parent alkene or alkyne name with the suffix *-oic* acid. Indicate the position of the multiple bond with a prefix.



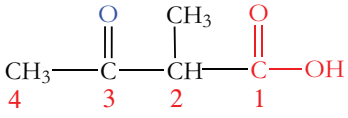
4--methyl-2-pentynoic acid

4. The carboxylic acid functional group has a higher priority than aldehyde, ketone, halogen, hydroxyl, and alkoxy groups. Indicate the names and locations of these groups with prefixes to the name of the parent carboxylic acid.



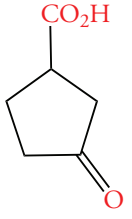
3-hydroxy-2-methylbutanoic acid

5. If a carboxylic acid contains an aldehyde or ketone, the names of the carbonyl group is *-oxo*. The priority order is aldehyde > ketone.

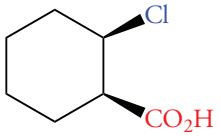


2-methyl-3-oxobutanoic acid

6. Name compounds that have a —COOH group bonded to a cycloalkane ring as derivatives of the cycloalkane with the suffix *carboxylic acid*. The ring atom to which the carboxyl group is attached is C-1. Do *not* include this number in the name.

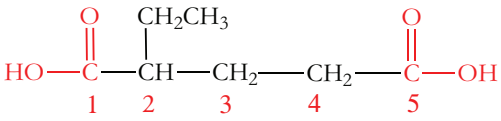


3-oxocyclopentanecarboxylic acid

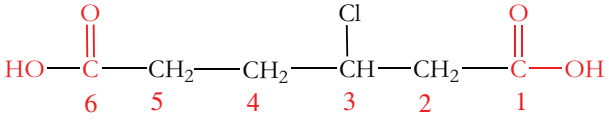


cis-2-chlorocyclohexanecarboxylic acid

7. Name dicarboxylic acids by adding the suffix *dioic acid* to the name the parent alkane that contains both carboxylic acid groups. Number the chain starting with the carboxyl carbon closest to the first substituent.



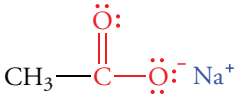
2-ethylpentanedioic acid



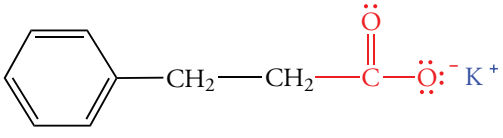
3-chlorohexanedioic acid

Names of Carboxylate Anions

The conjugate base of a carboxylic acid is a **carboxylate anion**. The common name of the conjugate base is obtained by changing the *-ic* acid ending to *-ate*. The IUPAC name of the conjugate base is obtained by changing the *-oic* acid ending to *-oate*. The name of the carboxylate anion is preceded by the name of the metal ion in the salt of a carboxylic acid.



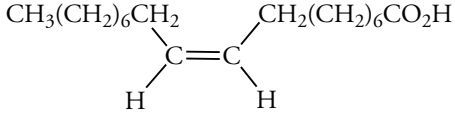
sodium ethanoate
(sodium acetate)



potassium 3-phenylpropanoate
(potassium β-phenylpropionate)

Problem 20.2

The structure of oleic acid, an unsaturated carboxylic acid present as an ester in vegetable oils, is shown below. What is the IUPAC name of oleic acid?

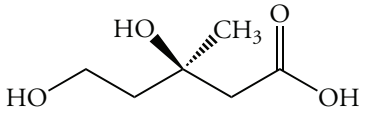


Sample Solution

First, determine the length of the continuous chain that contains the -COOH group. It contains 18 carbon atoms. The double bond is located at C-9, numbering from the carboxyl group on the right. Thus, the compound is a 9-octadecenoic acid. The configuration about the double bond is *Z*, and therefore the complete name is (*Z*)-9-octadecenoic acid.

Problem 20.3

Mevalonic acid is required to form isopentenyl pyrophosphate, an intermediate in terpene synthesis. It has the following structure. What is its IUPAC name?

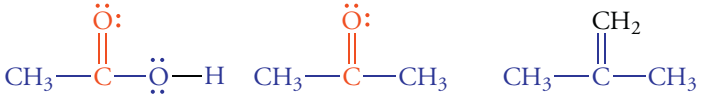


20.3 PHYSICAL PROPERTIES OF CARBOXYLIC ACIDS

The first property usually associated with liquid carboxylic acids is their sharp, unpleasant odor. For example, butanoic acid occurs in rancid butter and aged cheese. Caproic, caprylic, and capric acids have the odor of goats. (The Latin word for goat, *caper*, is the source of the common names of these acids.) Differences in biological effects of these compounds, such as odor, depend on physiological responses that differ from person to person. However, physical properties such as boiling points, melting points, and solubility directly relate to structure. We can understand these properties by considering the types of intermolecular interactions in these compounds.

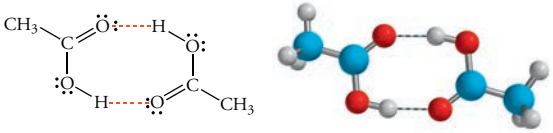
Boiling Points

Low molecular weight carboxylic acids are liquids at room temperature. Those with higher molecular weights are waxy solids. The boiling points of carboxylic acids are much higher than compounds with the same molecular weight and similar structures.



bp 118 °C bp 56.5 °C bp –7 °C

Carboxylic acids have high boiling points because they form hydrogen-bonded dimers. The hydroxyl group of one molecule acts as a proton donor to the carbonyl oxygen atom of the second molecule. The hydroxyl group of the second molecule acts as a proton donor to the carbonyl oxygen atom of the first molecule.



Acetic acid, hydrogen-bonded dimer

The two hydrogen bonds stabilize the dimer, and its structure remains even in the gas phase. As a result, the boiling points of carboxylic acids are higher than those of substances of comparable molecular weights because hydrogen bond dimerization doubles their effective molecular weight. Table 20.2 gives the boiling points of some common carboxylic acids.

Table 20.2
Boiling Points of Carboxylic Acids

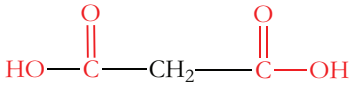
IUPAC Name	*Common Name*	*Boiling Point, °C*
Methanoic acid	Formic acid	101
Ethanoic acid	Acetic acid	118
Propanoic acid	Propionic acid	141
Butanoic acid	Butyric acid	164
2-Methylpropanoic acid	Isobutyric acid	155
Pentanoic acid	Valeric acid	186
3-Methylbutanoic acid	Isovaleric acid	177
2,2-Dimethylpropanoic acid	Pivalic acid	164
Hexanoic acid	Caproic acid	205
Octanoic acid	Caprylic acid	239
Decanoic acid	Capric	270
Dodecanoic acid	Lauric acid	299

Melting Points

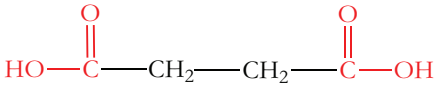
Saturated carboxylic acids with more than eight carbon atoms are solids at room temperature (Table 20.3). Their melting points increase with increasing chain length, as expected, because London forces increase with increasing chain length. The hydrocarbon chains of saturated acids pack tightly in the solid. The melting points of dicarboxylic acids are very high because they can form twice as many hydrogen bonds as carboxylic acids.

Table 20.3
Melting Points of Carboxylic Acids

Number of Carbon Atoms	*IUPAC Name*	*Common Name*	*Melting Point, °C*
10	Decanoic acid	Capric acid	31.3
12	Dodecanoic acid	Lauric acid	43.2
14	Tetradecanoic acid	Myristic acid	54.4
16	Hexadecanoic acid	Myristic acid	62.8
18	Octadecanoic acid	Isobutyric acid	69.9
20	Eicosanoic acid	Arachidic acid	75.4
22	Docosanoic acid	Behenic acid	79.9
24	Tetracosanoic acid	Lignoceric acid	84.2
26	Hexacosanoic acid	Ceratoic acid	87.7

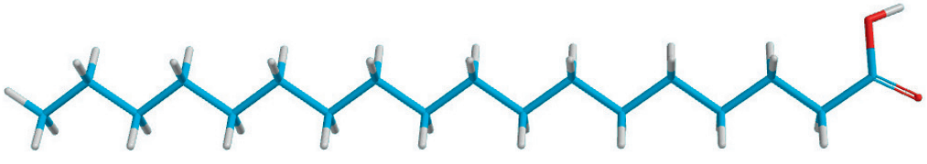


malonic acid
mp 136 °C

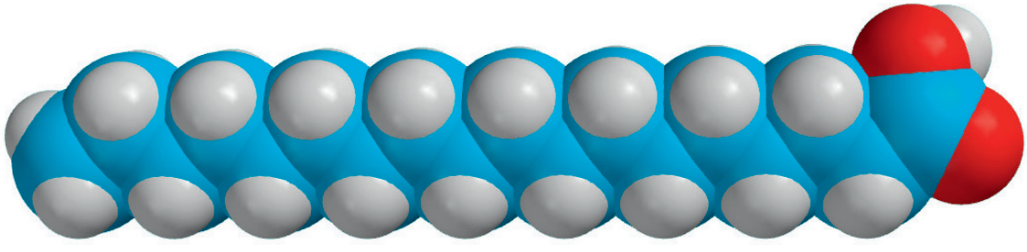


succinic acid
mp 185 °C

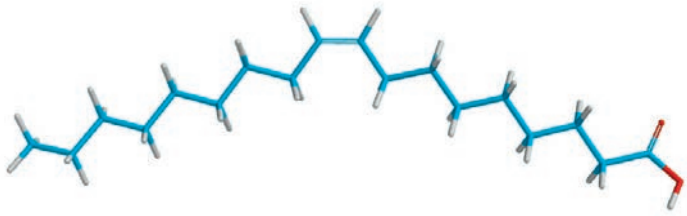
Unsaturation lowers the melting points of carboxylic acids, especially if the configuration around the double bond is *cis*. These unsaturated acids are bent molecules because of the geometry around the double bonds. The bends hinder efficient molecular packing, so London forces in unsaturated fatty acids are weaker than those in saturated fatty acids.



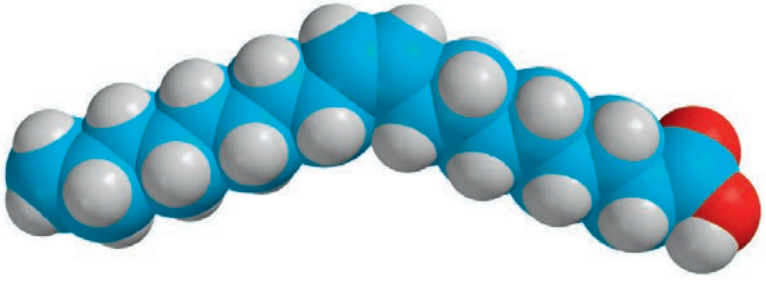
stearic acid



stearic acid

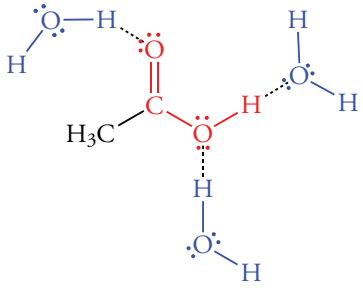


oleic acid



Solubilities

Carboxylic acids with low molecular weights dissolve in water because the carboxyl group forms several hydrogen bonds with water. A carboxylic acid acts both as a hydrogen bond donor through its hydroxyl hydrogen atom and as a hydrogen bond acceptor through the lone pair electrons of both oxygen atoms. The solubility of carboxylic acids, like that of alcohols, decreases with increasing chain length because long nonpolar hydrocarbon chains dominate the physical properties of the acid.



hydrogen bonds between acetic acid and water in aqueous solution

Carboxylic acids dissolve in common alcohol solvents such as ethanol. This solubility results from intermolecular hydrogen bonds between solute and solvent, and from van der Waals attractions between the ethyl group of ethanol and the nonpolar tail of the carboxylic acid. Nonpolar solvents, such as chloroform, are also excellent solvents for carboxylic acids. In these solvents, the carboxylic acids exist as relatively nonpolar hydrogen-bonded dimers that are compatible with the solvent.

Problem 20.4

(a) Rank toluene, benzyl alcohol, benzaldehyde, and benzoic acid in order of increasing boiling point. (b) Rank them in increasing order of solubility in water.

20.4 ACIDITY OF CARBOXYLIC ACIDS

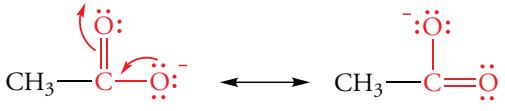
The ionization of an acid, HA, is reflected in the acid dissociation constant, K_a. It depends on both the strength of the H—A bond and the stability of the conjugate base, A^-, in the solvent. Although acetic acid and other carboxylic acids are weak acids, they are far more acidic than alcohols or phenols. For example, the K_a of acetic acid is about 10^{11} times larger than the K_a of ethanol.

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+ \quad K_a = 1 \times 10^{-16}$$

$$CH_3CO_2H + H_2O \rightleftharpoons CH_3CO_2^- + H_3O^+ \quad K_a = 1.8 \times 10^{-5}$$

Resonance Stabilization of the Carboxylate Ion

Carboxylic acids are much more acidic than alcohols because the ionization reaction yields a resonance-stabilized carboxylate anion. Dispersing the charge in the acetate ion between the two oxygen atoms makes acetic acid far more acidic than ethanol. In the ethoxide ion ($CH_3CH_2O^-$), a single oxygen atom carries the negative charge.



1 **2**

Resonance structures of acetate ion

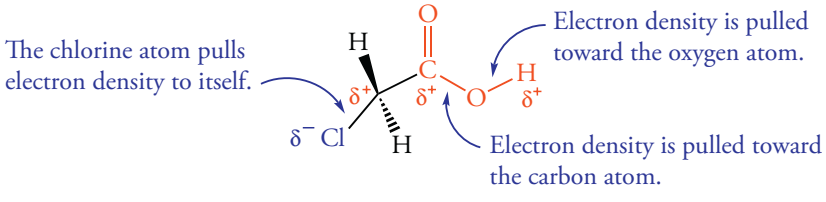
Electron delocalization in the acetate ion changes the lengths of the carbon–oxygen bonds. The lengths of both bonds in the acetate ion are 125 pm. Because both oxygen atoms are equivalent, each one bears one-half the negative charge. Acetic acid has two different carbon–oxygen bond lengths: the C—O single bond length is 136 pm and the C=O double bond length is 121 pm.

Inductive Effect on Acidity

The acidity of carboxylic acids is also partly the result of an inductive effect. The carbonyl group polarizes the H—O bond by attracting electrons through the σ-bonding network. Withdrawing electron density from the O—H bond weakens it, increasing the acidity of the hydrogen atom.

The inductive effect of an alkyl or aryl group attached to the carbonyl carbon atom also affects the acidity of carboxylic acids. An alkyl group is electron releasing with respect to hydrogen. This release of electron density to the carboxyl group stabilizes the acid and slightly destabilizes the conjugate base. Thus, acetic acid (pK_a 4.72) is weaker than formic acid (pK_a 3.75). Beyond the α carbon atom, additional carbon atoms do not significantly affect the pK_a (Table 20.4).

An electronegative group attached to the α carbon atom of a carboxylic acid also increases acidity. For example, halogen atoms pull electron density away from the carbonyl group and indirectly from the O—H bond. This weakens the O—H bond, and the pK_a value increases (Table 20.4).



As the distance between the halogen atom and the carboxyl group increases, the inductive effect falls off dramatically. For β- and γ-substituted acids, the pK_a values approach that of an unsubstituted carboxylic acid.

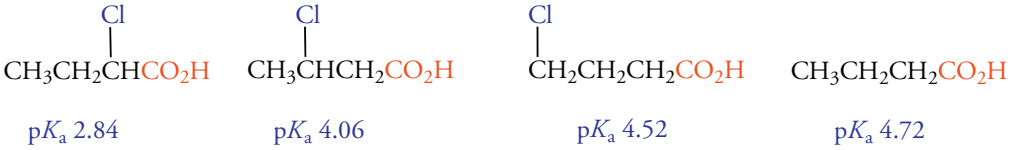


Table 20.4
pK_a Values of Carboxylic Acids

IUPAC Name	*Formula*	pK_a
Methanoic acid	HCO_2H	3.75
Ethanoic acid	CH_3CO_2H	4.72
Propanoic acid	$CH_3CH_2CO_2H$	4.87
Butanoic acid	$CH_3(CH_2)_2CO_2H$	4.82
2-Methylbutanoic acid	$(CH_3)_2CHCO_2H$	4.84
Pentanoic acid	$CH_3(CH_2)_3CO_2H$	4.81
2,2-Dimethylmethylpropanoic acid	$(CH_3)CCO_2H$	5.03
Fluoroethanoic acid	FCH_2CO_2H	2.59
Chloroethanoic acid	$ClCH_2CO_2H$	2.86
Bromoethanoic acid	$BrCH_2CO_2H$	2.90
Iodoacetic acid	ICH_2CO_2H	3.18
Dichloroethanoic acid	Cl_2CHCO_2H	1.24
Trichloroethanoic acid	Cl_3CCO_2H	0.64
Trifluoroethanoic acid	F_3CCO_2H	0.23
Methoxyethanoic acid	$CH_3OCH_2CO_2H$	3.55
Cyanoethanoic acid	$CNCH_2CO_2H$	2.46
Nitroethanoic acid	$NO_2CH_2CO_2H$	1.72

Table 20.5 lists the pK_a values for the first and second ionization constants of dicarboxylic acids. The effect of one electron-withdrawing carboxyl group on the acidity of the other carboxyl group decreases with distance between the two groups. The pK_a for the second ionization is larger than for the first ionization because the charged carboxylate group withdraws electrons more strongly than a protonated carboxyl group.

Table 20.5
pK_a Values of Dicarboxylic Acids

IUPAC Name	*Formula*	pK_{a1}	pK_{a2}
Oxalic acid	HO_2CCO_2H	1.27	4.27
Malonic acid	$HO_2CCH_2CO_2H$	2.85	5.70
Succinic acid	$HO_2C(CH_2)_2CO_2H$	4.35	5.64
Glutaric acid	$HO_2C(CH_2)_3CO_2H$	4.41	5.41
Adipic acid	$HO_2C(CH_2)_4CO_2H$	4.42	5.42
Pimelic acid	$HO_2C(CH_2)_5CO_2H$	4.51	5.42
Suberic acid	$HO_2C(CH_2)_6CO_2H$	4.52	5.41
Azelaic acid	$HO_2C(CH_2)_7CO_2H$	4.54	5.41
Sebacic acid	$HO_2C(CH_2)_8CO_2H$	4.55	5.40

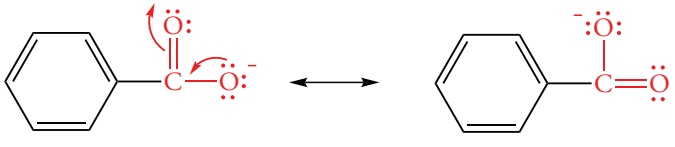
Acidity of Aromatic Carboxylic Acids

An aryl group is electron withdrawing relative to an alkyl group because the sp^2-hybrid orbitals of the aromatic Ar—CO_2H bond draws the bonding electrons toward the aryl group. Thus, benzoic acid (pK_a 4.19) is a stronger acid than acetic acid. Table 20.6 lists the pK_a values of some aromatic carboxylic acids.

Table 20.6
pK_a Values of Substituted Benzoic Acids

Substituent	*Ortho*	*Meta*	*Para*
CH_3O	4.06	4.10	4.47
CH_3	3.91	4.27	4.37
H	4.20	4.20	4.20
Cl	2.92	3.82	3.98
NO_2	2.17	3.49	3.42

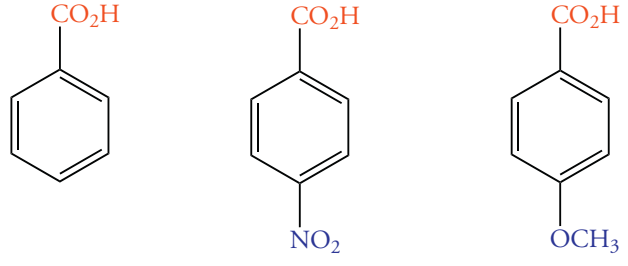
Substituents on an aromatic ring affect the reactivity of the ring toward electrophilic substitution by a combination of inductive and resonance effects (Section 13.5). Electron-withdrawing groups decrease the electron density of the ring. Electron-donating groups increase the electron density of the ring. However, the major resonance forms of the benzoate ion have the negative charge on the oxygen atoms. This negative charge cannot be delocalized into the aromatic ring.



1 2

Resonance structures of benzoate ion

Nevertheless, substituents bonded to an aromatic ring alter the acidity of benzoic acids. An electron-withdrawing group, such as —NO_2, decreases the electron density at the carbon atom to which the carboxylate group is bonded. As a result, the O—H bond is polarized, and its acidity increases. The decrease in electron density also stabilizes the resulting carboxylate ion. Electron-donating groups, such as —OCH_3, have the opposite effect.



pK_a = 4.20 pK_a = 3.42 pK_a = 4.47

The effect of a *para* substituent reflects both inductive and resonance contributions to the carbon atom bearing the carboxyl group. The effect of a *meta* substituent results only from inductive effects. The contribution of groups *ortho* to the carboxyl group is not easily interpreted because of steric effects on the conformation of the carboxyl group as well as solvation effects.

Problem 20.5

Explain why $CH_2{=}CHCH_2CO_2H$ (pK_a 4.3) is a stronger acid than butanoic acid (pK_a 4.8).

Sample Solution

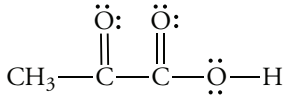
The vinyl group bonded to the α carbon atom is electron withdrawing relative to the ethyl group bonded to the α carbon atom of butanoic acid. The sp^2-hybridized carbon atom of the vinyl group draws electron density of the carbon–carbon bond away from the α carbon atom. Thus, the acidity of the unsaturated acid is greater, and the pK_a is smaller.

Problem 20.6

Explain why *p*-nitrobenzoic acid is a stronger acid than *m*-nitrobenzoic acid.

Problem 20.7

Explain why pyruvic acid (pK_a 4.7) is about 100 times more acidic than propanoic acid (pK_a 2.5). Pyruvic acid is a key metabolic intermediate in oxidative processes that provide energy for the growth and maintenance of cells.



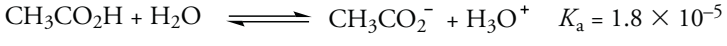
pyruvic acid

20.5 CARBOXYLATE ANIONS

What is the ratio of the concentrations of the carboxylate ion to nonionized carboxylic acid, RCO_2^-/RCO_2H, in aqueous solution? The answer depends on the pK_a of the carboxylic acid and the pH of the solution. In this section, we consider three cases (1) water, (2) solutions buffered at pH = 7, and (3) strongly basic solutions.

Carboxylate Ions in Water

The ionization of a weak acid, such as acetic acid, produces a very low concentration of acetate ion. The ionization reaction gives an acetate ion and hydronium ion.



$$CH_3CO_2H + H_2O \rightleftharpoons CH_3CO_2^- + H_3O^+ \quad K_a = 1.8 \times 10^{-5}$$

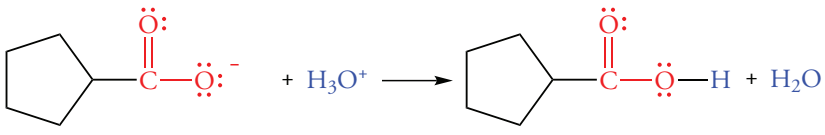
Since carboxylic acids are week acids, a dilute aqueous solution contains very little acetate. For example, the acetate ion concentration is only 1.3×10^{-3} M.

Carboxylate Ions in Basic Solution

When a carboxylic acid dissolves in a basic solution, the ratio of carboxylate ion to carboxylic acid increases dramatically. Thus, when acetic acid is placed into a solution of sodium bicarbonate at pH 8.5, less than 0.020 of the carboxylic acid remains. Since carboxylate ions have a negative charge, they are more soluble than carboxylic acids. Thus, carboxylic acids readily dissolve in sodium bicarbonate solution. Weaker acids such as phenols (pK_a 10) are not converted to their conjugate bases at pH = 8, so phenols are less soluble than carboxylic acids in sodium bicarbonate.

Separation and Purification of Carboxylic Acids

Since carboxylic acids are weak acids, carboxylates are relatively strong bases. Carboxylate salts react with hydronium ion to form the carboxylic acid. The carboxylic acid is insoluble in acid solution and therefore can be separated from the mixture.



We can proceed in the opposite direction too. Consider, for example, a mixture of 1-decanol and decanoic acid. 1-Decanol is not soluble in water and does not react with sodium hydroxide. However, decanoic acid reacts with sodium hydroxide and thus dissolves in the basic solution.

$CH_3(CH_2)_8CH_2OH + HO^- \xrightarrow{X} CH_3(CH_2)_8CH_2O^- + H_2O$

Insoluble in water — No reaction

$CH_3(CH_2)_8CO_2H + HO^- \longrightarrow CH_3(CH_2)_8CO_2^- + H_2O$

Insoluble in water — Soluble in water

Undissolved 1-decanol is physically separated from the basic solution. Then, HCl is added to neutralize the basic solution, and insoluble decanoic acid separates from the aqueous solution.

$CH_3(CH_2)_8CO_2^- + H_3O^+ \longrightarrow CH_3(CH_2)_8CO_2H + H_2O$

Soluble in water — Insoluble in water

This procedure is very useful in isolating acids from complex mixtures. It is also used to purify acids produced by chemical synthesis in the laboratory.

Problem 20.8

Ibuprofen, the active ingredient in Motrin, Advil, and Nuprin, is a carboxylic acid with $pK_a = 5.2$. Determine the ratio of the conjugate base to acid in stomach acid at (a) pH = 2 and (b) blood at pH = 7.4.

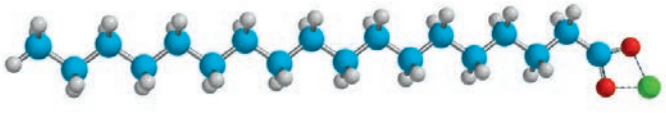
Soaps and Detergents

Soaps are salts of long-chain acids called fatty acids. The best soaps are carboxylate salts made from saturated acids with 14–18 carbon atoms. Soaps fabricated as bars are usually sodium salts, whereas the potassium salts, which are softer, are used in liquid soaps and shaving creams.

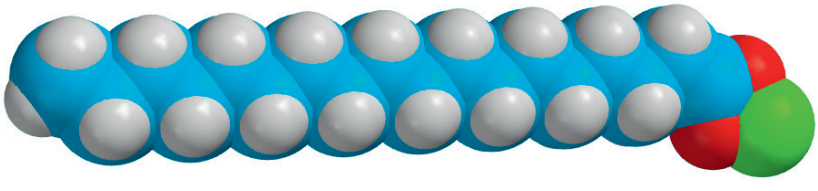
$CH_3(CH_2)_{16}CO_2^- Na^+$

Oil-soluble hydrocarbon "tail" — Water-soluble carboxylate "head"

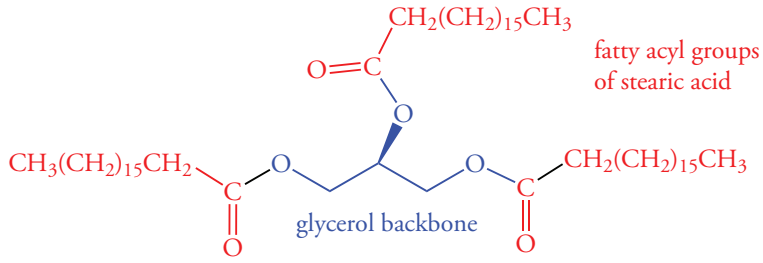
sodium stearate



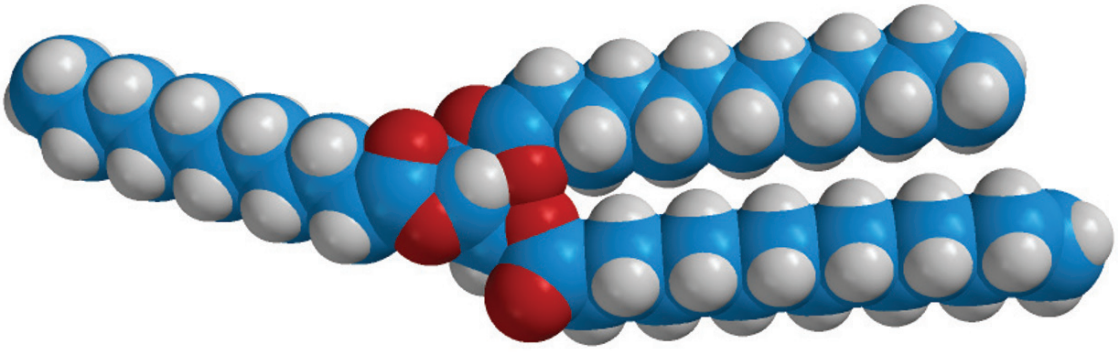
sodium stearate



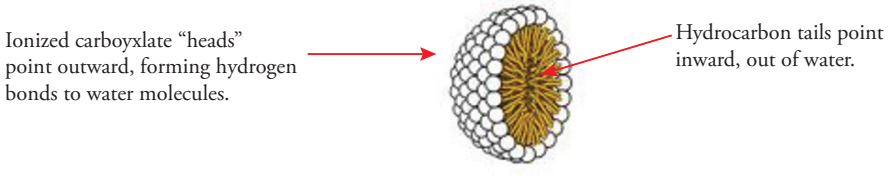
Soaps were originally produced from animal fats, triesters of glycerol and carboxylic acid containing 12–18 carbon atoms. The glycerol triester called myristin contains three acyl group of stearic acid.



myristin
(a triacylglycerol of stearic acid)



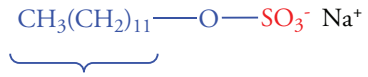
The carboxylate salts of fatty acids have long, nonpolar, hydrocarbon chains. Therefore, they do not form solutions of individual ions, but are dispersed as weakly associated structures called **micelles**, which are spherical aggregations of molecules or ions. In a micelle of carboxylate salts, the nonpolar hydrocarbon chains occupy the interior of the sphere, and the polar carboxylate "heads" lie on the surface of the sphere. This spherical arrangement encloses the maximum amount of "hydrocarbon" material in the smallest surface area. Therefore, a micelle disrupts the hydrogen-bonded structure of water to the smallest extent possible.



The nonpolar hydrocarbon tail of a fatty acid avoids water and is **hydrophobic**. In contrast, the polar carboxylate head forms hydrogen bonds to water and is **hydrophilic**. London forces among the hydrocarbons in a micelle hold it together. The tendency of nonpolar solutes to aggregate in aqueous solution is called the **hydrophobic effect**. The micelle surface, which might hold as many as 100 carboxylate groups, has many negative charges. Thus, micelles repel one another and remain suspended in water.

An example of a hydrophobic substance is grease, which does not dissolve in water because it is nonpolar. However, grease dissolves in the nonpolar interior of a micelle. This process accounts for the cleaning action of a soap.

Micelles also interact with the ions in hard water, which contains relatively high concentrations of calcium and magnesium ions. These ions bind the carboxylate groups of soaps and form precipitates that reduce the cleansing power of a soap. For this reason detergents, which are sulfate esters of long-chain alcohols, work better than soaps in hard water. Like soaps, detergents have long, hydrophobic tails. However, they do not form precipitates with calcium and magnesium ions.



Hydrophobic hydrocarbon "tail" dissolves grease.

Hydrophilic sulfate "head" does not bind Mg^{2+} and Ca^{2+}.

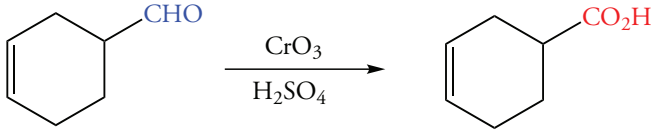
sodium dodecyl sulfate (SDS)

20.6 SYNTHESIS OF CARBOXYLIC ACIDS

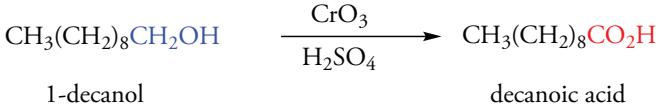
In this section, we first consider oxidative methods of preparing carboxylic acids. Then, we discuss two general methods that are useful in preparing carboxylic acids from starting materials containing one less carbon atom than the product. These methods, the carboxylation of a Grignard reagent and the hydrolysis of a nitrile, are based in part on reactions we have studied in earlier chapters.

Oxidative Methods

We recall that aldehydes and primary alcohols are oxidized by Jones reagent (Section 15.4) to produce carboxylic acids. The oxidation of alcohols proceeds by way of aldehydes, which are in turn more readily oxidized to carboxylic acids.

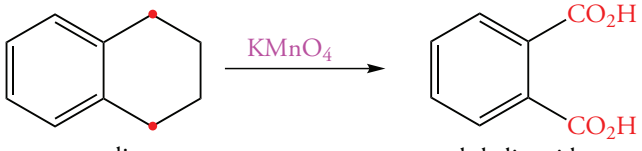


3-cyclohexenecarbaldehyde → 3-cyclohexenecarboxylic acid



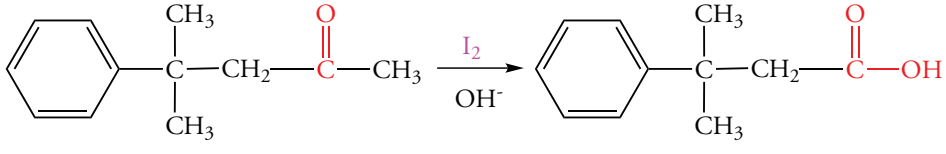
1-decanol → decanoic acid

Alkylbenzenes are oxidized by potassium permanganate to give benzoic acids. We recall that the entire side chain is oxidized in this reaction. For example, potassium permanganate oxidizes tetralin, which has a benzene ring fused to a cyclohexane ring, to produce phthalic acid.



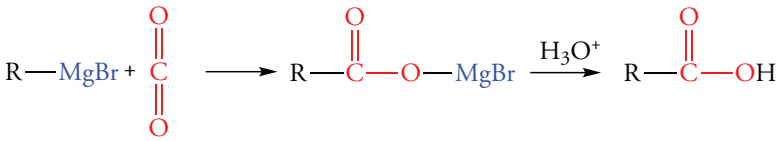
tetralin → phthalic acid

The haloform reaction (Section 21.5) is also an oxidative reaction. In this reaction, the methyl group of a methyl ketone is converted to a haloform such as iodoform, and the carbonyl carbon atom is oxidized to a carboxylic acid.



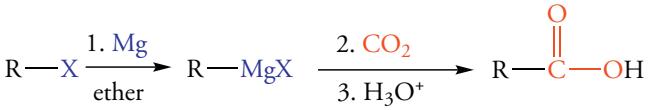
Carboxylation of Grignard Reagents

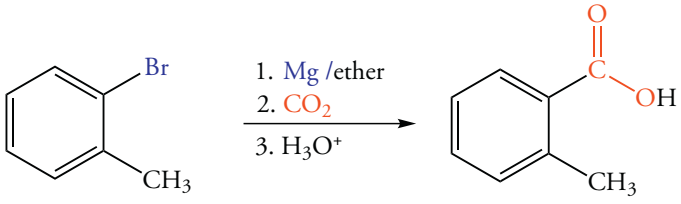
In Chapter 15, we saw that a Grignard reagent is a nucleophile, and that it reacts with the electrophilic carbonyl group of aldehydes or ketones. A similar reaction occurs between a Grignard reagent and the carbon—oxygen double bond of carbon dioxide to yield the magnesium salt of a carboxylic acid. Acidification gives the carboxylic acid. This reaction is called **carbonylation**.



Starting from the haloalkane, the reaction sequence requires three steps.

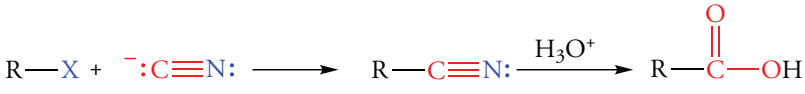
1. The haloalkane is converted to a Grignard reagent.
2. The ether solution of the Grignard reagent is poured over solid carbon dioxide (dry ice).
3. In the final step, the reaction mixture is acidified.



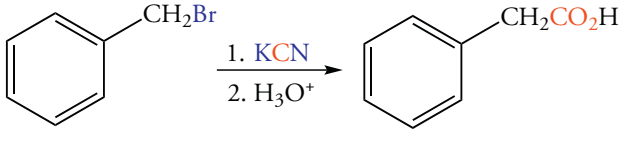


Hydrolysis of Nitriles

Another reaction that adds one carbon atom to the parent chain is the reaction of a haloalkane with cyanide ion by an S_N2 reaction (Section 9.10). The resulting product, called a nitrile (RCN), can be hydrolyzed to produce a carboxylic acid. (We will discuss the chemistry of nitriles in Chapter 21.)

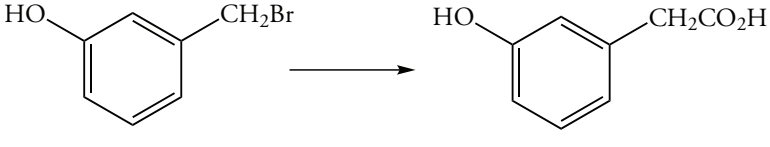


We recall that S_N2 reactions are most effective with primary haloalkanes. Elimination reactions decrease the yield for secondary haloalkanes.



Problem 20.9

Suggest a synthetic sequence for the following transformation.

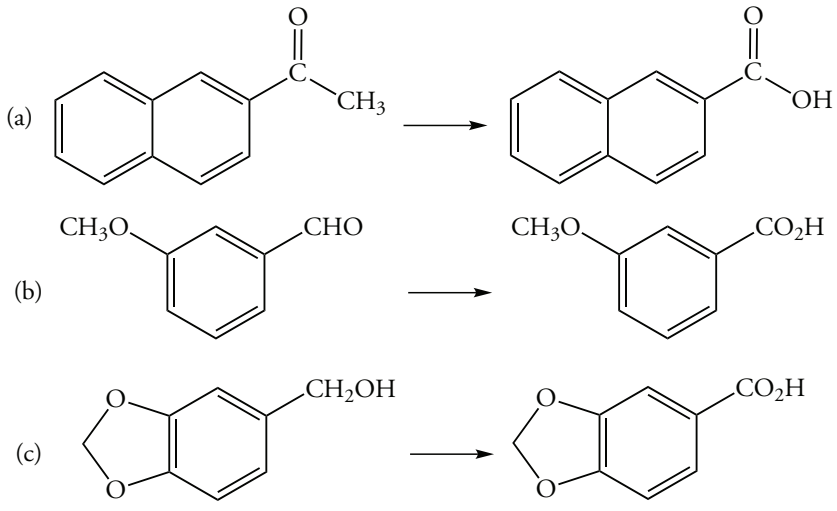


Sample Solution

One carbon atom in the form of a carboxyl group must be added to the side chain of the aromatic compound. We cannot use a Grignard reaction followed by carbonation because the acidic phenolic hydroxyl group would destroy the Grignard reagent (unless we protect it first). However, benzyl bromide is a primary haloalkane that readily reacts with cyanide ion in an S_N2 reaction to give a nitrile. Hydrolysis of the nitrile under acidic conditions gives the desired carboxylic acid.

Problem 20.10

Suggest synthetic sequences for the following reactions.

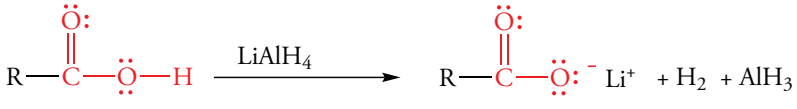


20.7 REDUCTION OF CARBOXYLIC ACIDS

Reduction with Lithium Aluminum Hydride

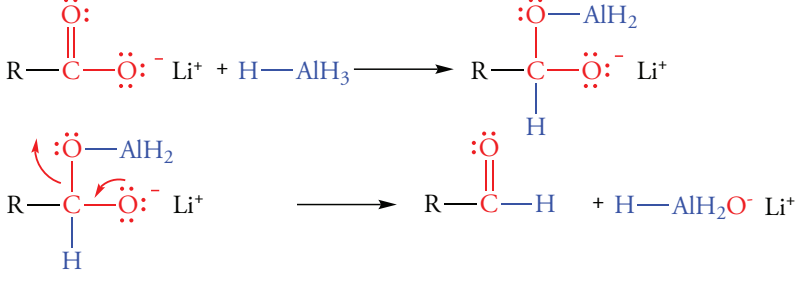
We recall that $LiAlH_4$ reduces esters of carboxylic acids, yielding primary alcohols (Section 15.9). An aldehyde occurs as an intermediate in the reaction, but cannot be isolated because lithium aluminum hydride reduces it more readily than the ester. Sodium borohydride does not reduce esters.

Carboxylic acids are also reduced by lithium aluminum hydride. However, the acidic proton of the carboxylic acid reacts with one equivalent of hydride ion to generate hydrogen gas and a lithium salt of the carboxylic acid. This reaction destroys part of the hydride reagent.



The continued reaction of the remaining aluminum hydride with the carboxylate salt requires higher temperatures and longer reaction times because the hydride ion must react with a carbonyl carbon atom of the carboxylate, which is less electrophilic than the carbonyl carbon atom of an ester.

The first step in the reduction of the carboxylate is a hydride addition reaction to the carbonyl group. This reaction is similar to the addition reaction of aldehydes and ketones. A subsequent elimination reaction forms an aldehyde. This reaction is analogous to the elimination reaction of a hemiacetal, which also has two oxygen atoms bonded to the same carbon atom, to give the more stable carbonyl compound.

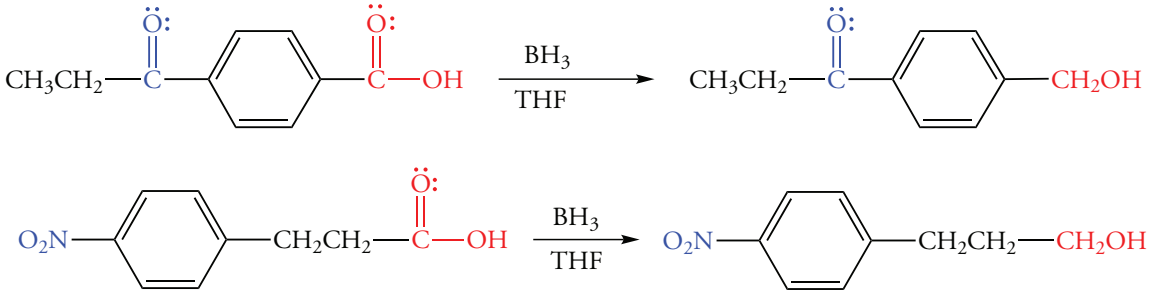


However, the aldehyde does not survive under these reaction conditions because it is reduced by $LiAlH_4$ or by remaining hydride in species such as AlH_3 or AlH_2O^-.

Reduction with Diborane

Carboxylic acids are reduced to primary alcohols using diborane in an ether solvent such as THF. The reaction occurs very rapidly even at room temperature. The major advantage of this reagent is its selectivity. For example, it reduces a carboxylic acid at a faster rate than a ketone or ester. It very slowly reduces a nitrile, but does not reduce a nitro group.

Diborane cannot be used if the substrate contains a double bond, because hydroboration would occur.



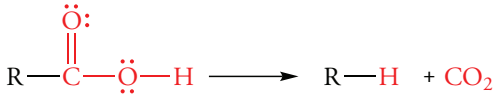
Lithium aluminum hydride would reduce both the carboxylic acid and the keto group, and it would reduce the carboxyl group to an alcohol and the nitro group to an amine.

Problem 20.11

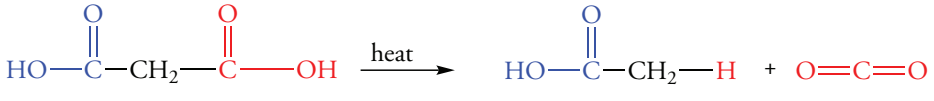
What is the product of the reaction of 3-(*p*-cyanophenyl)propanoic acid with $LiAlH_4$? What is the product using B_2H_6?

20.8 DECARBOXYLATION REACTIONS

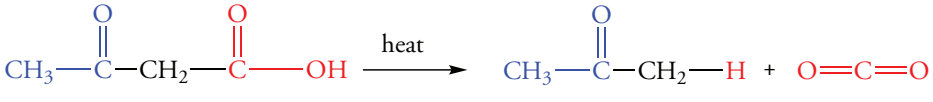
In a decarboxylation reaction, a CO_2 group is lost and is replaced by a hydrogen atom.



Decarboxylation does not occur readily for simple carboxylic acids. However, carboxylic acids containing a β-carbonyl group decarboxylate at relatively low temperatures. Two compounds of this type are acetoacetic acid and malonic acid.

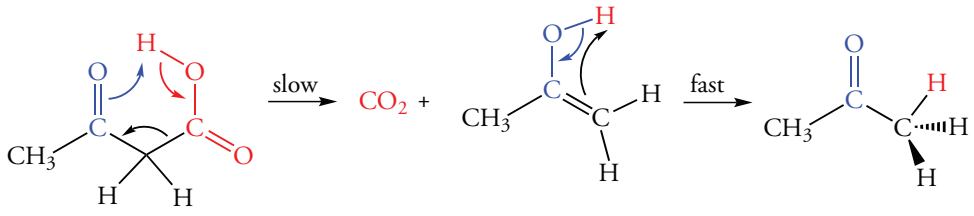


malonic acid

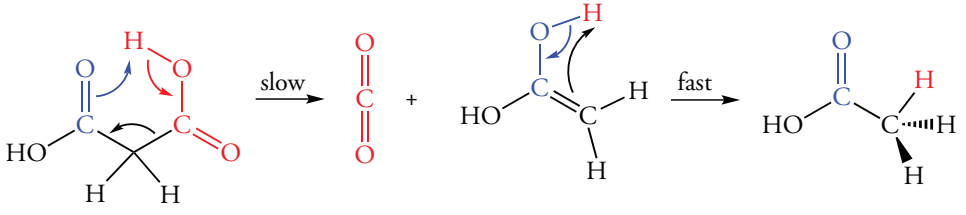


acetoacetic acid

The decarboxylation of acetoacetic acid, a β-keto acid, occurs by way of a cyclic transition state in which a proton is transferred from the carboxylate atom to the carbonyl oxygen to give an enol that rapidly tautomerizes to give acetone.

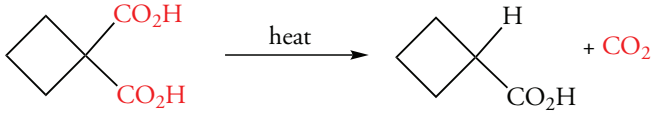


Malonic acid decarboxylates by way of a similar transition state to give an enol of acetic acid that tautomerizes to acetic acid.

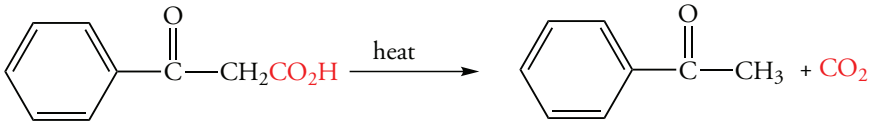


Neither reaction occurs for the conjugate base of these acids because a proton is required for transfer between oxygen atoms. If the conjugate base is carefully neutralized, the carboxylic acid can be isolated at room temperature without decarboxylation.

Groups bonded to C-2 of either acetoacetic acids or malonic acids, or to C-4 of acetoacetic acids, do not participate in the mechanism of the reaction. Both types of compounds are produced in condensation reactions of the related esters (Chapter 21). Hydrolysis of these esters yields carboxylic acids that are then heated to decarboxylate them.



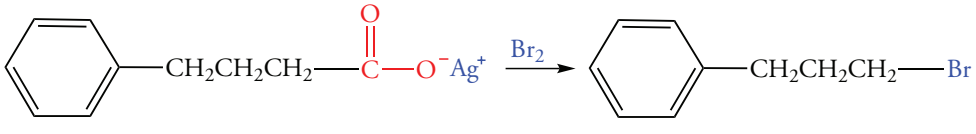
1,1-cyclobutanedicarboxylic acid cyclobutanecarboxylic acid



3-phenyl-3-oxopropanoic acid 1-phenyl-ethanone

The Hunsdiecker Reaction

If the silver salt of a carboxylic acid is treated with bromine, the salt decarboxylates and a bromoalkane forms. This process is called the **Hunsdiecker reaction**. The decarboxylation reaction can also be carried out using the carboxylic acid and mercury(II) oxide.

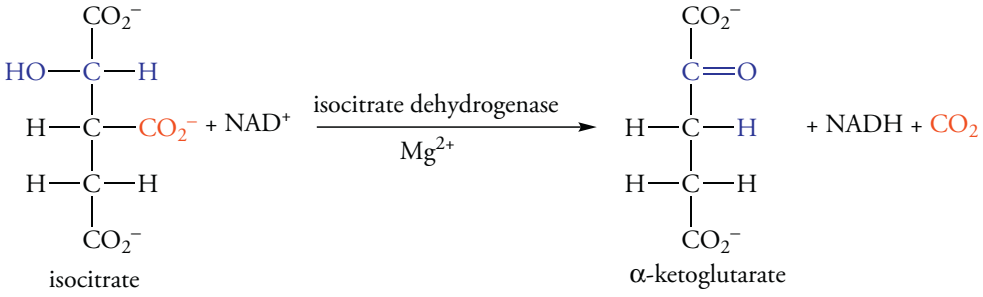


Problem 20.12

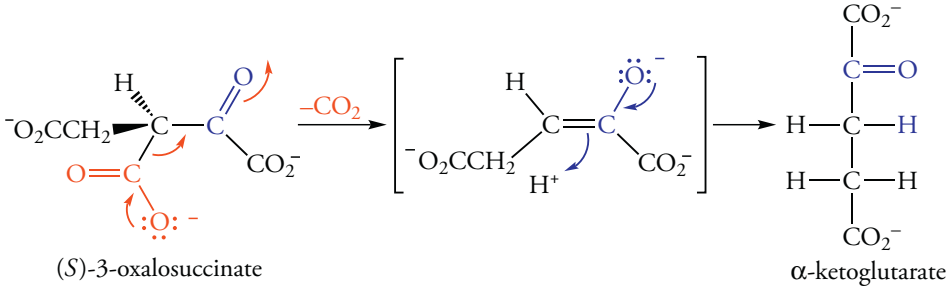
Heating 4-methyl-1,1-cyclohexanedicarboxylic acid yields a mixture of two isomers. (a) Draw their structures and (b) explain their origin.

Biochemical Decarboxylation Reactions

The decarboxylation of β-keto acids is an important biochemical reaction. The conversion of isocitric acid to α-ketoglutarate in the citric acid cycle is one example. This reaction is catalyzed by isocitrate dehydrogenase, an NAD^+-dependent dehydrogenase.



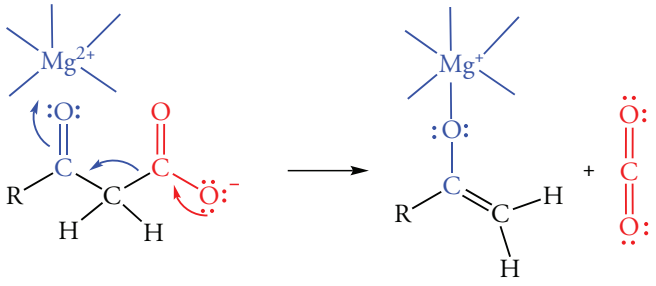
The first step is oxidation of the hydroxyl group to a carbonyl group, which gives oxalosuccinate, which is a β-keto acid. This metabolic intermediate undergoes decarboxylation.



The biological decarboxylation of a β-keto acid presents a slight difficulty. We recall that carboxylic acids exist as carboxylate anions at pH 7. And, the decarboxylation of β-keto acids occurs from the carboxylic acid, not the anion. Why, then, is this decarboxylation a favorable process? Decarboxylation of oxalosuccinate produces an enolate anion. An enolate anion has a pK_a of –20 and is very unstable at pH 7. A reaction that produces an unstable intermediate has a high activation energy and is slow. Thus, the enzyme-catalyzed decarboxylation of the anionic form of a β-keto acid has to stabilize the enolate anion intermediate. Isocitrate dehydrogenase requires Mg^{2+} ions. An Mg^{2+} ion forms a complex with the carbonyl group of the β-keto acid. This has two effects.

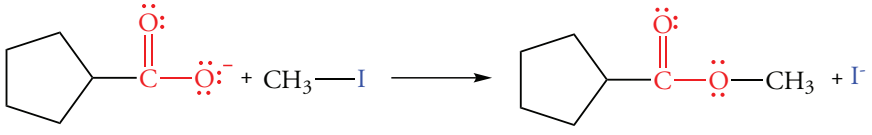
1. Mg^{2+} polarizes the carbonyl bond, making it more electron withdrawing. That is, it acts as an "electron sink" that withdraws electron density from the carboxylate group. This facilitates loss of CO_2.
2. The Mg^{2+} ion stabilizes the enolate anion intermediate by coordination with the negatively charged oxygen. Stabilization of the enolate lowers the energy of the transition state, increasing the rate of the reaction.

The mechanism of the decarboxylation reaction is shown below. The enolate picks up a proton from an acidic group at the enzyme active site and tautomerizes to the keto form.



20.9 REACTIONS OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES: A PREVIEW

Carboxylic acids are not nucleophiles. However, the carboxylate ion is a nucleophile. Since the charge on the carboxylate is delocalized, it is not a very strong nucleophile. A carboxylate anion reacts with a primary alkyl halide to give an ester in an S_N2 reaction

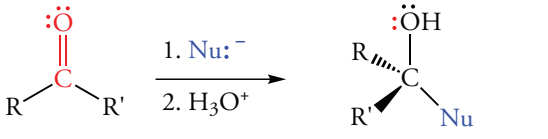


cyclopentanecarboxylate

methyl cyclopentanecarboxylate

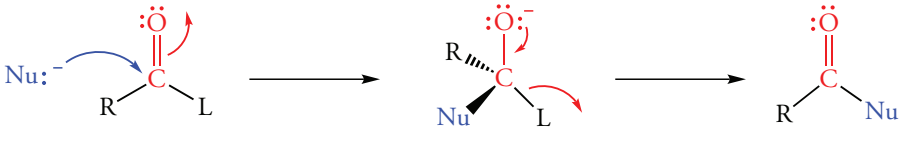
Nucleophilic Acyl Substitution

In the addition reactions of aldehydes and ketones, a tetrahedral product forms because of attack of a nucleophile at the carbonyl carbon atom. Examples include the formation of hemiacetals with alcohols, and the synthesis of alcohols using the Grignard reagent.



tetrahedral product

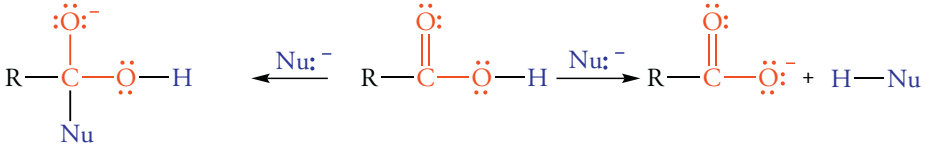
Carboxylic acids and acyl derivatives also react with nucleophiles. In these reactions, the nucleophile attacks the carbonyl carbon atom to generate an unstable *tetrahedral intermediate* that loses an OH group to form a different acyl derivative. The overall process is **nucleophilic acyl substitution**.



tetrahedral intermediate

The rate-determining step is usually nucleophilic attack at the carbonyl carbon atom to form a tetrahedral intermediate. The loss of the leaving group occurs in a second, faster step. The overall process is an **addition–elimination reaction**.

Only certain types of nucleophiles attack carboxylic acids. Most are bases that can either react with the acidic hydrogen atom of the carboxylic acid or attack the carbonyl carbon atom.



addition reaction

acid–base reaction

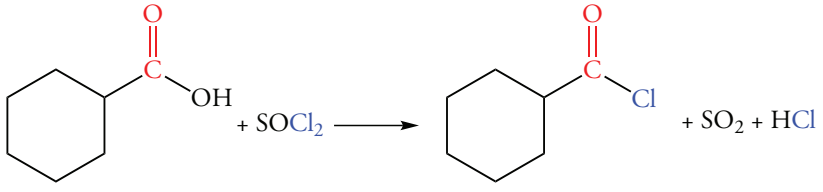
Because carboxylic acids are acidic, the acid–base reaction with nucleophile often predominates. However, an addition–elimination reaction is common for acyl derivatives because they do not have an acidic hydroxyl hydrogen atom.

20.10 CONVERSION OF CARBOXYLIC ACIDS INTO ACYL HALIDES

Carboxylic acids are converted into acyl halides for use in nucleophilic acyl substitution reactions for two reasons.

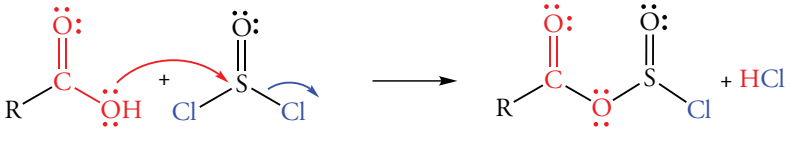
1. First, the competing reaction of nucleophiles with the acidic proton of carboxylic acids is eliminated.
2. Second, a chloride ion is a better leaving group than a hydroxide ion.

We recall that the best way to replace hydroxyl group of an alcohol with chlorine is to convert the hydroxyl group into a better leaving group. Similarly, we can use thionyl chloride to convert a carboxylic acid to an acyl halide. It reacts with an alcohol to give a chlorosulfite ester (Section 15.3).

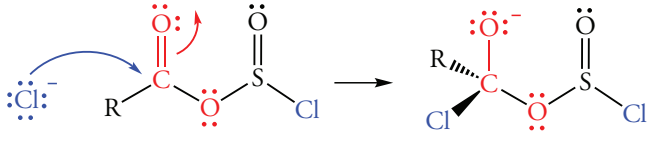


The mechanism for the reaction of $SOCl_2$ with carboxylic acids occurs in three steps, and it resembles the mechanism for the reaction of $SOCl_2$ with alcohols.

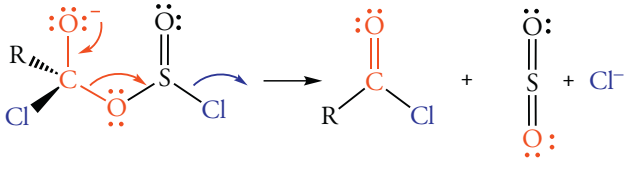
1. In the first step, the hydroxyl oxygen of the acid reacts with $SOCl_2$ to give chlorosulfite derivative as a result of nucleophilic substitution.



2. Chloride attacks the highly polarized carbonyl carbon of the chlorosulfite ester. A tetrahedral intermediate forms. It can exist either as an anion, as shown, or it can be protonated by the acid formed in the first step of the mechanism.



3. The third step is a concerted process in which the chlorosulfite group decomposes into an acyl chloride, sulfur dioxide, and chloride ion.



Problem 20.13

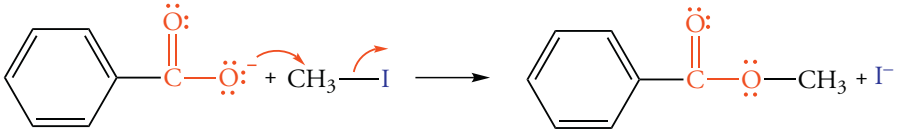
Carboxylic acids can be converted into acyl bromides by reaction with PBr_3. Write a mechanism for the reaction of PBr_3 with carboxylic acids.

20.11 CONVERSION OF CARBOXYLIC ACIDS INTO ESTERS

We can picture the formation of an ester as the joining of an acyl group carbon and an alkyl or aryl group carbon by way of an oxygen bridge. Either the acyl carbon or the alkyl (aryl) carbon can supply the oxygen atom. We will show examples of both methods.

Alkylation of Carboxylate Anions

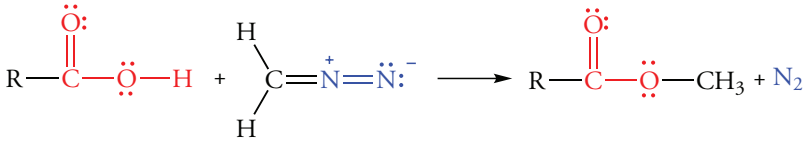
We recall that an alkoxide with a primary alkyl halide in an S_N2 reaction called the Williamson ether synthesis (Section 16.6). We can classify this reaction as "alkylation of oxygen." A similar alkylation reaction can occur with a carboxylate as the nucleophile. The product is an ester. However, because carboxylates are resonance-stabilized, they are weaker nucleophiles than alkoxide. On the other hand, they are also less basic, so a competing elimination reaction is less likely to occur and for a methyl halide they cannot occur.



Since the reaction occurs by an S_N2 mechanism and since the carboxylate is a poor nucleophile, the reaction works best for primary alkyl halides.

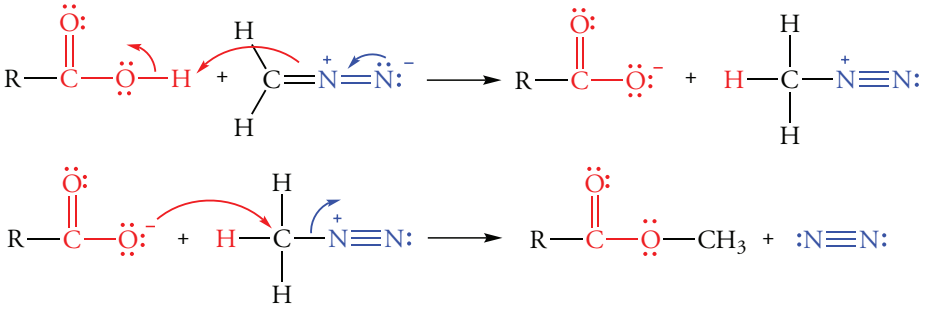
Esterification with Diazomethane

The laboratory synthesis of methyl esters can be quickly carried out by treating a carboxylic acid with diazomethane



This method is limited to small-scale laboratory synthesis because diazomethane is a toxic, explosive gas that is prepared only in small quantities. The ether is isolated as a pure compound by evaporating the solvent. The nitrogen by-product is released as a gas, and any excess diazomethane is also released.

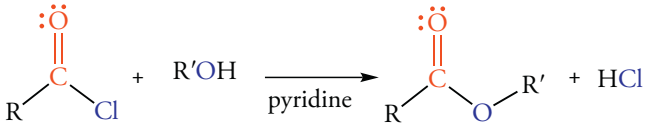
The mechanism of the reaction of diazomethane with a carboxylic acid shows why diazomethane must be handled with great care. The methylene group of diazomethane reacts with the proton of the carboxylic acid to give a methyl diazonium ion. This ion reacts rapidly with carboxylates to give an ester, but the nitrogen gas that is released is very stable, and is therefore an excellent, neutral leaving group.



Cellular molecules such as DNA, RNA, and proteins, which all have nucleophilic groups, can also react with diazomethane. The alkylation of DNA, RNA, and proteins has devastating consequences for the cell.

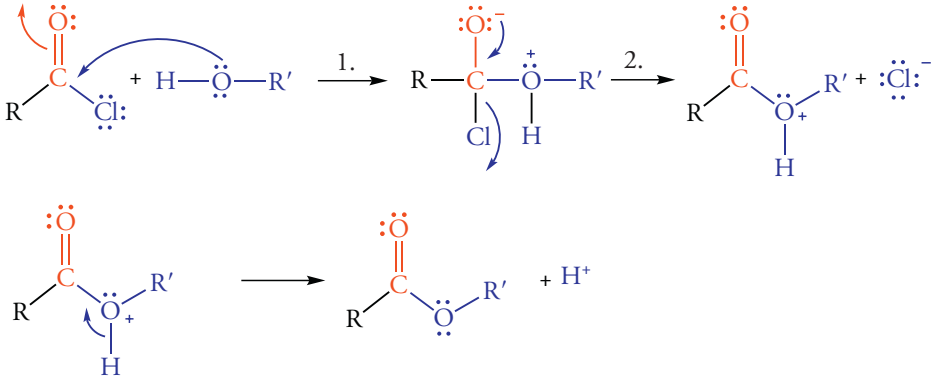
Reaction of Acyl Chlorides with Alcohols

Acyl chlorides, prepared by the reaction of carboxylic acids with thionyl chloride, react readily with alcohols to give ester. Pyridine is used as a base to neutralize the HCl that forms in the reaction.

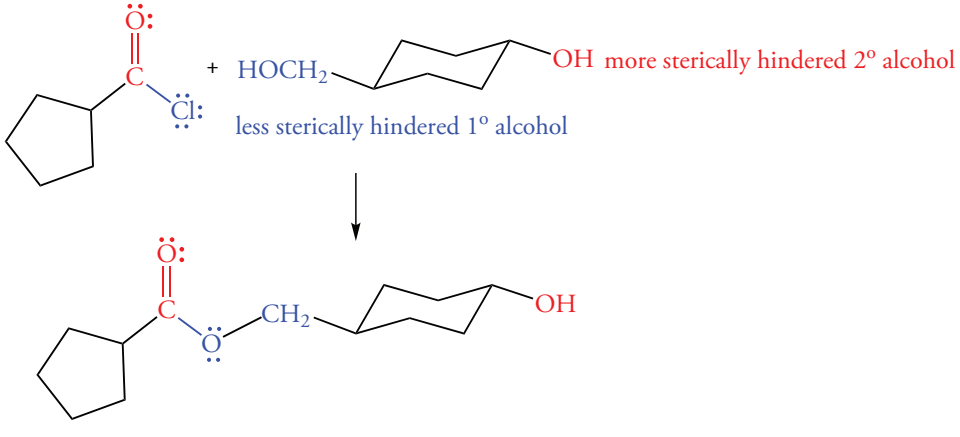


The reaction occurs in two steps.

1. First, the alcohol acts as a nucleophile that attacks the electrophilic acyl carbon atom to give a tetrahedral intermediate.
2. Second, the tetrahedral intermediate loses chloride, which is followed by rapid loss of a proton to give the ester.

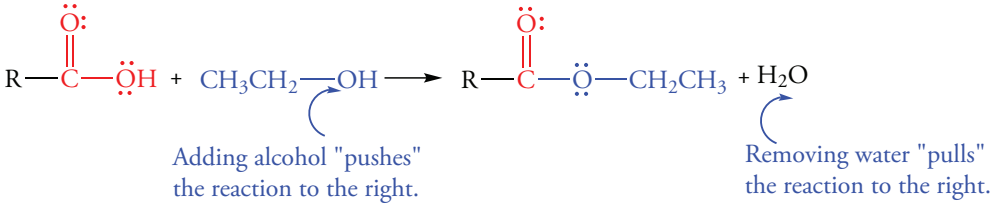


The bridging oxygen atom of the ester is provided by the alcohol. We recall that the nucleophilicity of alkoxides depends on the steric environment near the oxygen atom. A similar effect is found for the nucleophilic attack of an alcohol at an acyl carbon atom. The rate of reaction is primary > secondary > tertiary. The difference in rate often allows the selective formation of an ester of an unhindered alcohol in the presence of a hindered alcohol. For example, reaction of a diol with a primary hydroxyl group and a secondary hydroxyl group gives the ester of the primary alcohol.



Fischer Esterification

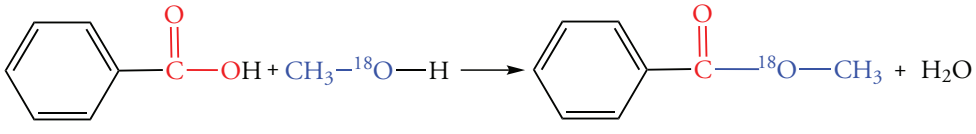
Carboxylic acids react directly with alcohols to give esters in a process called **Fischer esterification**. The reaction is catalyzed by inorganic acids such as hydrogen chloride or sulfuric acid. Both the carboxylic acid and its ester exist in substantial amounts at equilibrium. The equilibrium constants for esters of primary alcohols are approximately 1.0. However, distilling the water out of the reaction mixture or adding excess alcohol increases the yield of ester. Removing water or adding alcohol shifts the equilibrium toward the product, in accord with Le Chatelier's principle. Ethyl esters of acids are obtained by using ethanol as a solvent. Under these conditions, the high concentration of ethanol favors a high conversion of the acid to the ester.



Esters cannot be prepared from tertiary alcohols using the Fischer esterification method because these alcohols tend to dehydrate under acid conditions. Esters of phenols also cannot be prepared by Fischer esterification because the equilibrium constant for the reaction is about 10^{-4}.

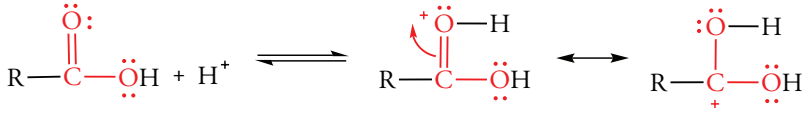
20.12 MECHANISM OF ESTERIFICATION

Does the oxygen atom linking the acyl and alkyl carbon atoms of an ester come from the oxygen of the acid or the alcohol? From a different perspective, does the water come from the hydroxyl group of the alcohol and the hydrogen of the acid or from the hydrogen atom of the alcohol and the hydroxyl group of the acid? Studies on the mechanism of the acid-catalyzed esterification reaction using ^{18}O-labeled methanol answer these related questions. When methanol reacts with benzoic acid, the oxygen-18 is contained in the ester, not in the water. Therefore, the acyl O—H bond of the acid, rather than the O—H bond, is cleaved. Also, the O—H bond of the alcohol is cleaved rather than the C—O bond.

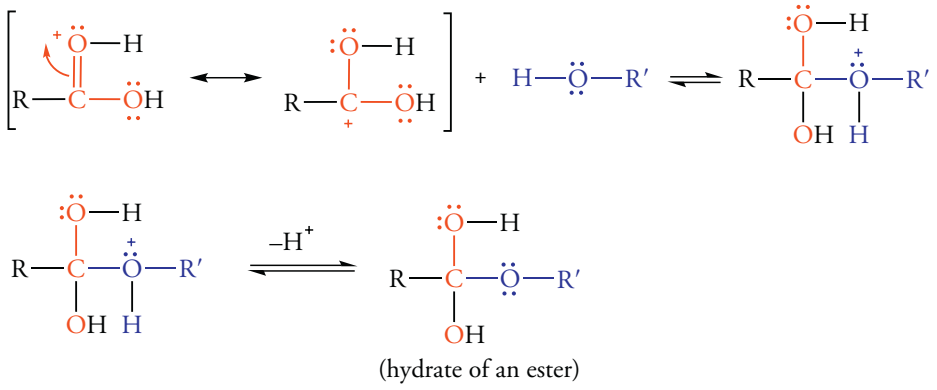


The data obtained from isotopic labeling studies and several other observations have clearly established the mechanism of the acid-catalyzed esterification of carboxylic acids. The reaction occurs in four steps.

1. In the first step, protonation occurs at the lone pair of electrons of the carbonyl oxygen atom. This reaction increases the electrophilicity of the carbonyl carbon atom, which otherwise is less reactive than the carbonyl carbon atom of an acyl chloride.

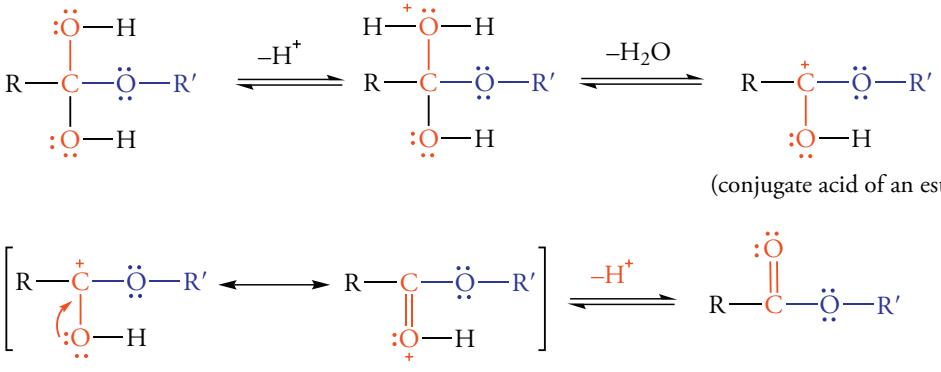


2. Nucleophilic attack by the alcohol gives a tetrahedral intermediate, the conjugate acid of a hydrate of an ester. This step is analogous to the acid-catalyzed nucleophilic addition of an alcohol to an aldehyde to give a hemiacetal or addition of water to give a hydrate. The addition product loses a proton in a solvent-mediated step to give the hydrate.



(hydrate of an ester)

3. The hydrate of the ester loses water in acid-catalyzed steps similar to those for loss of water from the hydrate of an aldehyde or ketone. Protonation of one of the two hydroxyl groups prepares it to leave as water. Loss of a proton from the remaining hydroxyl group in a solvent-mediated reaction gives the ester.



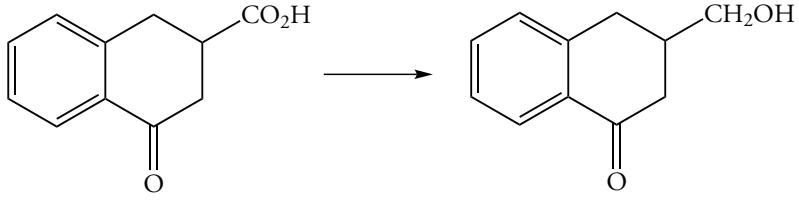
(conjugate acid of an ester)

4. The configuration of a chiral alcohol is retained in this esterification reaction because the bond to the oxygen atom of the alcohol is not cleaved.

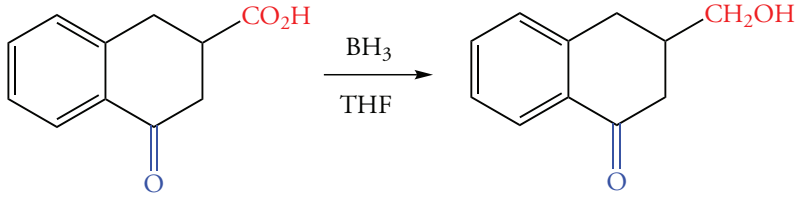
20.13 BRIEF SYNTHETIC REVIEW

Functional Group Modifications in Organic Synthesis

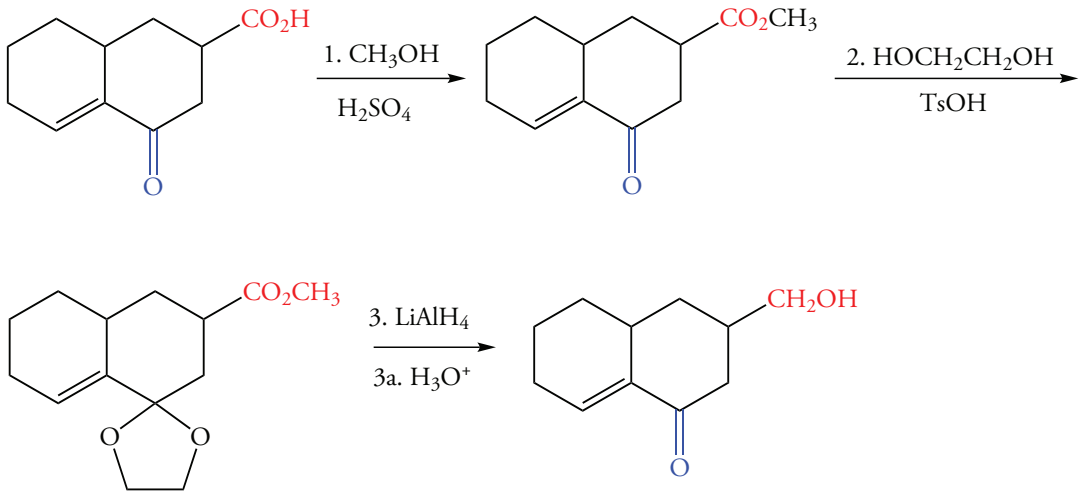
In Section 17.10, we saw that functional group modification plays an important role in organic synthesis. We can use the reactions we discussed in this chapter and in Chapter 19 to carry out the transformation shown below.



This transformation can be carried out in a single step by hydroboration because BH_3 regioselectively reduces the carboxylic acid in the presence of the β-keto group.



Suppose, however, that the carboxylic acid we wish to reduce to an alcohol is present in a molecule that has a keto group and alkenyl group. In that case, we cannot use diborane because it would also reduce the alkene. An example is shown below.



We could carry out the transformation in three steps.

1. Convert the carboxylic acid to a methyl ester by Fischer esterification.
2. Block the β-keto group by making a cyclic acetal with ethylene glycol. *p*-Toluene sulfonic acid, TsOH, is the acid catalyst for this reaction. We would not use aqueous acid because that would hydrolyze the ester.
3. Reduce the ester with lithium aluminum hydride. The workup of this step also hydrolyzes the acetal.

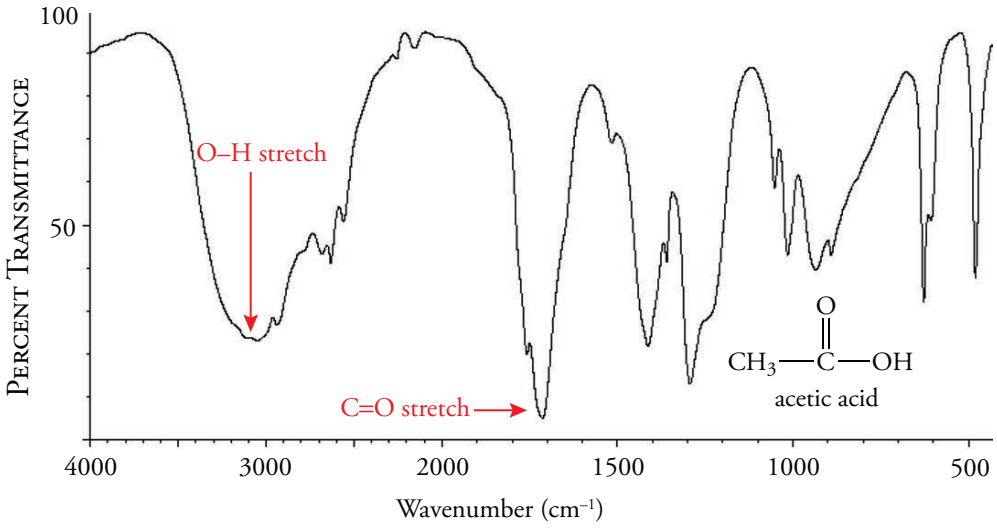
20.14 SPECTROSCOPY OF CARBOXYLIC ACIDS

Infrared Spectroscopy

For either a pure liquid or in solution, the C=O stretching absorption of carboxylic acids occurs near 1710 cm^{-1}. Under these conditions, a carboxylic acid exists as a hydrogen-bonded dimer. Thus, the position of the C=O stretching absorption is close to that of aldehydes and ketones. However, the absorption of carboxylic acids is much broader than those of aldehydes and ketones, and this characteristic is one of the hallmarks of the infrared spectra of carboxylic acids.

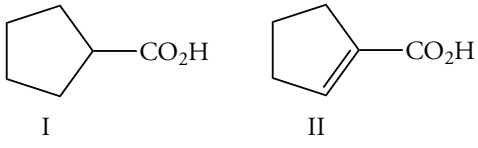
The O—H stretching absorption of carboxylic acids is also a highly characteristic feature. It occurs in the same region of the spectrum as that of alcohols. However, as in the case of the C=O absorption, the O—H absorption is very broad (2400–3600 cm^{-1}). As a consequence, this absorption strongly overlaps the region of C—H stretching absorption, which is often largely obscured. The presence of broad absorptions in both the 3000 and the 1700 cm^{-1} regions clearly identifies carboxylic acids (Figure 20.2).

Figure 20.2
Infrared Spectrum of Acetic Acid



Problem 20.14

How can the following two carboxylic acid isomers be distinguished by infrared spectroscopy?



I II

Proton NMR Spectroscopy

Like aldehydes and ketones, the protons of carboxylic acids have NMR absorptions in the 2.0–2 5 δ region, depending on the degree of substitution of the α carbon atom. Therefore, an absorption in this region is not a characteristic that can be used to identify a carboxylic acid. The resonance of the O—H hydrogen atom depends on the acidity of the individual carboxylic acid as well as its concentration in the solvent used to determine the spectrum. In most cases, the hydroxyl proton resonance occurs in the 9–12 δ region. This strong deshielding effect is a consequence of the strong hydrogen bonding in the dimer (Figure 20.3). Although this resonance is in the same region as the aldehydic hydrogen atom of aldehydes, the two are easily distinguished. Like the hydroxyl hydrogen atom of alcohol, the hydrogen atom of carboxylic acids rapidly exchanges with deuterium in D_2O. If the resonance in the 9–12 δ region disappears after adding some D_2O to the NMR sample, we know that the compound is a carboxylic acid and not an aldehyde.

Carbon-13 NMR Spectroscopy

As in aldehydes and ketones, the carbon NMR spectra of carboxylic acids have a low field absorption due to the carbonyl carbon atom and a slightly deshielded carbon atom. Both absorptions resemble those of aldehydes and ketones, but those of carboxylic acids are at somewhat higher field.

Based on the electronegativity of the oxygen atom, we might expect the hydroxyl group of a carboxylic acid to inductively withdraw electrons from the carbonyl carbon atom and cause deshielding of both it and the α carbon atom. However, the carboxylic acid group is somewhat resonance-stabilized. This shields both the carbonyl carbon atom and the α carbon atom of carboxylic acids relative to the carbonyl carbon atom of aldehydes and ketones, so their resonances appear at higher field (Figure 20.4).

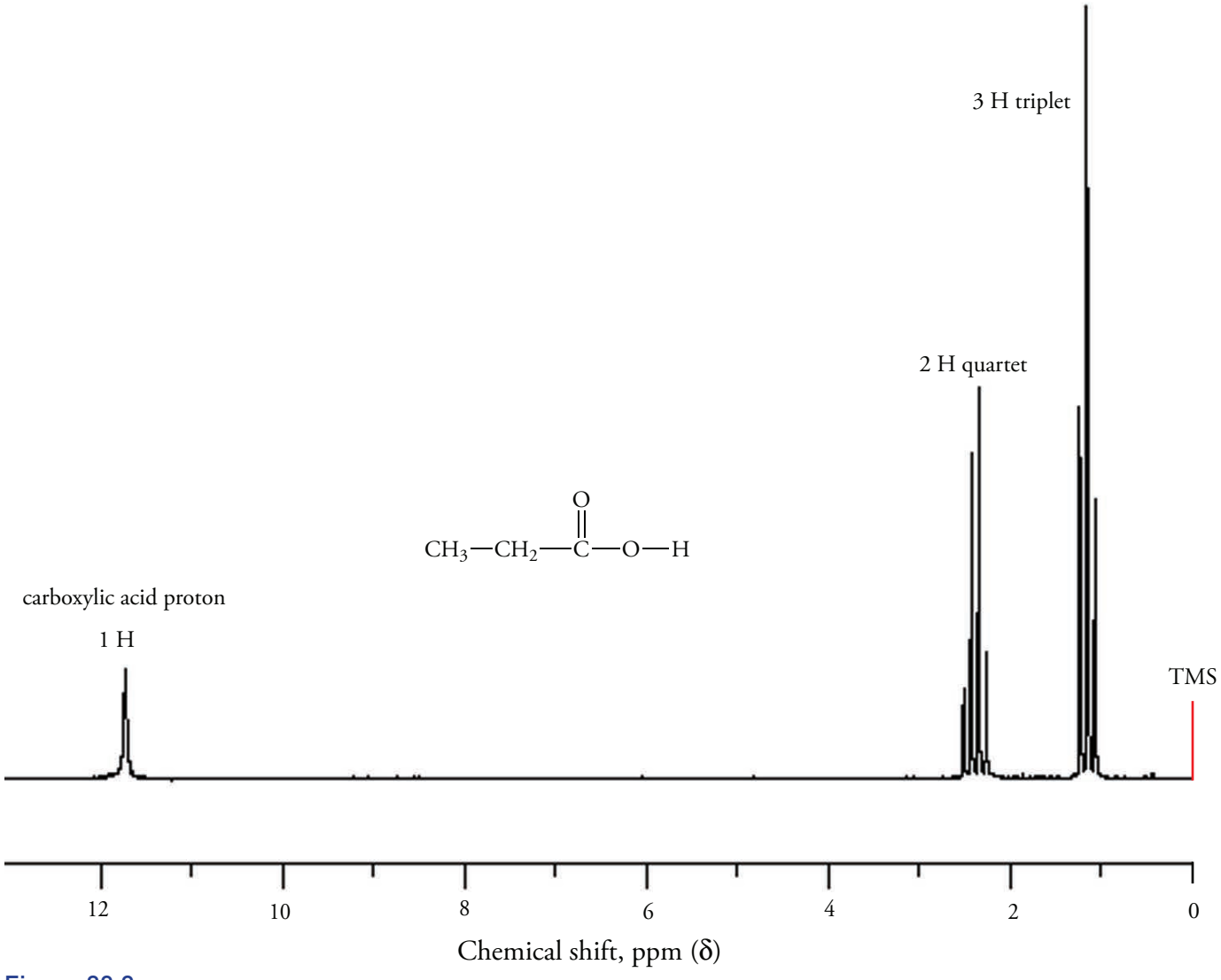
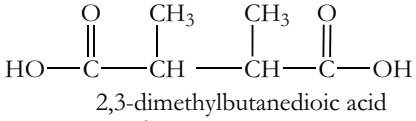


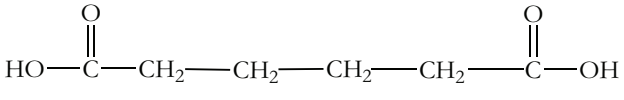
Figure 20.3
Proton NMR Spectrum of Propanoic Acid

Problem 20.15

How could the following two isomers be distinguished using proton NMR spectroscopy?



2,3-dimethylbutanedioic acid
(α,β-dimethylsuccinic acid)



hexanedioic acid
(adipic acid)

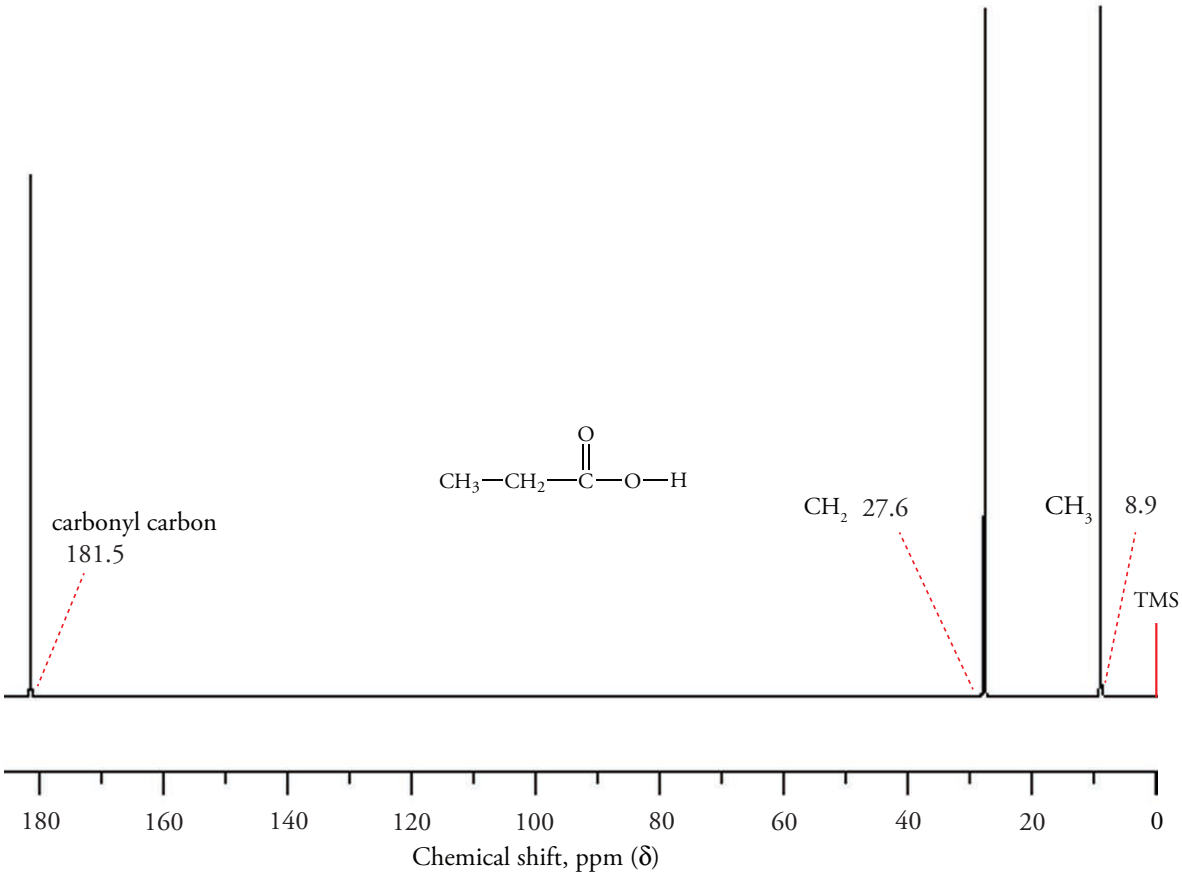


Figure 20.4
C-13 NMR Spectrum of Propanoic Acid

Problem 20.16

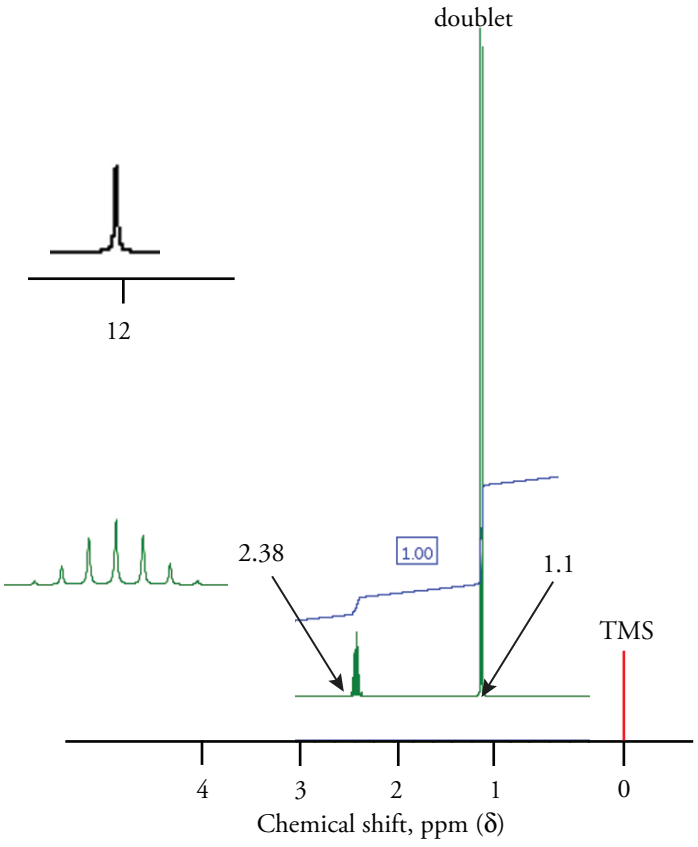
Deduce the structure of a compound with molecular formula $C_8H_8O_2$ based on the following C-13 NMR data.

C-13 Chemical Shift Data:

21.2 ppm, 128.1 ppm , 129.1 ppm , 129.4 ppm, 143.0 ppm, 167.4 ppm

Problem 20.17

Identify the compound with molecular formula $C_4H_8O_2$ using the following hydrogen NMR spectrum.


doublet
12
2.38
1.00
1.1
TMS
4
3
2
1
0
Chemical shift, ppm (δ)

EXERCISES

Nomenclature

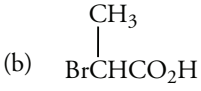
20.1 Give the common name for each of the following acids.

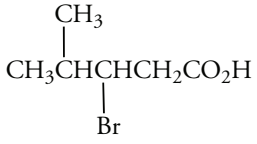
(a) $CH_3CH_2CO_2H$ (b) HCO_2H (c) $CH_3(CH_2)_4CO_2H$

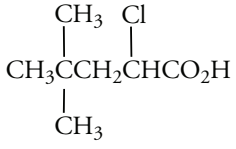
(d) $CH_3(CH_2)_{10}CO_2H$ (e) $CH_3(CH_2)_{16}CO_2H$ (f) $CH_3(CH_2)_{14}CO_2H$

20.2 Give the common name for each of the following acids.

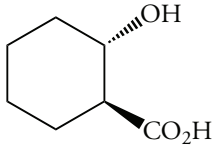
(a) 

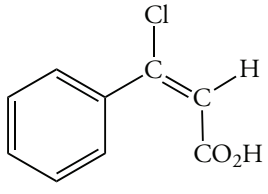
(b) 

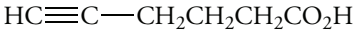
(c) 

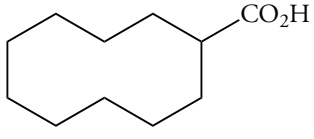
(d) 

20.3 Give the IUPAC name for each of the following acids.

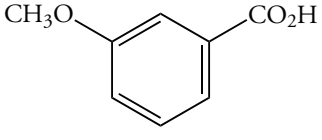
(a) 

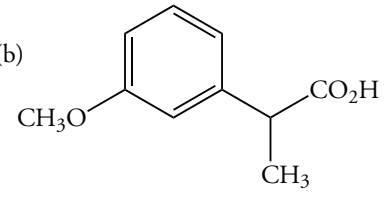
(b) 

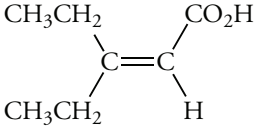
(c) 

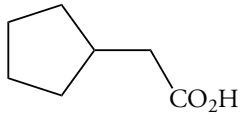
(d) 

20.4 Give the IUPAC name for each of the following acids.

(a) 

(b) 

(c) 

(d) 

20.5 The IUPAC name of ibuprofen, the analgesic in Motrin, Advil, and Nuprin, is 2-(4-isobutylphenyl)propanoic acid. Draw its structure.

Molecular Formulas

20.6 What is the general molecular formula for each of the following classes of compounds?

(a) saturated acyclic carboxylic acid

(b) saturated acyclic dicarboxylic acid

(c) saturated monocyclic carboxylic acid

(d) monounsaturated acyclic carboxylic acid

20.7 Draw the structure of two isomers having the following characteristics.
(a) dicarboxylic acids with molecular formula $C_4H_4O_4$
(b) carboxylic acids with molecular formula $C_4H_8O_2$
(c) saturated carboxylic acids with molecular formula $C_5H_8O_2$

20.8 10-Undecenoic acid is the antifungal agent contained in Desenex and Cruex. Write the structure.

Properties of Acids

20.9 Explain why 1-butanol is less soluble in water than butanoic acid.

20.10 Explain why adipic acid is much more soluble in water than hexanoic acid.

20.11 Explain why the boiling point of decanoic acid is higher than that of nonanoic acid.

20.12 Explain why the boiling point of 2,2-dimethylpropanoic acid (164 °C) is lower than that of pentanoic acid (186 °C).

20.13 Explain why the boiling point of 4-methoxybenzoic acid (278 °C) is higher than that of 2-methoxybenzoic acid (200 °C).

20.14 Explain why the boiling point of *trans*-2-butenoic acid (185 °C) is higher than that of *cis*-2-butenoic acid (169 °C).

Acidity of Carboxylic Acids

20.15 The K_a of methoxyacetic acid is 2.7×10^{-4}. Explain why this value differs from the K_a of acetic acid (1.8×10^{-5}).

20.16 The K_a values of benzoic acid and *p*-nitrobenzoic acid are 6.3×10^{-5} and 3.8×10^{-4}, respectively. Explain why these values differ.

20.17 Estimate the pK_a values of the two carboxyl groups in 3-chlorohexanedioic acid.

20.18 The pK_a of 3-cyanobutanoic acid is 4.44. Using the pK_a values of chlorine-substituted butanoic acids as a guide, estimate the pK_a of 2-cyanobutanoic acid.

20.19 The pK_a for the first dissociation of dicarboxylic acids levels off at approximately 4.85. The pK_a of long-chain carboxylic acids levels off at approximately 4.55. What relationship exists between these two numbers? What structural features are responsible for this difference?

20.20 The difference between the pK_a values for dissociation of the first and second protons of the long-chain dicarboxylic acids is about 1 unit. The difference between the pK_a values for both oxalic and malonic acids is about 3 units. Explain these data, focusing on the pK_a for the second ionization step.

20.21 The methoxy group is an effective donor of electrons and as a consequence is an activating group in electrophilic aromatic substitution. Explain why the pK_a of methoxyacetic acid (3.5) is less than that of acetic acid (4.7).

20.22 The pK_a values of cyanoacetic acid and nitroacetic acid are 2.45 and 1.65, respectively. What do these data indicate about the substituent properties of —CN and —NO_2?

20.23 The substituent effects of the hydroxyl and methoxy groups are quite similar, as evidenced by the pK_a values of *p*-hydroxy- and *p*-methoxybenzoic acids, which are 4.48 and 4.47, respectively. However, the pK_a values of *o*-hydroxy- and *o*-methoxybenzoic acids are 2.97 and 4.09, respectively. Explain why the values for the *ortho* isomers are so different.

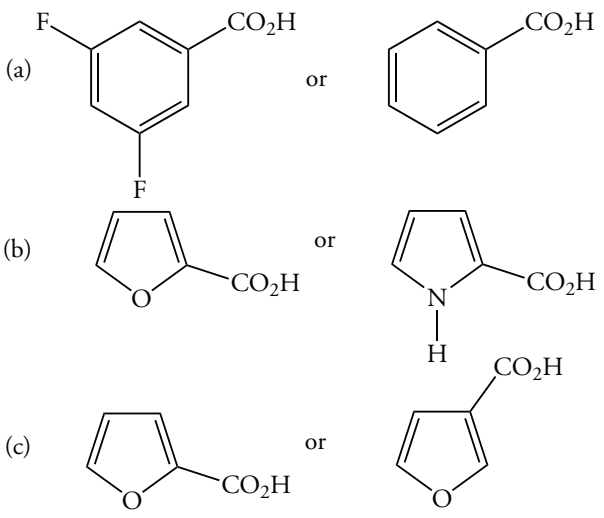
20.24 The pK_a values of *para*-substituted benzoic acids for the —PCl_2 and —$Si(CH_3)_3$ groups are 3.6 and 4.3, respectively. Based on these data, determine whether these groups are activating or deactivating in electrophilic aromatic substitution.

20.25 *p*-Methoxybenzoic acid is a weaker acid than benzoic acid, but *p*-(methoxymethyl)benzoic acid is a stronger acid than *p*-methylbenzoic acid. Why does the methoxy group have opposite effects in these two cases?

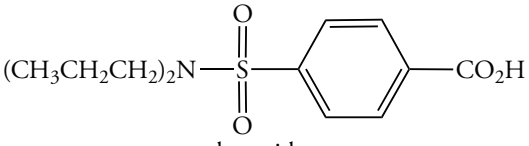
20.26 The van der Waals radii of fluorine and hydrogen atoms arc similar. The pK_a values of *o*-, *m*-, and *p*-fluorobenzoic acids are 4.1, 3.9, and 3.3, respectively. The pK_a value of benzoic acid is 4.2. Explain the order of the pK_a values of the fluorobenzoic acids. Estimate the contribution of fluorine as an electron donor in terms of resonance.

20.27 Compare the pK_a values of biphenyl-3-carboxylic acid (4.14) and biphenyl-4-carboxylic acid (4.21) to that of benzoic acid (4.20), and explain the different effect of the phenyl group on the pK_a values.

20.28 Which is the stronger acid in each of the following pairs of aromatic carboxylic acids? What accounts for the difference in acid strength?

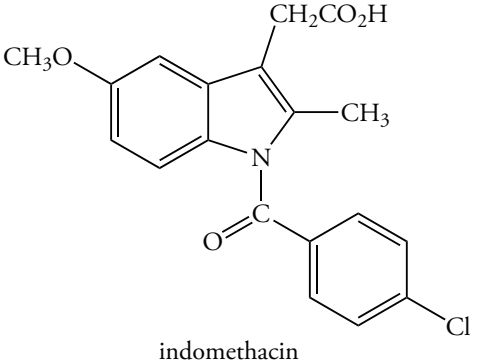


20.29 The pK_a of benzoic acid is 4.2. The pK_a of probenecid is 3.4. Explain why probenecid is the stronger acid. (Probenecid is a drug that is used to treating gout and hyperuricemia.)



probenecid

20.30 Predict the pK_a of indomethacin, an anti-inflammatory agent.



indomethacin

Carboxylate Anions

20.31 The pK_a of penicillin G is 2.8. Is it more soluble in stomach acid (pH ~2) or in blood (pH =7.4)?

20.32 Sodium benzoate is used as a preservative in foods, but only if the pH is greater than 5. In what form is the compound present at pH 7?

20.33 Explain why benzoic acid with an ^{18}O isotopic label in the hydroxyl oxygen atom can be prepared, but that it cannot be used in mechanistic studies in aqueous solutions.

Synthesis of Carboxylic Acids

20.34 Outline the steps required to prepare cyclohexanecarboxylic acid from each of the following reactants.
(a) bromocyclohexane (b) cyclohexanol (c) cyclohexene
(d) vinylcyclohexane (e) cyclohexylmethanol

20.35 Outline the steps required to prepare hexanoic acid from each of the following reactants.
(a) 1-chloropentane (b) 1-hexanol (c) hexanal
(d) 1-hexene (e) 1-heptene

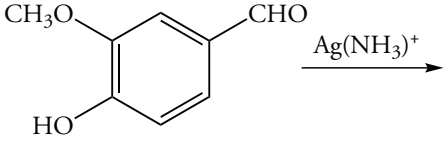
20.36 Outline the steps required to convert methylenecyclohexane to each of the following compounds.
(a) cyclohexanecarboxylic acid (b) cyclohexylacetic acid
(c) 1-methylcyclohexanecarboxylic acid

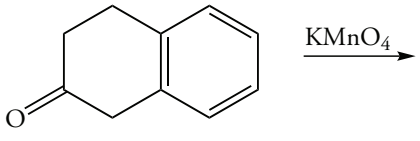
20.37 Outline the steps required to convert *p*-ethylanisole into each of the following compounds.
(a) *p*-methoxybenzoic acid (b) 2-(*p*-methoxyphenyl)propanoic acid
(c) 3-(*p*-methoxyphenyl)butanoic acid

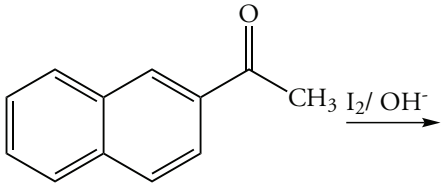
20.38 Fatty acids from natural sources are long-chain unbranched carboxylic acids that contain an even number of carbon atoms. Outline the steps to convert the readily available dodecanoic acid (lauric acid) into the rare tridecanoic acid

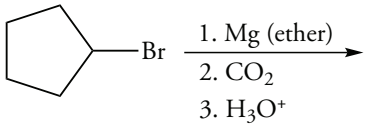
20.39 Pivalic acid, $(CH_3)_3CCO_2H$, can be prepared from *tert*-butyl chloride. What method should be used?

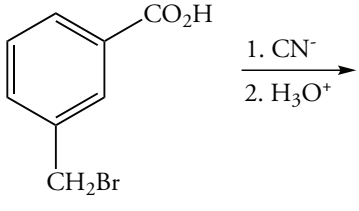
20.40 What is the structure of the product of each of the following reactions?

(a) 

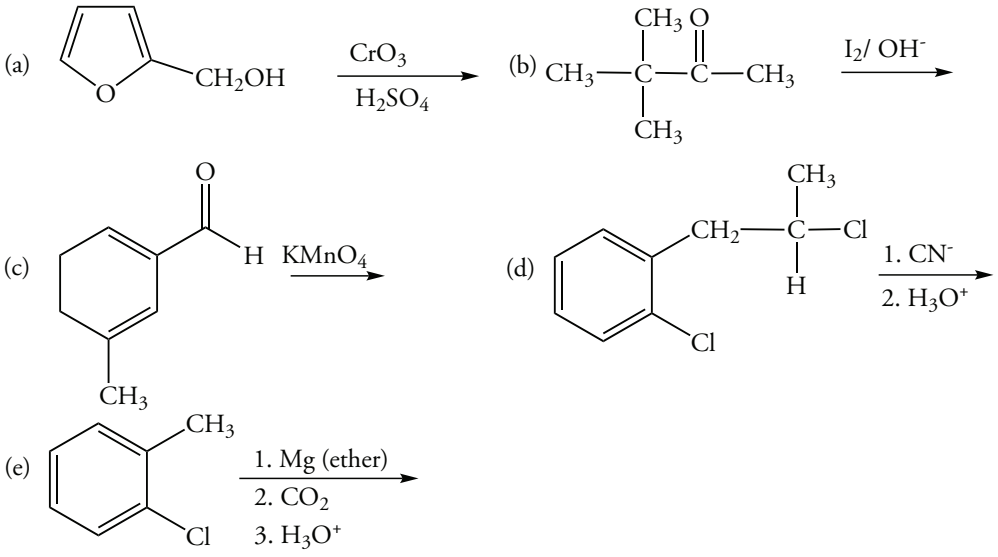
(b) 

(c) 

(d) 

(e) 

20.41 What is the structure of the product of each of the following reactions?

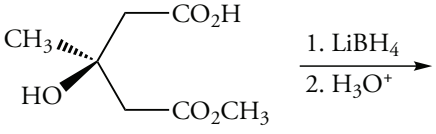


Reduction of Carboxylic Acids

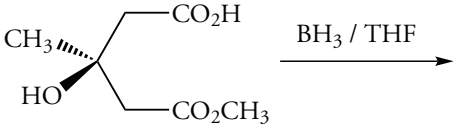
20.42 Metal hydride reductions occur by nucleophilic attack at the carbonyl carbon atom of acyl derivatives. Reduction of carboxylic acids with hydride reagents occurs slowly, but reduction by diborane occurs rapidly. Based on the structure of BH_3, the active reagent in diborane reductions, suggest the structure of the first intermediate formed in the reaction.

20.43 Diborane slowly reduces nitriles to amines, but rapidly reduces aldehydes and ketones. Using the structure of BH_3 and the mechanism your wrote in Exercise 20.42, explain why nitriles react more slowly than aldehydes and ketones.

20.44 Lithium borohydride is a more active reducing agent than sodium borohydride, but less active than lithium aluminum hydride. Lithium borohydride reduces the ester group of the following compound selectively. Explain this selectivity.



20.45 Draw the structure of the product of the following reaction. What relationship exists between this compound and the product of the reaction of Exercise 20.44?

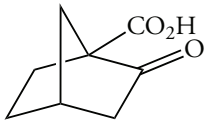


Decarboxylation

20.46 Could the Hunsdiecker reaction be used to decarboxylate an unsaturated carboxylic acid?

20.47 Which carboxylic acid should decarboxylate more easily in a Hunsdiecker reaction, benzoic acid or cyclohexanecarboxylic acid?

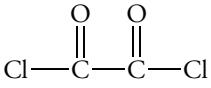
20.48 The following β-keto acid does not decarboxylate on heating. Based on the mechanism for the reaction, explain this observation.



20.49 Saturated carboxylic acids do not decarboxylate, but β,γ-unsaturated carboxylic acids do. Explain why, using a mechanism to show the decarboxylation of 3-butenoic acid. Use your mechanism to predict the product of decarboxylation of (*E*)-4-methyl-3-pentenoic acid.

Acyl Halides

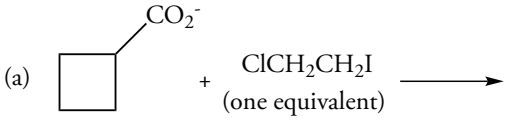
20.50 Acyl halides can be prepared by reaction of a carboxylic acid with one equivalent of oxalyl chloride. The by-products of the reaction are HCl, CO_2, and CO. Write a mechanism for this reaction.



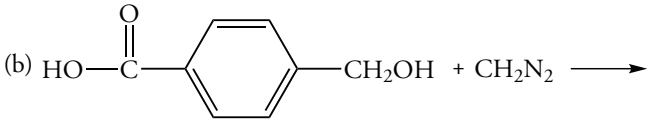
20.51 Explain why acyl halides of hydroxy acids cannot be prepared using thionyl chloride.

Synthesis of Esters

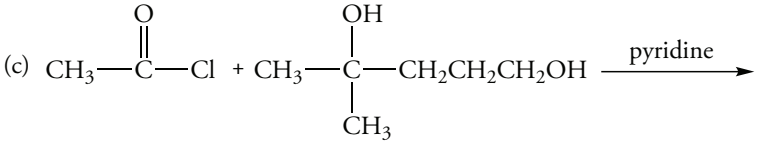
20.52 Draw the structure of the product of each of the following reactions.



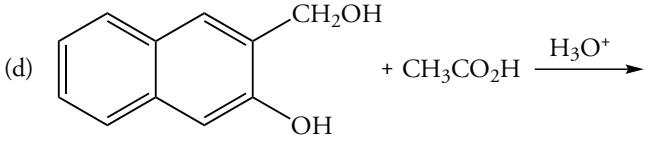
(a) CO_2^- + $ClCH_2CH_2I$ (one equivalent) ⟶



(b) HO—C(=O)— —CH_2OH + CH_2N_2 ⟶

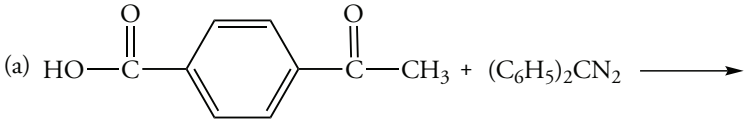


(c) CH_3—C(=O)—Cl + CH_3—C(OH)(CH_3)—$CH_2CH_2CH_2OH$ —pyridine⟶

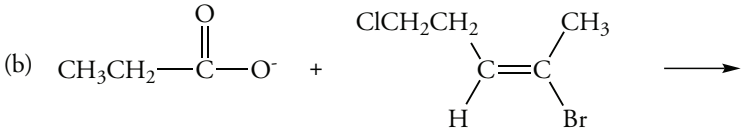


(d) + CH_3CO_2H —H_3O^+⟶

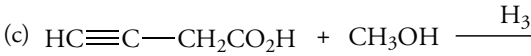
20.53 Draw the structure of the product of each of the following reactions.



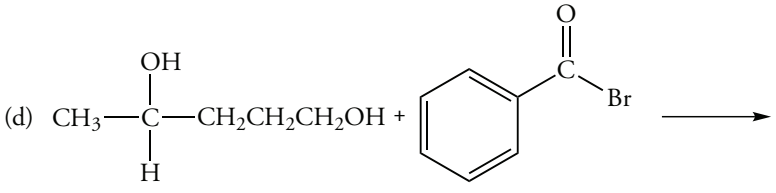
(a) HO—C(=O)— —C(=O)—CH_3 + $(C_6H_5)_2CN_2$ ⟶



(b) CH_3CH_2—C(=O)—O^- + $ClCH_2CH_2$, CH_3, C=C, H, Br ⟶

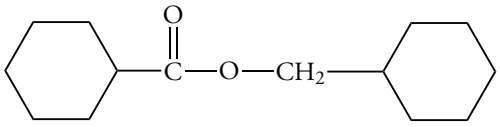


(c) HC≡C—CH_2CO_2H + CH_3OH —H_3O^+⟶

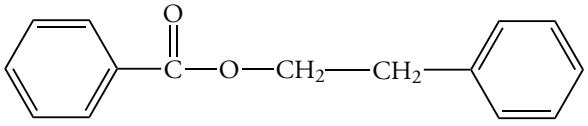


(d) CH_3—C(OH)(H)—$CH_2CH_2CH_2OH$ + —C(=O)—Br ⟶

20.54 Outline the steps necessary to prepare the following compound from cyclohexanecarboxylic acid.



20.55 Outline the steps necessary to prepare the following compound from benzoic acid.

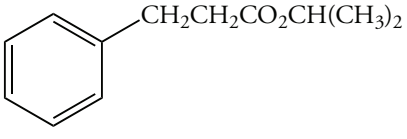


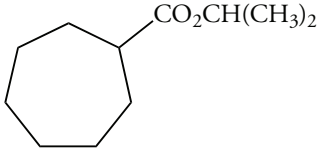
20.56 What alcohol and acid are required to form each of the following esters by Fischer esterification?

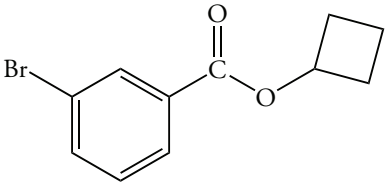
(a) $CH_3CH_2CH_2CH_2-C(=O)-O-CH_2CH_2CH_3$ (b) $CH_3-C(=O)-O-CH_2CH_2CH_3$

(c) $CH_3CH_2-C(=O)-O-CH_2CH_2CH_3$

20.57 What alcohol and acid or acyl derivative are required to form each of the following esters?

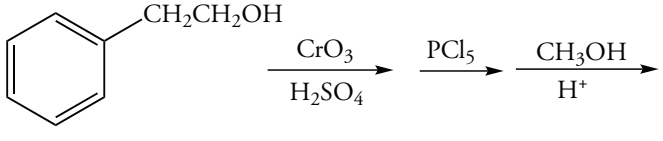
(a) 

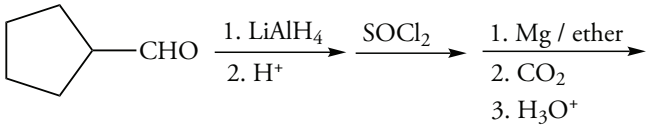
(b) 

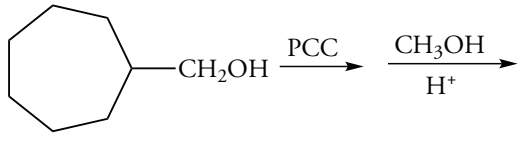
(c) 

Multistep Synthesis

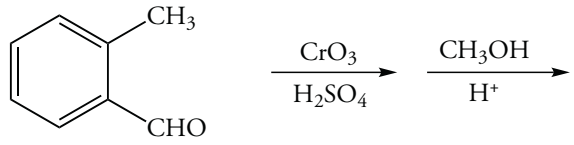
20.58 Write the structure of the final product of each of the following sequences of reactions.

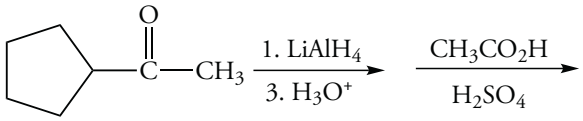
(a) 

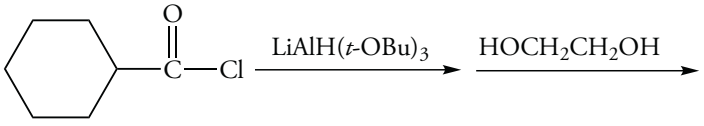
(b) 

(c) 

20.59 What reactants are required to form each of the following structures?

(a) 

(b) 

(c) 

NMR Spectroscopy of Carboxylic Acids

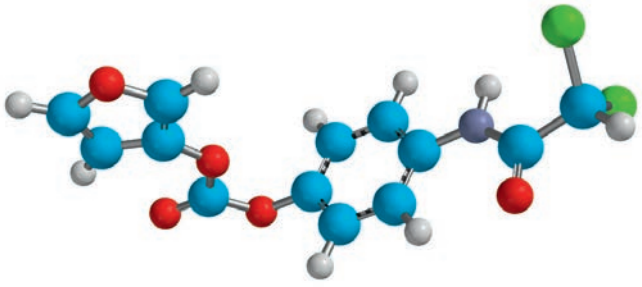
20.60 Each of the following compounds has a resonance due to a single hydrogen atom at a lower field position than 10 δ. Based on the molecular formula and the indicated remaining resonances, propose a structure for each compound The number of hydrogen atoms and multiplicity are given in parentheses.
(a) $C_5H_{10}O_2$, 1.25 ppm (9H singlet)
(b) $C_3H_5ClO_2$, 1.75 ppm (3H doublet), 4.45 ppm (1H quartet)
(c) $C_8H_8O_2$, 1.4 ppm (3H singlet), 4.0 ppm (3H singlet)
(d) $C_3H_6O_3$, 3.4 ppm (2H singlet), 4.0 ppm (3H singlet)
(e) $C_9H_{10}O_3$, 2.7 ppm (2H triplet), 4.2 ppm (2H triplet), 7.4 ppm (5H complex multiplet)

20.61 Each of the following compounds has a resonance due to a single hydrogen atom at a lower field position than 10 δ. Based on the molecular formula and the indicated remaining resonances, propose a structure for each compound The number of hydrogen atoms and multiplicity are given in parentheses.
(a) $C_6H_{12}O_2$, 1.07 ppm (9H singlet), 2.21 ppm (2H singlet)
(b) $C_3H_5ClO_2$, 2.85 ppm (2H triplet), 3.80 ppm (2H triplet)
(c) $C_8H_8O_2$, 3.6 ppm (2H singlet), 7.25 ppm (5H singlet)
(d) $C_3H_6O_3$, 3.4 ppm (2H singlet), 4.0 ppm (3H singlet)
(e) $C_9H_{10}O_3$, 2.7 ppm (2H triplet), 4.2 ppm (2H triplet), 7.4 ppm (5H complex multiplet)

20.62 Deduce the structure of each of the following compounds based on the molecular formula and the carbon-13 NMR data.
(a) $C_6H_{12}O_2$, 9.3 ppm, 24.6 ppm, 33.5 ppm, 42.7 ppm, 185.5 ppm
(b) $C_6H_6O_2$, 128.7 ppm, 129.6 ppm, 131.2 ppm, 133.0 ppm, 167.7 ppm
(c) $C_4H_8O_2$, 13.4 ppm, 18.5 ppm, 36.3 ppm, 179.6 ppm

20.63 Deduce the structure of each of the following compounds based on the molecular formula and the carbon-13 NMR data.
(a) $C_5H_{10}O_2$, 13.5 ppm, 22.0 ppm, 27.0 ppm, 34.1 ppm, 179.7 ppm
(b) $C_7H_6O_3$, 115.8 ppm, 121.9 ppm, 132.7 ppm, 162.5 ppm, 169.0 ppm

21 Carboxylic Acid Derivatives



Dioxanide furanoate (an antibiotic)

In this chapter, we will continue the discussion of carboxylic acid derivatives that we began in Chapter 20. Each class of carboxylic acid derivatives has a potential leaving group bonded to a carbonyl carbon atom, and each carbonyl group can undergo a nucleophile addition reaction. We have already discussed the properties of leaving groups and nucleophiles, and we will apply this knowledge in this chapter. We have also discussed the reactivity of the carbonyl group toward nucleophilic addition, and the effect of structure on that reactivity. A common theme for the mechanisms of the reactions of carboxylic acid derivatives unifies this discussion.

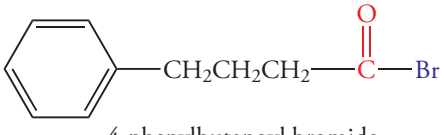
21.1 NOMENCLATURE OF CARBOXYLIC ACID DERIVATIVES

The Acyl Group and Acid Derivatives

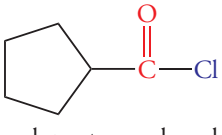
We recall that the "RCO" unit in a carboxylic acid and its derivatives is an **acyl group**. In the previous chapter, we briefly discussed the names of acyl derivatives. Now, we will describe their nomenclature in greater detail.

Names of Acid Halides

In an acid halide, a halogen atom is attached to an acyl group. In the IUPAC names of acid halides, the ending *-oyl halide* replaces the ending *-oic acid* of carboxylic acids. The name of the halide is appended as a separate word. An acid halide functional group bonded to a cycloalkane ring is named as a *carbonyl halide*. Common names of acid halides replace the *-ic acid* ending with *-yl halide*.



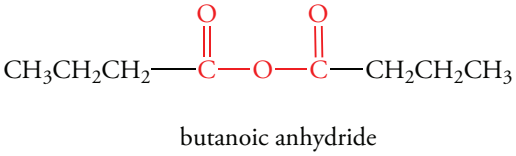
4-phenylbutanoyl bromide



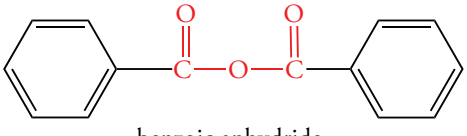
cyclopentanecarbonyl chloride

Names of Acid Anhydrides

An acid anhydride consists of two acyl groups bonded through a bridging oxygen atom. Although acid anhydrides can have two different acyl groups, compounds containing identical acyl groups are more common. They are named by replacing the suffix *-oic acid* with *-oic anhydride*. Common names are derived by replacing the term acid with anhydride.



butanoic anhydride

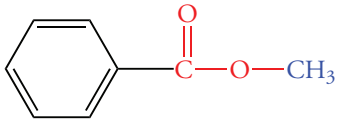


benzoic anhydride

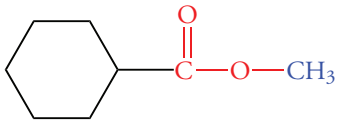
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00021-8
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Names of Esters

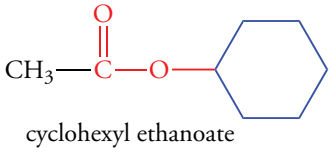
To name an ester, we first write the name of the alkyl group bonded to oxygen (—OR or —OAr) The acyl portion of the ester is named as a carboxylate in which *-ate* replaces *-ic acid*. In the three examples given below, the alkyl portion of each molecule is shown on the right side of each structure. However, the alkyl name is written first in the name of the ester regardless of how the structure is drawn.



methyl benzoate

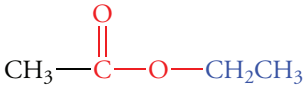


methyl cyclohexanecarboxylate

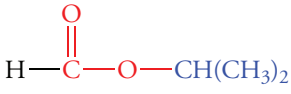


cyclohexyl ethanoate

As we observed for carboxylic acids, common names are often used for esters. This is especially true for esters of acetic acid and formic acid.

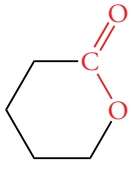


ethyl acetate

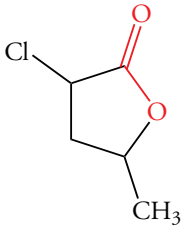


isopropyl formate

Lactones are cyclic esters of hydroxy acids. Five- and six-membered lactones commonly occur in nature. The IUPAC name of a lactone is constructed by adding lactone to the name of the related hydroxy acid. The common name is derived by changing the suffix *-ic acid* to *–olactone*. A Greek letter designates the position of the bridging oxygen atom that closes the lactone ring, α, β ,γ, etc.



5-hydroxypentanoic acid lactone
(δ-valerolactone)

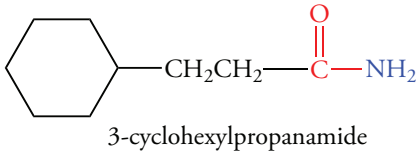


4-hydroxy-2-chloropentanoic acid lactone
(α-chloro-γ-valerolactone)

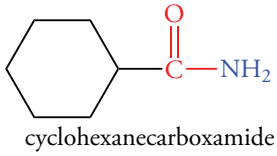
Names of Amides

In an amide, a group such as —NH_2, —NHR, or —NR_2 is attached to an acyl group. Amides are named by replacing the suffix for the acid (*-oic acid*) with the name *–amide*. The suffix *-carboxamide* indicates amides derived from cycloalkanecarboxylic acids.

In a **primary amide**, an —NH_2 group is bonded to the acyl carbon.



3-cyclohexylpropanamide

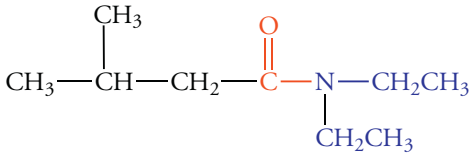


cyclohexanecarboxamide

In **secondary** and **tertiary amides**, the prefix *N-* or *N,N-* indicates that one or more alkyl or aryl groups are bonded to the nitrogen atom.

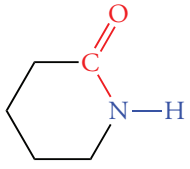


N-ethylpropanamide
(*N*-ethylpropionamide)

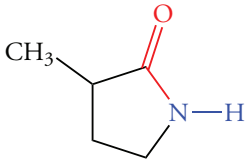


N,N-diethyl-3-methylbutanamide
(*N,N*-diethyl-β-methylbutyramide)

Lactams are cyclic amides formed from amino acids. The IUPAC name of a lactam is obtained by adding *lactam* to the name of the related amino acid. The common name is obtained by changing the suffix *-ic acid* to *–olactam*. As in lactones, a Greek letter designates the position of the bridging nitrogen atom closing the lactone ring. The prefix *N-* indicates substituents on the nitrogen atom.



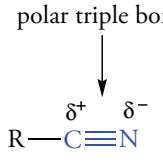
5-aminopentanoic acid lactam
(δ-valerolactam)



4-amino-2-methylbutanoic acid lactam
(α-methyl-γ-butryolactam)

Nitriles

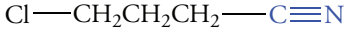
A nitrile is a compound in which a cyano group is bonded to an alkyl or aryl group. The reactions of nitriles resemble those of acyl derivatives in important ways. The sp-hybridized carbon of the nitrile is highly electrophilic. Therefore, nucleophiles add to the cyano group carbon as they do to carbonyl carbons. Both acyl derivatives and nitriles have three bonds to electronegative elements.



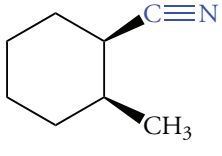
nitrile

Names of Nitriles

Acyclic nitriles are named by adding *-nitrile* as a suffix to the alkane name that includes the carbon atom of the nitrile. The carbon atom of the nitrile is C-1. Cyclic compounds with the —CN group bonded to the ring are named using the suffix *-carbonitrile*. The ring carbon bearing the cyano group is C-1, but that number is not included in the name.



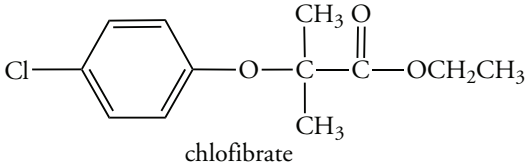
4-chlorobutanenitrile



cis-2-methylcyclohexanecarbonitrile

Problem 21.1

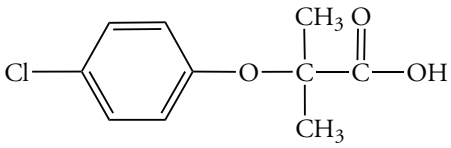
What is the IUPAC name of clofibrate, a drug used to lower the concentration of blood triglycerides and cholesterol?



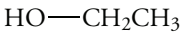
clofibrate

Sample Solution

First, identify the alcohol portion of the ester, which is located at the right of the molecule. The alcohol portion contains two carbon atoms, so the compound is an ethyl ester.

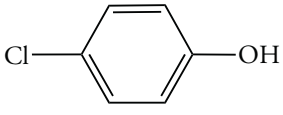


acid part of ester

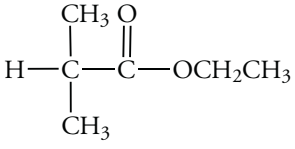


ethanol

The acid portion is a substituted propanoic acid with a methyl group and an aryl-containing group at C-2. Imagine removing the aryl-containing group from the acid and adding a hydrogen atom to its oxygen atom. The resulting compound is *p*-chlorophenol. The original group is a *p*-chlorophenoxy group.



p-chlorophenol



ethyl 2-methylpropanoate

The name of the acid is 2-(*p*-chlorophenoxy)-2-methylpropanoic acid. Now change the *-ic* ending of the acid to *–ate* and write the name of the alkyl group of the alcohol as a separate word in front of the modified acid name. The ester is named ethyl 2-(*p*-chlorophenoxy)-2-methylpropanoate.

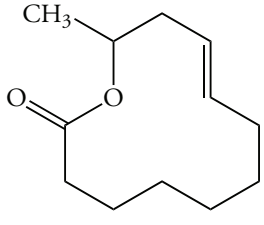
Problem 21.2

Write the structure of each of the following compounds.

(a) benzyl 2-methylbutanoate
(b) *N*,*N*-dimethylcyclobutanecarboxamide
(c) 2-chlorobutanoyl bromide
(d) 4-ethoxyhexanenitnle
(e) 3,3,3-trifluoropropanoic anhydride
(f) 6-aminohexanoic acid lactam

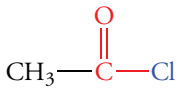
Problem 21.3

What is the name of the following large-ring lactone, which has been isolated from a species of fungus?

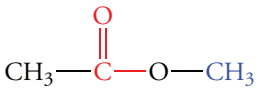


21.2 PHYSICAL PROPERTIES OF ACYL DERIVATIVES

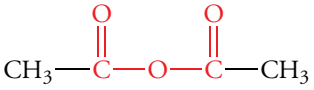
Acyl halides, such as acetyl chloride, and acid anhydrides, such as acetic anhydride, are used exclusively as reagents rather than as solvents. Consequently, their physical properties, such as boiling points and dielectric constants, are of less interest than those of other acyl derivatives. Because neither acyl halides nor acid anhydrides form intermolecular hydrogen bonds, their boiling points are similar to structurally related carbonyl compounds of approximately the same molecular weight.



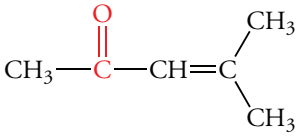
mol wt 68.6
bp 50.9 °C



mol wt 70.4
bp 57 °C



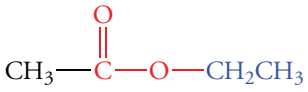
mol wt 102
bp 140 °C



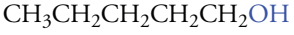
mol wt 102
bp 130 °C

Esters

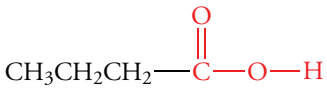
Esters are polar molecules, but their boiling points are lower than those of carboxylic acids and alcohols of similar molecular weight because there is no intermolecular hydrogen bonding between ester molecules.



ethyl acetate
bp 77 °C



1-pentanol
bp 138 °C



butanoic acid
bp 164 °C

Esters can form hydrogen bonds through their oxygen atoms to the hydrogen atoms of water molecules. As a result, esters are slightly soluble in water. However, because esters do not have a hydrogen atom to form a hydrogen bond to an oxygen atom of water, they are less soluble than carboxylic acids. Table 21.1 lists the solubilities and boiling points of some esters.

Table 21.1
Physical Properties of Esters

IUPAC Name	*Boiling Point, °C*	*Solubility, g/100 g H_2O*
Methyl methanoate	32	Miscible
Methyl ethanoate	57	24.4
Methyl propanoate	80	1.8
Methyl butanoate	102	0.5
Methyl pentanoate	126	0.2
Methyl hexanoate	151	0.06
Ethyl methanoate	54	Miscible
Ethyl ethanoate	77	7.4
Ethyl propanoate	99	1.7
Ethyl butanoate	120	0.5
Ethyl pentanoate	145	0.2
Propyl ethanoate	102	1.9
Butyl ethanoate	125	1.0
Methyl benzoate	199	0.1
Ethyl benzoate	213	0.08

The odors of esters are distinctly different from those of the corresponding acids. Acids have unpleasant smells, but esters have fruity smells. In fact, esters are responsible for the odors of many fruits. For example, ethyl ethanoate occurs in pineapples, 3-methylbutyl ethanoate in apples and bananas, 3-methylbutyl-3-methylbutanoate in apples, and octyl ethanoate in oranges.

The demand in our society for processed foods that are expected to taste and smell "fresh" has created problems for the food industry. Esters have low boiling points, and they evaporate during heating. To make processed food more attractive, processors add esters back to the food. In some cases, the esters are the same as those lost in heating. Nevertheless, government regulations require that the added esters be identified as additives on the label.

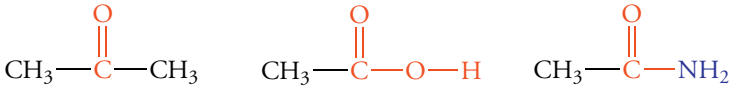
The esters used in some products are not necessarily the same as those in natural fruits, but they produce the same odor or taste. The choice of esters may be dictated by their cost and availability. Table 21.2 lists some of these esters. Although the esters are not the same as those that occur naturally in the fruit, the product is not dangerous. The structures are similar to those of naturally occurring esters.

Table 21.2
Esters Used as Flavoring Agents

IUPAC Name	*Flavor*
Methyl butanoate	Apple
Pentyl butanoate	Apricot
Pentyl ethanoate	Banana
Octyl ethanoate	Orange
Ethyl butanoate	Pineapple
Ethyl methanoate	Rum

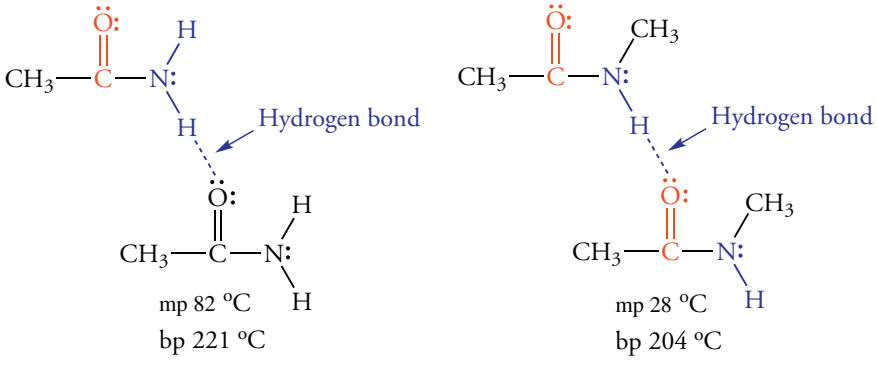
Amides

Amides form strong intermolecular hydrogen bonds between the amide hydrogen atom of one molecule and the carbonyl oxygen atom of a second molecule. This intermolecular interaction is responsible for the high melting and boiling points of primary amides compared to other compounds of similar molecular weight and structure.



bp 56.5 °C, mp –94 °C | bp 118 °C, mp 16.7 °C | bp 221°C, mp 82 °C

Substitution of the hydrogen atoms on the nitrogen atom by alkyl or aryl groups reduces the number of possible intermolecular hydrogen bonds and lowers their melting and boiling points. Tertiary amides cannot form intermolecular hydrogen bonds.



mp 82 °C, bp 221 °C | mp 28 °C, bp 204 °C | mp –20 °C, bp 166 °C

Amides having low molecular weights readily dissolve in water because hydrogen bonds form between the amide group and water. Even low molecular weight tertiary amides dissolve in water because the carbonyl oxygen atom can form hydrogen bonds to the hydrogen atoms of water.

The dielectric constants of amides are higher than those of carboxylic acids and esters of similar structure. The dielectric constants of formamide and dimethylformamide are 111 and 37, respectively. Dimethylformamide (DMF) is an excellent polar aprotic solvent. It dissolves inorganic salts such as halides used in S_N2 reactions.

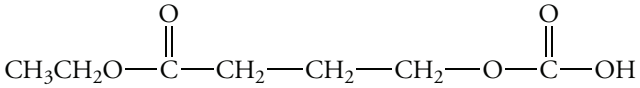
Nitriles

Nitriles are very polar compounds because the carbon–nitrogen triple bond includes three pairs of shared electrons, polarized toward the electronegative atom. Even though oxygen is more electronegative than nitrogen, the bond moment of the carbonyl group is smaller than that of the nitrile group. The dipole moment of acetonitrile is 3.4 D.

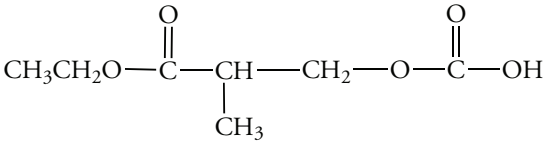
Although nitriles have an unshared pair of electrons, they are not effective hydrogen bond acceptors because the electrons occupy an sp^2-hybridized orbital. However, because acetonitrile is very polar, it is miscible in water. Propionitrile is moderately soluble in water. Acetonitrile is an excellent polar, aprotic solvent. It has a relatively high boiling point (81.5 °C) for a low molecular weight compound, and a high dielectric constant (38).

Problem 21.4

Explain why one of the following compounds is more soluble in water than the other.



I



II

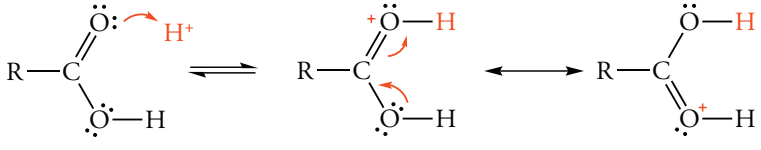
Problem 21.5

Explain why the dipole moment of methyl acetate (1.7 D) is smaller than the dipole moment of acetone (2.9 D).

21.3 BASICITY OF CARBOXYLIC ACID DERIVATIVES

We recall that the first step in the acid-catalyzed addition reaction of carbonyl compounds is protonation of the carbonyl oxygen atom. However, the carbonyl oxygen atom is a weak base because its lone pair electrons occupy an sp^2-hybridized orbital, and therefore they are more strongly attracted to the nucleus than lone pair electrons in an sp^3-hybridized atom.

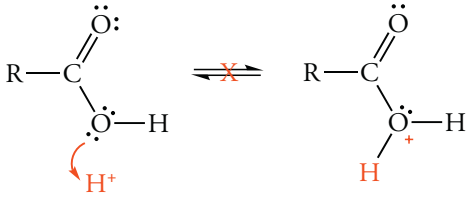
Protonation of a carboxylic acid occurs at the carbonyl oxygen atom because the resulting conjugate acid is resonance stabilized.



resonance-stabilized conjugate acid

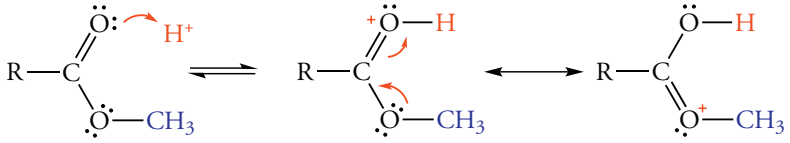
$pK_a = -6$

Protonation does not occur at the hydroxyl oxygen atom, even though the lone pair electrons occupy an sp^3-hybridized orbital, because the resulting conjugate acid is not resonance stabilized.



conjugate acid, *not* resonance stabilized

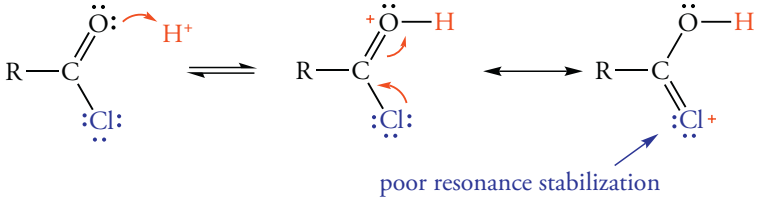
The basicity of an ester approximately equals that of the structurally related carboxylic acid.



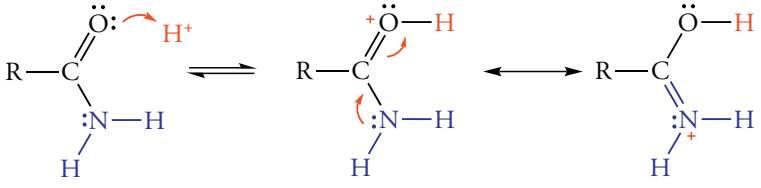
resonance-stabilized conjugate acid of an ester

$pK_a = -6$

Acyl chlorides are much less basic than carboxylic acids or esters because the chlorine atom does not stabilize the conjugate acid by resonance. An inductive effect destabilizes the conjugate acid.



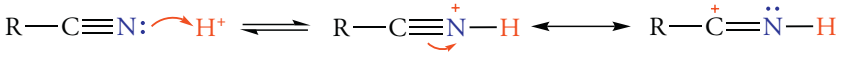
Amides are the most basic acid derivatives because the nitrogen atom provides effective resonance stabilization of the positive charge of the conjugate acid.



resonance-stabilized conjugate acid of an amide

$pK_a = -1$

Nitriles are extremely weak bases. Consequently, the conjugate acids of nitriles are very strong. The low basicity of nitriles reflects the hybridization of the orbital containing the lone pair electrons. Even though nitrogen is more basic than oxygen, the sp orbital holds electrons close to the nucleus, so they are less available to form a conjugate acid. Also, the alternate resonance form of the conjugate acid does not have a Lewis octet at each atom.



resonance-stabilized conjugate acid of a nitrile

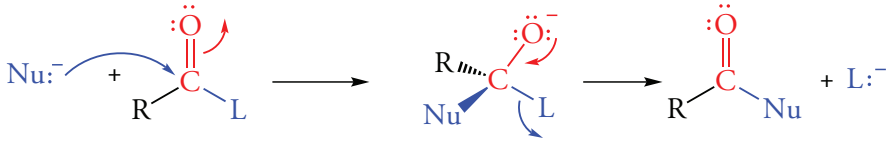
$pK_a = -10$

Problem 21.6

The pK_a of the conjugate acid of propanone is –7.1. Why is this species a stronger acid than the conjugate acid of ethanoic acid ($pK_a = -6$)?

21.4 MECHANISM OF NUCLEOPHILIC ACYL SUBSTITUTION

Acyl derivatives react with nucleophiles in an addition reaction to generate an unstable tetrahedral intermediate. The intermediate decomposes by an elimination reaction in which a group leaves to form a different acyl derivative. The overall process is called **nucleophilic acyl substitution**. The process is also called an **acyl transfer reaction** because it transfers an acyl group from one group (the leaving group) to another (the nucleophile).

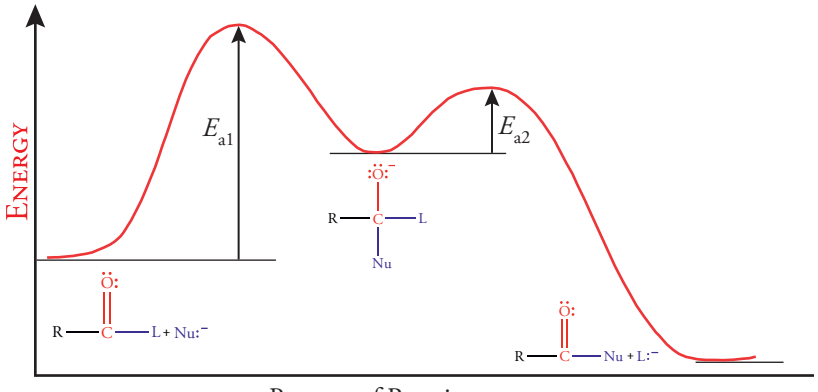


tetrahedral intermediate

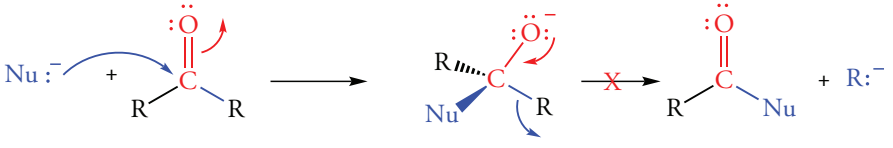
The net result is a substitution reaction whose stoichiometry resembles that of an S_N2 substitution reaction of haloalkanes. However, the resemblance is only superficial. An S_N2 reaction is a concerted process in which the nucleophile forms a bond to the carbon atom as the leaving group departs. In contrast, nucleophilic acyl substitution occurs in two steps.

1. The rate-determining step is usually nucleophilic attack at the carbonyl carbon atom to form a tetrahedral intermediate.
2. The leaving group departs in an elimination reaction in a fast second step (Figure 21.1).

Figure 21.1
Mechanism of Nucleophilic Acyl Substitution



Why don't acyl derivatives behave like aldehydes and ketones and form stable tetrahedral products? The answer is that the intermediate formed from an acyl derivative has a good leaving group. In the case of an acid chloride, the leaving group is the weakly basic chloride ion. We recall that leaving group abilities are inversely related to base strength. An intermediate derived from a ketone does not have a good leaving group. A carbanion, the conjugate base of a hydrocarbon, is an extremely strong base and, therefore, a very poor leaving group.



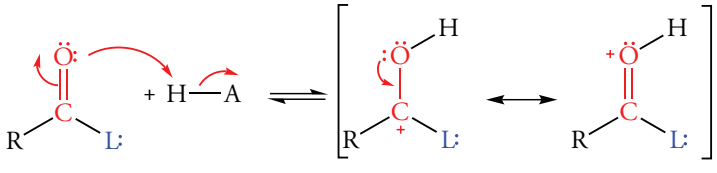
tetrahedral intermediate

The mechanism of nucleophilic acyl substitution reactions depends on the identity of the nucleophile and the leaving group. The mechanisms for acid and base catalysis are not the same. We now consider both acid- and base-catalyzed nucleophilic acyl substitution.

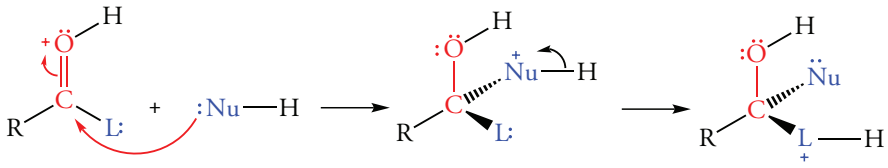
Acid-Catalyzed Acyl Substitution Reactions

Acid-catalyzed acyl substitution reactions occur in three steps.

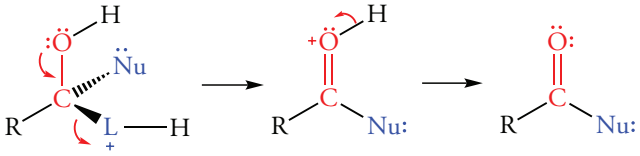
1. Protonation of the Acyl Oxygen. An acid, H—A, protonates the oxygen atom of an acyl group to form a resonance-stabilized carbocation intermediate that is more electrophilic than the original acyl derivative.



2. Nucleophilic Addition. As a result of the increased electrophilicity of the protonated carbonyl group carbon, it reacts with a nucleophile to give a tetrahedral intermediate.



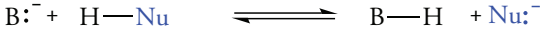
3. Proton transfer, followed by departure of the protonated leaving group, L—H, gives the new acyl derivative.



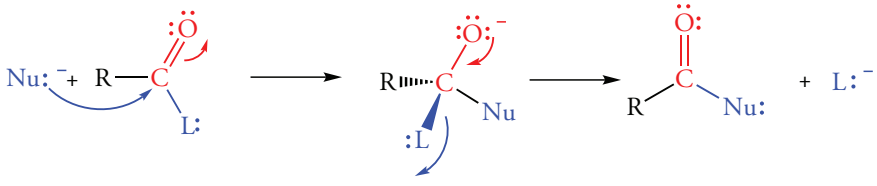
Base-Catalyzed Acyl Substitution Reactions

Base-catalyzed acyl substitution reactions also occur in three steps.

1. Deprotonation of the Nucleophile. An base, B^-, removes a proton from a nucleophile H—Nu to give Nu^-, which is significantly more reactive than the neutral nucleophile.



2. Nucleophilic Addition. The nucleophile attacks the carbonyl carbon atom, yielding a tetrahedral intermediate.



3. Regeneration of the Nucleophile. An acid–base reaction between the leaving group and the conjugate acid of the base, B—H, which was generated in Step 1, regenerates the base catalyst, B^-.



Relative Reactivity of Acyl Derivatives

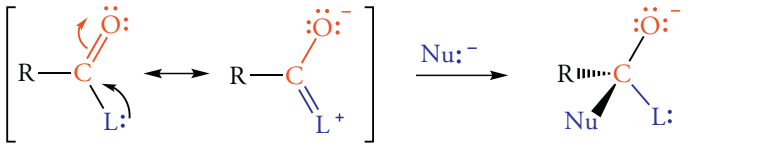
There are tremendous variations in the rates of acyl substitution reactions with a common nucleophile such as water. The order of reactivity in a hydrolysis reaction is acyl chloride > acid anhydride > ester > amide (Table 21.3).

Table 21.3
Relative Reactivities of Acyl Derivatives

Acyl Compound	*Relative Rate of Hydrolysis*
Acetyl chloride	10^{13}
Acetic anhydride	10^{9}
Ethyl acetate	10^{2}
Acetamide	1

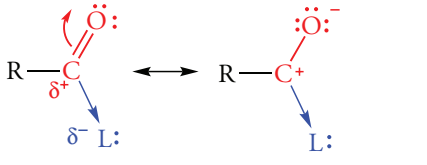
This order of reactivity might seem to reflect the leaving group abilities of these compounds, which we know are related to their basicities. We know, for example, that HCl is a strong acid and that Cl^- is a weak base. Therefore, Cl^- is a good leaving group. We also know that NH_3 is a very weak acid, NH_2^- is a very strong base, and that it is therefore a poor leaving group. However, nucleophilic acyl substitution occurs in two steps (Figure 21.1). In the first step, the nucleophile attacks the acyl carbon and a tetrahedral intermediate forms. This is the rate-determining step in the reaction. Because the leaving group departs in a second, fast step, it does *not* affect the overall rate of reaction.

The order of reactivities of acyl derivatives parallels the resonance stabilization of the reactant. Donation of an electron pair by an atom bonded to the acyl carbon decreases the partial positive charge on the carbon atom and decreases its electrophilicity. Resonance stabilization is impossible in the tetrahedral intermediate.

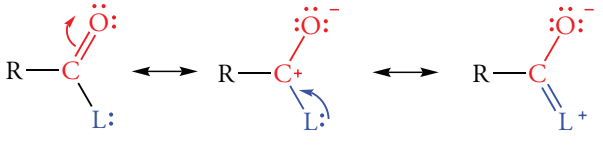


We can explain the effect of the group bonded to the acyl carbon atom on the observed order of reactivity of acyl compounds using concepts we discussed in the context of electrophilic aromatic substitution in Chapter 13. We recall that electronegative, second-row elements, such as oxygen and nitrogen, withdraw electron density from the aromatic ring by an inductive effect, but that they donate electron density by resonance. Furthermore, nitrogen is a better electron donor than oxygen because oxygen is more electronegative and can more effectively donate its nonbonded electrons. We also recall that chlorine, a third-row element, withdraws electron density by an inductive effect, but is not very effective in donating electrons by resonance because of poor overlap of its 3p orbitals and the 2p orbital of carbon.

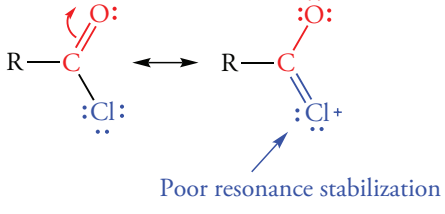
Inductive electron withdrawal from the acyl carbon by the electronegative chlorine atom destabilizes the acyl chloride. A reaction that leads to another acyl derivative with less severe electron withdrawal from the acyl carbon atom is therefore favorable.



However, donation of electrons by resonance stabilizes the carbonyl group. Therefore, a reaction that leads to an acyl derivative with more effective electron donation to the acyl carbon is favored.



Resonance stabilization by the chlorine atom is not effective, and acyl halides are the most reactive acyl derivatives.



Amides are much more stable than acid chlorides even though nitrogen and chlorine have about the same electronegativities. Therefore, their inductive effects should also be about the same. Nitrogen, however, is a second-row element, and it effectively donates electron density to the acyl carbon by resonance.

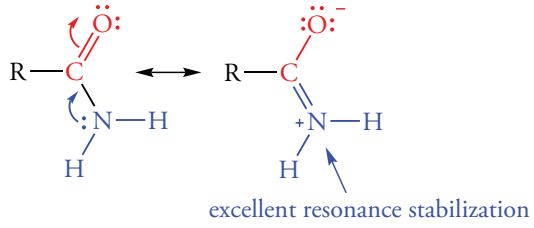
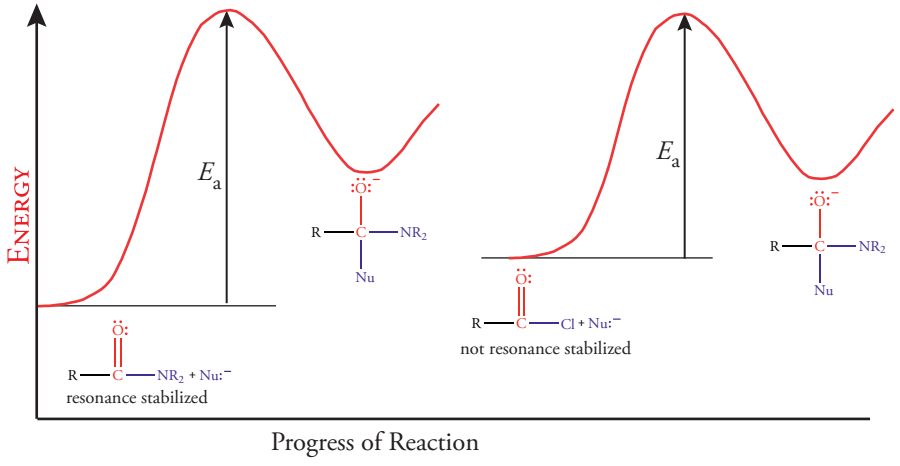
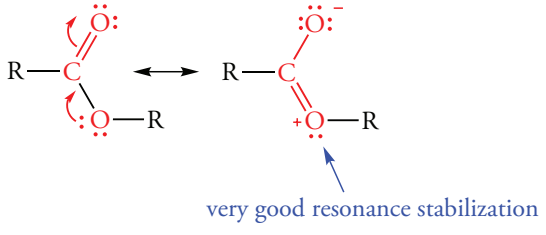


Figure 21.2 shows energy profiles for reactions of a nucleophile with an amide and with an acid chloride. The relative energies of transition states and tetrahedral intermediates for the two reactions are about the same because neither intermediate is resonance stabilized. However, because the amide reactant is resonance stabilized and the acid chloride is not, the reaction of the acid chloride is faster because it is the less stable reactant.

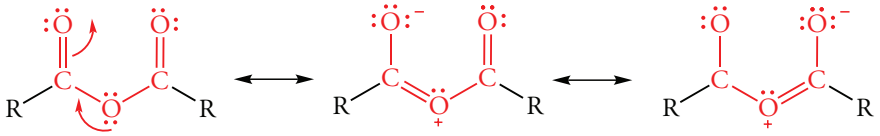
Figure 21.2
Reactivity of Acyl Derivatives



Next, let's consider acyl derivatives containing oxygen. Esters and anhydrides are both more reactive than amides, and anhydrides are more reactive than esters. We can explain these facts using the resonance contribution of the nonbonded electrons of oxygen. Oxygen is a second-row element like nitrogen, but oxygen does not donate electron density in resonance forms as well as the less electronegative nitrogen. We could characterize the donation of electrons by oxygen as "very good."



The oxygen atom of an anhydride is less effective than the oxygen atom of an ester in supplying electrons by resonance because the second carbonyl carbon atom also competes for the same lone pair electrons of oxygen. Neither carbonyl group is as stable as the single carbonyl group of an ester.

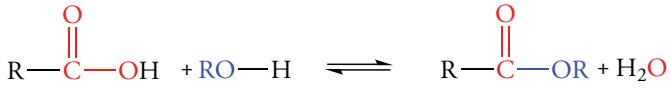


good resonance stabilization

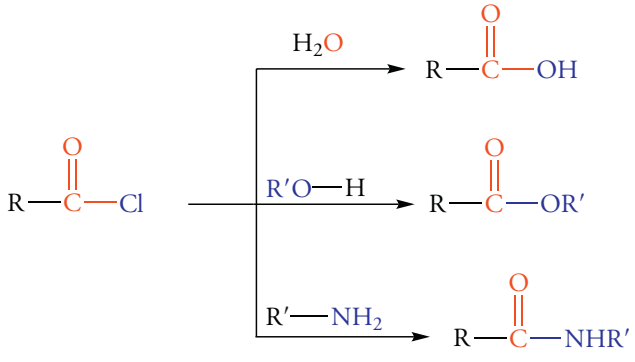
Predicting the Direction of a Nucleophilic Acyl Substitution Reaction

Since we know the relative stabilities of acyl derivatives, we can predict the position of a nucleophilic acyl substitution reaction. The same factors that affect the relative reactivity of acyl derivatives also control their stabilities. The identity of the groups bonded to the tetrahedral carbon atom affects the stabilities of the reactants and products. Thus, destabilizing the reactant and stabilizing the product increase the equilibrium constant. We conclude that the less stable acyl derivative is more reactive and can be converted into a more stable, less reactive acyl derivative. The relative stabilities of acyl derivatives enable us to understand most of the chemical reactions discussed in this chapter.

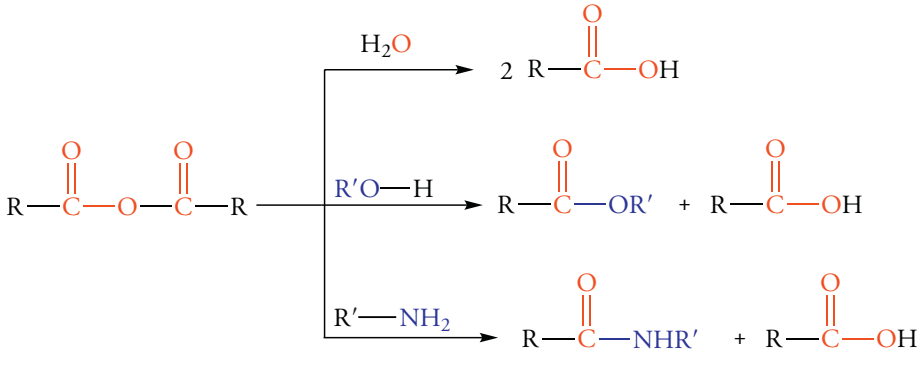
Because acids and esters have similar reactivities, they can be readily interconverted in equilibrium processes. For example, the reaction conditions may be selected to favor either the esterification of an acid or the hydrolysis of an ester.



Acid chlorides react rapidly and quantitatively with most nucleophiles, and they are hydrolyzed by the moisture in air. Reaction of an acid chloride with an alcohol gives an ester. Reaction with acid chlorides readily converts amines into amides.

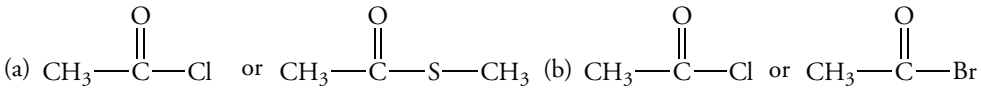


Acid anhydrides are less reactive than acid chlorides, but they are still very active acylating agents. Water hydrolyzes acid anhydrides to acids, alcohols react to give esters, and amines give amides. The by-product in each case is one molar equivalent of a carboxylic acid.



Problem 21.7

Which member of each of the following pairs of compounds reacts faster with water?



Problem 21.8

Explain why the carbonyl carbon–oxygen single bond of esters is about 7 pm shorter than the carbon–oxygen bond of an ether. Using this interpretation, determine whether the difference between the carbonyl carbon–nitrogen bond of an amide and the carbon–nitrogen bond of an amine will be larger or smaller than 7 pm.

Sample Solution

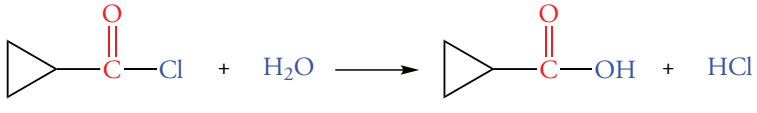
The contribution of dipolar resonance forms of esters increases the bond order of the carbonyl carbon–oxygen single bond of esters. Increased double bond character results in a decrease in bond length. The contribution of dipolar resonance forms of amides is greater than that of esters because nitrogen is more effective than oxygen in donating electrons by resonance. Thus, the carbonyl carbon–nitrogen bond has more double bond character, which leads to a further decrease in bond length. The difference between the carbonyl carbon–nitrogen bond of an amide and the carbon–nitrogen bond of an amine is larger than 7 pm.

21.5 HYDROLYSIS OF ACYL DERIVATIVES

The hydrolysis of acyl derivatives yields an acid as one of the products. Recalling the order of reactivity of acyl derivatives, we expect the reaction of acyl chlorides and anhydrides to have favorable equilibrium constants. The reaction of an ester with water is an equilibrium reaction that can be forced to completion by using favorable experimental conditions and taking into account Le Chatelier's principle. Amides are so stable that the hydrolysis requires harsh conditions to drive the reaction to completion. It is also difficult to hydrolyze nitriles.

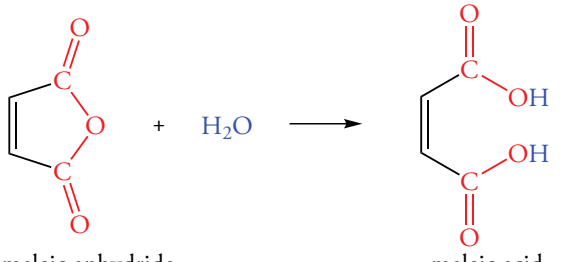
Hydrolysis of Acid Chlorides and Anhydrides

An acid chloride reacts spontaneously with water to give a carboxylic acid and HCl. The reaction requires no acid or base catalyst. There is no synthetic advantage to this reaction because acid chlorides are prepared from carboxylic acids. Acid chlorides must be protected from the moisture in air because they react readily with water.



cyclopropanecarbonyl chloride — cyclopropanecarboxylic acid

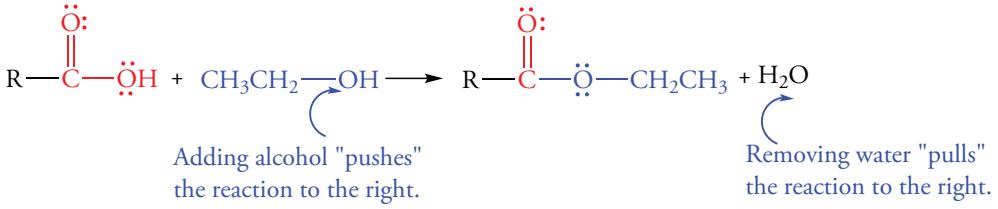
Although acid anhydrides are less reactive than acid chlorides, they still react spontaneously with water to give carboxylic acids.



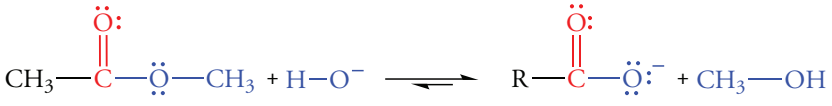
maleic anhydride — maleic acid

Hydrolysis of Esters

The acid-catalyzed hydrolysis of an ester produces an acid and an alcohol. Ester hydrolysis, then, is just the reverse of the Fischer esterification reaction, which is also catalyzed by strong acids. A large excess of water favors the reaction.

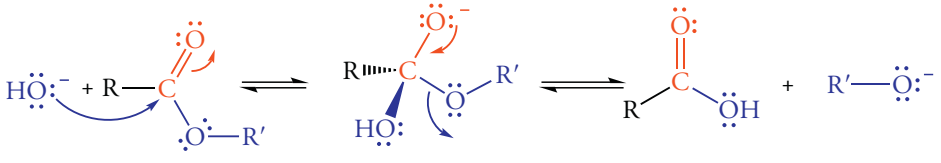


The hydrolysis of an ester by a strong base is called saponification (from Latin *sapon*, soap) because this reaction is used to make soaps from esters of long-chain carboxylic acids. Methyl acetate reacts with a strong base to give acetate ion and methanol.

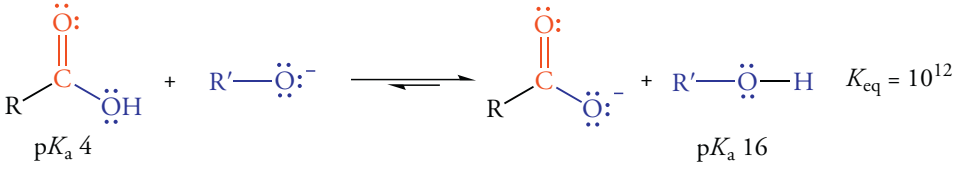


There is an important difference between ester hydrolysis and saponification. In hydrolysis, the hydronium ion acts as a catalyst, but in saponification hydroxide is a reagent; that is, it is not regenerated at the end of the reaction. Equal numbers of moles of ester and hydroxide react, and since hydroxide is a strong base, the equilibrium lies overwhelming on the side of the products.

Saponification occurs by nucleophilic attack on the acyl carbon by hydroxide ion to form a tetrahedral intermediate. The intermediate can then eliminate hydroxide to regenerate the ester or eliminate an alkoxide anion to form an alkoxide and a carboxylic acid.

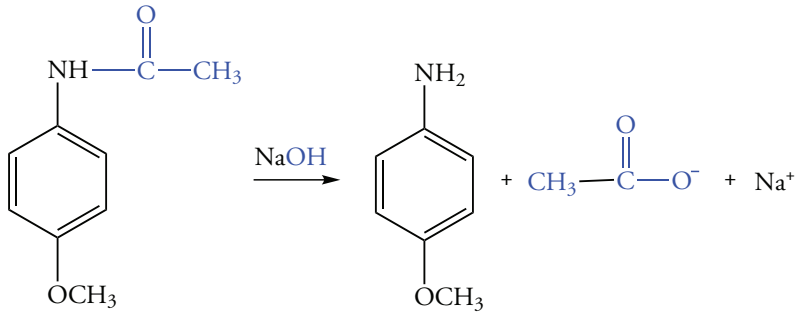


Since alkoxide is a stronger base than hydroxide, acid–base reaction occurs to give a carboxylate anion and an alcohol. The equilibrium constant for this reaction lies far on the right, and it pulls the saponification reaction to completion.

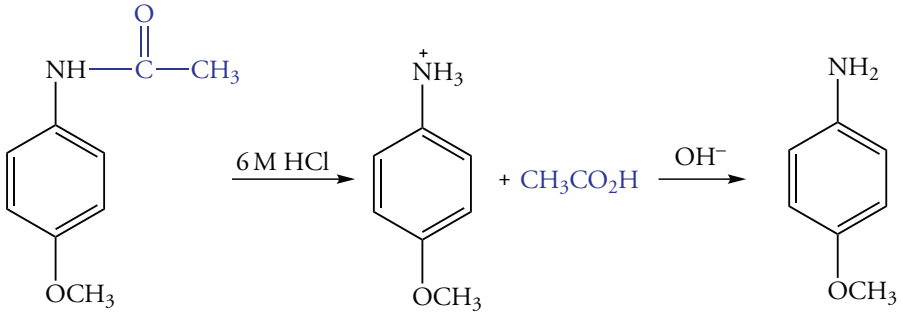


Hydrolysis of Amides

Hydrolysis of an amide breaks the carbon–nitrogen bond and produces a carboxylic acid and either ammonia or an amine. The reaction resembles esters hydrolysis, but there are important differences. Ester hydrolysis occurs relatively easily, but amides resist hydrolysis. Under acid conditions, 6 M HCl and refluxing for 24 hours are required. Under basic conditions, a 40% solution of sodium hydroxide is used. Under these conditions, the salt of a carboxylate anion is produced. As in saponification of esters, an acid–base reaction to form the carboxylate anion pulls the reaction to completion.



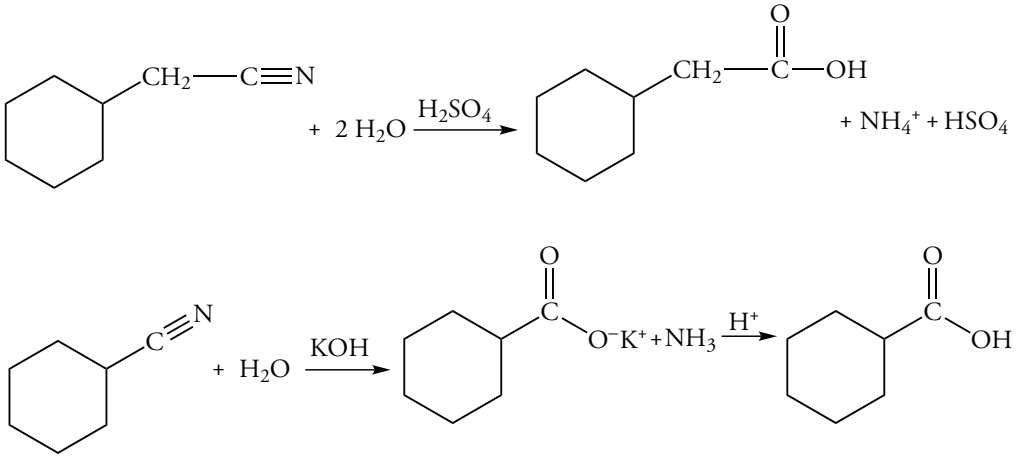
When amide hydrolysis is carried out under acid conditions, the ammonium salt of the amine forms, and a mole of acid reacts with each mole of the amide. The formation of the conjugate acid of the amine drives the reaction to completion. The free amine forms in a subsequent neutralization reaction with base.



The stability of amides has important biochemical consequences since the amino acid residues in proteins are linked by amide bonds. Because amides are stable, proteins do not hydrolyze at physiological pH and body temperature without an enzyme catalyst.

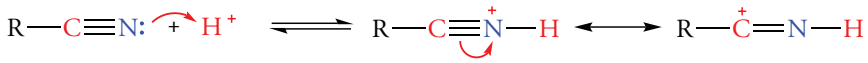
Hydrolysis of Nitriles

Nitriles hydrolyze to form carboxylic acids when treated with either concentrated acid or concentrated base. As in the case of amides, the reaction is slow and requires elevated temperatures. Amides form as intermediates in the hydrolysis process, and continued reaction converts them to carboxylic acids.

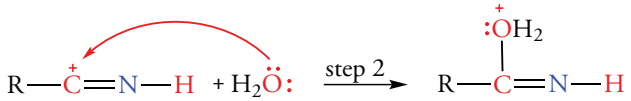


The mechanisms of the acid- and base-catalyzed reactions of the triple bonds of nitriles resemble those of the acid- and base-catalyzed reactions of the double bonds of aldehydes and ketones. The acid-catalyzed reaction proceeds in three steps, as we have seen for other kinds of acyl derivatives.

1. Protonation of the lone pair on nitrogen. The product is a resonance-stabilized ion. Protonation increases the electrophilicity of the cyano carbon atom.

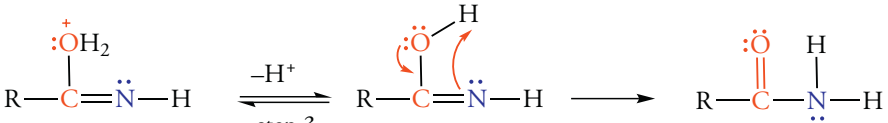


2. Nucleophilic Addition. As a result of the increased electrophilicity of the protonated acyl oxygen, a neutral nucleophile that does not react with the original acyl derivative can now react with the protonated species to give a tetrahedral intermediate. Solvent-mediated proton transfers can occur between two sites in the tetrahedral intermediate.



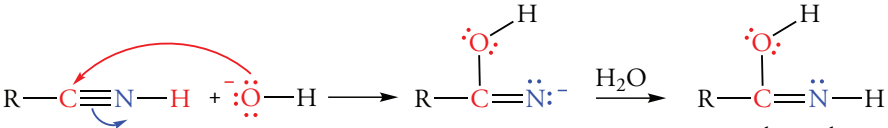
conjugate acid of an imidic acid

3. Loss of a proton and tautomerization. The conjugate acid of the imidic acid loses a proton, and the resulting imidic acid tautomerizes to give an amide. The amide continues to react by the mechanism of acid-catalyzed amide hydrolysis we discussed above.



imidic acid

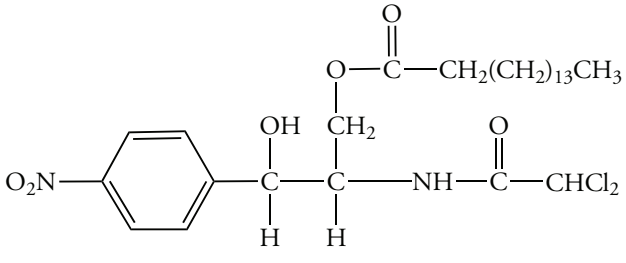
In the base-catalyzed hydration of a nitrile, the first step of the process is nucleophilic attack of hydroxide at the electrophilic carbon atom. Subsequent protonation of nitrogen by water yields an imidic acid. The imidic acid tautomerizes to give an amide that hydrolyzes to yield the carboxylic acid.



imidic acid

Problem 21.9

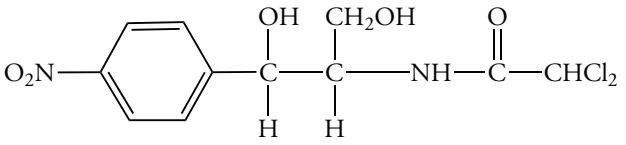
The antibiotic chloramphenicol has a bitter taste. Its palatability for children is improved by using a suspension of the palmitate ester. Enzymes in the intestine hydrolyze the ester. Given the structure of the ester, write the structure of the antibiotic.



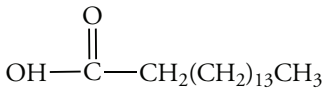
chloramphenicol palmitate

Sample Solution

First, locate the ester functional group by examining the carbonyl carbon atoms. The carbonyl group in the center of the structure is bonded to a nitrogen atom. This is an amide. The carbonyl carbon atom at the top of the structure is bonded to an oxygen atom. This is the ester. The carbon chain to the right of the carbonyl group is part of palmitic acid, which contains a total of 16 carbon atoms. Chloramphenicol is bonded in the ester through its primary hydroxyl group.



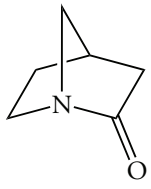
chloramphenicol



palmitic acid

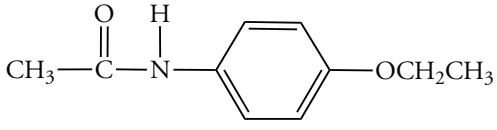
Problem 21.10

Give two reasons why the following bicyclic amide is easily hydrolyzed.



Problem 21.11

What are the products of the hydrolysis of phenacetin by a base? Phenacetin was once used in APC analgesic tablets consisting of aspirin, phenacetin, and caffeine.



phenacetin

Problem 21.12

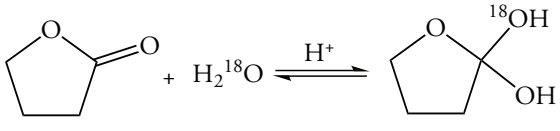
The principal component of the wax of the sperm whale is an unbranched ester that hydrolyzes to give $C_{16}H_{34}O$ and $C_{16}H_{32}O_2$. Write the structure of the ester.

Problem 21.13

The lactone of 4-hydroxybutanoic acid is stable in aqueous acid solution. However, when it is dissolved in aqueous acid labeled with ^{18}O, the lactone incorporates ^{18}O. Which oxygen atom of the lactone is labeled?

Sample Solution

First, the acid protonates the carbonyl oxygen atom. Second, the nucleophilic oxygen of a water molecule attacks the carbonyl carbon atom give a tetrahedral intermediate that is a hydrate of the ester.



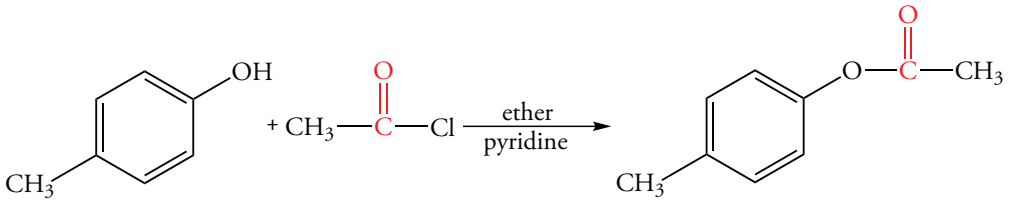
The hydroxyl groups are structurally equivalent. Thus, the reverse of the hydration reaction can eliminate either group in the water released. The ^{18}O can be retained in the carbonyl group or released back into the solution.

21.6 REACTION OF ACYL DERIVATIVES WITH ALCOHOLS

The mechanism of the reaction of alcohols with each of the acyl derivatives is similar to the corresponding mechanism for the hydrolysis of acyl derivatives.

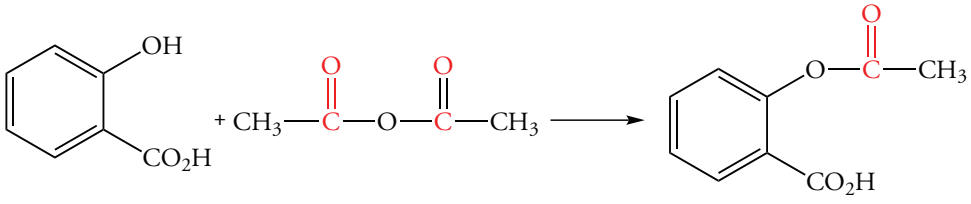
Acid Chlorides

We recall that esters of alcohols can be prepared by Fischer esterification (Section 20.12). Esters of phenols cannot be prepared by this method because the equilibrium constant is not favorable. However, acid chlorides react with of both alcohols and phenols to give esters. The reaction produces HCl, and pyridine is added to the reaction mixture to neutralize the HCl.

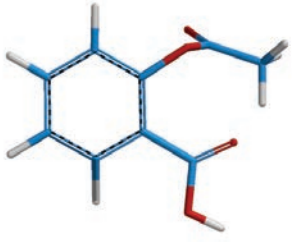


Acid Anhydrides

Acid anhydrides react with alcohols in much the same way as acid chlorides. However, only one of the two acyl groups of the anhydride reacts with nucleophiles. Because an acid anhydride is usually prepared from two equivalents of a carboxylic acid, one of those equivalents is wasted when the acid anhydride reacts with an alcohol. Acetic anhydride, an inexpensive and commercially available reagent, is used in industry to acetylate alcohols and phenols. Drug manufacturers prepare aspirin from salicylic acid by this method.



acetyl salicylic acid (aspirin)



aspirin

Esters

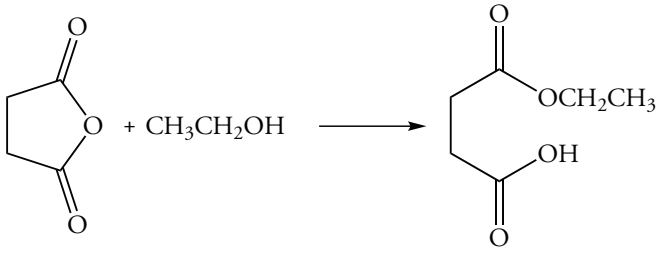
The reaction of an ester with an alcohol in an acid-catalyzed reaction yields an ester of the alcohol by an exchange of alkoxy groups. This transesterification reaction has little synthetic utility because any desired ester can usually be prepared in better yield from another acid derivative, such as an acid chloride.

Problem 21.14
Why are the esters of tertiary alcohols prepared by reaction with acid chlorides rather than by the Fischer esterification method?

Problem 21.15
Write the product of the reaction of succinic anhydride with ethanol.

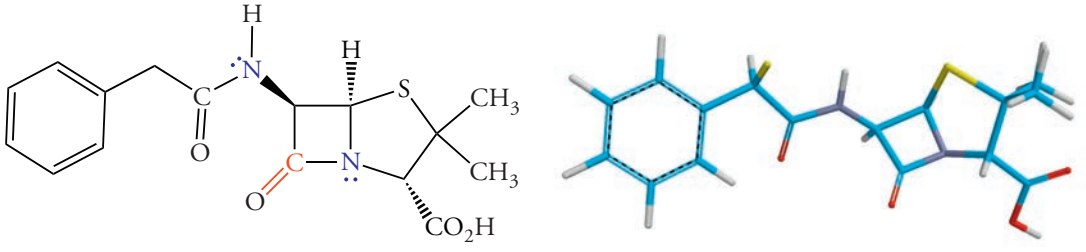
Sample Solution

Reaction of an alcohol with an acyclic anhydride to form an ester releases one equivalent of a carboxylic acid. Because succinic anhydride is a cyclic anhydride, the carboxyl group is not released. It remains as part of the ester. Because carboxylic acids are less reactive than anhydrides, the carboxyl group does not react with a second equivalent of ethanol. The product is the monoethyl ester.



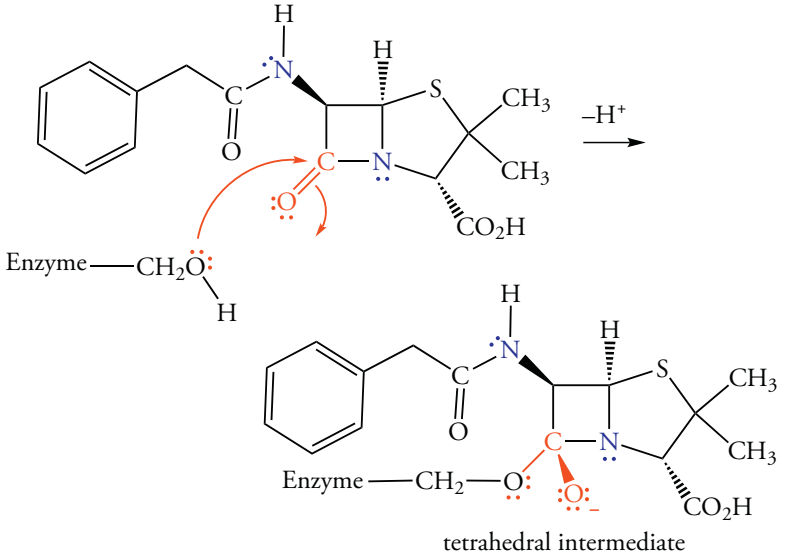
Biochemical Hydrolysis of Penicillin

Penicillins and cephalosporins are two classes of bactericides that contain a four-membered lactam (a β-lactam). Although representatives of both types of compounds were originally isolated from fungi, derivatives are now produced by structural modification in the laboratory. We will focus our attention upon penicillin G.



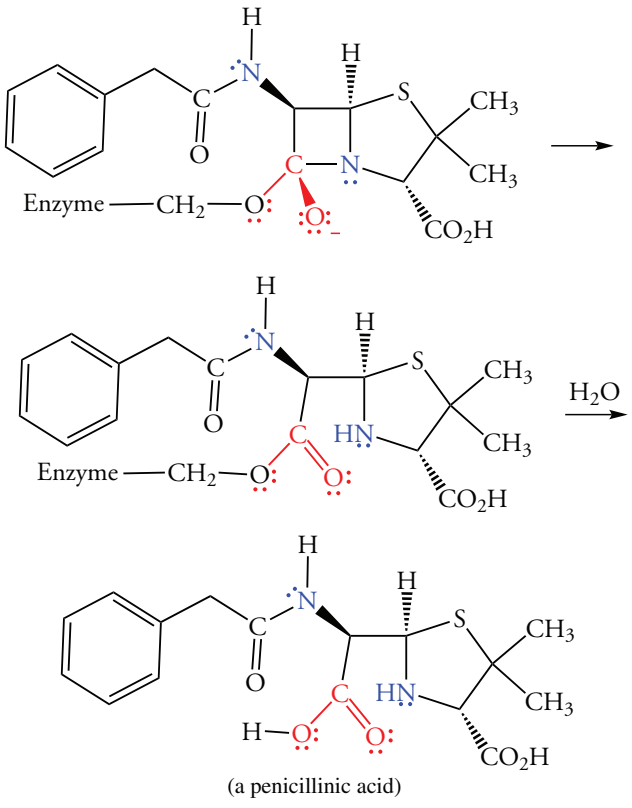
Penicillin G

Penicillin G inhibits the synthesis of bacterial cell walls, causing growing cells to burst. The enzyme *transpeptidase* catalyzes reactions that form the cell wall. The enzyme forms a complex with penicillin G, and the carbonyl group reacts with a serine hydroxyl group contained in the active site of the enzyme. The first step of the reaction is formation of a tetrahedral intermediate.



tetrahedral intermediate

The tetrahedral intermediate then collapses to give an acyl enzyme, which hydrolyzes to give a penicillinic acid.



(a penicillinic acid)

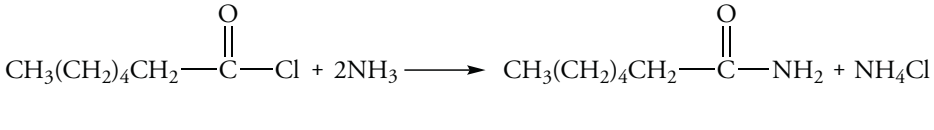
Most amides are ineffective acylating agents. However, the four-membered ring of a β-lactam is strained. Relief of strain provides the driving force for its reaction with nucleophiles.

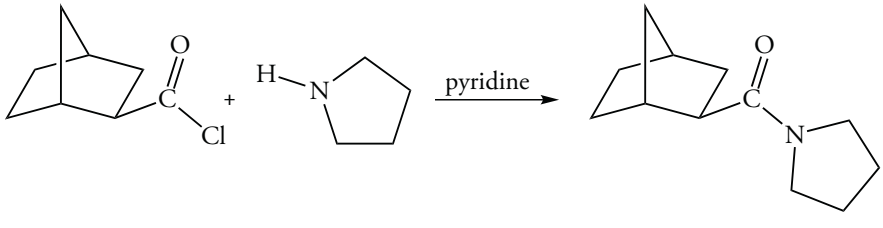
21.7 REACTION OF ACYL DERIVATIVES WITH AMINES

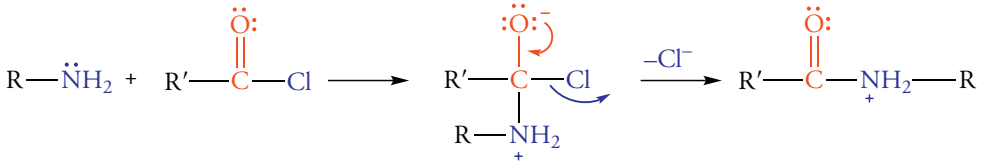
Ammonia and amines are better nucleophiles than water or alcohols because the nitrogen atom is less electronegative than oxygen. Therefore, amines are stronger bases. Because amides are the most stable acyl derivatives, ammonia and amines react with acyl halides, anhydrides, and esters to give amides.

Acid Chlorides

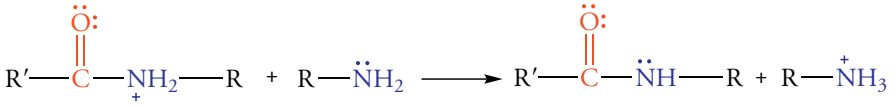
Acid chlorides react with ammonia, a primary amine, or a secondary amine to give primary, secondary, and tertiary amides, respectively. Tertiary amines do not react with acid chlorides to give amides.







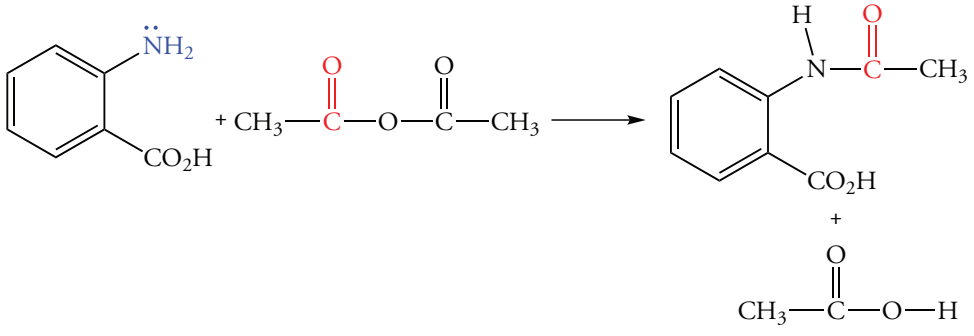
An amide is a weak base. Thus, the conjugate acid of the amide formed in the synthetic reaction transfers a proton to the reactant amine.



The ammonium ion, unlike the original amine, is not nucleophilic. Therefore, one equivalent of amine is consumed for every equivalent of amine converted to the amide. Such a process is wasteful, and impractical for all but the least expensive amines. Therefore, a tertiary amine, such as pyridine, is used to react with the proton released in the reaction.

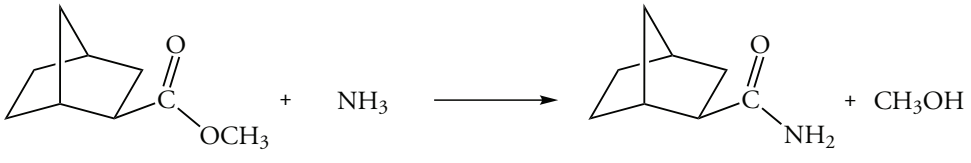
Acid Anhydrides

Ammonia, primary amines, and secondary amines all react easily with acid anhydrides to form amides. The by-product is the carboxylic acid used to originally form the anhydride. Acetic anhydride in acetic acid is an inexpensive reagent for the acetylation of amines.

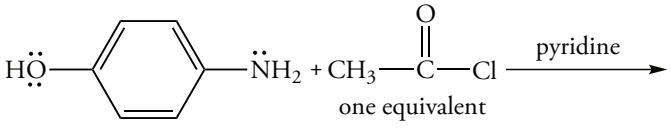


Esters

Esters react with ammonia of primary or secondary amines to yield amides by the same general mechanism as for the reaction of nitrogen compounds with acid chlorides or acid anhydrides. However, the preparation of amides from esters is not used synthetically because amides are better prepared by reaction with the more reactive acyl derivatives.



Problem 21.16
Draw the structure of the product of the following reaction.



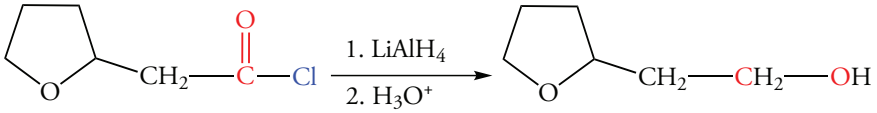
Problem 21.17
Draw the structure of the product of the reaction of maleic anhydride with methylamine (CH_3NH_2).

21.8 REDUCTION OF ACYL DERIVATIVES

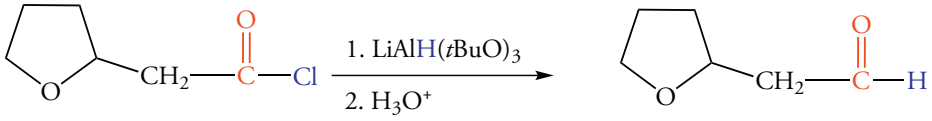
Carboxylic acids and their acyl derivatives are relatively difficult to reduce. These reactions require strong reducing agents. In this section, we will review some of these reductions, which we studied earlier as methods to synthesize alcohols and aldehydes.

Reduction of Acid Chlorides

Acid chlorides are the most reactive acyl derivatives toward the nucleophilic hydride ion provided by metal hydrides. Acid chlorides are rapidly reduced to aldehydes. However, lithium aluminum hydride is such a strong reducing agent that the aldehydes produced from acid chlorides are further reduced to primary alcohols under the reaction conditions.

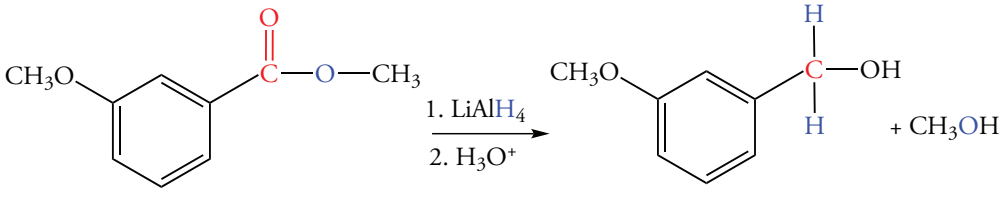


The milder reducing agent lithium aluminum tri(*tert*-butoxy) hydride reduces acid chlorides to yield aldehydes without further reduction to an alcohol.



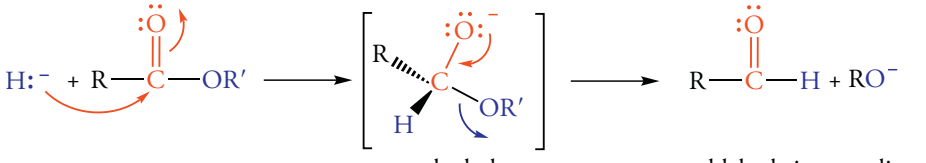
Reduction of Esters

The reduction of esters requires the strong reducing agent lithium aluminum hydride. The milder reagent sodium borohydride does not reduce esters.

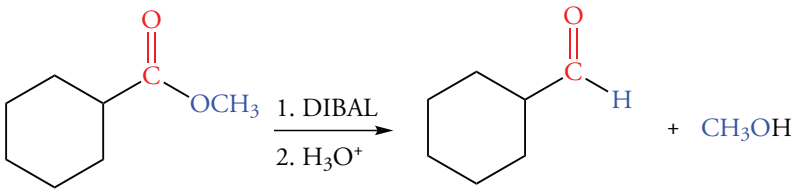


The alcohol portion of the ester is a by-product of the reaction. The esters typically reduced by lithium aluminum hydride contain a low molecular weight alkyl group that was introduced in the conversion of an acid to an ester. The alcohol obtained by reduction of the acid portion of the ester is easily separated from the low molecular weight, water-soluble alcohol.

The mechanism of the reduction of an ester occurs by nucleophilic attack of a one molar equivalent of a hydride ion on the carbonyl carbon atom. However, the aluminum atom is bonded to the oxygen atom and participates in the reaction. For simplicity, the structures do not show the aluminate ion. Attack by the hydride ion produces a tetrahedral intermediate whose negatively charged oxygen atom is bonded to the aluminum atom. The tetrahedral intermediate loses an alkoxide ion, and the resulting aldehyde is even more rapidly reduced than the original ester by a second molar equivalent of hydride ion. Two molar equivalents of hydride ion or one-half molar equivalent of lithium aluminum hydride is required for the reduction.

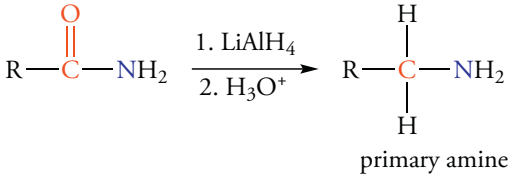


Esters are reduced to aldehydes using the mild reducing agent diisobutylaluminum hydride (DIBAL). To avoid subsequent reduction of the aldehyde, exactly one equivalent of the reagent is used, and the reaction is carried out at –78 °C.

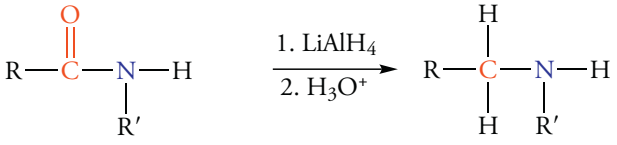


Reduction of Amides

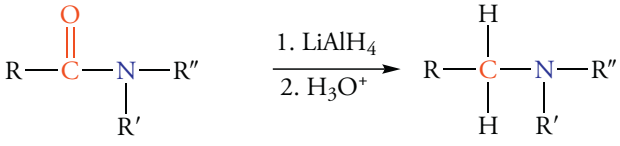
Lithium aluminum hydride reduces amides to amines regardless of the degree of substitution of the amide. Primary, secondary, and tertiary amides yield primary, secondary, and tertiary amines, respectively.



primary amine



secondary amine

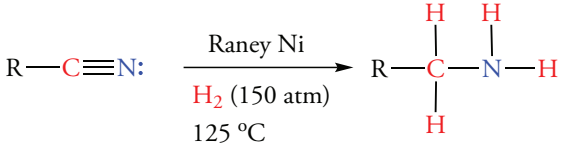


tertiary amine

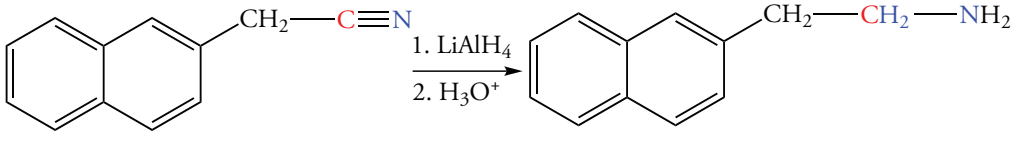
There is an important difference between the reductions of esters and amides. In esters, the oxygen atom retained in the product is the original carbonyl oxygen atom. The bridging oxygen atom to the alkyl group leaves as an alkoxy group. If a similar mechanism occurred with amides, the nitrogen atom would leave, but it does not. In the reduction of amides, the carbonyl oxygen atom is replaced by two hydrogen atoms.

Reduction of Nitriles

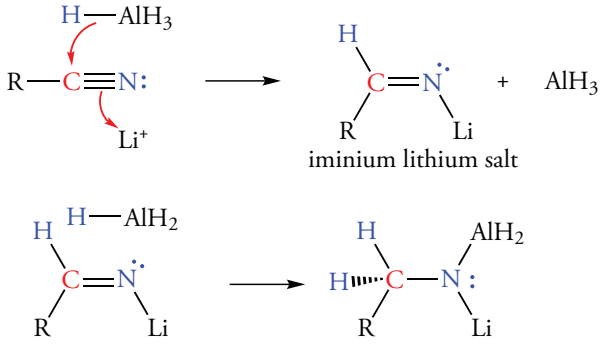
Nitriles are difficult to reduce by catalytic hydrogenation. The conditions of high temperature and high pressure of hydrogen are similar to those required for catalytic reduction of carbonyl compounds.



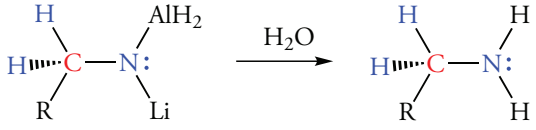
The intermediate in the reaction is an imine, which is rapidly reduced to the amine. However, lithium aluminum hydride reduces nitriles to primary amines.



The first step in the mechanism of the reduction of a nitrile produces a lithium iminium adduct, which then reacts with a second equivalent of hydride.

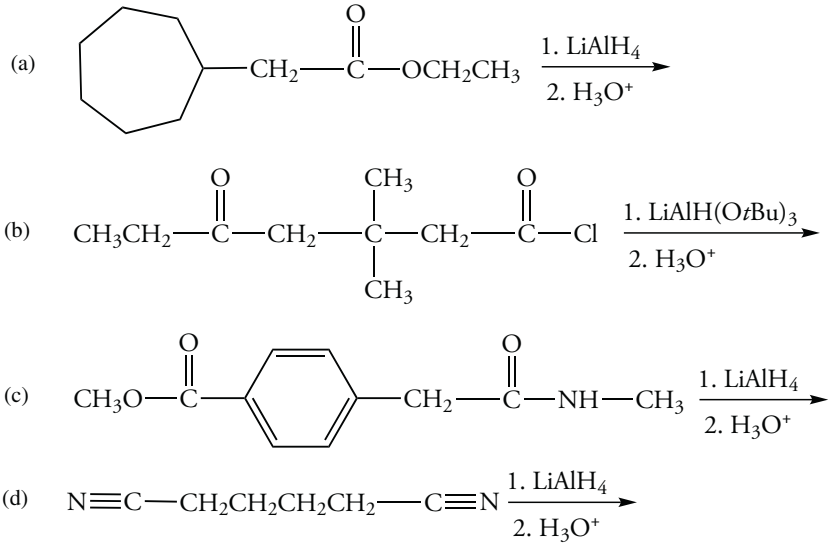


The N—Li and the N—Al bonds are protonated in the subsequent hydrolysis step.



Problem 21.18

Draw the structure of the product of each of the following reactions.



Problem 21.19

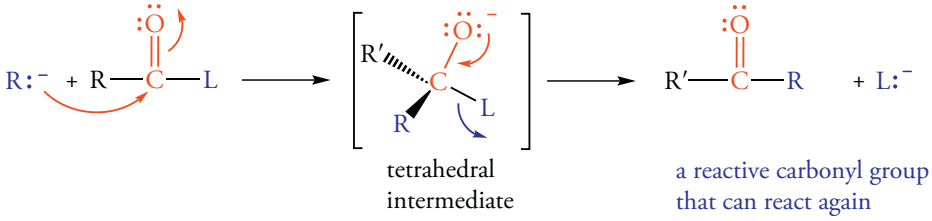
Reduction of cyclohexanecarboxamide with $LiAlD_4$ followed by aqueous workup gives $C_7H_{13}D_2N$. What is the structure of the product?

Problem 21.20

Reduction by $LiAlH_4$ of a substance with molecular formula $C_{12}H_{20}O_2$ obtained from a fungus gives (*E*)-4-dodecene-2,12-diol. Write the structure of the compound.

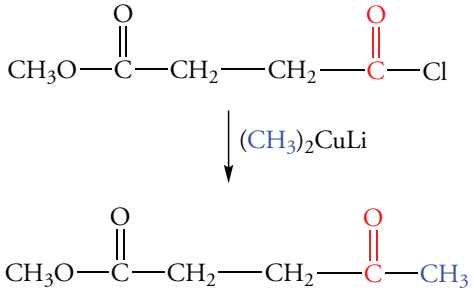
21.9 REACTION OF ACYL DERIVATIVES WITH ORGANOMETALLIC REAGENTS

The carbonyl group of acid derivatives reacts with the nucleophilic carbanion available from organometallic reagents. However, the reactions of the individual classes of compounds are not as straightforward as the addition reactions of organometallic compounds with aldehydes and ketones. Addition of a carbanion to the acyl carbon atom generates a tetrahedral intermediate that can decompose to give a ketone that will react further with another equivalent of the carbanion.



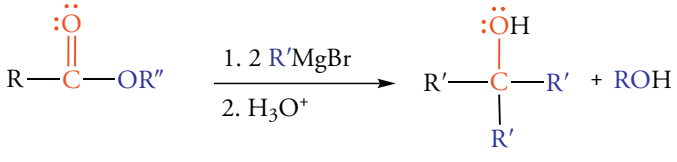
Acid Chlorides

Addition reactions of Grignard reagents to acid chlorides are not useful synthetic procedures because the reactions are difficult to control. However, lithium dialkylcuprates (Gilman reagents) are less reactive and react by a different mechanism than Grignard reagents (Section 17.2). Gilman reagents replace chloride by a "carbanion" to give a ketone. Because Gilman reagents react only slowly with ketones, the reaction can be stopped at this stage. The method is an excellent way to prepare ketones. The Gilman reagent does not react with esters because they are less susceptible to nucleophilic acyl substitution than acid chlorides.

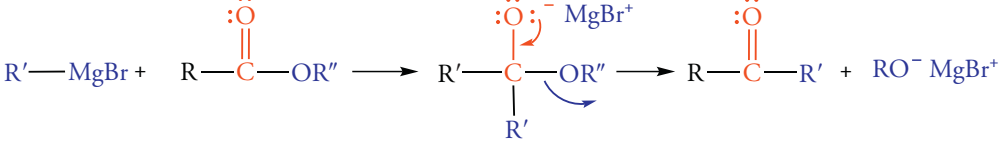


Esters

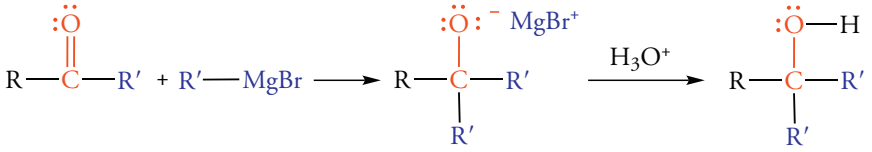
The reaction of an ester with a Grignard reagent to give a tertiary alcohol that contains two equivalents of the alkyl group of the organometallic reagent is an important synthetic procedure.



The first step of the reaction is addition of the Grignard reagent to the carbonyl group to give a tetrahedral intermediate. It releases an alkoxide ion complexed with magnesium bromide. Thus, the reaction is a typical nucleophilic acyl substitution reaction.



The carbon atom of the carbonyl group of ketones is more electrophilic than the acyl carbon atom of esters. Therefore, a second mole of Grignard reagent adds to the ketone to give a tertiary alcohol.

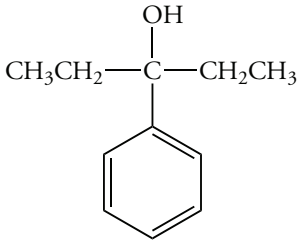


Problem 21.21

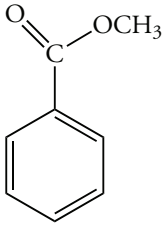
Propose a synthesis of 3-phenyl-3-pentanol using the addition reaction of a Grignard reagent to an ester.

Sample Solution

The carbon atom that bears the hydroxyl group has two ethyl groups and a phenyl group bonded to it.



The two ethyl groups can come from a Grignard reagent that can add to the carbonyl carbon of an ester. The ester must have a phenyl group bonded to the carbonyl carbon atom; it is a benzoate ester. The benzoate ester can contain any alkyl group such as in methyl benzoate or ethyl benzoate. Adding two equivalents of ethylmagnesium bromide followed by addition of aqueous acid gives the product, 3-phenyl-3-pentanol.



methyl benzoate

Problem 21.22

Explain how symmetrical secondary alcohols of the type R_2CHOH can be prepared by adding a Grignard reagent to an ester.

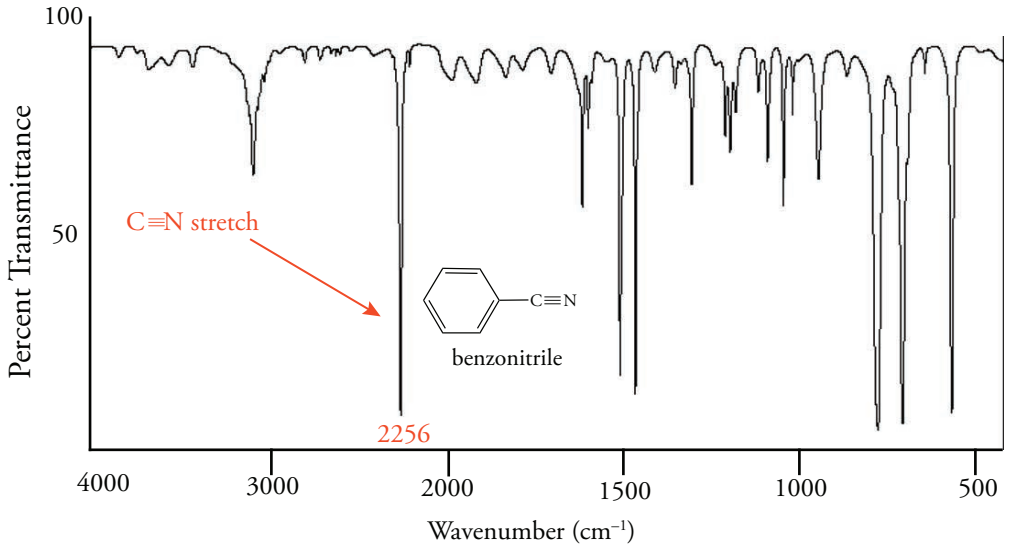
21.10 INFRARED SPECTROSCOPY OF ACYL DERIVATIVES

Nitriles

The C≡N stretching frequency occurs in a rather isolated part of the spectrum in the 2100–2200 cm^{-1} region. In contrast to the C≡C absorption, which is very weak and even absent in nearly symmetrical alkynes, the C≡N stretching absorption is very intense (Figure 21.3).

All acid derivatives having a carbonyl group have strong C=O stretching absorptions in the 1700–1800 cm^{-1} region. Simple esters as well as six-membered lactones (δ lactones) have an absorption at 1735 cm^{-1}, a higher wavenumber than aldehyde and ketone absorptions. The C=O stretching absorption of unsaturated esters occurs at slightly lower wavenumber (1720–1725 cm^{-1}).

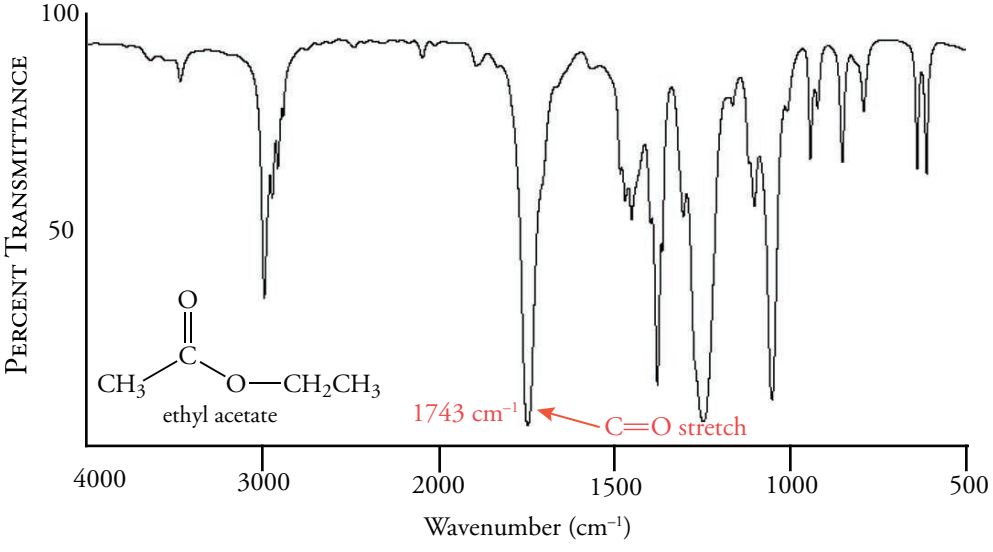
Figure 21.3
Infrared Spectrum of Benzonitrile



Esters

As in ketones, a decrease in ring size increases the wavenumber position of the C=O stretching absorption. The absorptions of five-membered lactones (γ-lactones) and four-membered lactones (β-lactones) occur at 1770 and 1840 cm^{-1}, respectively. Esters also have a C—O stretching absorption in the 1000–1300 cm^{-1} region. Because other absorptions also occur in this region, such data are useful only as a confirmation when an ester is suspected from other data such as the carbonyl stretching absorption. We recall that alcohols, ethers, and carboxylic acids have C—O absorptions in the same region. Figure 21.4 shows the infrared spectrum of ethyl acetate.

Figure 21.4
Infrared Spectrum of Ethyl Acetate



Acid Chlorides

Acyl chlorides have C=O stretching absorptions at higher wavenumber (1800 cm^{-1}) than esters, and amides have C=O stretching absorptions at lower wavenumber (1650–1655 cm^{-1}). These different values reflect the contribution of inductive and resonance effects in the stabilization of the Lewis structure of a carbonyl group compared to the dipolar resonance form. The chlorine atom of acyl chlorides inductively withdraws electrons from the carbonyl carbon and destabilizes the dipolar resonance form, thus leading to an increase in the double bond character of the carbonyl group. Figure 21.5 shows the infrared spectrum of acetyl chloride.

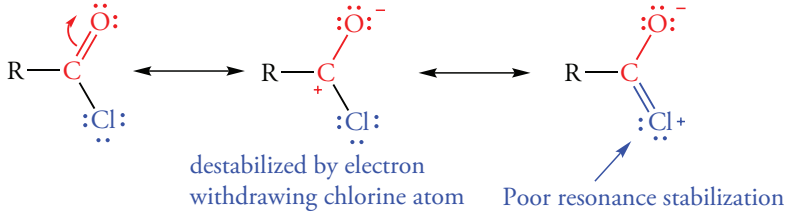
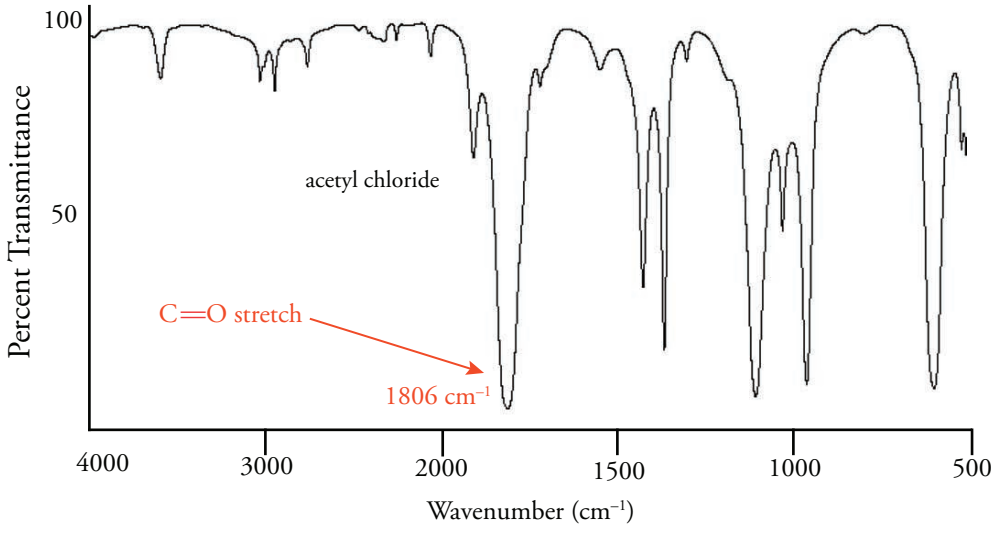
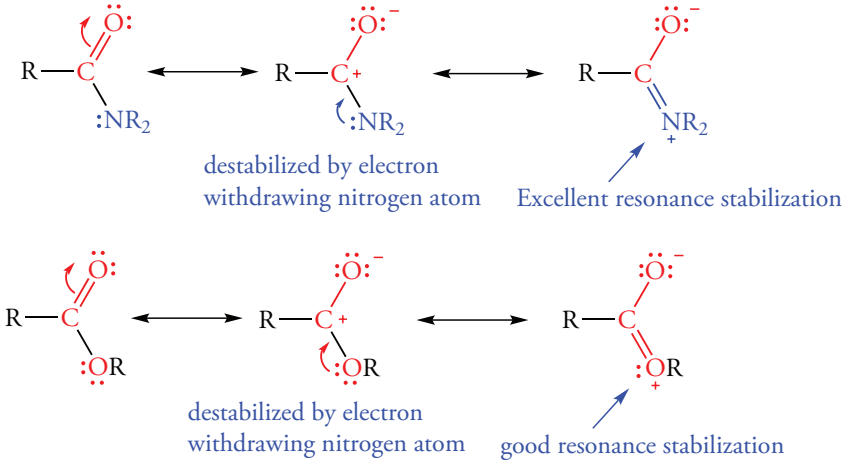


Figure 21.5
Infrared Spectrum of Acetyl Chloride



Amides

The position of the C=O stretching absorption of amides, like that of esters, reflects contributions of both inductive electron withdrawal by electronegative atoms and donation of electron density by resonance. The oxygen atom of esters and the nitrogen atom of amides destabilize the dipolar resonance form compared to that of ketones as a result of inductive withdrawal of electron density. If only inductive effects were important, both amides and esters would have C=O stretching absorptions at higher wavenumber positions than ketones, as is indeed observed for acyl chlorides. However, unlike chlorine, both nitrogen and oxygen can donate electrons by resonance and stabilize a dipolar resonance form that has a C—O single bond. As a result, the C=O stretching absorptions of esters and amides occur at higher wavenumber than acyl chlorides. Because nitrogen is less electronegative than oxygen, nitrogen supplies its lone pair electrons more easily and the dipolar resonance form is better stabilized in amides than in esters. As a consequence, the carbonyl group in amides has less double bond character than esters, and less energy is required to stretch the C=O bond in amides compared to esters.



In addition to the characteristic C=O stretching absorption of amides, primary and secondary amides also have N—H stretching absorptions in the 3200–3400 cm^{-1} region. Amides without alkyl or aryl groups bonded to nitrogen (primary amides) have two N—H absorptions; secondary amides have one N—H absorption. Of course, tertiary amides have no absorption in this region. Figures 21.6 and 21.7 show the infrared spectra of acetamide, a primary amide, and *N*-methylacetamide, a secondary amide.

Figure 21.6
Infrared Spectrum of Acetamide

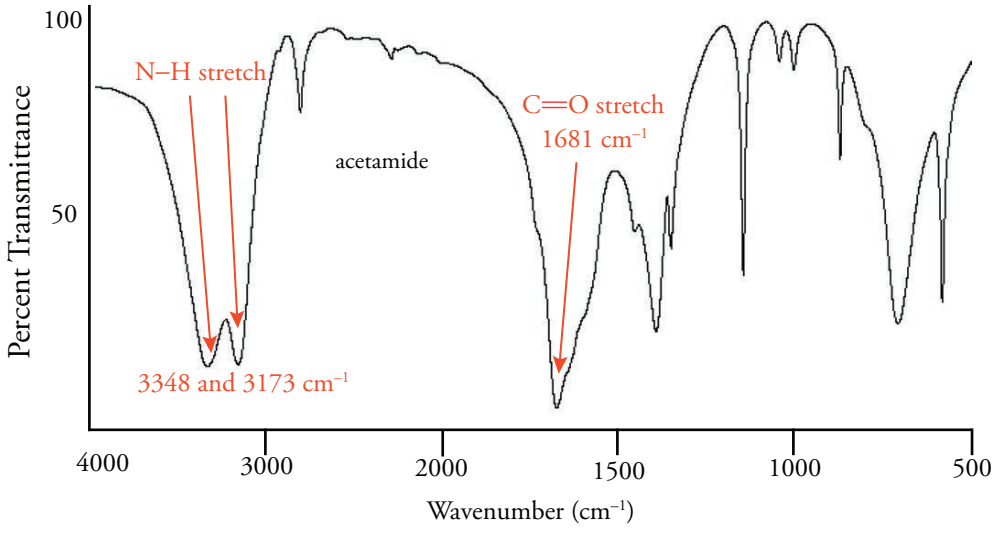
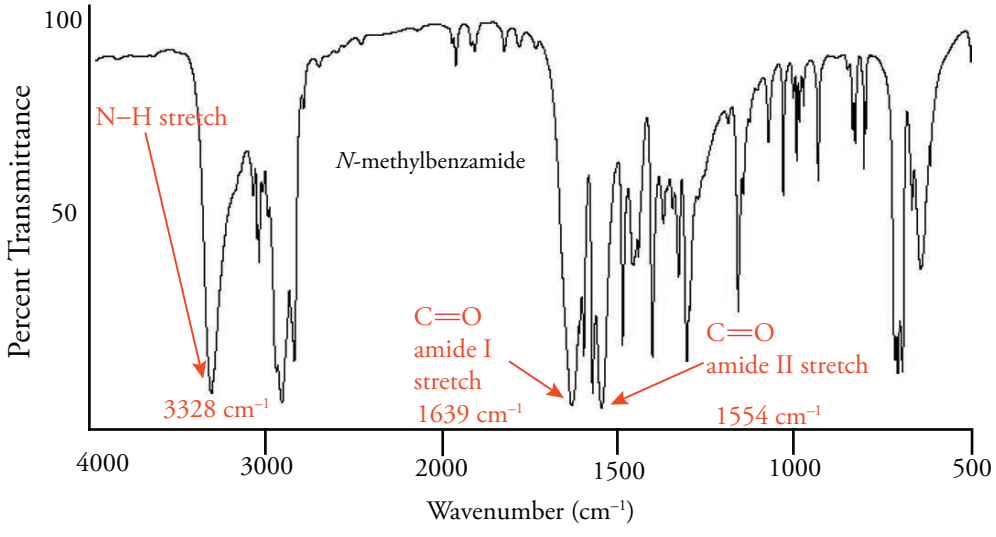


Figure 21.7
Infrared Spectrum of *N*-Methylbenzamide

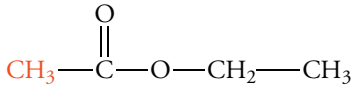


21.11 NMR SPECTROSCOPY OF ACYL DERIVATIVES

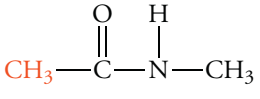
Proton NMR Spectroscopy

The α hydrogen atoms of all acid derivatives are somewhat deshielded by the carbonyl group, and the proton resonance occurs in the 2 δ region, as illustrated by the following simple structures. Substitution of alkyl groups on the α carbon causes a further down field shift.

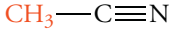
The chemical shift of hydrogen atoms on the alkyl carbon atom bonded directly to oxygen in esters is at about 0.6 ppm to lower field than the corresponding hydrogen atom of alcohols and ethers. This deshielding is the result of partial positive charge on the oxygen atom of esters that is a consequence of inductive electron withdrawal by the carbonyl carbon atom and donation of electrons of oxygen by resonance. Figure 21.8 shows the proton NMR of ethyl acetate.



δ ~ 2.0 ppm



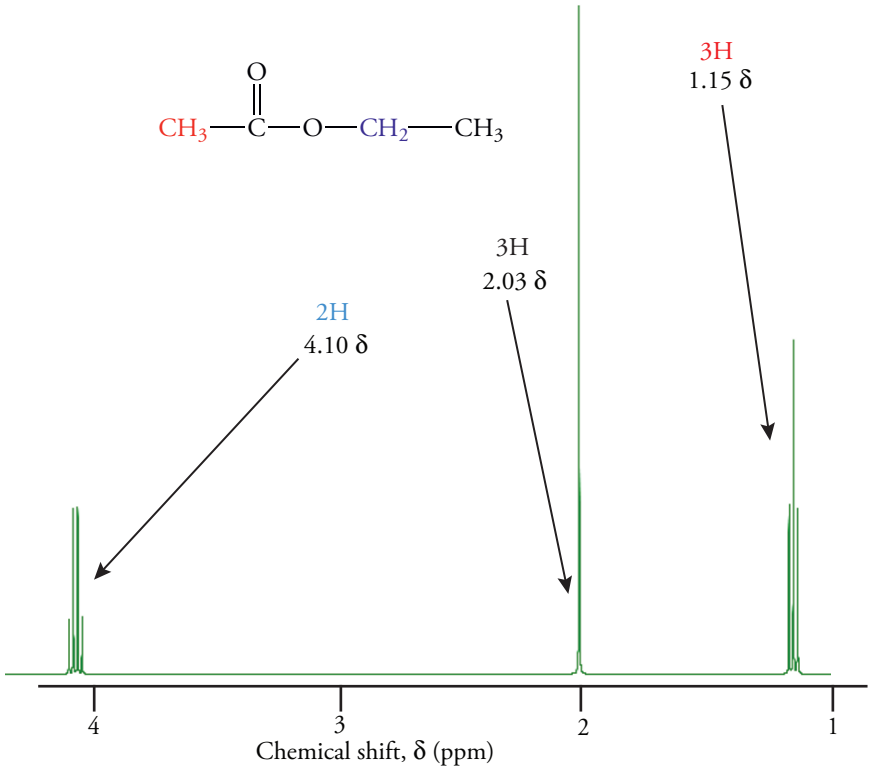
δ ~ 2.0 ppm



δ ~ 2.0 ppm

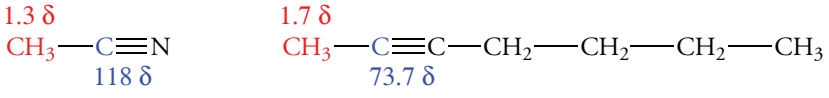
The chemical shift of hydrogen atoms on the alkyl carbon atom bonded directly to nitrogen in amides is in the 2.6–3.0 δ region. The proton(s) bonded to nitrogen are in the 7.5–8.5 δ region. Like the resonances of hydrogen atoms bonded to oxygen, the resonances of N—H groups are not split because they exchange protons with one another. As in alcohols, these N—H atoms can be exchanged by deuterium using D_2O.

Figure 21.8
Proton NMR Spectrum of
Ethyl Acetate

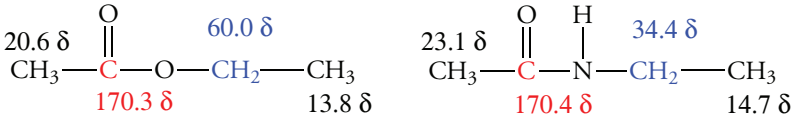


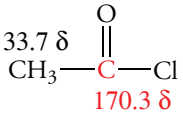
Carbon-13 NMR Spectroscopy

The chemical shift of the carbon atom bonded to nitrogen in nitriles occurs in the 115–120 δ range. These values illustrate that the carbon atom is more deshielded than the triple-bonded carbon atom of acetylenes, a direct consequence of the electronegativity of the nitrogen atom. The chemical shift of the carbon atom bonded to the nitrile carbon atom is at high field, as is also the case for the carbon atom bonded to the acetylenic carbon atom of alkynes. The reason for this phenomenon, which is related to an effect of the π elections of a triple bond, is a specialized topic that we will not consider further.



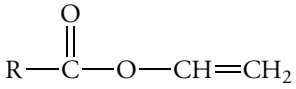
The resonance of the carbonyl carbon atom of acid derivatives, like that of carboxylic acids, occurs in the 165–180 δ region. The resonances of the α carbon atom of all acid derivatives are in the 20 δ region and at lower field with increased substitution of alkyl groups. The carbon atom bonded to oxygen of esters and the carbon atom bonded to nitrogen of amides are deshielded, compared to other saturated carbon atoms, as a result of the inductive effect of the electronegative oxygen and nitrogen atoms.





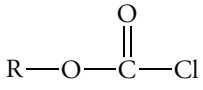
Problem 21.23

Although esters of unsaturated acids have carbonyl stretching absorptions at 1720 cm^{-1}, a lower value than the esters of saturated acids, the carbonyl stretching absorption of unsaturated esters of the following type is at 1760 cm^{-1}. Explain why.



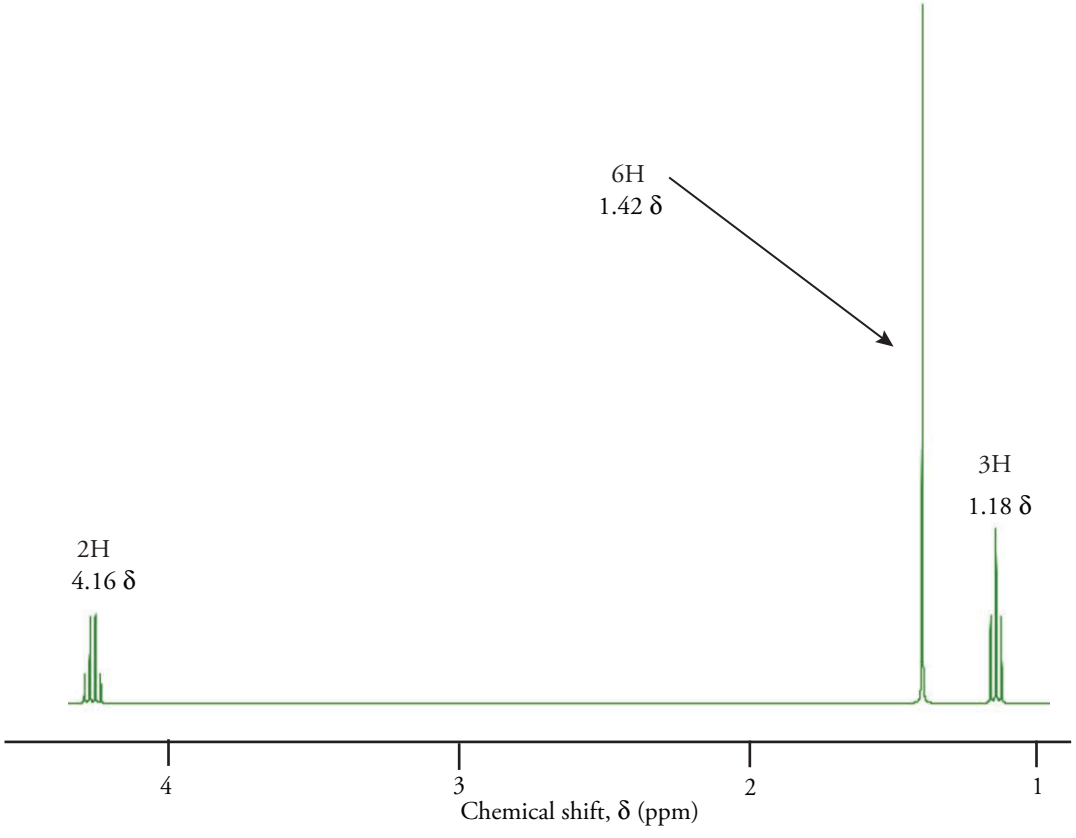
Problem 21.24

Explain why chlorocarbonates have carbonyl stretching absorptions at 1780 cm^{-1}, a lower wavenumber value than shown by acyl chlorides.



Problem 21.25

Deduce the structure of a compound with molecular formula $C_6H_{11}BrO_2$ with a carbonyl stretching absorption at 1730 cm^{-1} and having the following hydrogen NMR spectrum.



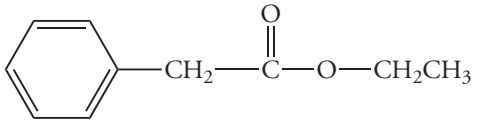
Problem 21.26

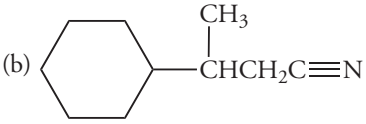
Deduce the structure of a compound with molecular formula $C_4H_6O_2$ that has a carbonyl stretching absorption, and whose carbon-13 NMR spectrum has resonances at 178.1, 22.3, 27.8, and 68.8 ppm.

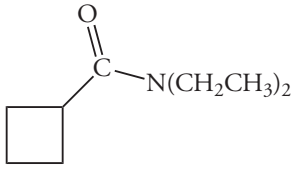
EXERCISES

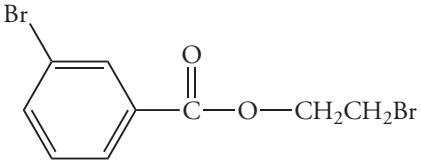
Nomenclature

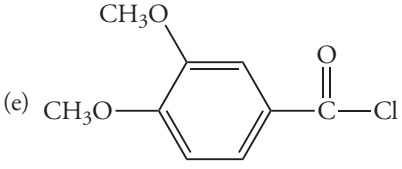
21.1 Give the IUPAC name for each of the following carboxylic acid derivatives.

(a) 

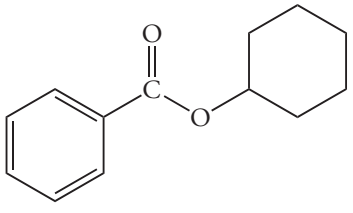
(b) 

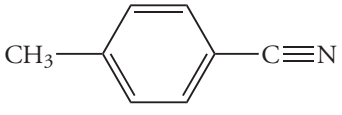
(c) 

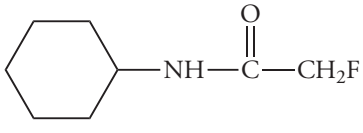
(d) 

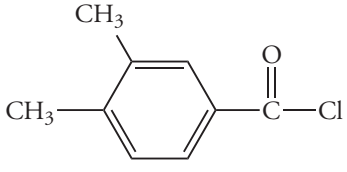
(e) 

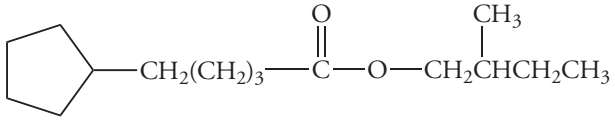
21.2 Give the IUPAC name for each of the following carboxylic acid derivatives.

(a) 

(b) 

(c) 

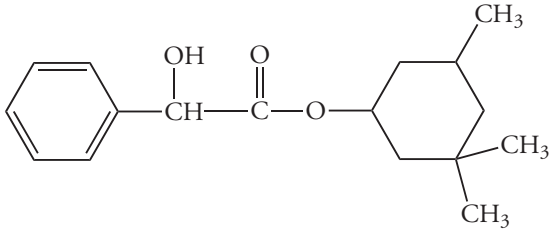
(d) 

(e) 

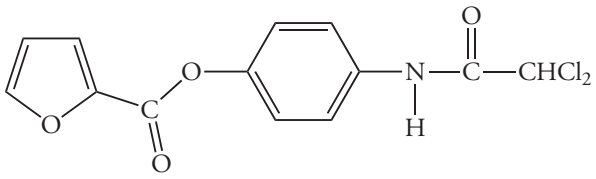
21.3 Write the structure of each of the following compounds.
(a) phenyl octanoate (b) butanoic anhydride (c) *N*-ethyl-4,4-dimethylcyclohexanecarboxamide
(d) 2-bromo-3-methylbutanoyl chloride (e) *trans*-4-methylcyclohexanecarbonitrile

21.4 Write the structure of each of the following compounds.
(a) 2-chloropropyl 3-bromobutanoate (b) 4-methoxyphthalic anhydride (c) *N*,*N*-dimethyl-3-cyclopropylpentanamide
(d) cyclobutanecarbonyl bromide (e) (*R*)-2-methylbutanenitrile

21.5 The common name of the vasodilator cyclandelate is 3,5,5-trimethylcyclohexyl mandelate. Give the structure and name of the acid contained in the ester.



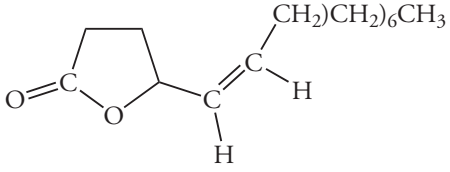
21.6 Hydrolysis in the body is required for diloxanide furanoate to be effective against intestinal amebiasis. What is the acid component of the drug? Considering the name of the drug, name the acid.



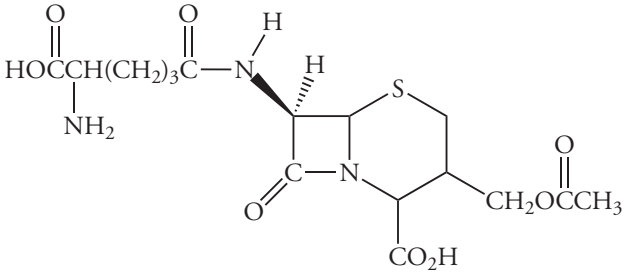
diloxanide furanoate

Cyclic Acyl Derivatives

21.7 (a) Identify the oxygen-containing functional group in the following structure of a sex pheromone of the female Japanese beetle. (b) What is the configuration around the carbon–carbon double bond?

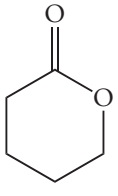


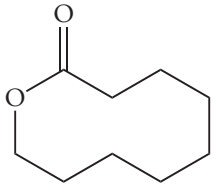
21.8 Identify the nitrogen-containing functional group within the four-membered ring of cephalosporin C, antibiotic.

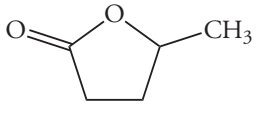


cephalosporin C

21.9 Name each of the following lactones.

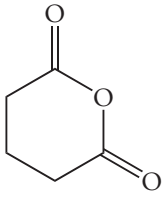
(a) 

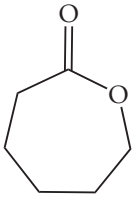
(b) 

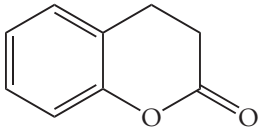
(c) 

21.10 Draw the structure of each of the following lactams.
(a) 3-aminopropanoic acid lactam (b) 4-aminopentanoic acid lactam (c) 5-aminopentanoic acid lactam

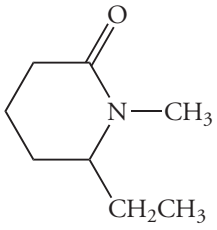
21.11 Which of the following compounds are lactones?

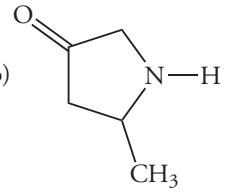
(a) 

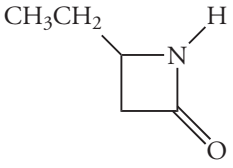
(b) 

(c) 

21.12 Which of the following compounds are lactams?

(a) 

(b) 

(c) 

Properties of Acid Derivatives

21.13 The boiling points of methyl pentanoate and butyl ethanoate are 126 and 125 °C, respectively. Explain the similarity of these boiling points.

21.14 The boiling points of methyl pentanoate and methyl 2,2-dimethylpropanoate are 126 and 102 °C, respectively. Explain why these values differ.

21.15 The boiling points of acetonitrile and 1-propyne are 81.5 and –23 °C, respectively. Account for this difference in boiling point between two compounds with similar molecular weights.

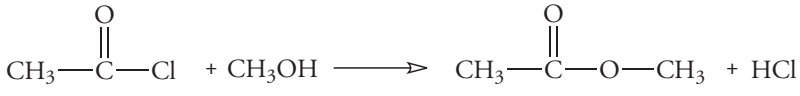
21.16 The boiling points of acetamide and acetic acid are 221 and 118 °C, respectively. Account for this difference in boiling point between two compounds with similar molecular weights.

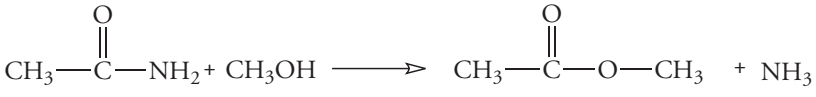
21.17 Explain why protonation of *N*,*N*-dimethylformamide occurs at the oxygen atom rather than the nitrogen atom.

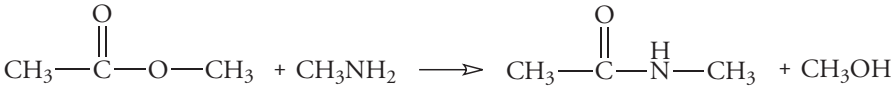
21.18 The rotational barrier around the nitrogen-carbonyl carbon bond of *N*,*N*-dimethylformamide is approximately 87 kJ $mole^{-1}$. Why is this energy barrier substantially higher than values for other single bonds?

Nucleophilic Acyl Substitution

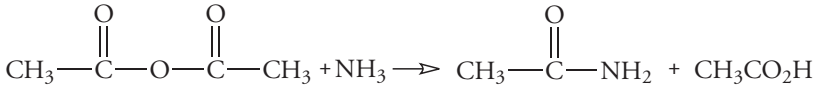
21.19 Indicate whether each of the following reactions will occur.

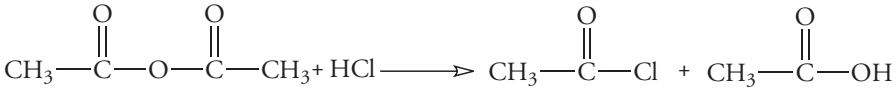
(a) 

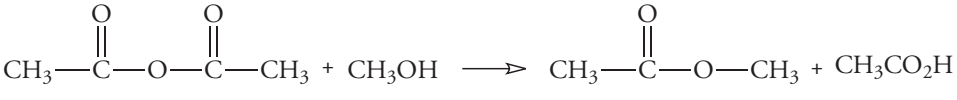
(b) 

(c) 

21.20 Indicate whether each of the following reactions will occur.

(a) 

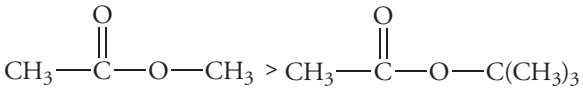
(b) 

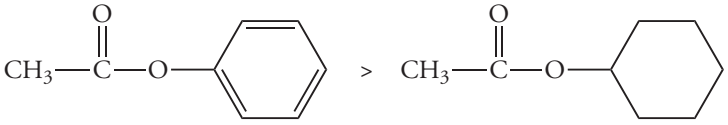
(c) 

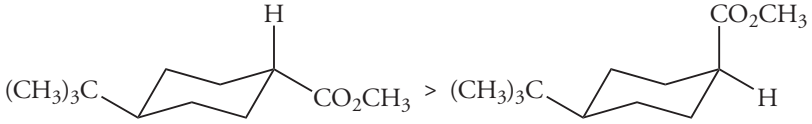
21.21 Considering the stability of the reactant, explain why thioesters react more readily than esters in acyl substitution reactions.

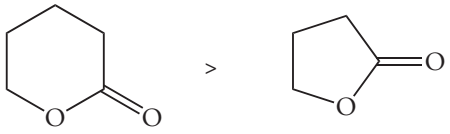
21.22 Considering the stability of the reactant, explain why thioesters are less reactive than acid chlorides in acyl substitution reactions.

21.23 Explain the order of reactivity in saponification reactions of each of the following pairs of compounds.

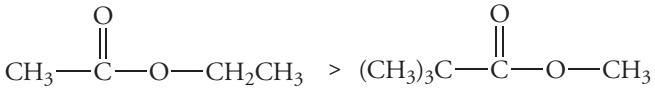
(a) 

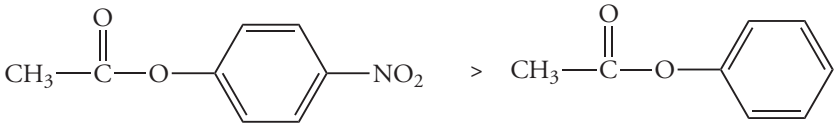
(b) 

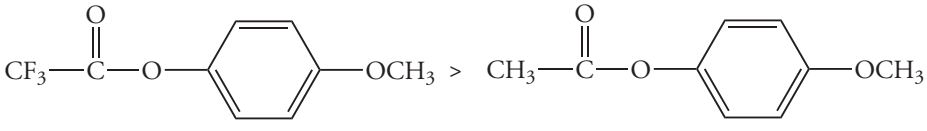
(c) 

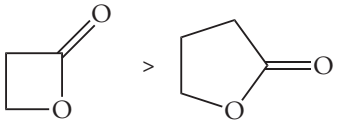
(d) 

21.24 Explain the order of reactivity in saponification reactions of each of the following pairs of compounds.

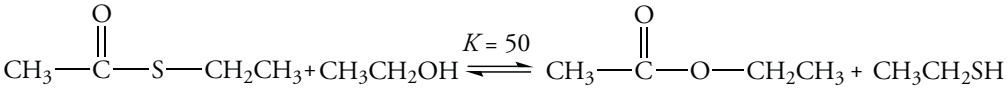
(a) 

(b) 

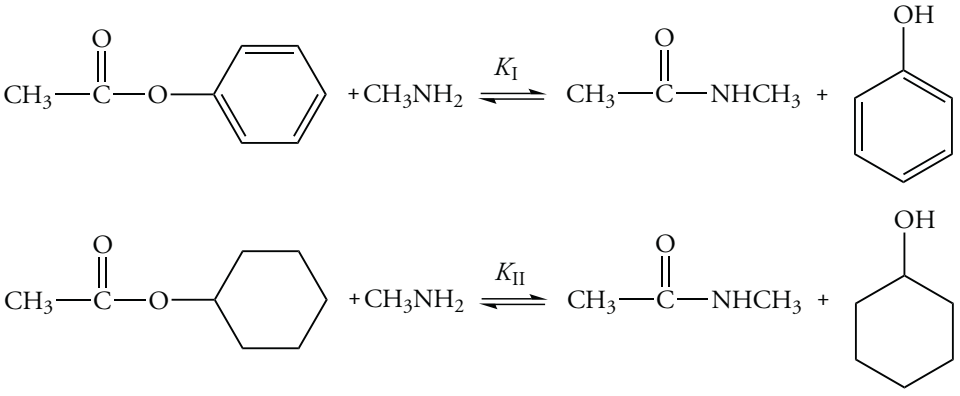
(c) 

(d) 

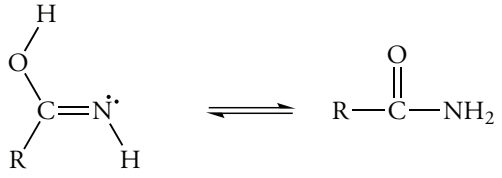
21.25 Explain the position of the following equilibrium. That is, why does it lie so far to the right?



21.26 Which equilibrium constant for the following reactions is larger, K_I or K_{II}?

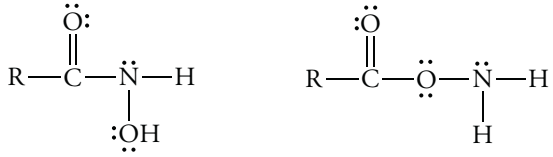


21.27 Explain why the tautomeric equilibrium between an imidic acid and an amide lies on the side of the amide.



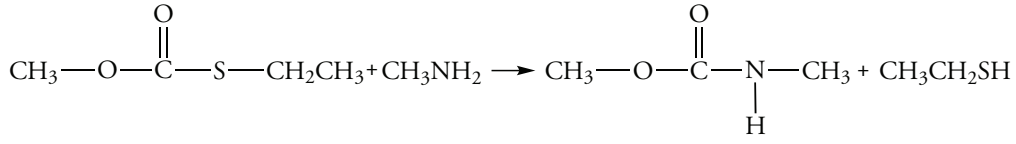
imidic acid amide

21.28 Explain why esters react with hydroxylamine (NH_2OH) to give hydroxamic acids rather than *O*-acyl hydroxyl amines.

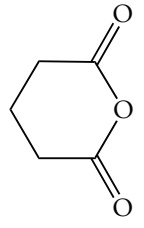


(an hydroxamic acid) (an *O*-acyl hydroxyl amine)

21.29 One equivalent of methylamine reacts with *S*-ethyl-*O*-methylthiocarbonate as shown by the following equation. What other product is possible? Explain the observed selectivity of the reaction.

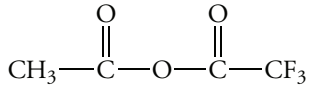


21.30 Methanol reacts with glutaric anhydride to give a good yield of a monomethyl ester. Explain why the diiester does not form.

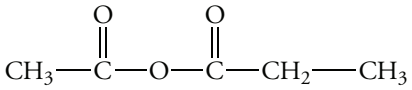


glutaric anhydride

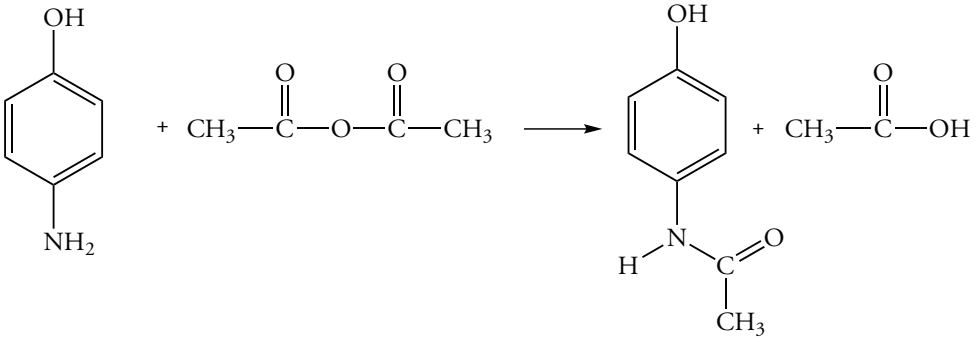
21.31 Explain why alcohols react with the following mixed anhydride to give good yield of acetate esters.



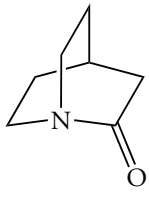
21.32 Ethanol reacts with the following mixed anhydride to give two esters in a 36:64 ratio. Which of the two possible esters forms in the larger amount?



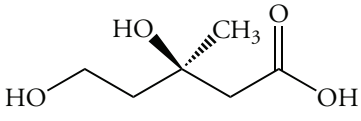
21.33 *p*-Hydroxyaniline reacts with acetic anhydride to give *N*-(4-hydroxyphenyl)acetamide. Explain why the reaction is selective and acetylation does not occur at oxygen.



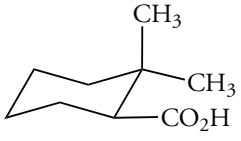
21.34 Explain why the following bicyclic lactam is hydrolyzed at a significantly faster rate than 5-aminopentanoic acid lactam.



21.35 Mevalonic acid readily forms a lactone when heated. Draw two possible structures for the lactone. Which of the two is formed?



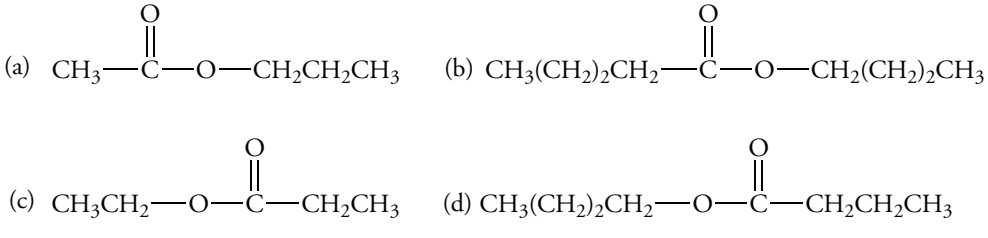
21.36 Explain why the rate of acid-catalyzed esterification of 2,2-dimethylcyclohexanecarboxylic acid is slower than that of cyclohexanecarboxylic acid.



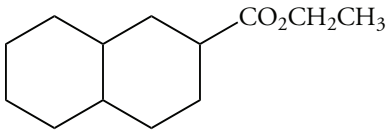
2,3-dimethylcyclohexanecarboxylic acid

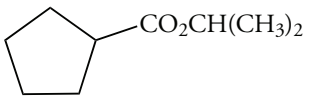
Reactions of Acyl Derivatives

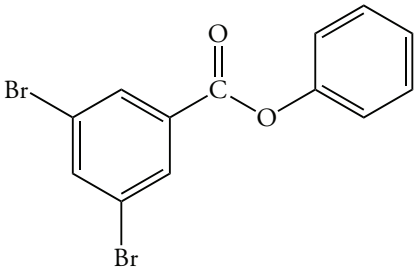
21.37 Draw the structures of the products of hydrolysis of each of the following esters.

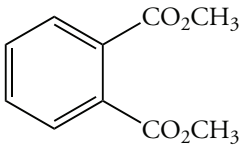


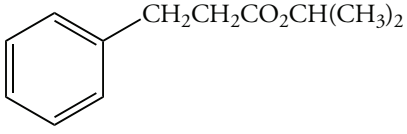
21.38 Draw the structures of the hydrolysis products of each of the following esters.

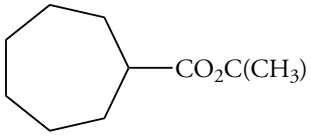
(a) 

(b) 

(c) 

(d) 

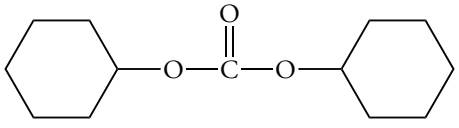
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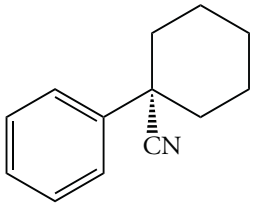
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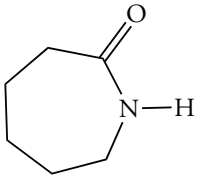
21.39 Hydrolysis of ambrettolide, contained in hibiscus, yields (*E*)-16-hydroxy-7-hexadecenoic acid. Draw the structure of ambrettolide.

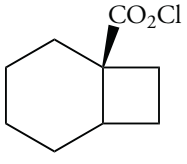
21.40 Hydrolysis of beeswax gives a mixture containing unbranched acids with 26 and 28 carbon atoms and unbranched alcohols with 30 and 32 carbons atoms. Draw the structures of all possible components of beeswax

21.41 Draw the structures of the hydrolysis products of each of the following compounds.

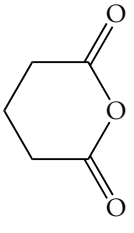
(a) 

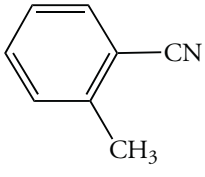
(b) 

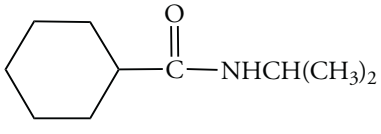
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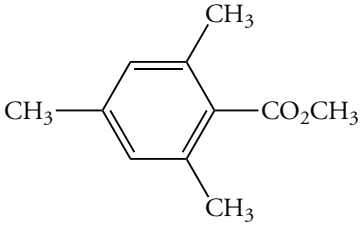
(d) 

21.42 Draw the structures of the acid-catalyzed hydrolysis products of each of the following compounds.

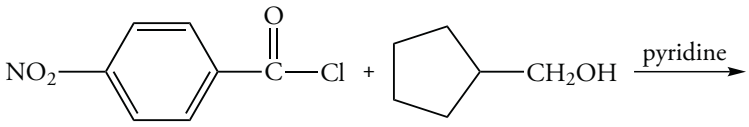
(a) 

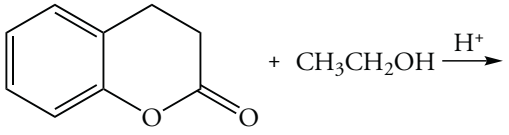
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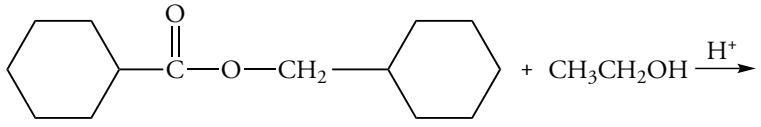
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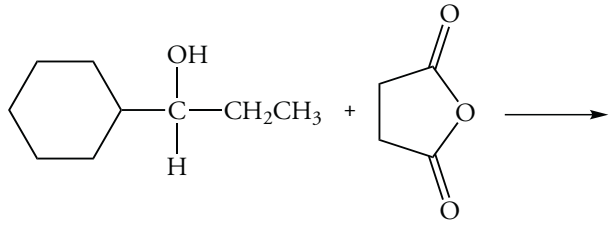
(d) 

21.43 Draw the structure of the product of each of the following reactions.

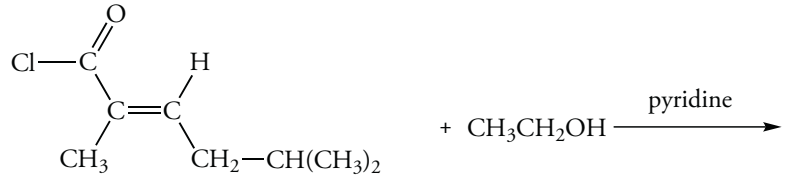
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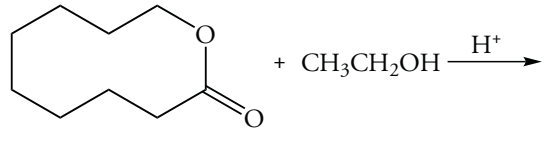
(b) 

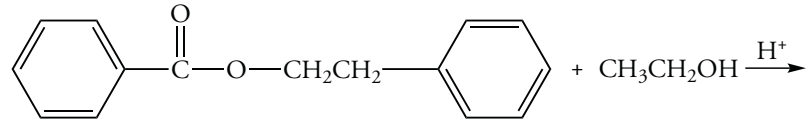
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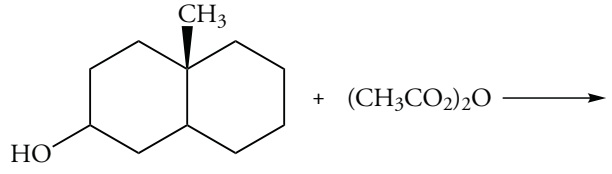
(d) 

21.44 Draw the structure of the product of each of the following reactions.

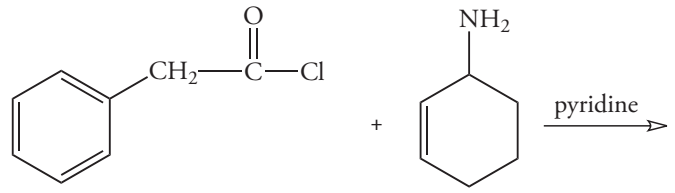
(a) 

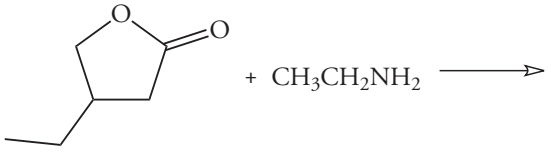
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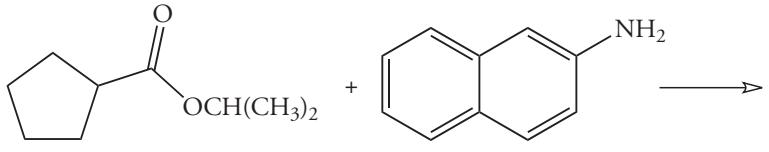
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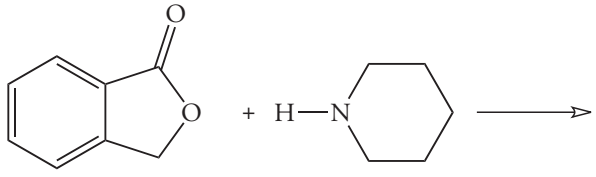
(d) 

21.45 Draw the structure of the product of each of the following reactions.

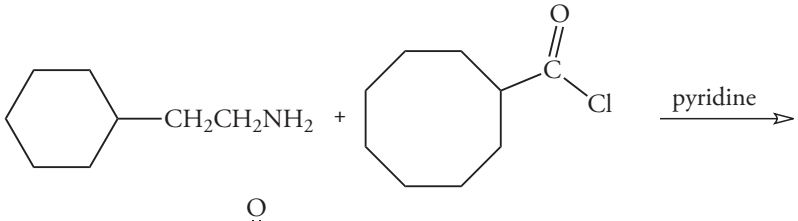
(a) 

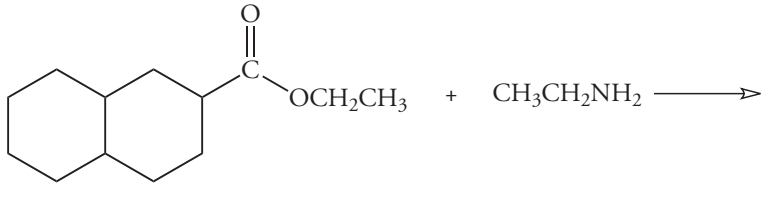
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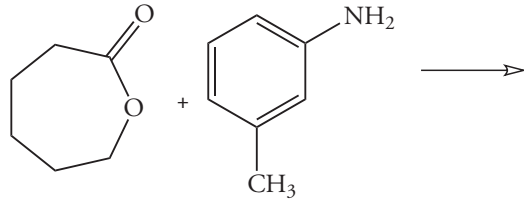
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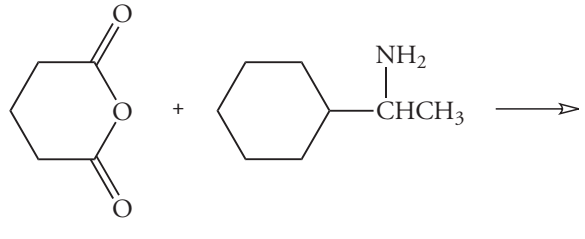
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21.46 Draw the structure of the product of each of the following reactions.

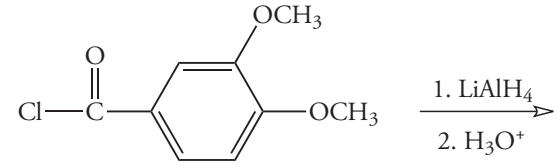
(a) 

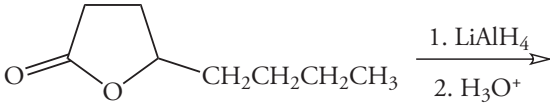
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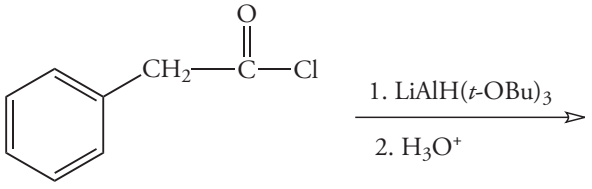
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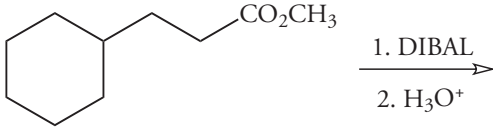
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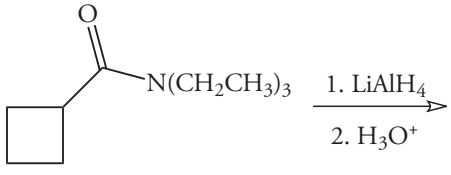
21.47 Draw the structures of the products of each of the following reactions.

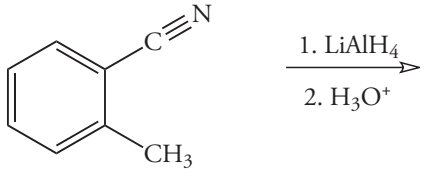
(a) 

(b) 

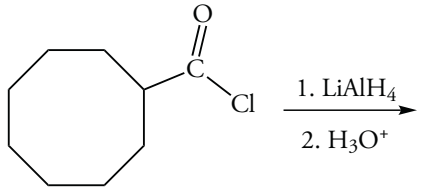
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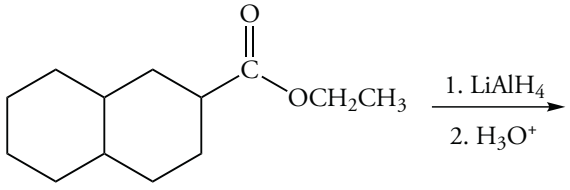
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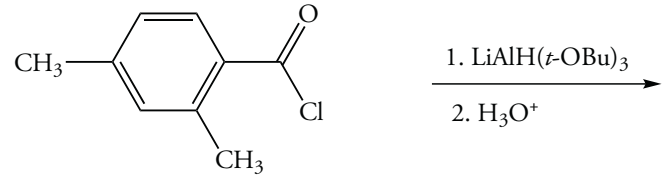
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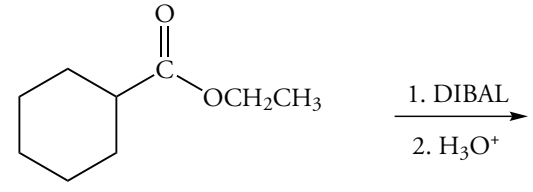
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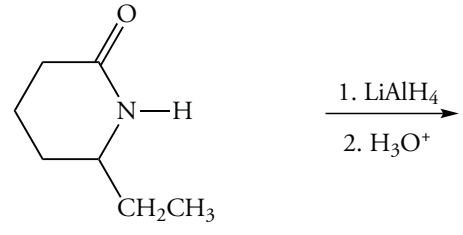
21.48 Draw the structure of the product of each of the following reactions.

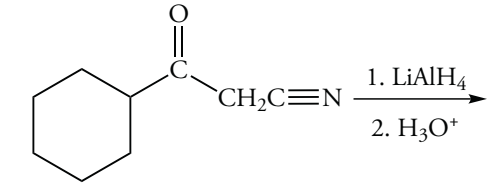
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

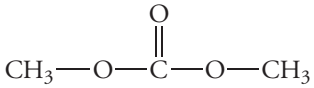
21.49 A compound obtained from the wax of the sperm whale has the molecular formula $C_{32}H_{64}O_2$. Reduction by $LiAlH_4$ gives 1-hexadecanol. Draw the structure of the compound.

21.50 A compound obtained from hibiscus has the molecular formula $C_{16}H_{28}O_2$. Reduction by $LiAlH_4$ gives (*E*)-7-hexadecen-1,16-diol. Draw the structures of two possible compounds that could yield this diol.

Reactions with Organometallic Compounds

21.51 What ester is required to produce alcohols of the general structure R_2CHOH using a Grignard reagent.

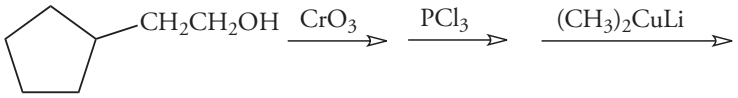
21.52 Dimethyl carbonate reacts with Grignard reagents to give tertiary alcohols with the general structure R_2CHOH. Write the structures of the intermediates formed after the addition of 1 and 2 moles of the Grignard reagent

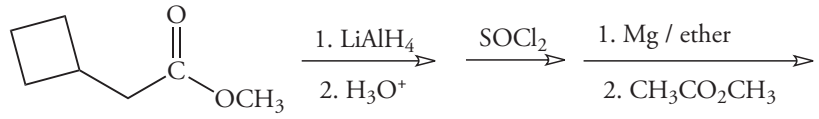


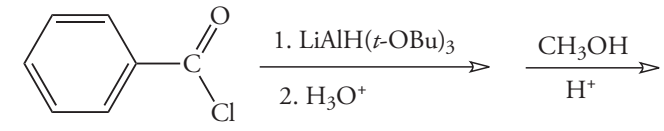
dimethyl carbonate

Multistep Synthesis

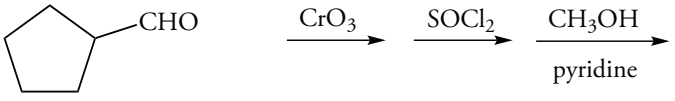
21.55 Draw the structure of the final product of each of the following reaction sequences.

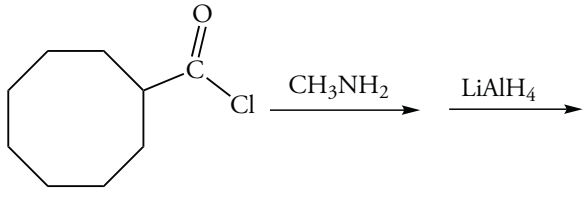
(a) 

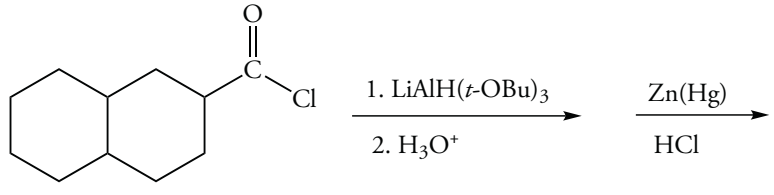
(b) 

(c) 

21.56 Draw the structure of the final product of each of the following reaction sequences.

(a) 

(b) 

(c) 

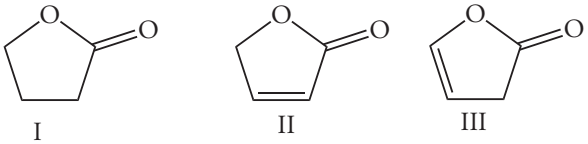
Spectroscopy of Acid Derivatives

21.57 Would you expect the carbonyl stretching absorption of acyl bromides to occur at higher or lower wavenumber than the carbonyl stretching absorption of acyl chlorides?

21.58 Explain why the carbonyl stretching absorption of thioesters occurs at 1690 cm^{-1}, whereas that of acyl chlorides occurs at 1800 cm^{-1}.

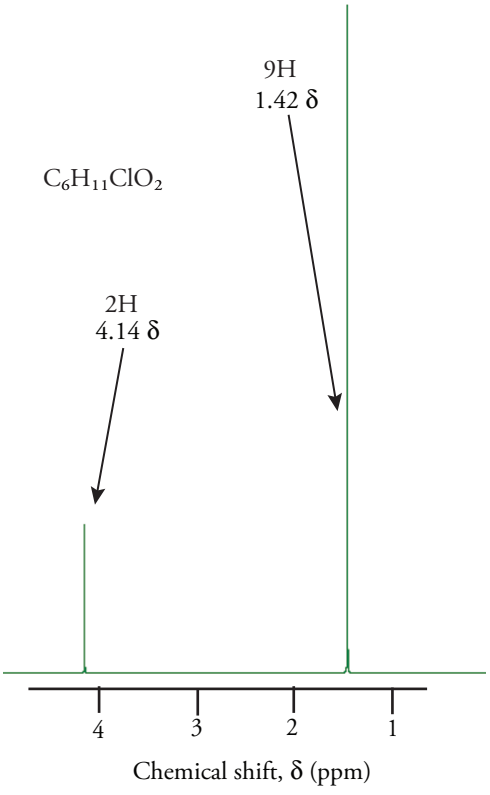
21.59 A compound with molecular formula C_4H_5N has a strong absorption at 2250 cm^{-1}. Suggest two possible structures and explain how they could be distinguished by other infrared absorptions.

21.60 A compound with molecular formula C_4H_5N has a strong absorption at 2250 cm^{-1}. Suggest two possible structures and explain how they could be distinguished by other infrared absorptions.

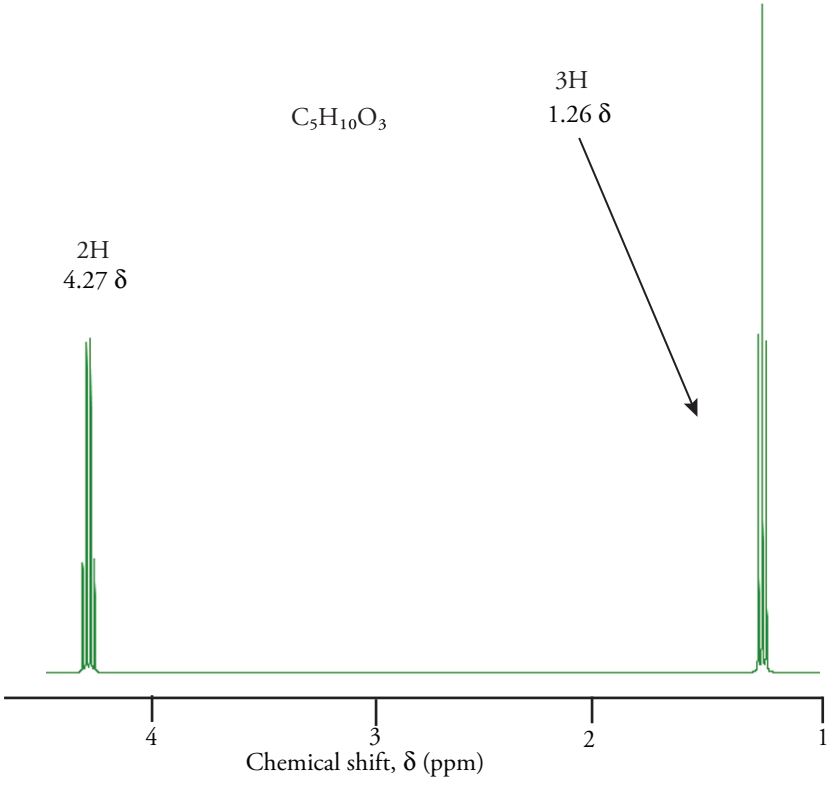


I II III

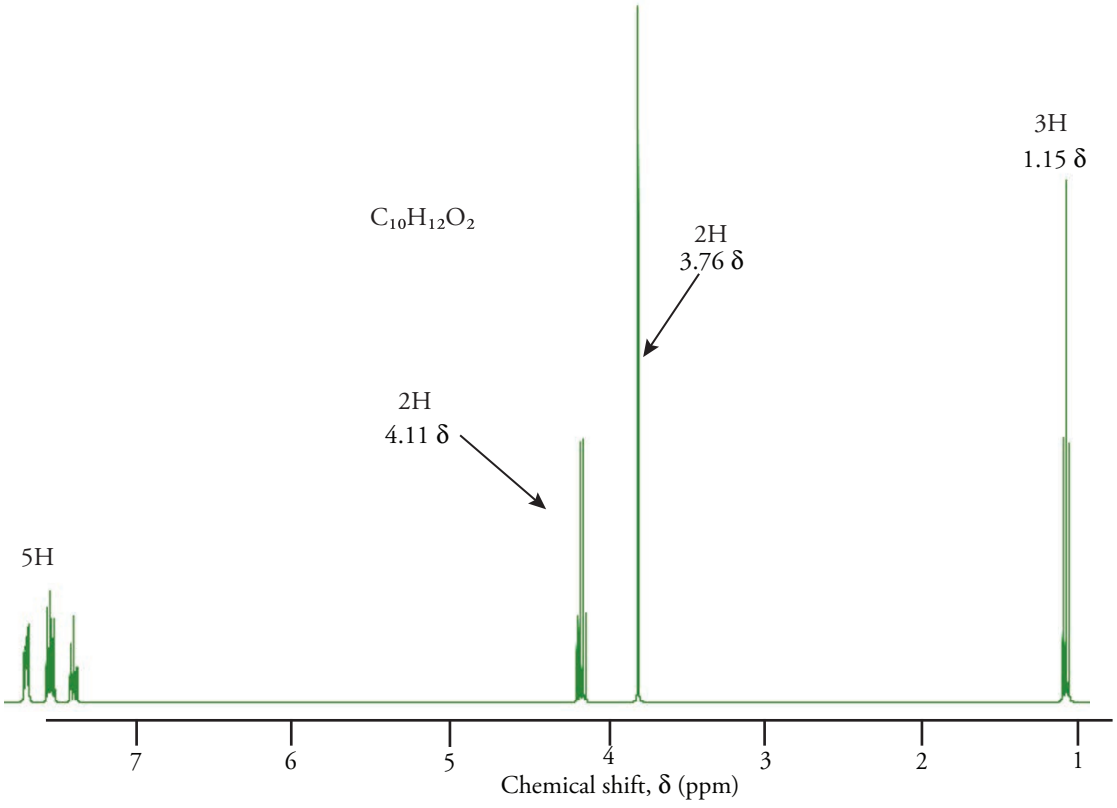
21.61 Deduce the structure of the following compound based on the molecular formula and the following proton NMR spectrum.



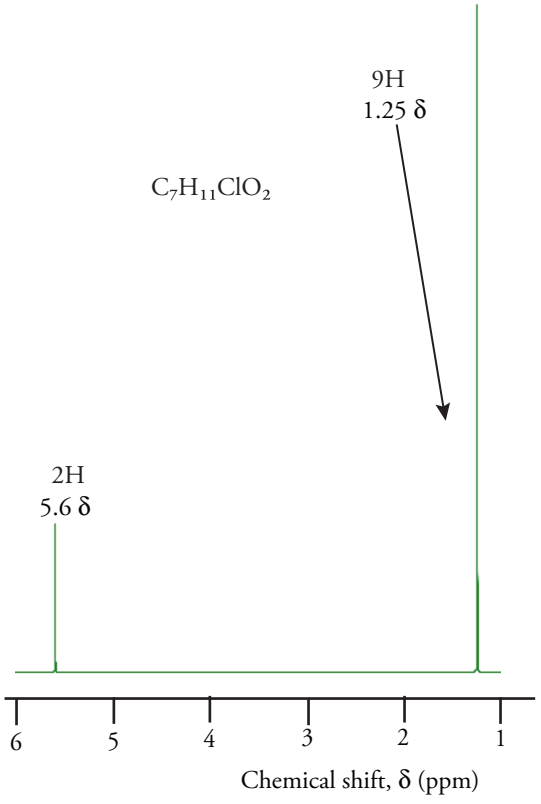
21.62 Deduce the structure of the following compound based on the molecular formula, $C_5H_{10}O_3$, and the following proton NMR spectrum.



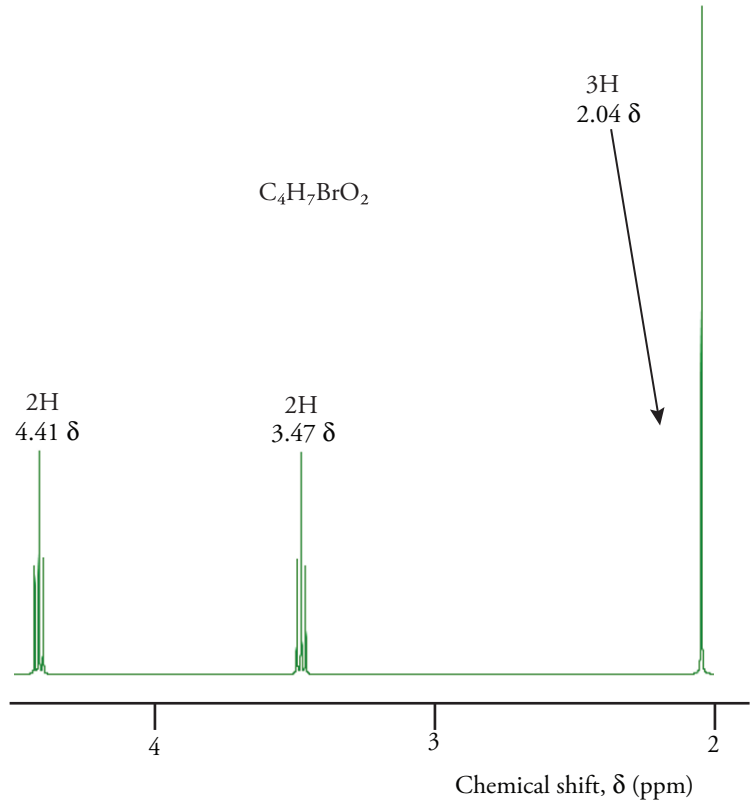
21.63 Deduce the structure of the following compound based on the molecular formula and the following proton NMR spectrum.



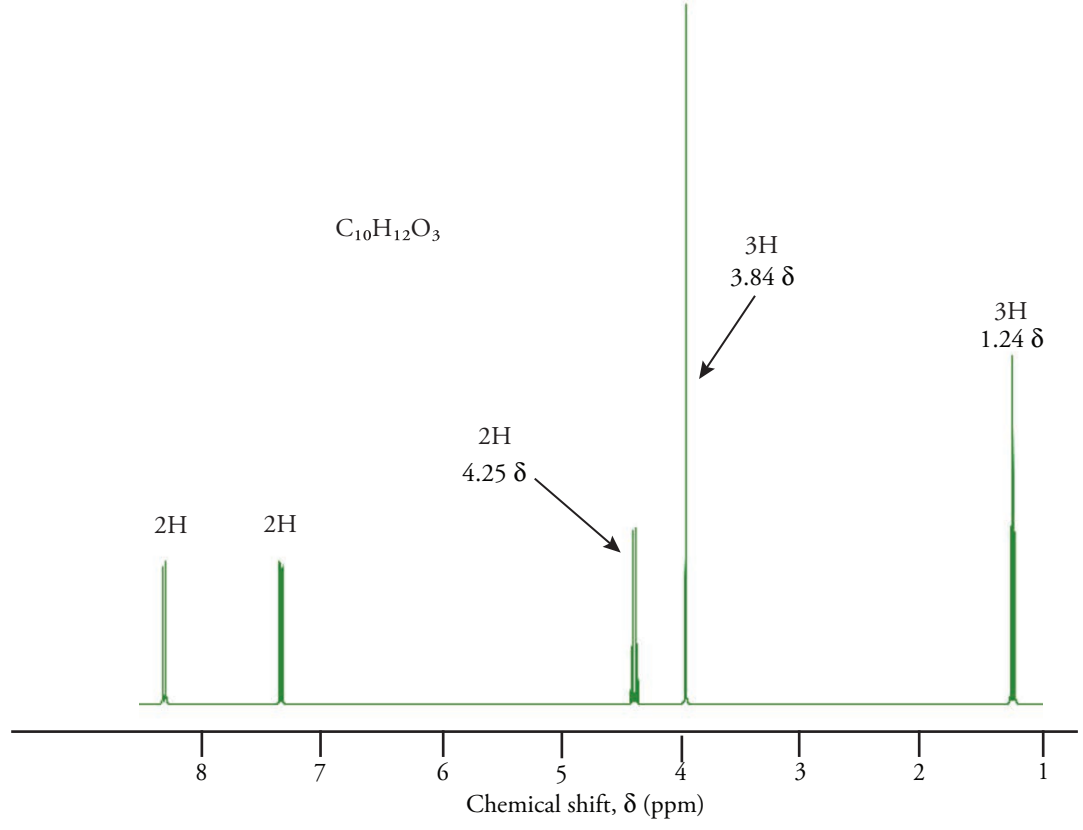
21.64 Deduce the structure of the following compound based on the molecular formula and the following proton NMR spectrum.



21.65 Deduce the structure of the following compound based on the molecular formula and the following proton NMR spectrum.



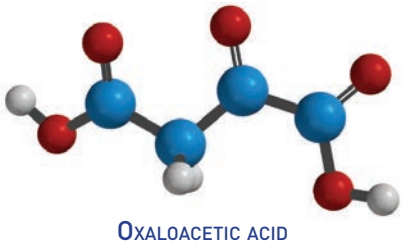
21.66 Deduce the structure of the following compound based on the molecular formula and the following proton NMR spectrum.



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22

Condensation Reactions of Carbonyl Compounds

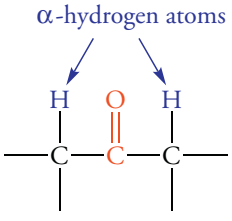


Oxaloacetic acid

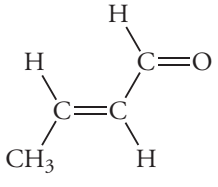
The synthesis of complex molecules is one of the goals of organic chemistry. The synthesis of a complex molecule often is carried out by constructing large molecules from smaller precursors. The reactions of functional groups that we have discussed in preceding chapters play an important part in this process, but the critical component of an organic synthesis is often the formation of new carbon–carbon bonds. Carbon–carbon bonds can be made in many different ways, as we saw in Chapter 17 when we discussed organometallic chemistry. In this chapter, we first consider condensation reactions of aldehydes and ketones; then we examine condensations of reactions of esters as methods for making carbon–carbon bonds. Hydrogen atoms bonded to the α-carbons of these compounds, which give rise to enols and enolate anions, play a critical role in these reactions.

22.1 THE α-CARBON ATOM OF ALDEHYDES AND KETONES

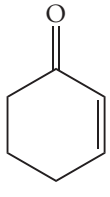
In Chapters 18 and 19, we considered the reactions of carbonyl compounds, where we focused upon the carbonyl carbon itself. Now we will discuss the chemistry of the α-carbon atom, a reactive site of carbonyl compounds. The hydrogen atom bonded to the α-carbon, called the α-hydrogen, is slightly acidic. Removing this hydrogen gives a nucleophilic α-carbon atom.



We also consider unsaturated carbonyl compounds in which a carbon–carbon double bond is conjugated to the carbonyl bond. These are α,β-unsaturated aldehydes and ketones. They react in ways that we can partly anticipate from our discussion of conjugated alkenes in Chapter 11.



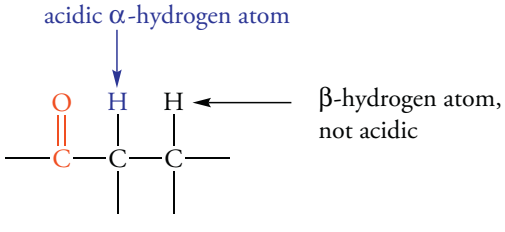
α,β-unsaturated aldehyde



α,β-unsaturated ketone

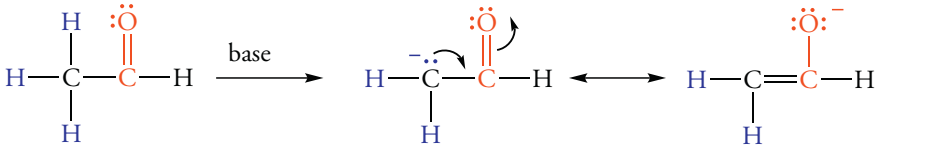
Acidity of α-Hydrogens

We know that the carbonyl bond is polar, that it has a partial positive charge. This partial positive charge decreases the electron density in adjacent bonds by an inductive effect. This inductive effect is transmitted to the α-hydrogen atoms. As a result, the α-hydrogens are more acidic than hydrogen atoms further away from the carbonyl carbon.



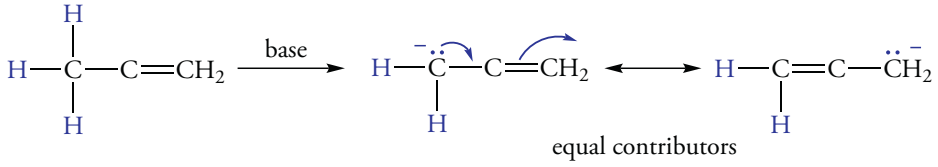
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00022-X
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The pK_a values of the α-hydrogens of acetaldehyde and acetone are 19.7 and 19, respectively. Thus, the α-hydrogen is 10^{30} times more acidic than the C—H bond of alkanes, whose pK_a values are approximately 50. This tremendous difference in acidity reflects more than the inductive effect of the carbonyl group. When an α-hydrogen is removed from a carbonyl compound in an acid–base reaction, the product is a resonance-stabilized **enolate anion**. One resonance form has a negative charge on the oxygen atom, and the other has a negative charge on the α-carbon atom. Since the charge of the enolate anion is delocalized, an enolate anion is more stable than a carbanion such as $CH_3CH_2^-$, in which no resonance stabilization is possible.



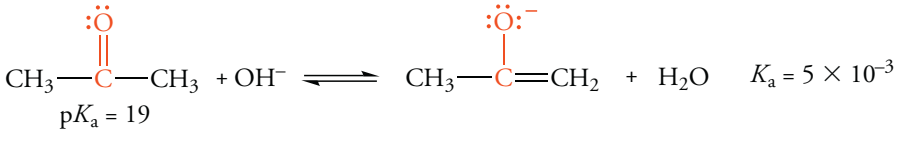
resonance structures of the enolate anion of acetaldehyde

The major resonance form of the enolate ion has a negative charge on the more electronegative oxygen atom. This form contributes strongly to the stability of enolate anion, which is the conjugate base of the carbonyl compound. We can appreciate the significance of this stabilization by comparing the acidity of acetaldehyde to that of propene. The allylic hydrogen atom of propene has a pK_a of 42, about 10^8 times more acidic than an alkane. Resonance stabilization of the allyl anion accounts for the greater acidity, but neither allyl anion resonance form tolerates a negative charge as well as the oxygen atom of the enolate ion.

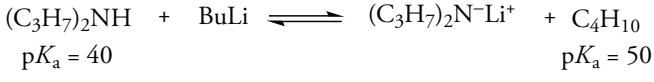


Formation of Enolates

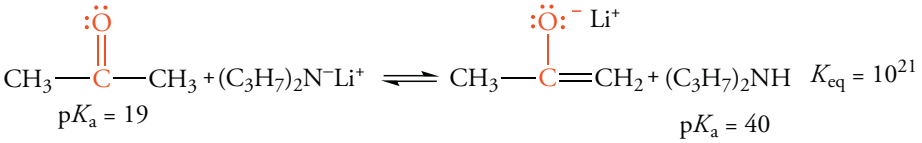
What is the strength of the base required to produce an enolate anion from a carbonyl compound? The strongest base that can exist in aqueous solution is the hydroxide ion. Because the pK_a of water is 15.7 and the pK_a of acetone is 19, the amount of the enolate anion of acetone that can form in a 1 M NaOH solution is very small. Although the concentration of enolate is low, it may be sufficient for some reactions. As the enolate reacts, more enolate forms, maintaining the equilibrium.



If acetone is treated with the conjugate base of a much weaker acid than acetone, the enolate forms in high concentrations. Lithium diisopropylamide, $(i\text{-}C_3H_7)_2N^-Li^+$, commonly abbreviated LDA, is such a base. It is prepared from diisopropylamine and butyllithium in ether as a solvent.



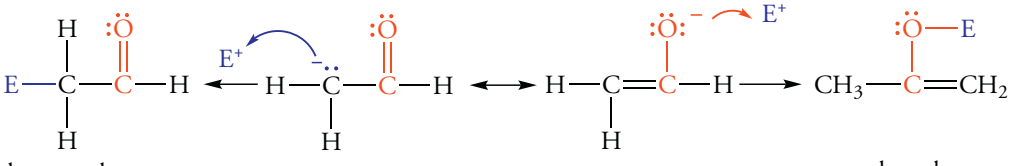
The enolate is produced in a stoichiometric amount when LDA is used as the base because diisopropylamine is a much weaker base than acetone.



Therefore, enolates may be prepared in ether solution and used in subsequent reactions. The only limitation is that the solutions must be protected from moisture or other weak acids that instantly react with the enolate anion converting it to the aldehyde or ketone from which it was derived.

Reactions of Enolates

The charge in enolates is distributed between two sites—a condition called *ambidentate* ("two fanged" Latin *ambi*, both + *dens*, tooth)—and the enolate can react with an electrophile at either site. We recall that the resonance forms used to depict charge distribution do not exist as independent nucleophilic entities. However, we may use these forms to show how different products result by reaction at each site. An electrophile can react with the nucleophilic enolate to give two possible isomeric compounds, a keto product and an enol product.



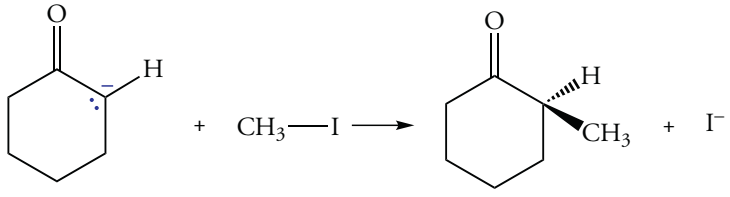
The products of enolate reactions are stable enough to isolate in some cases. Many factors determine the relative amounts of these isomers. We might be tempted to predict that the enol product would form readily because of the greater electron density on the oxygen atom of the enolate compared to the α-carbon atom. The enol forms when the electrophile is a proton, but the enol product spontaneously rearranges to the isomeric keto form. For most other electrophiles, the keto product forms directly. This preference for the keto product over the enol product reflects the relative energies of the respective transition states leading to each product. The transition state energies reflect the stabilities of the products formed. Therefore, let's consider the bonds that start to form in the transition state. For the enol isomer, formation of a single bond between oxygen and the electrophile is accompanied by formation of a carbon–carbon double bond. For the keto isomer, formation of a single bond between carbon and the electrophile is accompanied by formation of a carbon–oxygen double bond. The difference in the bond energies of C—H and O—H is much less than the difference in the bond energies of C=C and C=O bonds. We recall that the carbon–oxygen double bond is considerably stronger than a carbon–carbon double bond (Section 18.1). *The keto isomer forms in preference to the enol isomer mostly because of the greater stability of the carbonyl group.*

Problem 22. 1

(a) Draw the product expected for the reaction of the enolate of cyclohexanone with iodomethane. (b) How might the reaction of 2-iodopropane with the same nucleophile differ from the first reaction?

Sample Solution

(a)The α-carbon atoms of cyclohexanone are equivalent, and only one enolate can form. The enolate acts as a nucleophile and displaces iodide ion from iodomethane, giving 2-methyl-cyclohexanone.



2-methylcyclohexanone

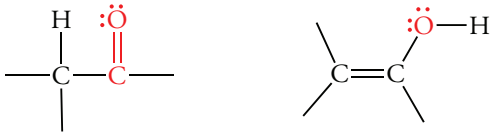
(b) 2-Iodopropane is a secondary alkyl halide, and strong bases tend to give dehydrohalogenation products rather than substitution products. Propene and cyclohexanone would be the major products of the reaction.

Problem 22. 2

Chlorotrimethylsilane, $(CH_3)_3SiCl$, reacts with enolates to give the enol product with silicon bonded to oxygen. (a) Draw the product of the reaction with the enolate of cyclohexanone. (b) Explain why this product forms rather than the keto product.

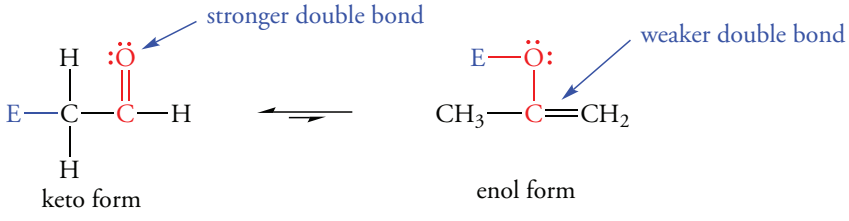
22.2 KETO–ENOL EQUILIBRIA OF ALDEHYDES AND KETONES

If the electrophile that reacts with an enolate is a proton, the products are called the keto and enol forms for both aldehydes and ketones. These species are isomers, not resonance forms.



keto form enol form

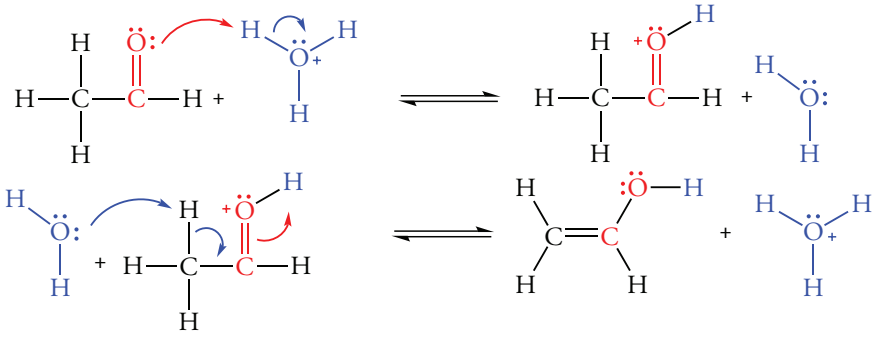
It is not necessary to protonate an enolate to obtain these two isomers. They exist in equilibrium with each other by a proton transfer reaction known as **keto–enol tautomerism**. Tautomerization describes the interconversion of two isomeric structures that differ in the location of a hydrogen atom. Tautomerization requires a change in the kinds of bonds between at least two other sets of atoms in the structures. We encountered this phenomenon in the isomerization reaction of the enol formed in the hydration of an alkyne (Chapter 7). We know that the keto form is more stable than the enol form. As we saw in the last section, this order of stabilities results primarily from the difference between the bond strengths of a carbon–oxygen double bond and a carbon–carbon double bond.



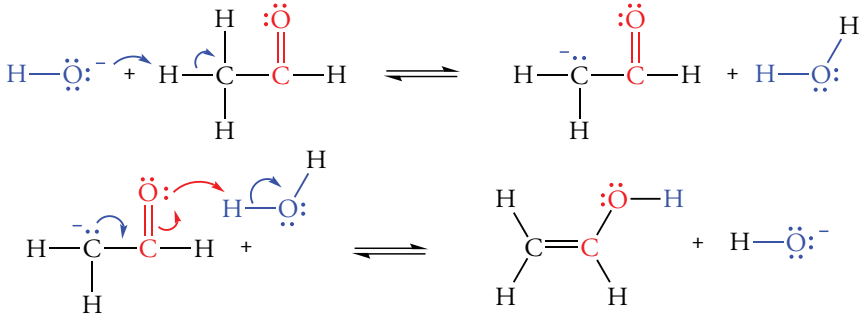
Mechanism of Tautomerization

Tautomerization does not occur by the intramolecular transfer of a proton between carbon and oxygen atoms. Rather, a series of proton transfer steps between each tautomer, and the solvent occurs. The solvent acts as a mediator, accepting a proton from one form and giving it to the other form. Either acid or base can catalyze proton transfer. Hence, tautomerization occurs by two different mechanisms.

In the first step of acid-catalyzed tautomerization of the keto form, hydronium ion protonates the carbonyl oxygen atom. Then, water removes the α-hydrogen atom to give the enol. Each of the reactions is reversible, so the acid-catalyzed conversion of the enol into the keto form occurs by the reverse of each step of the mechanism.

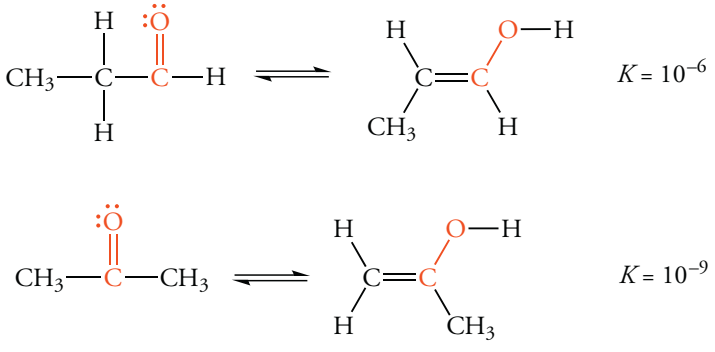


In the first step of base-catalyzed tautomerization of the keto form, hydroxide ion removes the α-hydrogen atom to give the enolate anion. Then, water reacts with the enolate anion to give the enol. To simplify the bond line structures for the reaction, the step that forms the enolate shows one resonance form and the second step shows the alternate resonance form. Each of the reactions is reversible, so the base-catalyzed conversion of the enol into the keto form occurs by the reverse of each step of the mechanism.



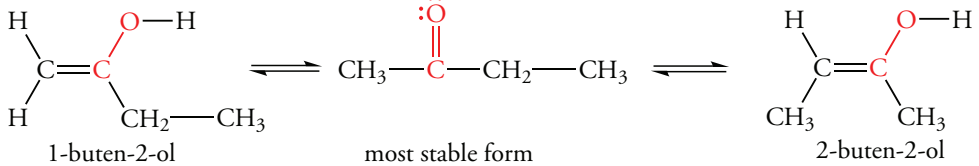
Stability of Enols

The amount of enol in equilibrium with the carbonyl compound depends on structural factors that affect the stability of both the carbonyl compound and the enol. For example, aldehydes tend to have much higher concentrations of enols than ketones.



The stability of the carbonyl compound explains this difference in the two equilibrium constants. We recall that a ketone is more stable than an aldehyde because two alkyl groups donate electron density to the carbonyl carbon atom of a ketone versus only one for an aldehyde.

Only one α-carbon atom exists in an aldehyde. However, two α-carbon atoms may form enols of a ketone. In general, the relative stabilities of the double bonds of the two enols account for the amount of each enol formed. The enol with the more substituted double bond predominates because alkyl groups stabilize double bonds. However, the concentration of either enol is much smaller than the concentration of the keto form.

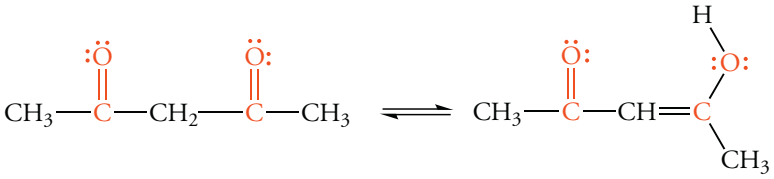


1-buten-2-ol
(less stable enol)

most stable form

2-buten-2-ol
(more stable enol)

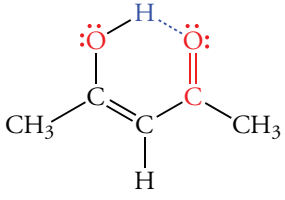
β-Diketones provide a more dramatic demonstration of the effect of double bond stability on the concentration of the enol form. The 1,3 arrangement of the carbonyl carbon atoms in β-diketones results in a conjugated system in the enol, greatly increasing its stability.



4-hydroxy-3-penten-2-one

$K = 5$

We recall that conjugation of two carbon–carbon double bonds of butadiene results in resonance stabilization of approximately 15 kJ mole^{-1}. A similar stabilization is reasonable for a carbon–carbon double bond in conjugation with a carbonyl group. However, a second structural feature further increases the concentration of 4-hydroxy-3-penten-2-one in equilibrium with 2,4-pentanedione. There is a strong intramolecular hydrogen bond between the enol hydrogen atom and the oxygen atom of the carbonyl group. An intramolecular hydrogen bond can stabilize a structure by approximately 20 kJ mole^{-1}.



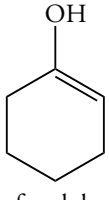
intramolecular hydrogen bond of an enol of a β-diketone

Problem 22. 3

The equilibrium constant for formation of the enol of cyclohexanone is approximately 10^{-5}. Explain why this value is larger than the equilibrium constant for acetone.

Sample Solution

The carbon–carbon double bond of the enol of cyclohexanone is more highly substituted than the carbon–carbon double bond of the enol of acetone. Thus, the double bond of the enol of cyclohexanone is more stable, and the formation of the enol is more favorable.



enol of cyclohexanone

Problem 22. 4

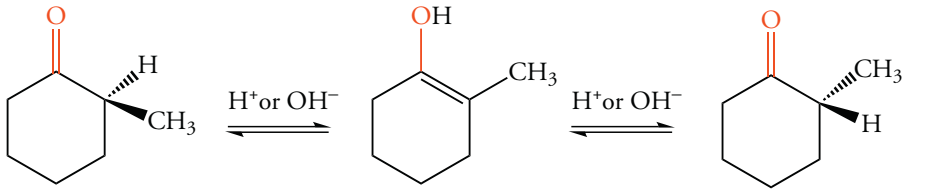
Draw three possible enols for 2-methyl-3-pentanone and describe their relative stabilities.

Problem 22. 5

An enol of 2,4-pentanedione can form an intramolecular hydrogen bond. Draw its structure and explain why it occurs in substantially smaller concentration than 4-hydroxy-3-penten-2-one.

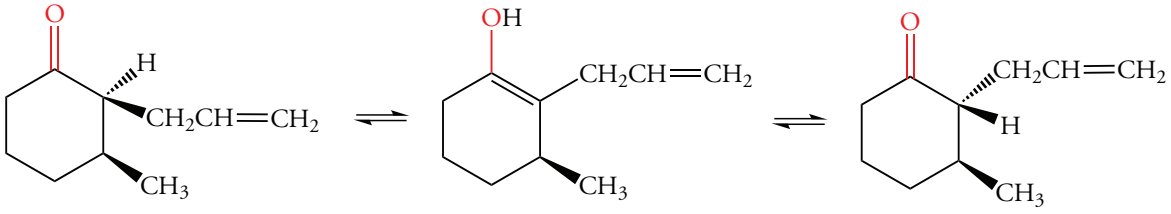
22.3 CONSEQUENCES OF ENOLIZATION

A hydrogen atom located on an α-carbon atom can be lost to a solvent molecule and then regained in equilibrium reactions that occur by way of formation of the enol. This α-hydrogen atom is called an **enolizable hydrogen atom**. If the enolizable hydrogen atom is located at a stereogenic center, formation of the enol destroys the configuration of the center. For this reason, stereogenic centers located next to a carbonyl group readily racemize in enolization reactions catalyzed by both acid and base. The equilibrium for formation of the enol of (*R*)-2-methylcyclohexanone illustrates this phenomenon.



(*R*)-2-methylcyclohexanone achiral enol (*S*)-2-methylcyclohexanone

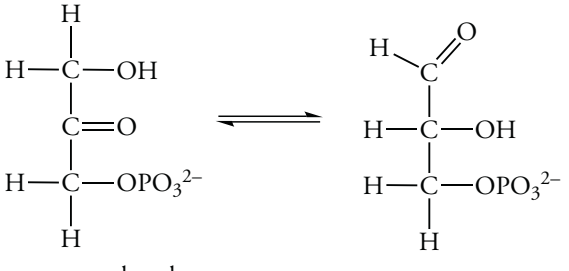
Because there is no stereogenic center in the enol of 2-methylcyclohexanone, the transfer of a proton back to C-2 can occur equally well from either side of the plane of the double bond to give a racemic mixture of enantiomers. If stereogenic centers occur elsewhere in the molecule, the result is an unequal mixture of diastereomers. For example, the enolization of *cis*-2-ally1-3-methylcyclohexanone, which has two stereogenic centers, isomerization the less sterically hindered *trans* isomer by enolization. In the enol, C-2 is no longer a stereogenic center. The enol can be protonated from either of two sides. However, attack at the top of the ring is not equivalent to attack at the bottom because of the stereogenic center at C-3. Hence, the two isomers do not form in equal amounts.



less stable isomer enol more stable isomer

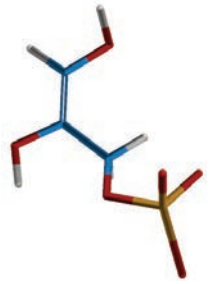
Tautomerization in Metabolic Reactions

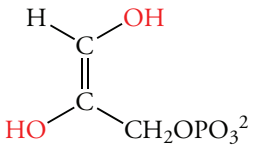
Tautomerism is important in the chemistry and metabolism of carbohydrates (Chapter 26). For example, glyceraldehyde 3-phosphate and dihydroxyacetone phosphate are two intermediates in glycolysis, a metabolic pathway in almost all organisms.



dihydroxyacetone phosphate glycerladehyde-3-phosphate

These compounds are isomers that are interconverted enzymatically by way of an enediol intermediate that has a hydroxyl group on the α-carbon atom of both the ketone and the aldehyde.





enediol intermediate

The enediol intermediate is produced from dihydroxyacetone phosphate by transfer of a proton from the α-carbon atom bearing the hydroxyl group to water and a transfer of a proton from water to the carbonyl oxygen atom. Similarly, the enediol intermediate is also produced from glyceraldehyde 3-phosphate by transfer of a proton from its α-carbon atom to water and transfer of a proton from water to the carbonyl oxygen atom.

Because dihydroxyacetone phosphate and glyceraldehyde 3-phosphate enolize to give a common intermediate, they exist in equilibrium. The enzyme triose phosphate isomerase efficiently catalyzes the isomerization. Although the enediol intermediate is chiral, the enzyme forms only the *R* enantiomer of glyceraldehyde 3-phosphate. In aqueous solution, an acid-catalyzed reaction would yield a racemic mixture of aldehyde 3-phosphate.

At equilibrium, a mixture contains 3% dihydroxyacetone phosphate because the ketone carbonyl group is more stable than the aldehyde carbonyl group of glyceraldehyde 3-phosphate. Only glyceraldehyde-3-phosphate reacts in subsequent steps of glycolysis. However, as it is removed from the equilibrium mixture, more dihydroxyacetone phosphate is converted to glyceraldehyde-3-phosphate. Similar isomerization enediol intermediates occur in many enzyme-catalyzed reactions of carbohydrates.

Problem 22. 6

Determine whether each of the following chiral compounds may enolize to produce a racemic mixture.

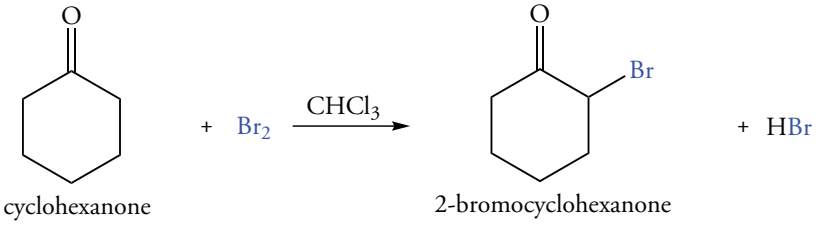
(a) (*R*)-2-ethyl-2-methylcyclopentanone
(b) (*S*)-3-ethylcyclohexanone
(c) (*S*)-3-phenyl-2-butanone

Problem 22. 7

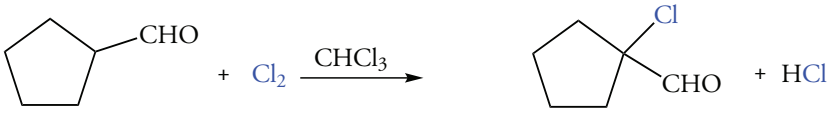
How can 2-methylcyclohexanone and 3-methylcyclohexanone be distinguished by acid-catalyzed enolization in D_2O?

22.4 α-HALOGENATION REACTIONS OF ALDEHYDES AND KETONES

Chlorine and bromine react with aldehydes and ketones to give α-halogenated compounds. The number of halogen atoms incorporated depends on reaction conditions.



cyclohexanone — 2-bromocyclohexanone



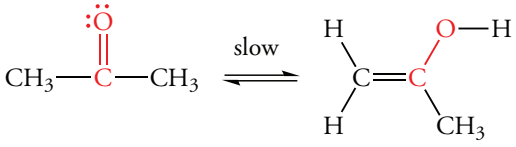
cyclopentanecarbaldehyde — 1-chlorocyclopentanecarbaldehyde

The halogenation reaction can be carried out under either acidic or basic conditions, but not with the same efficiency or experimental results. Under acidic conditions, the reaction can be used to substitute one hydrogen atom without significant complications of multiple substitutions. However, under basic conditions, α-halogenation reactions occur very much more rapidly, and substitution of a single hydrogen atom is not possible.

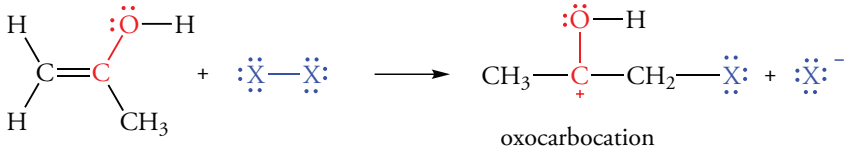
Acid-Catalyzed Halogenation

Very little acid is required to generate acidic conditions because one of the products of the halogenation reaction is an acid that catalyzes the reaction. After the halogen and the ketone are mixed, there is an induction period during which no apparent reaction occurs. However, as the hydrogen halide forms, the reaction becomes autocatalytic and proceeds faster.

Nearly a century ago, it was found that the rates of iodination, bromination, and chlorination of acetone are the same. The reaction is first order in acetone and is independent of the concentration of the halogen. These results are consistent with a mechanism in which an enol intermediate forms in the rate-determining step. The enol reacts with the halogen in a second, more rapid step to give the α-halogenated acetone.

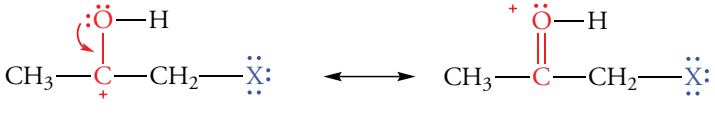


The formation of an enol in the rate-determining step is an acid-catalyzed reaction. Because the acid-catalyzed exchange of deuterium also occurs by way of an enol, the rate of deuterium exchange is identical to the rate of the acid-catalyzed halogenation. The addition of an electrophilic halogen atom to the double bond of the enol is analogous to the addition to alkenes we discussed in Chapter 7. However, the double bond of an enol is more reactive because the oxygen atom releases electron density by resonance.



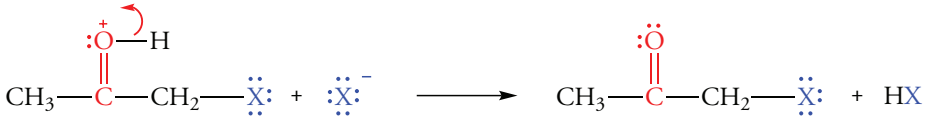
oxocarbocation
(conjugate acid of product)

Delocalization of a lone pair of electrons of the oxygen atom results in a resonance-stabilized oxocarbocation, which is a conjugate acid of the product. The protonated carbonyl resonance form is the more important contributor to the structure because the carbon and oxygen atoms both have octets of electrons.

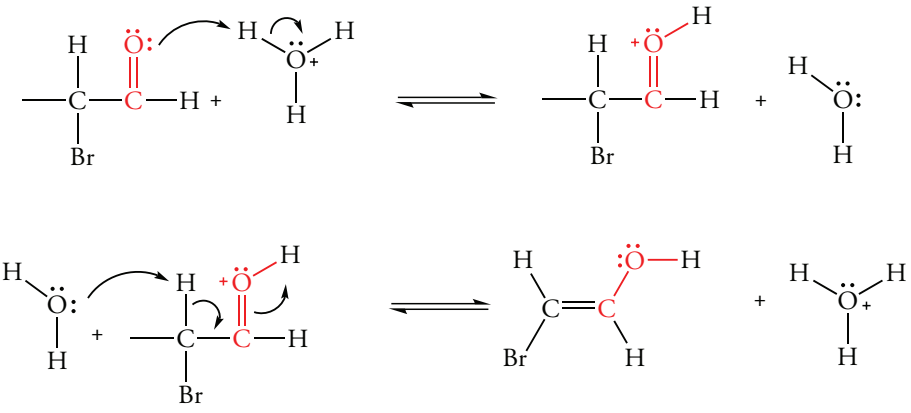


major contributor

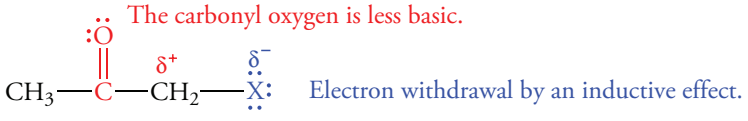
The conjugate acid of the α-halogenated ketone loses a proton to give the product.



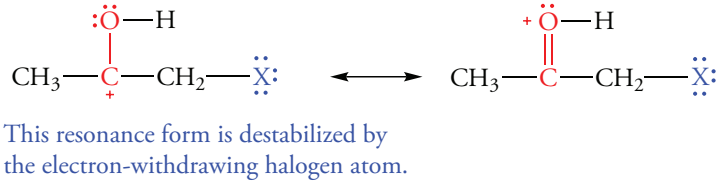
Although multiple halogen substitution for all may occur, a single halogen atom substitution does not occur readily under acidic conditions. Since the reaction rate depends on the rate of formation of the enol, we need only to compare the mechanistic step for the incorporation of a second halogen atom to the halogenation step for the original ketone.



We recall that chlorine and bromine are deactivating groups in electrophilic aromatic substitution because they withdraw electron density by an inductive effect but are ineffective in the donation of electron density by resonance. The same features are important in controlling the rate of the second step of ketone halogenation. The bromine atom withdraws electron density from the carbonyl carbon atom, making the carbonyl oxygen atom less basic. Therefore, the enol forms more slowly in the second step.

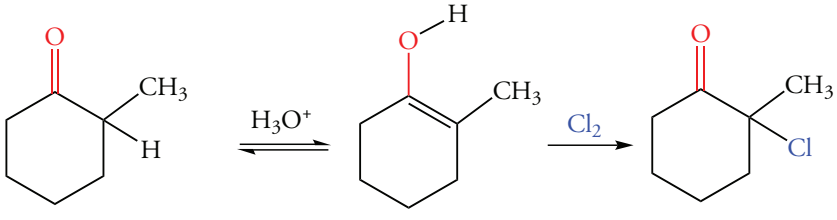


The bromine atom also destabilizes the conjugate acid of the halogenated ketone, which also decreases the equilibrium constant for formation of the enol.



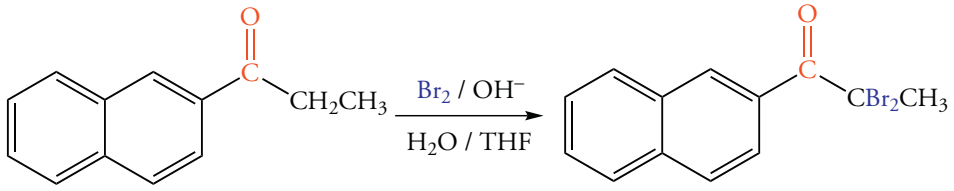
The bromine atom decreases the stability of the ketone and increases the K_a of its conjugate acid. As a result, the reaction of an α-halogenated ketone with a second halogen is slow. Further halogenation occurs only after the original carbonyl compound has reacted completely.

When the ketone has two nonequivalent α-carbon atoms, the acid-catalyzed reaction yields the α-haloketone with the halogen on the more substituted atom. We can explain this observation by considering the two possible enol intermediates. The more highly substituted site gives the more highly substituted double bond of the enol. Because halogenation under acidic conditions requires the formation of an enol, the stability of the enol controls the formation of the halogen product.

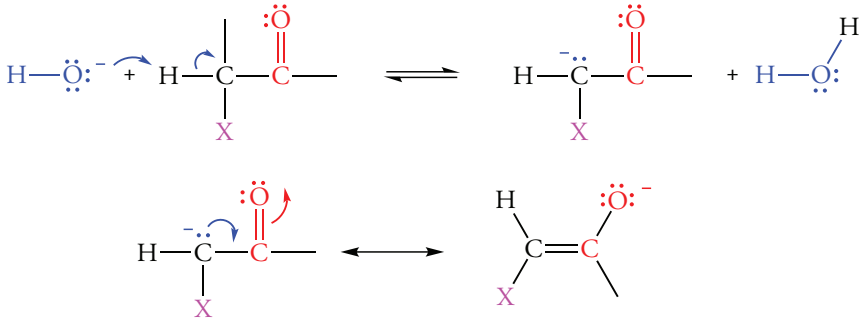


Base-Catalyzed Halogenation

Alpha halogenation of aldehydes and ketones occurs readily under basic conditions and does not stop with the replacement of a single hydrogen atom. All α-hydrogen atoms are substituted.



Multiple substitution occurs because the initial α-haloketone formed is even more reactive than the original ketone. We can explain this phenomenon by examining the structure of the enolate formed from the α-haloketone and comparing its reactivity to the enolate of the original ketone.

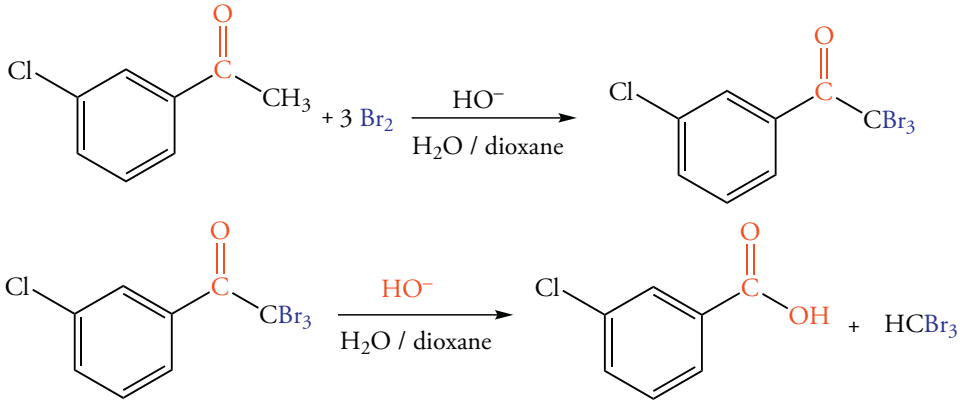


The electron-withdrawing halogen atom stabilizes the enolate ion, which increases the equilibrium constant for formation of this conjugate base of the α-haloketone compared to the original ketone. We can also explain the experimental results by considering the inductive effect of the halogen on the acidity of the α-hydrogen atom. The halogen draws the bonding electrons of the C—H bond toward carbon, increasing the acidity of the hydrogen atom.

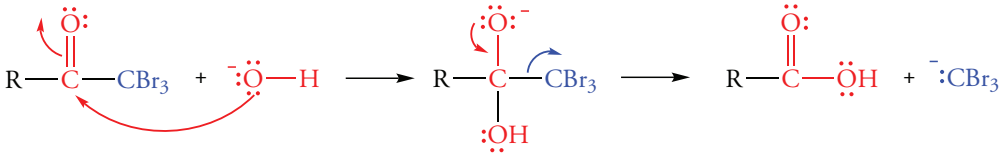
The enhanced reactivity of an α-carbon atom caused by the α-halogen atom results in multiple substitution at that site, but not at an alternate α-carbon atom, until the first site is fully halogenated. Therefore, 2,2-dibromo-3-pentanone forms faster than 2,4-dibromo-3-pentanone. When the two α-hydrogen atoms are nonequivalent, the more acidic hydrogen determines the site of the first halogenation. The acidity of C—H bonds decreases in the order 1° > 2° > 3°.

The Haloform Reaction

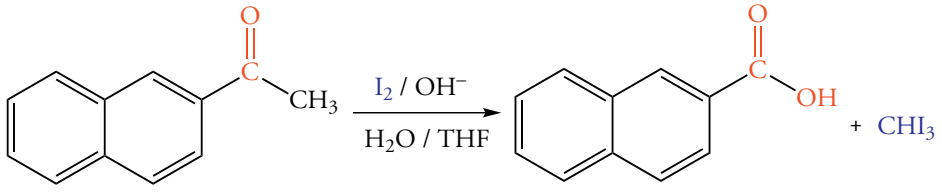
When a methyl ketone is halogenated in basic solution, the halogen replaces all three α-hydrogen atoms. This trihaloketone reacts further, resulting in the cleavage of a carbon–carbon bond. After acidification, the products are a carboxylic acid and a trihalomethane known as a **haloform**. The haloforms for chlorine, bromine, and iodine are chloroform, bromoform, and iodoform.



The cleavage of the carbon–carbon bond occurs by a two-step mechanism in which hydroxide ion attacks the carbonyl carbon atom to give a tetrahedral intermediate that subsequently releases the tribromomethyl carbanion. If iodine reacts with a methyl ketone, iodoform, CHI_3, forms. It is a bright yellow, insoluble solid.



Under basic conditions, the carboxylic acid product shown exists as an anion. However, after neutralization in the workup of the reaction mixture, the products are a carboxylic acid and $CHBr_3$. The haloform reaction can be used as a synthetic method to prepare carboxylic acids.



Problem 22.8

Which of the following compounds will give a positive iodoform test?

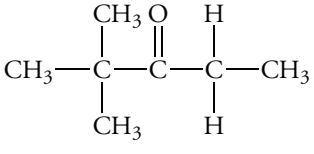
(a) 3-pentanone (b) 2-pentanone (c) 2-methyl-3-pentanone (d) 2-methylcyclohexanone

Problem 22.9

Write the product of the reaction of bromine with 2,2-dimethy1-3-pentanone under acidic and basic conditions.

Sample Solution

Only one of the two α-carbon atoms has hydrogen atoms that may be replaced by a halogen atom.



Under acidic conditions, one bromine atom replaces a hydrogen atom at C-4 to give 2-bromo-4,4-dimethyl-3-pentanone. Under basic conditions, the reaction continues to replace the second hydrogen atom faster than the first, and a dibromo compound is obtained.

Problem 22.10

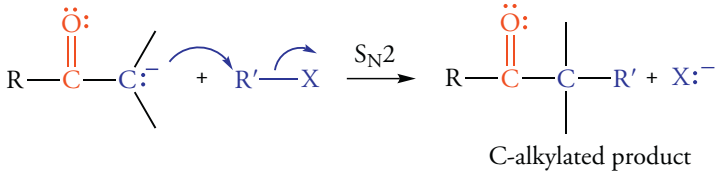
Based on the structural factors that affect the stability of an enol, predict the product of the reaction of 3-methyl-2-butanone with bromine under acidic conditions.

22.5 ALKYLATION OF ENOLATE IONS

The reaction of a nucleophilic carbon atom with an electrophilic carbon atom of a second species is one of the most important reactions in organic chemistry because it results in formation of a carbon–carbon bond. We now extend our repertoire of these reactions by using enolates as the nucleophile that forms a bond to an electrophilic carbon atom.

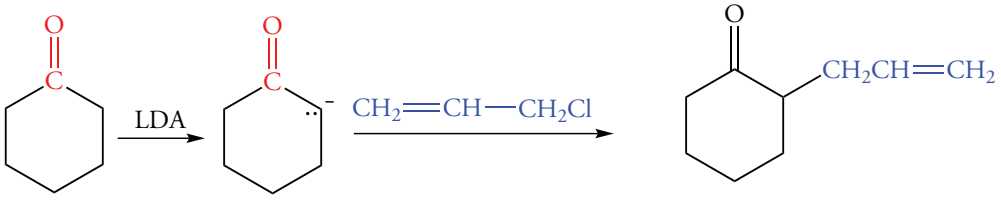
In some respects, the alkylation of enolate anions resembles nucleophilic substitution. We recall that many nucleophiles displace leaving groups from primary alkyl halides by an S_N2 mechanism (Section 9.3). A similar reaction occurs with secondary alkyl halides, but competing elimination reactions also occur. Primary alkyl halides react with carbanions, such as the alkynide ion, by an S_N2 mechanism. (Secondary alkyl halides react not only in displacement reactions but also in elimination reactions because the alkynide ion is a strong base.)

An enolate is a nucleophile that can displace a leaving group from a primary alkyl halide by an S_N2 mechanism. Although the enolate has two sites of reactivity, we have already seen that reaction of an electrophile with an enolate. The reaction usually occurs at the α-carbon atom to give a substituted keto product called the C-alkylated product. The reaction at oxygen to give an O-alkylated product is much less common.

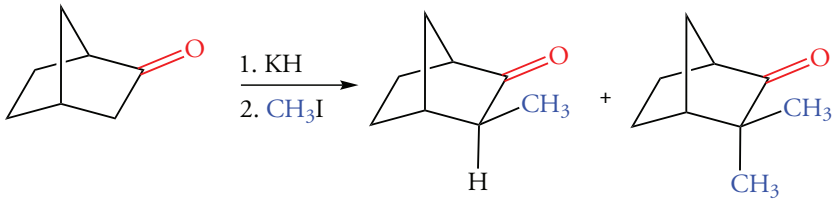


We recall that hydroxide ion is not basic enough to form an enolate ion in high concentration. Alkoxide anions cannot provide a high concentration of the enolate ion either. With these bases, the enolate ion is not the predominant basic species in solution. Hydroxide ion or alkoxide ion would substitute for the leaving group and give an alcohol or ether.

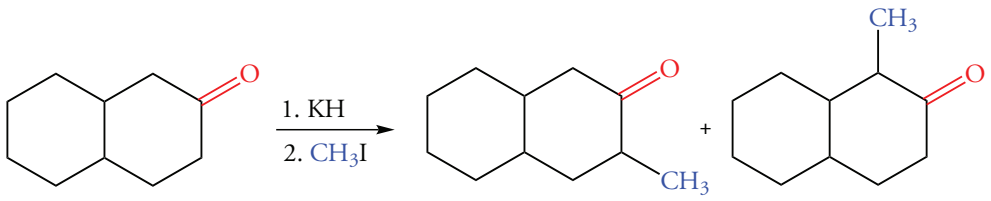
Strong bases, such as potassium hydride or lithium diisopropyl amide (LDA), are used to obtain stoichiometric quantities of enolates. Then, an alkyl halide is added to the solution of the enolate to give the C-alkylated product.



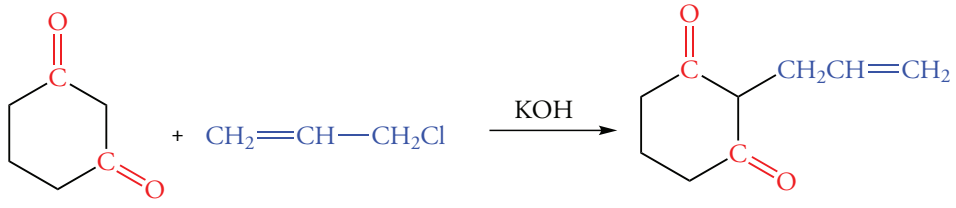
Dialkylation can occur because an enolate of the monoalkylated product can form by proton transfer from the original enolate. This enolate reacts with the alkyl halide to give the dialkylated product. For example, methylation of bicycle[2.2.1]heptan-2-one gives a mixture of mono- and dialkylated products.



When the two α-hydrogen atoms are nonequivalent, removing the more acidic hydrogen atom determines which alkylated product forms. The strong base abstracts the more acidic hydrogen atom. We recall that the acidity of C—H bonds decreases in the order 1° > 2° > 3°. When both α-carbon atoms have the same degree of substitution, a mixture of products results.



Alkylation of β-diketones gives excellent yields of product. This reaction does not require a strong base because the two carbonyl groups greatly increase the acidity of the C—H bond located between them.



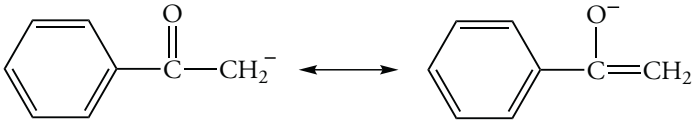
Alkylation of aldehydes is not a useful reaction because side reactions occur in which the nucleophilic enolate attacks the electrophilic carbonyl carbon atom of the aldehyde of another molecule. This reaction does not compete with the alkylation of ketones because ketones are less susceptible to nucleophilic attack at the carbonyl carbon atom.

Problem 22.11

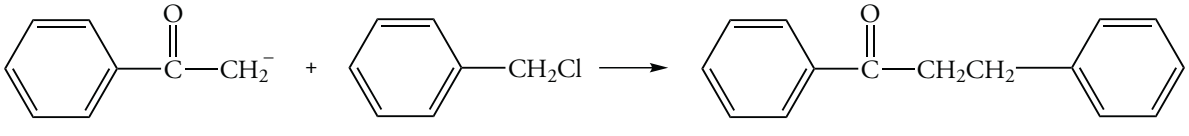
Draw the product of the reaction of acetophenone with KH followed by reaction with benzyl chloride.

Sample Solution

Only one of the two α-carbon atoms has bonded hydrogen atoms. Removing a proton from the methyl group of acetophenone by KH gives a resonance-stabilized enolate anion.



Benzyl chloride is very reactive in substitution reactions. The enolate displaces chloride ion in an S_N2 reaction that results in carbon–carbon bond formation.

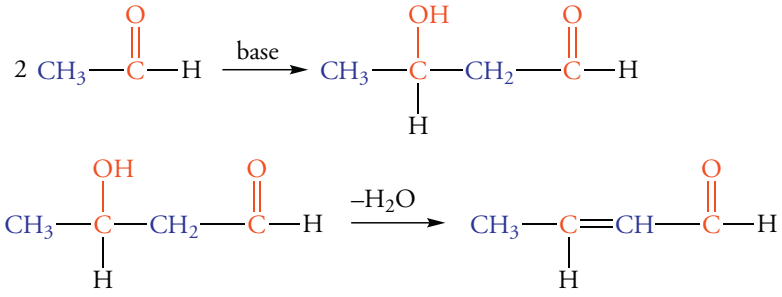


Problem 22.12

Draw the products of the reaction of 2-methylcylopentanone with LDA by reaction with allyl chloride.

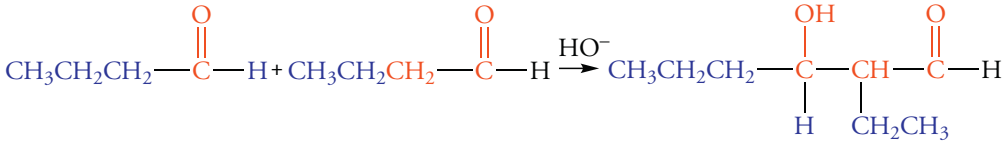
22.6 THE ALDOL CONDENSATION OF ALDEHYDES

Two molecules of an aldehyde can join in a reaction called an **aldol condensation**. This base-catalyzed reaction gives a product that is both an aldehyde and an alcohol, called an **aldol**. The aldol can be isolated, but it can also react further to form a conjugated unsaturated carbonyl compound and water.



The combination of two molecules to give a larger molecular weight product and a smaller molecule, such as water, is called a **condensation reaction**. In that sense, only the final unsaturated aldehyde product qualifies as a condensation product. However, the reaction of two carbonyl compounds is often termed a condensation reaction even if the aldol is the major product. We will distinguish between these two reactions by calling the product of the first step an addition product, and the product of the second step the condensation product. Specific structural features and experimental conditions favor one product over the other.

In the addition step of an aldol condensation, a new carbon–carbon bond forms between the α-carbon atom of one carbonyl compound and the carbonyl of the other. The addition product has just one carbon atom between the aldehyde and alcohol carbon atoms. The aldol product derived from butanal illustrates this relationship.

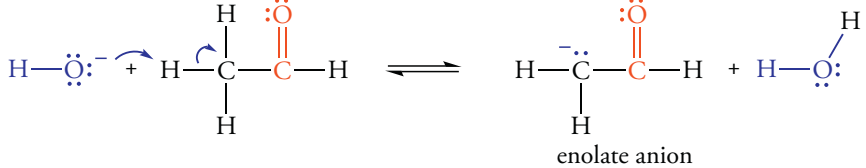


Both steps of the aldol condensation are reversible. Thus, it is often necessary to manipulate the experimental conditions to drive the reaction toward product. At equilibrium, the conversion of acetaldehyde to its aldol is less than 50%. The equilibrium concentration of the addition product is seldom above 1% for ketones.

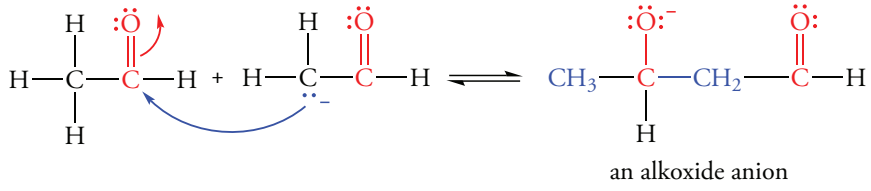
Mechanism of the Addition Reaction

The addition step of the aldol condensation occurs at room temperature when an aldehyde is treated with an aqueous solution of sodium hydroxide. The reaction occurs in a three-step process.

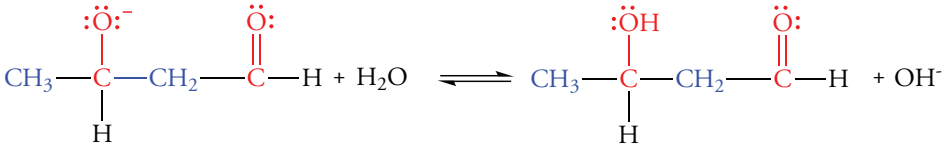
1. One aldehyde molecule reacts with base (OH^-) at it is a C—H bond to give a nucleophilic enolate anion.



2. The nucleophilic enolate anion reacts with the carbonyl carbon atom of another aldehyde molecule. The alkoxide ion product is the conjugate base of an aldol.



3. The alkoxide anion extracts a proton from the solvent, water, which regenerates a hydroxide anion.

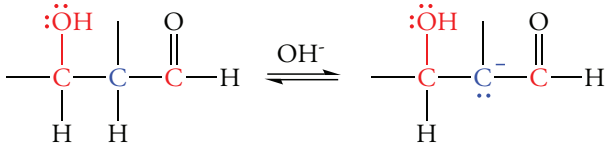


Under the conditions of the reaction, little of the carbonyl compound is converted to the enolate. The aldehyde and the enolate are in equilibrium, and the enolate is replaced as it reacts. The enolate is present in an excess of aldehyde, so its nucleophilic carbon atom is surrounded by many electrophilic carbon atoms. The hydroxide ion is a catalyst, and its concentration does not change.

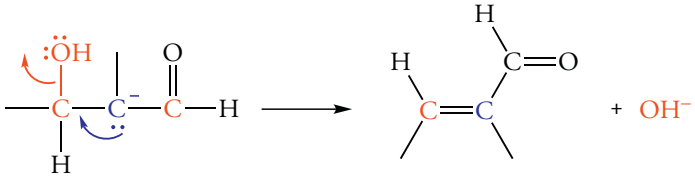
Dehydration of Aldols

If the aldol reaction mixture is heated under basic conditions, the dehydrated product forms. The dehydration of the aldol under basic reaction conditions drives reaction to completion. The aldol may also be isolated and dehydrated like any other alcohol by using a strong acid. The mechanism of acid-catalyzed dehydration of an aldol is exactly like that of alcohols. However, the base-catalyzed dehydration that occurs in the aldol reaction is an E2 process that does not occur for simple alcohols. The base-catalyzed dehydration reaction occurs in two steps.

1. The base removes an α-hydrogen atom to give a resonance-stabilized enolate ion. This step would not occur for an ordinary alcohol because the C—H bond at the α-carbon of an alcohol is not sufficiently acidic.



2. The hydroxide ion leaves in the second step of this E2 mechanism. This step might be regarded as unusual because we know that the hydroxide ion is not a good leaving group. However, in this case, the loss of a hydroxide ion generates a conjugated unsaturated aldehyde. The resonance stabilization of conjugated multiple bonds makes this step exothermic.



Problem 22.13

Draw the product of the aldol condensation of 3-phenylpropanal.

Problem 22.14

A commercial process for the preparation of 1-butanol starts with an aldol condensation of acetaldehyde. Write the additional steps required to produce 1-butanol.

Sample Solution

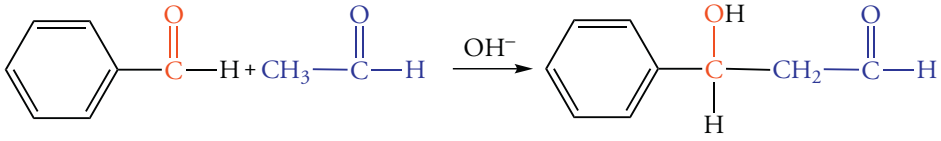
Under conditions favoring dehydration, the product of the aldol condensation of acetaldehyde is 2-butenal. The desired product, 1-butanol, is more saturated than 2-butenal. Reduction of both the carbonyl group and the carbon–carbon double bond is required. Catalytic hydrogenation simultaneously reduces both unsaturated sites.

Problem 22.15

A commercial process to produce the insect repellent 2-ethyl-1,3-hexanediol starts with an aldol condensation. What starting material is used? Write equations for the reactions required to form the diol.

22.7 MIXED ALDOL CONDENSATION REACTIONS

If two different aldehydes undergo an aldol condensation, the reaction is a **mixed aldol condensation**. In the aldol condensation reactions we described above, the same aldehyde provided both the enolate and the substrate attacked by the enolate anion. But if two different aldehydes are mixed and heated in a basic solution, the enolate anion of one can react with the carbonyl form of the other. Mixtures of products can result because any two aldehydes can react with each other. Thus, if the aldehydes are A_1 and A_2, aldol condensation can produce every possible combination: A_1A_1, A_2A_2, A_1A_2, and A_2A_1—in short, a dreadful mixture. This unhappy outcome can be avoided if one of the aldehydes lacks α-hydrogen atoms and the other aldehyde is less reactive. For example, an aldol condensation occurs between benzaldehyde and acetaldehyde to give a high yield of a single aldol product. Reaction between two benzaldehyde molecules cannot occur because benzaldehyde lacks α-hydrogen atoms. Therefore, benzaldehyde is mixed with a base, and acetaldehyde is then slowly added. The acetaldehyde is rapidly converted to an enolate anion. Because benzaldehyde is more reactive than acetaldehyde, and the concentration of free acetaldehyde in the mixture is much smaller than that of benzaldehyde, the enolate of acetaldehyde reacts with benzaldehyde. Only one product results.



no α-hydrogens

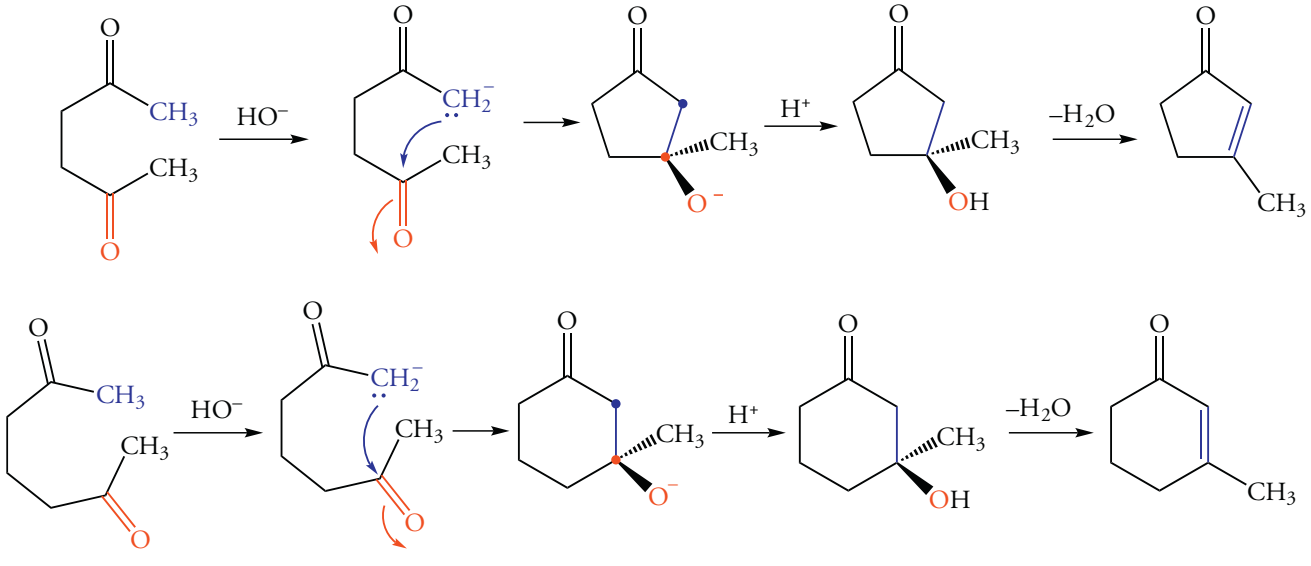
Problem 22.16

Acetophenone undergoes a condensation reaction with benzaldehyde to give a product with the molecular formula $C_{15}H_{12}O$. Draw its structure and explain why it forms.

22.8 INTRAMOLECULAR ALDOL CONDENSATION REACTIONS

In Section 22.7, we saw that the equilibrium constants for the condensation reactions of aldehydes are not large, and those for ketones are so small that the aldol condensation of a ketone is impractical. However, ketones can react in an intramolecular process to give cyclic aldol products.

The most favorable intramolecular reactions give five- or six-membered ring products. For example, 1,4-dicarbonyl compounds condense and dehydrate to give cyclopentenones. Similarly, 1,5-dicarbonyl compounds give cyclohexenones.

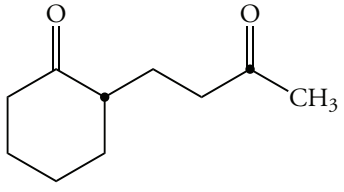


Would we expect smaller or larger rings to form in intramolecular aldol condensations? If the reactive sites required for an intramolecular aldol reaction are close to each other, the ring closure could occur to give four- and three-membered rings, but they would be strained. Rings larger than six carbon atoms are not likely because the probability of forming such a ring is lower than the formation of an alternate smaller ring. Furthermore, all possible aldol products form in equilibrium reactions, each of which can reverse to regenerate the original dicarbonyl compound. Therefore, the product formed at equilibrium is the more stable aldol.

Next, let's consider a problem similar to we encountered for mixed aldol condensations. Which α-carbon atom will react with which carbonyl carbon atom if rings of similar size could result? Under the reaction conditions, all possible enolates can form in low concentration. Thus, we can consider the various carbonyl groups and determine which is more likely to react with the nucleophilic carbon atom of an enolate. If one carbonyl group is an aldehyde and the other a ketone, the answer to the question is easy because the aldehyde carbonyl group is more susceptible to attack by a nucleophile.

Problem 22.17

Draw the structure of the final aldol product of 2-(3-oxobutyl)cyclohexanone.

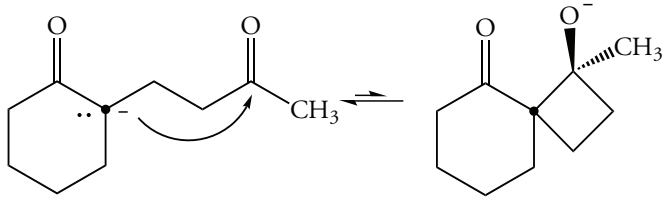


2-(3-oxobutyl)cyclohexanone

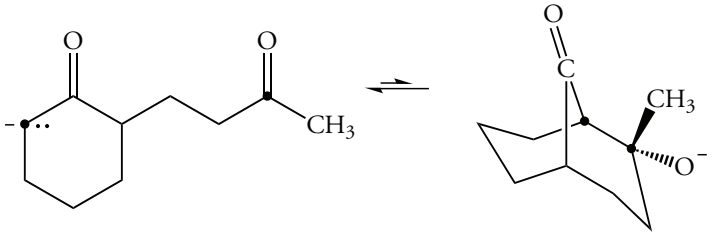
Sample Solution

Each carbonyl group has two α-carbon atoms. An enolate derived from C-2 or C-6 could react with the carbonyl group of the oxobutyl chain. An enolate derived from the C-2 or C-4 of the oxobutyl chain could react with the carbonyl group of the cyclohexane ring.

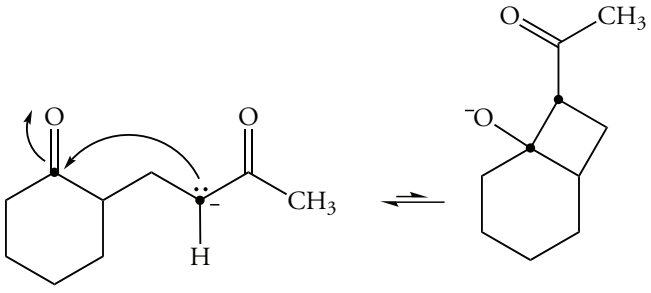
Neither of the enolates derived from C-2 or C-6 of the cyclohexanone ring should lead to a significant amount of product. The enolate derived from C-2 would produce a four-membered ring when it attacks the C-3 carbonyl carbon atom of the oxobutyl chain. And, the resulting aldol product cannot dehydrate to give a conjugated ketone because the ring is too small, and ring strain is prohibitive.



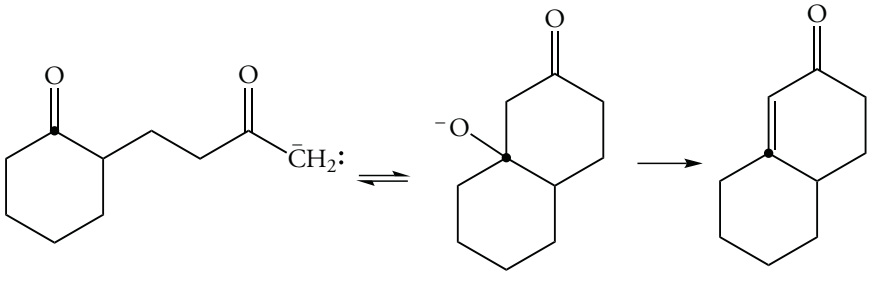
The enolate derived from C-6 could give a six-membered ring in a reaction with the C-3 carbonyl carbon atom to give a bicyclic product. However, this reaction can occur only by reaction with the oxobutyl chain in an axial conformation. The resulting aldol cannot dehydrate to give a conjugated carbonyl compound because a double bond at the bridgehead carbon atom would be very strained.



The enolate derived from C-2 could give a four-membered ring in a reaction with the carbonyl carbon atom on the cyclohexane ring. However, this reaction can occur only by reaction with the oxobutyl chain in an axial conformation. The resulting aldol cannot dehydrate to give a conjugated carbonyl compound because a double bond at the bridgehead carbon atom would be very strained.

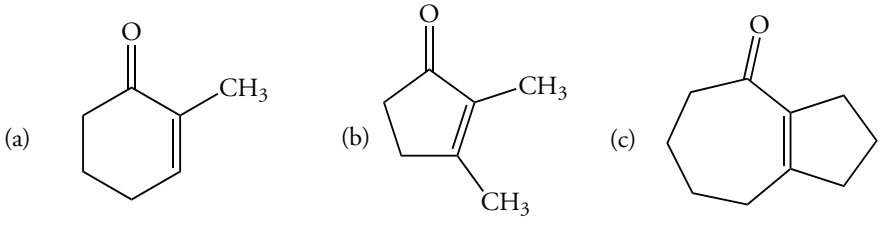


Attack of the enolate of the C-4 site of the oxobutyl chain on the carbonyl carbon atom of the cyclohexane ring gives a six-membered ring. This process is the most likely of the four processes outlined above because the product is the most stable. Dehydration of the aldol occurs to give a carbon–carbon double bond in conjugation with the carbonyl group.



Problem 22.18

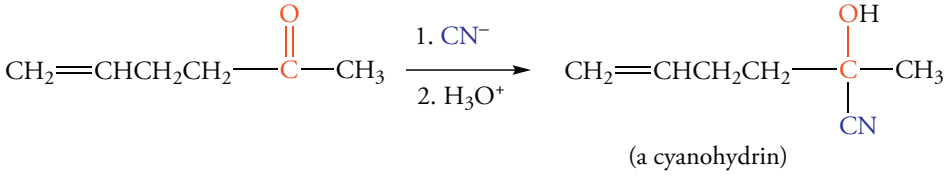
Draw the structure of the dicarbonyl compound required for synthesis of each of the following products by an aldol condensation.



22.9 CONJUGATION IN α–β-UNSATURATED ALDEHYDES AND KETONES

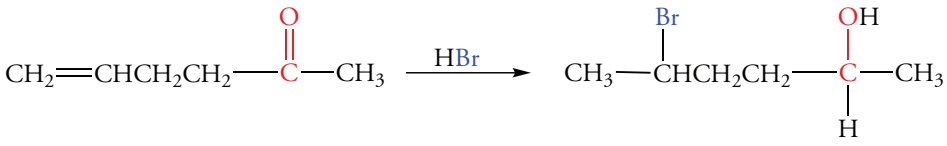
In chapter 11, we discussed the new properties that arise when dienes are conjugated, that is, when a π system has alternating single and double bonds (π–σ–π). Similarly, a conjugated π system arises when a carbonyl group is separated by a single σ bond from a π bond.

First, we will compare the chemical reactivities of a carbon–carbon double bond and a carbon–oxygen double bond in a nonconjugated molecule in a reaction with cyanide ion. The cyanide ion reacts at the carbonyl carbon atom. Carbon–carbon double bond does not react with nucleophiles such as cyanide. Thus, cyanide ion reacts with 5-penten-2-one to give a cyanohydrin.



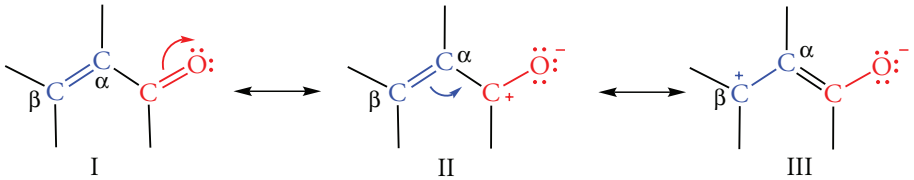
(a cyanohydrin)

The carbon–carbon double bond of this nonconjugated compound reacts with electrophilic reagents such as HBr. The carbon–oxygen double bond does not react with HBr.



Markovnikov addition product

α,β-Unsaturated aldehydes and ketones are more stable than nonconjugated unsaturated carbonyl compounds because the two π bonds interact. We recall that this "extra" stability is called the resonance energy. In Chapter 11, we showed that the resonance energy of dienes results from the distribution of electrons in molecular orbitals that extend over three or more atoms. Many of the physical and chemical properties of conjugated dienes can also be explained using Lewis structures. We will use Lewis structures to consider the physical and chemical properties of α,β-unsaturated aldehydes and ketones. An α,β-unsaturated carbonyl compound can be represented by one uncharged and two dipolar resonance forms.



I
most stable

II

III
least stable

Of the three resonance forms, structure III is the least stable. However, we shall see shortly that its contribution is important in explaining the special reactivity of α,β-unsaturated carbonyl compounds. In structure II, the carbonyl carbon atom has a positive charge; in structure III, the carbon atom has a positive charge. We used the partial positive charge of the carbonyl carbon atom to explain the addition reaction of carbonyl groups (Chapter 18). The partial positive charge of the β-carbon atom of the carbon–carbon double bond alters its characteristic reactivity.

The diminished electron density makes the carbon–carbon π bond less reactive toward an electrophile. However, for the same reason, the β-carbon atom is electrophilic and can react with nucleophiles. Addition reactions to conjugated systems are the subject of the next section.

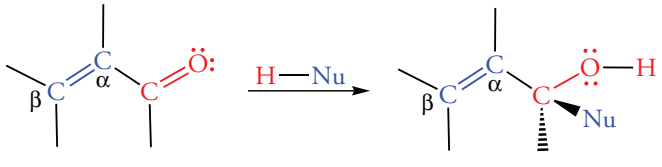
22.10 CONJUGATE ADDITION REACTIONS

We recall that many addition reactions of a nucleophile to a carbonyl compound are reversible because the carbon–nucleophile bond of the addition product is weak, and the nucleophile is a good leaving group. The addition of cyanide ion is one such example. However, strong bases, such as hydride ion or an alkyl carbanion, add irreversibly to the carbonyl group.

To understand the product distribution in addition reactions of carbonyl groups, we have to know whether the product results from kinetic control or thermodynamic control. If a reaction is irreversible, the product is "trapped" and results from kinetic control. However, the product distribution in reversible addition reactions depends on the relative stabilities of the products. We call this phenomenon thermodynamic control.

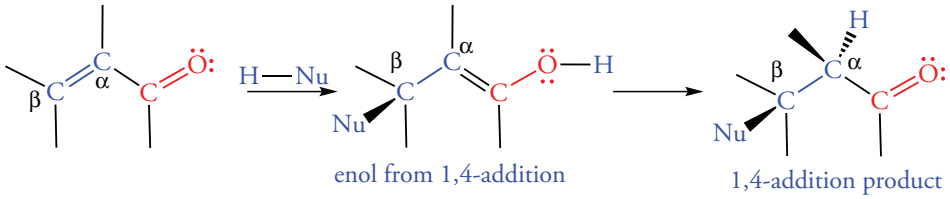
1,2- and 1,4-Addition Reactions

Like conjugated dienes, conjugated unsaturated carbonyl compounds can add reagents in two ways. 1,2-Addition is simply nucleophilic addiction to a carbonyl group, which we discussed in Chapter 18.



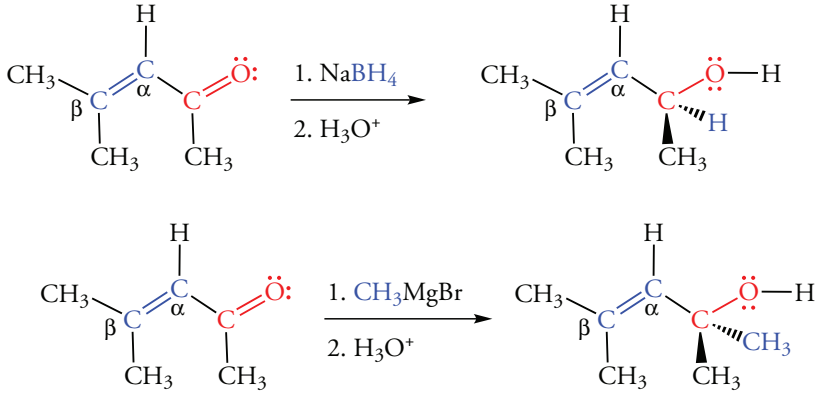
1,2-addition product

In a 1,4-addition reaction, the nucleophile adds to atom 4 (the β-carbon atom), and the electrophile adds to the carbonyl oxygen, atom 1. It is not immediately obvious that a 1,4-addition reaction has occurred with α,β-unsaturated carbonyl compounds because the initial product is an enol.

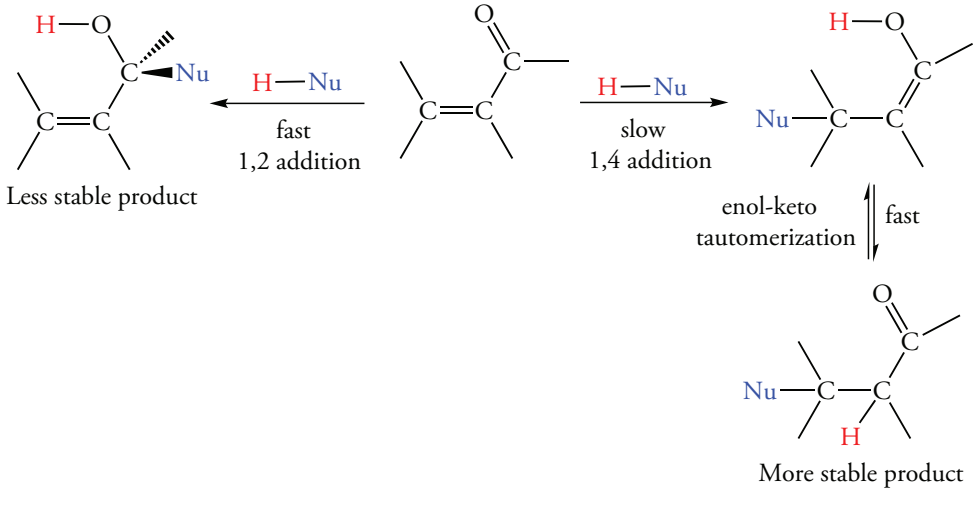


Thus, the nucleophile is bonded to the β-carbon atom, but the electrophile is bonded to the α-carbon atom. From the structure of the isolated product, the reaction appears to be simply the addition of H—Nu to a carbon–carbon double bond. However, we know that this could not have occurred. The atoms added are not in the places predicted by Markovnikov's rule. Furthermore, the presence of the electron-withdrawing carbonyl group should make the α-carbon susceptible to attack by the nucleophile, not the electrophile.

We already know that metal hydride reagents reduce carbonyl groups and not carbon–carbon double bonds. This reaction is a 1,2-addition. Similarly, a Grignard reagent adds to a carbonyl group, not to a carbon–carbon double bond. We conclude that strong nucleophiles such as hydride ion and carbanions undergo 1,2 addition. Neither reaction is reversible, and the products result from kinetic control.



1,4-Addition reactions occur with weak nucleophiles such as cyanide. 1,2-Addition would result from attack at the carbonyl carbon atom, which is more electrophilic than the β-carbon atom. However, the reaction is reversible, so the 1,2 addition product does not accumulate. Although the 1,4-addition product forms more slowly, it accumulates because it is thermodynamically more stable than the 1,2-addition product. The 1,4-addition product retains the carbon–oxygen double bond, which is more stable than the carbon–carbon double bond of the 1,2 addition product (Figure 22.1).



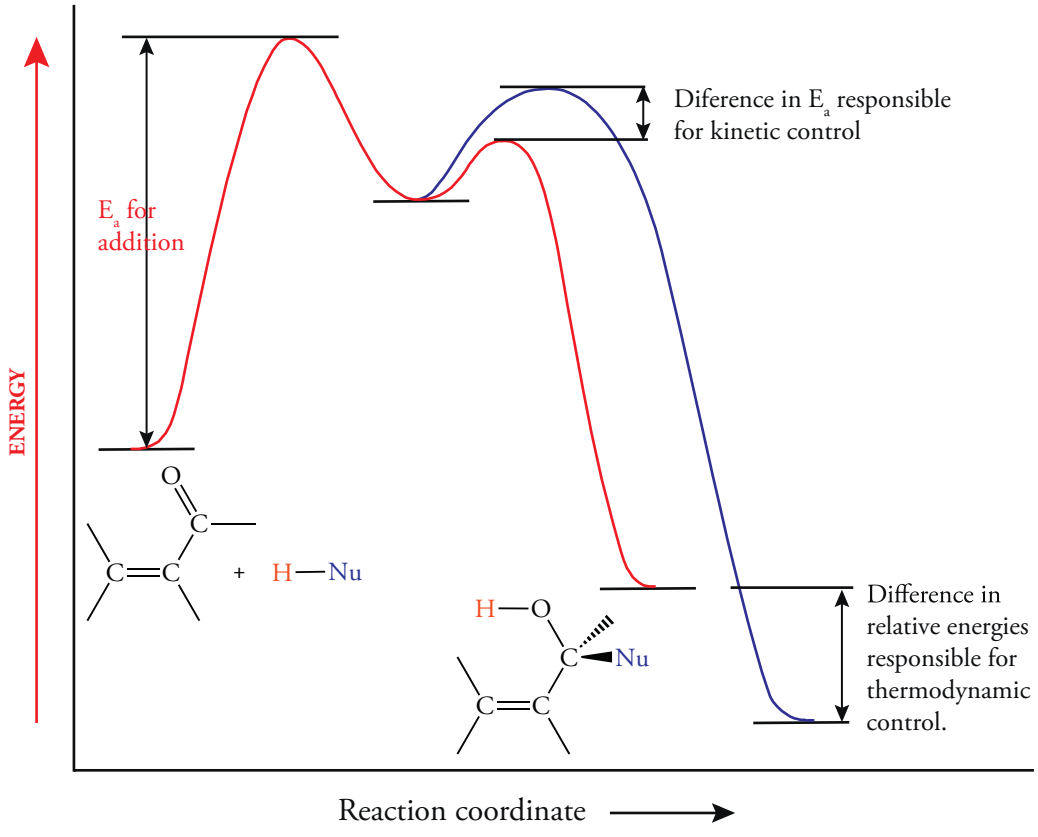
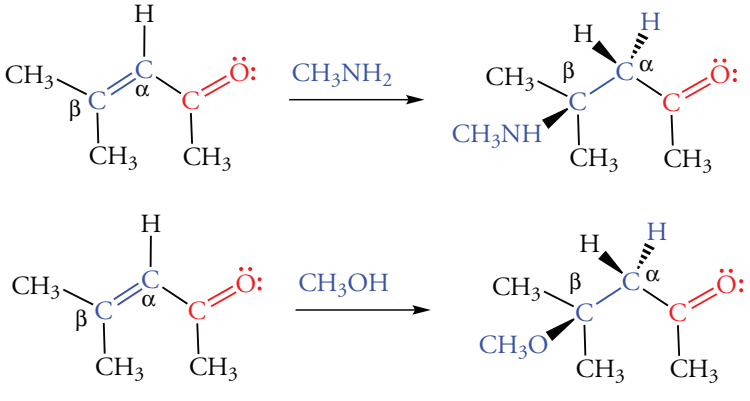
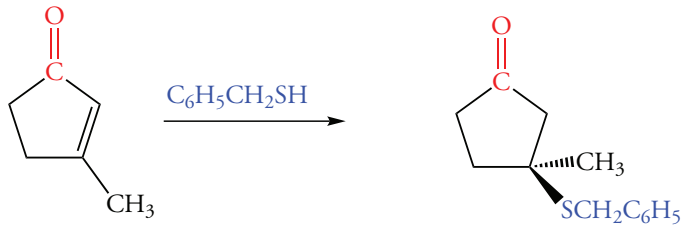


Figure 22.1 Kinetic vs. Thermodynamic Control of 1,2- and 1,4-Addition Reactions
Direct 1,2-addition occurs faster than 1,4-conjugate addition but gives a less stable product. The 1,4-addition product isomerizes to give a more stable product that retains the carbonyl group.

In Chapter 19, we saw that weak nucleophiles such as methyl-amine, methanol, and thiols add to the carbonyl group of aldehydes and ketones. However, these nucleophiles react with α,β-unsaturated carbonyl compound to give 1,4-addition products. We know that methylamine adds to a carbonyl group to give an imine. We also know that an imine is less stable than a carbonyl compound, so the equilibrium constant for the reaction is less than 1. Similarly, alcohols react with carbonyl compounds to give hemiacetals. Again, the equilibrium constant for the reaction is less than 1 unless the reaction is intramolecular. Thiols react with carbonyl compounds to give thioacetals or thioketals, but the reaction requires an acid catalyst. However, like cyanide ion, each of these reagents reacts with α,β-unsaturated carbonyl compounds to give 1,4-addition products.

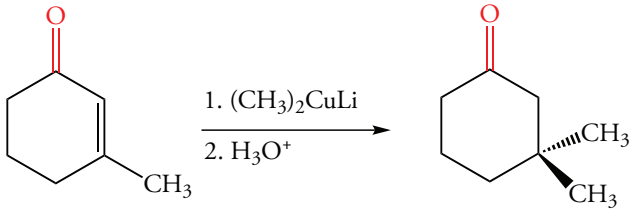




Conjugate Addition of Organometallic Reagents

We saw earlier that the Grignard reagent undergoes 1,2-addition reactions with α,β-unsaturated carbonyl compounds with few exceptions. Those exceptions occur when the carbonyl carbon atom of a ketone is sterically hindered compared to the β-carbon atom. Aldehydes always give 1,2-addition products. Organolithium reagents are more reactive than Grignard reagents, and they always give 1,2-addition products.

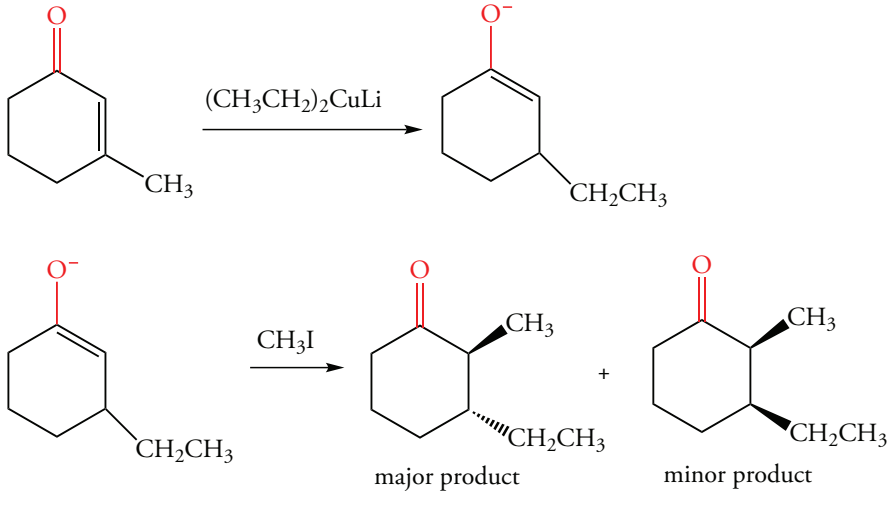
In Chapter 17, we saw that organocuprates (Gilman reagents) react with α,β-unsaturated carbonyl compounds to form 1,4-addition products.



3,3-dimethylcyclohexanone

The mechanism of this reaction is not simple nucleophilic attack of a carbanion at the β-carbon atom. We discussed the mechanism of this reaction in Chapter 17, and we will not repeat that discussion here. Nevertheless, we can ask why the Gilman reagent adds at the β-carbon in a 1,4 addition, but Grignard reagents add at the carbonyl carbon. To answer this question, we appeal to the notion of "hard" and "soft" nucleophiles. Grignard reagents and organolithium reagents are hard nucleophiles because the negative charge is concentrated on the carbon atom in the C—Mg or C—Li bond. In contrast, the charge in the Gilman reagent is delocalized across the d orbitals of the much larger copper ion. Thus, the organocuprate is more polarizable, and it reacts with the less polar β-carbon of the α,β-unsaturated compound. The product is a resonance-stabilized enolate anion.

The enolate can be trapped by adding an alkyl halide after the first step is complete, but before the reaction is worked up. This sequence of two reactions is synthetically useful because it results in alkylation at both the α- and β-carbon atoms.

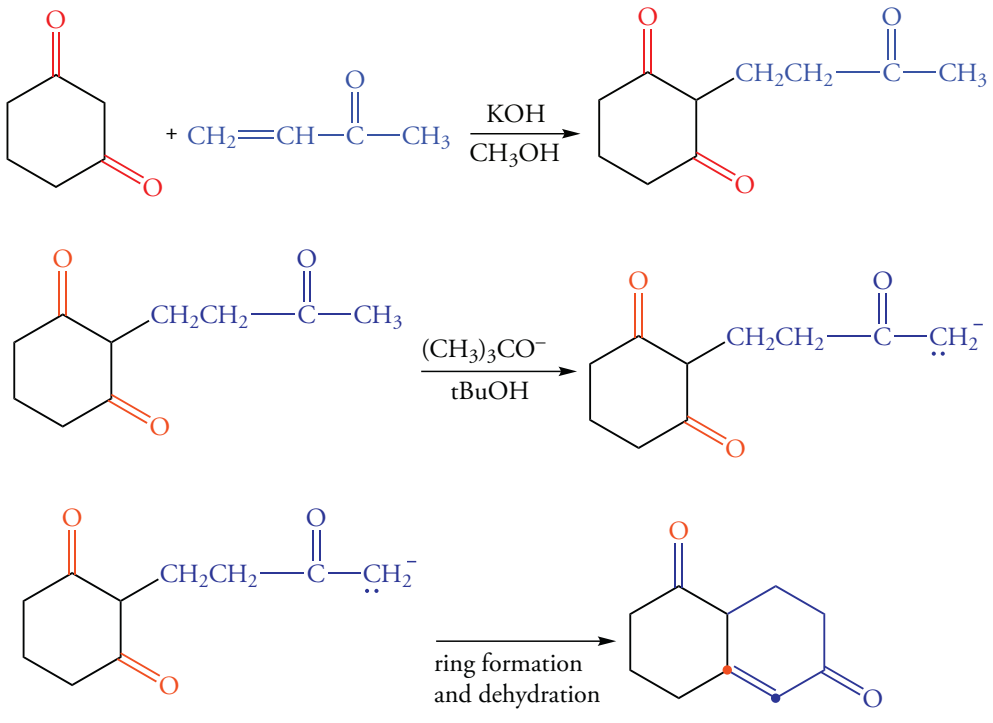


major product minor product

22.11 THE MICHAEL REACTION AND ROBINSON ANNULATION

We have seen that to synthesize a complex structure, we have to combine smaller molecules in a way that leaves functional groups that can be further modified in subsequent steps. In this section, we will discuss two reactions, the Michael reaction and the Robinson annulation, to illustrate this principle.

In the Michael reaction, an enolate acts as a nucleophile that undergoes 1,4 addition to an α,β-unsaturated carbonyl compound. 1,3-Dicarbonyl (β-dicarbonyl) compounds are most frequently used to provide the enolate because they are quite acidic, and alkoxide bases can abstract the hydrogen atom that is α to both carbonyl carbon atoms. The Michael addition product has a reactive α-carbon atom that can undergo an intramolecular aldol condensation with a carbonyl carbon atom. The product contains a new six-membered ring.



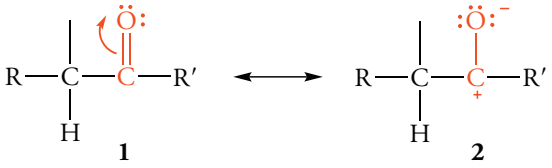
A Michael addition reaction followed by an intramolecular aldol condensation is known as the **Robinson annulation**, where the term annulation means "ring formation."

22.12 THE α-HYDROGEN ATOMS OF ACID DERIVATIVES

In Section 22.2, we saw that an enolate formed by deprotonation of the α-carbon atom of aldehydes or ketones is a nucleophile, and therefore a useful synthetic intermediate. The enolate reacts with the electrophilic carbon atom of an alkyl halide to give an alkylated product. The enolate reacts with the electrophilic carbon atom of a carbonyl group to yield an aldol product. Both of these processes generate carbon–carbon bonds.

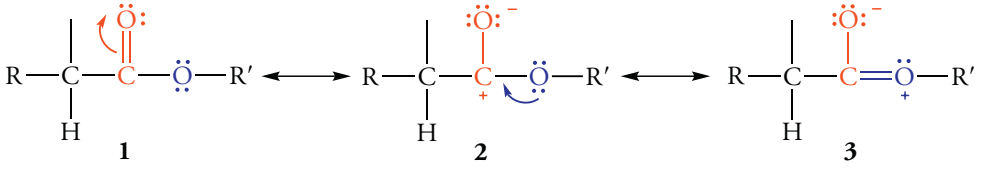
The electron-withdrawing effect of the positively charged carbonyl carbon atom also increases the acidity of the α-hydrogen atoms of acid derivatives. Their acidity also depends on resonance and inductive effects of the attached substituents (Table 22.1). Therefore, derivatives of carboxylic acids can form enolates that undergo reactions that resemble the condensation reactions of aldehydes and ketones.

In the following sections, we focus on condensation reactions at the α-carbon atom of esters. Reactions of these derivatives form carbon–carbon bonds and are useful in synthesis. Alkylation reactions using alkyl halides and reactions at carbonyl carbon atoms both occur with ester enolates. However, the reactions of enolates of acid derivatives differ somewhat from the reactions of enolates of aldehydes and ketones. For one thing, the α-hydrogen atoms of esters (pK_a 25) are less acidic than those of aldehydes and ketones (pK_a 20). Two resonance forms are written for aldehydes and ketones. The dipolar resonance form of a ketone has a positive charge on an electron-deficient carbonyl carbon atom. The contribution of this resonance form (2) to the resonance hybrid increases the acidity of the α-hydrogen atom as the result of inductive electron withdrawal.



1 **2**

Three resonance forms are written for esters, two of which are dipolar. Donation of electron density by the bridging oxygen atom yields a dipolar resonance form (3) with Lewis octets at all atoms. In this resonance form, the positive charge is located on the oxygen atom rather than the carbonyl carbon atom.



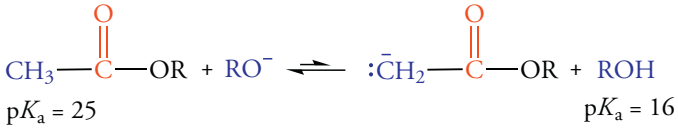
1 **2** **3**

Table 22.1
Acidity of α-Hydrogen Atoms

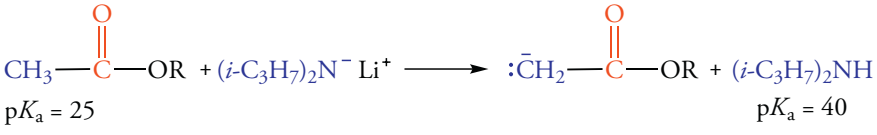
Compound	pK_a
CH_3CCl (O)	16
CH_3CCH_3 (O)	19
CH_3COCH_3 (O)	25
$CH_3C{\equiv}N$	25
$CH_3CN(CH_3)_2$ (O)	30

Formation of Ester Enolates

In Section 22.2, we considered the types of bases required to generate an enolate of aldehydes and ketones. We recall that relatively weak bases, such as alkoxide ions, give only low concentrations of the enolates of ketones. Because esters are weaker acids than ketones, even lower concentrations of ester enolates form in reactions with alkoxide ions. The alkoxide base *must* be the same as the alkoxy group contained in the ester to avoid exchange of alkoxy groups.



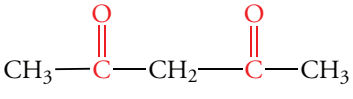
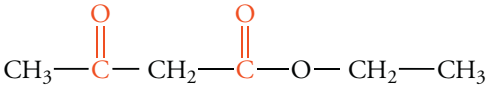
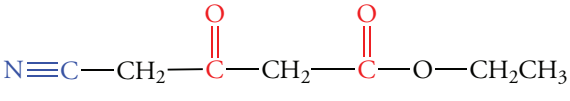
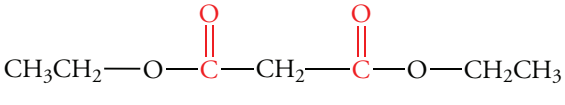
We recall that the conjugate base of an aldehyde must react with the aldehyde, which is present in a significantly greater concentration, to make an aldol condensation possible. A similar condensation reaction, called the **Claisen condensation**, occurs when low concentrations of ester enolates react with esters (Section 22.15). If an ester reacts with a very strong base, such as lithium diisopropylamide (LDA), high concentrations of the ester enolate form, and no ester would remain for a bimolecular self-condensation reaction. The ester enolate yield is stoichiometric when LDA is used as the base because diisopropylamine is a much weaker acid than an ester. Furthermore, LDA is a sterically hindered nucleophile, so it does not react with the electrophilic carbon atom of the ester.

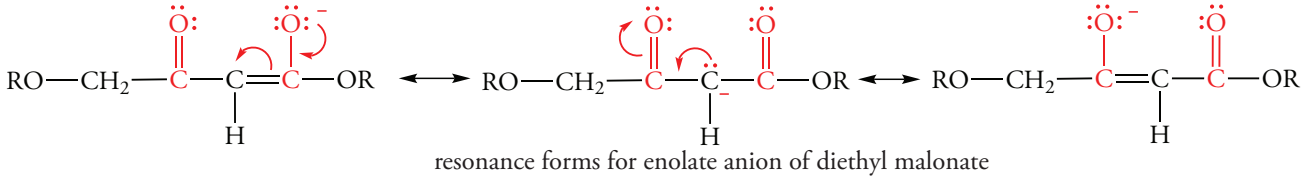


Enolates of β-Dicarbonyl Compounds

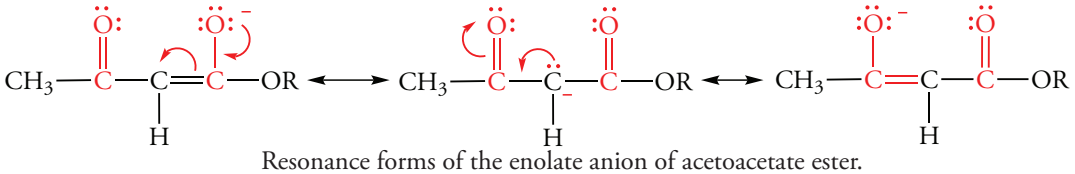
Compounds with a carbonyl group β to the carbonyl carbon atom of an ester are stronger acids than simple esters (Table 22. 2). When the α-hydrogen atom of a β-keto ester is removed, the negative charge of the conjugate base is delocalized from the β-carbon atom to two oxygen atoms. In an ester, the negative charge of the conjugate base is delocalized from the α-carbon atom to just one oxygen atom. Malonate esters and esters of acetoacetic acid form such resonance-stabilized enolate ions.

Table 22.2
Acidity of α-Hydrogen Atoms

Compound	*pK*$_a$	*Common Name*
	9	Acetylacetone
	11	Ethyl acetoacetate
	9	Ethyl cyanoacetate
	13	Diethyl malonate



resonance forms for enolate anion of diethyl malonate



Resonance forms of the enolate anion of acetoacetate ester.

Malonate esters and acetoacetate esters are more acidic than water or alcohols (Table 22.2). Thus, the hydroxide ion or an alkoxide ion is sufficiently basic to produce the conjugate base of either of these β-dicarbonyl compounds. The enolates of simple esters and β-keto esters are nucleophiles, and they undergo the condensation reactions we will discuss below.

Problem 22. 19

Rank the three resonance forms of the malonate ester in order of their stability. Are any two of the resonance forms equivalent?

Problem 22. 20

Why are malonate esters weaker acids than acetoacetate esters?

Sample Solution

The α-carbon atom of a malonate ester is bonded to the carbonyl carbon atoms of two ester functional groups, whereas the α-carbon atom of an acetoacetate ester is bonded to the carbonyl carbon atoms of an ester and a ketone. The α-carbon atom of esters are weaker acids than those of ketones because the alkoxy group donates electrons by resonance to the carbonyl carbon atom, thus decreasing its partial positive charge. Malonate esters have a smaller positive charge on the carbonyl carbon atom, and the adjacent α-hydrogen atoms are less acidic.

Problem 22. 21

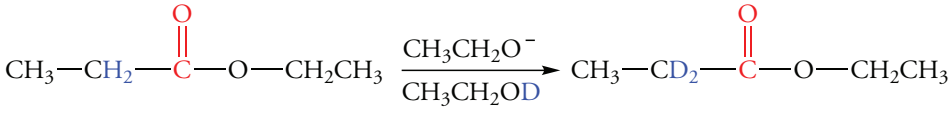
Calculate the equilibrium constant for the reaction of ethoxide ion with diethyl malonate.

22.13 REACTION AT THE α-CARBON OF ACID DERIVATIVES

The enolates of aldehydes and ketones undergo deuterium exchange, bromination, and alkylation reactions (Sections 22.4–22.6). Carboxylic acid derivatives react similarly. However, the added possibility of a competing nucleophilic acyl substitution reaction limits some of the substitution reactions at the α-carbon atom of acid derivatives. For example, acyl halides react with most bases in substitution reactions at the carbonyl carbon atom rather than by abstraction of the α-hydrogen atom. On the other hand, the pK_a of the α-hydrogen atoms of amides is very large, and these derivatives would require a very strong base for formation of enolates for synthetic reactions. Esters are the most convenient acyl derivatives for enolate formation and subsequent substitution at the α-carbon atom. The substituted ester can subsequently be converted into other acyl derivatives.

Deuterium Exchange

We recall that a hydrogen atom located on an α-carbon atom of an aldehyde or ketone can be lost to a solvent molecule and then regained in equilibrium reactions that occur by formation of an enol intermediate (Section 22.4). This hydrogen atom is called an *enolizable hydrogen atom*. The proton transfer equilibrium between a carbonyl compound and its enol is useful in the synthesis of isotopically labeled aldehydes or ketones using deuterium oxide (D_2O) and NaOD as a base. The same hydrogen–deuterium exchange occurs with esters. However, the exchange requires an alkoxide and its corresponding deuterated alcohol as solvent to avoid saponification of the ester.



Only α-hydrogen atoms are exchanged because the reaction occurs through an enolate ion intermediate. All possible enolizable hydrogen atoms are eventually replaced. The hydrogen atoms are lost in the solvent, which contains many more deuterium atoms than the number of hydrogen atoms transferred from the carbonyl compound.

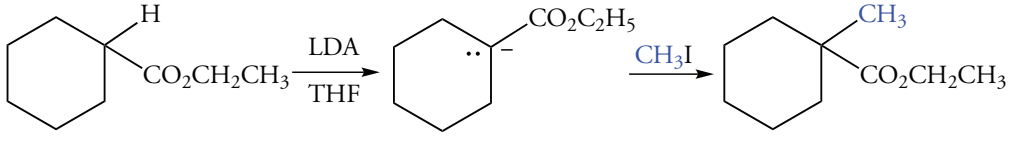
The rate of exchange of hydrogen by deuterium in esters is much slower than in ketones. Ketone exchange occurs at room temperature in a few minutes. Deuterium exchange reactions of esters require weeks at the same temperature. The exchange reaction is therefore usually carried out at the boiling point of the alcohol solvent.

Alkylation of Esters

We have seen that an enolate of a ketone is a nucleophile that can displace a leaving group from a primary alkyl halide. Although the enolate has two reactive sites, we have already learned that reaction of an electrophile with an enolate occurs at the α-carbon atom to give a substituted keto product called the C-alkylated product. The alternate reaction at the oxygen atom to give an O-alkylated product occurs much less commonly.

We also know that hydroxide ion or alkoxide ions are not basic enough to form the enolate ion in high concentration. Hence, the hydroxide ion or alkoxide ion would substitute for the halide ion of the alkyl halide to give an alcohol or ether. However, strong bases, such as potassium hydride or LDA, yield stoichiometric quantities of the enolate. An alkyl halide is then added to the solution of the enolate to give the α-alkylated product.

The α-hydrogen atoms of esters are less acidic than those of ketones. However, as in the case of ketones, LDA quantitatively removes α-hydrogen atoms of esters. Subsequent addition of an alkyl halide to the solution of the ester enolate yields an alkylated ester. Because the ester enolate is an even stronger base than enolates of ketones, only primary alkyl halides can be used as alkylating agents. Both secondary and tertiary alkyl halides undergo elimination reactions.

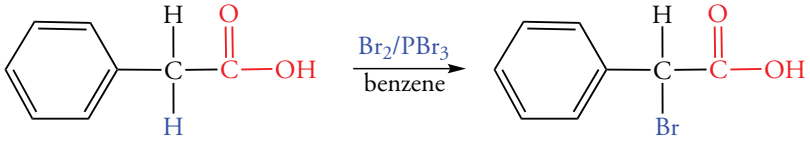


ethyl cyclohexanecarboxylate

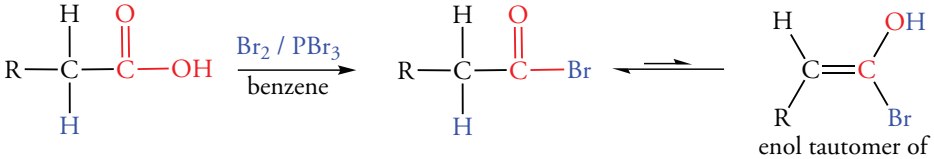
ethyl 1-methylcyclohexanecarboxylate

α-Bromination

Because the enol content of carboxylic acids is much lower than that of aldehydes and ketones, carboxylic acids do not react with halogens to give α-halo carboxylic acids. However, bromination does occur in the presence of a catalytic amount of PBr_3. The reaction also occurs in the presence of a small amount of phosphorus, which reacts with bromine to generate PBr_3 under the reaction conditions. Either variation of the method is called the **Hell—Volhard—Zelinsky reaction**.

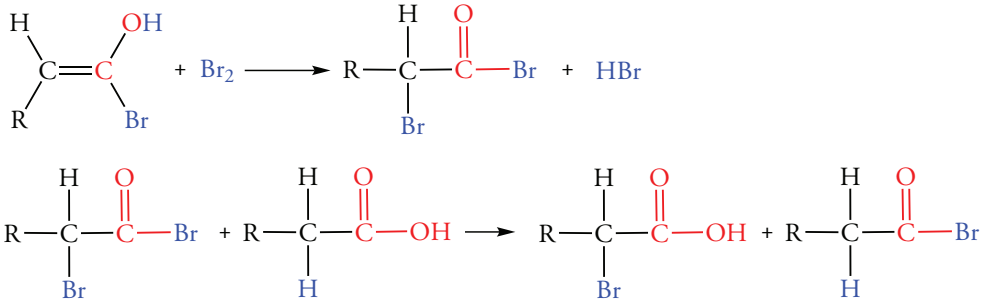


The carboxylic acid itself is not brominated in the Hell—Volhard—Zelinsky reaction. Rather, a small amount of the carboxylic acid is converted into an acid bromide, which has a substantially higher concentration of the enol tautomer than the carboxylic acid.

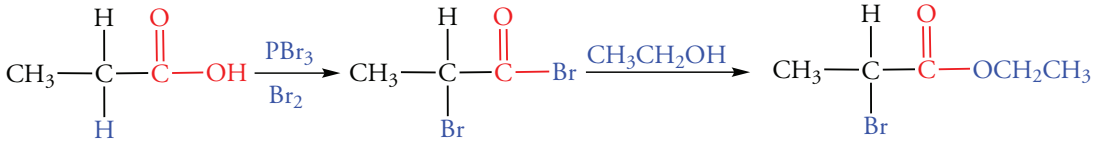


enol tautomer of an acid bromide

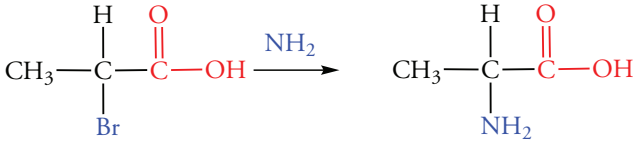
Reaction of the enol tautomer with bromine gives an α-bromo acyl bromide. An exchange reaction between the α-bromo acyl bromide and the unreacted carboxylic acid then occurs giving an α-bromo carboxylic acid. The second product, an acyl bromide, then reacts with bromine to form additional α-bromo acyl bromide. That is why only a catalytic amount of PBr_3 is required to convert all the carboxylic acid to an α-bromo derivative.



If one equivalent of PBr_3 is used in the Hell–Volhaid–Zelinsky reaction, an α-bromo acid bromide results. This acid halide can be used in the typical reactions of acid halides discussed in Chapter 21. For example, if an alcohol is added after completion of the reaction, an α-bromo ester results.



α-Bromo acids or esters undergo typical S_N2 substitution reactions. For example, bromide can be displaced by ammonia in aqueous solution to give an α-amino acid.



alanine
(an alpha amino acid)

Problem 22. 22

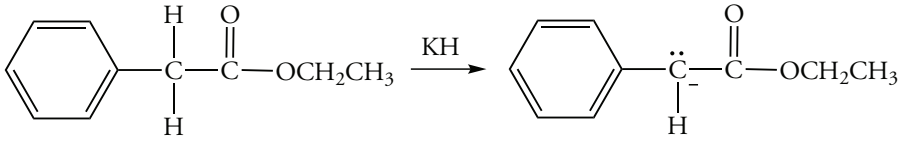
Predict the product of the reaction of 2-bromobutanoic acid with an aqueous sodium carbonate solution.

Problem 22. 23

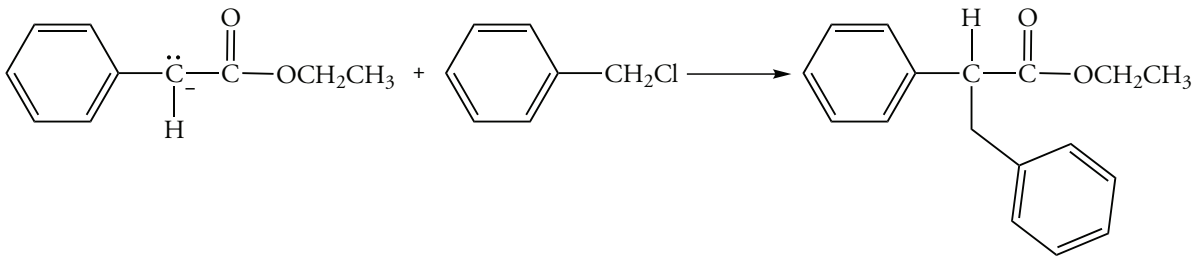
Draw the product of the reaction of ethyl 2-phenylacetate with KH followed by reaction with benzyl chloride.

Sample Solution

Potassium hydride is a strong base that removes the α-hydrogen atom and generates a resonance-stabilized carbanion.



Benzyl chloride is very reactive in S_N2 reactions and cannot undergo competitive elimination reactions because it has no α-hydrogen atoms. The carbanion derived from ethyl 2-phenylacetate reacts with benzyl chloride to give an alkylated product.

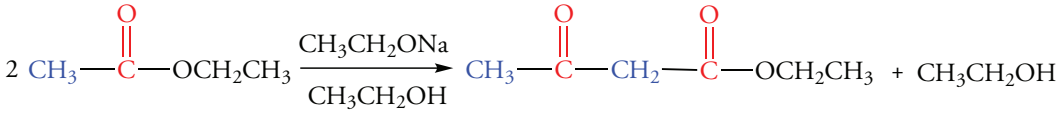


Problem 22. 24

Suggest two methods to prepare 2-isopropylpentanenitrile using an a lkylation reaction. Which would give the better yield?

22.14 THE CLAISEN CONDENSATION

Two molecules of an ester react in the presence of an alkoxide base to produce a condensation product. The reaction, which produces a β-keto ester, is called the **Claisen condensation**.



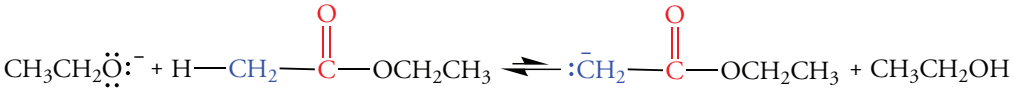
The ester must have two α-hydrogen atoms, as we will see in our discussion of the mechanism. One equivalent of base is required for the Claisen condensation, whereas only a catalytic amount is required for the aldol condensation. The base promotes the reaction, but does not act as a catalyst. That is, the base is consumed in the reaction.

Some of the steps in the mechanism of the Claisen condensation resemble those of the aldol condensation. For example, both mechanisms have several reversible steps. However, there are important differences. Several equilibria in the Claisen condensation are not favorable. The entire sequence becomes favorable only in the final step in an acid–base reaction. And, the Claisen condensation requires a molar equivalent of base.

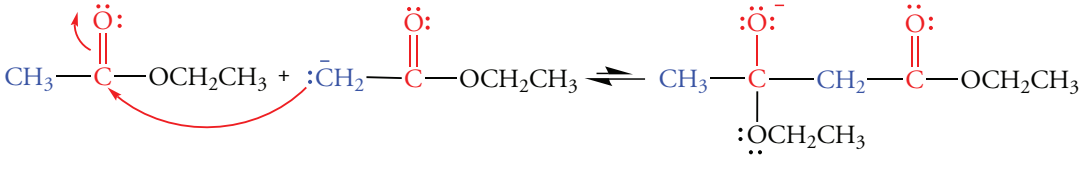
The acid dissociation constants of esters (pK_a = 25) are about 10^9 times smaller than the pK_a of ethanol, which is 16. Thus, the reaction of sodium ethoxide with an ester to produce an ester enolate and ethanol has an equilibrium constant of 10^{-9}, and only a minuscule amount of the enolate exists at equilibrium.

We will divide the mechanism into five steps.

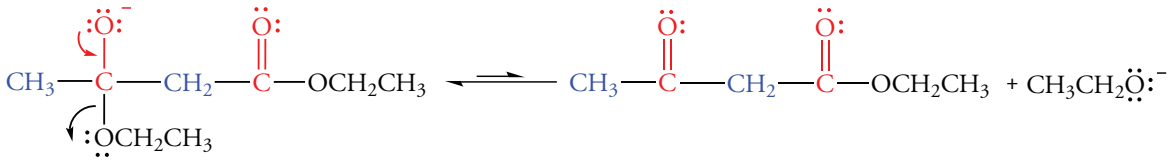
1. One equivalent of base removes an α-hydrogen from the ester to give an ester enolate.



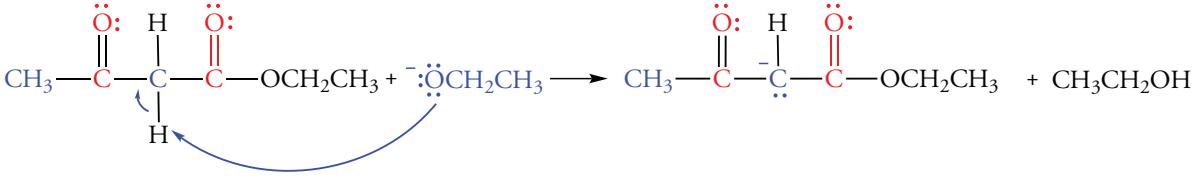
2. The ester enolate reacts with another molecule of ester to form a carbon–carbon bond in a nucleophilic addition reaction that gives a tetrahedral intermediate.



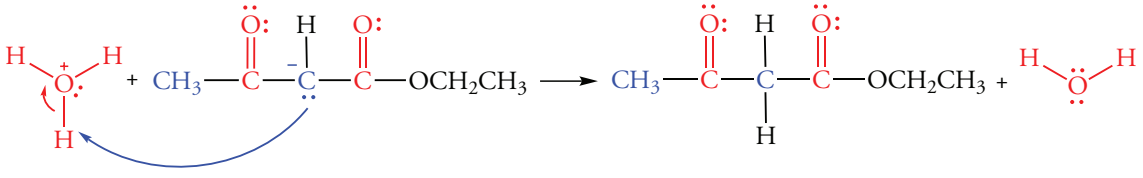
3. The addition product is the conjugate base of a hemiketal, which loses an alkoxide to give a β-keto ester.



4. β-Keto esters have pK_a values around 11 because the negative charge of the conjugate base can be delocalized over both carbonyl groups. Ethanol is a weaker acid than β-keto esters. Therefore, ethoxide ion quantitatively removes a proton from the product of the Claisen condensation. This final step drives the overall sequence of reactions to completion.

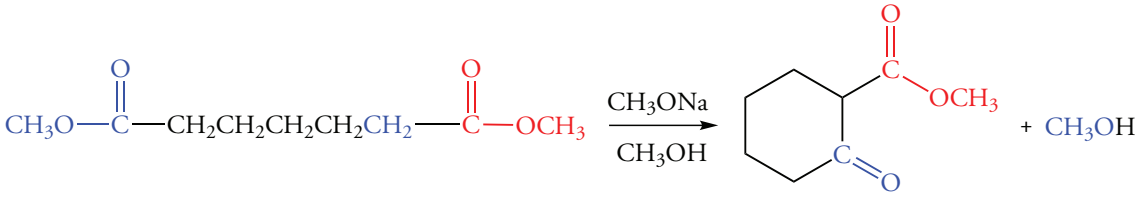


5. In the last step of the reaction, adding dilute acid converts the conjugate base of the β-keto ester to the product.



Dieckmann Condensation

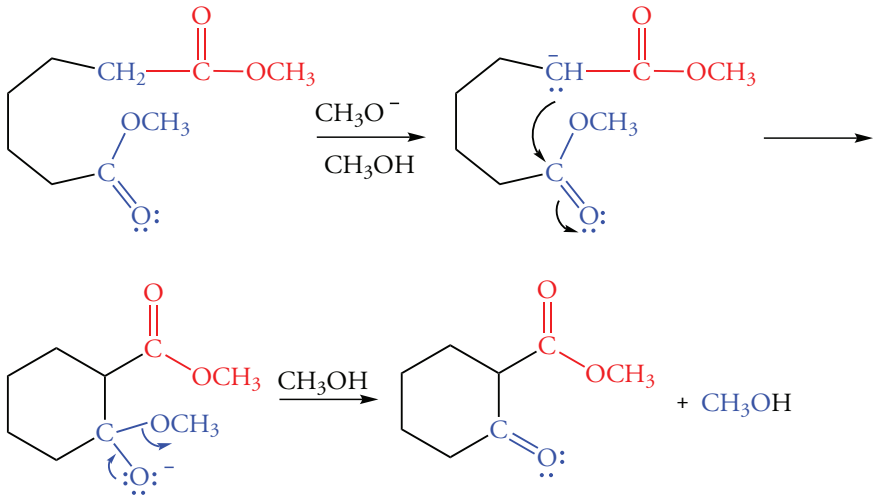
We recall that intramolecular aldol condensation reactions can occur to give five- or six-membered ring compounds (Section 22.9). An intramolecular Claisen condensation, known as the Dieckmann condensation, can also occur to give five- or six-membered ring compounds. The Dieckmann condensation is more favorable than the bimolecular Claisen condensation because it converts a single molecule of reactant into two molecules of product.



The mechanism of this intramolecular reaction exactly parallels the mechanism for the intermolecular Claisen condensation.

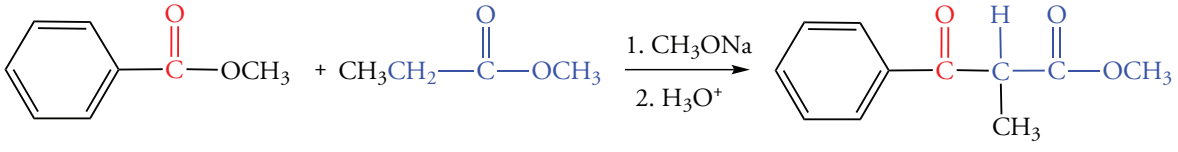
1. An alkoxide anion abstracts an α-hydrogen atom to give a carbanion.
2. This carbanion attacks the other carbonyl carbon atom to give a tetrahedral intermediate.
3. The tetrahedral intermediate eliminates an alkoxide anion.
4. The alkoxide anion abstracts an α-hydrogen to give another carbanion. Thus the original α-carbon atom must have *two* hydrogen atoms.
5. Adding acid protonates the carbanion, driving the reaction to completion.

The following mechanism omits steps 4 and 5.



Mixed Claisen Condensations

We recall that mixed aldol condensation reactions between two different aldehydes are successful only in limited cases (Section 22.8). Similar circumstances are required for the reaction of two different esters in a mixed Claisen condensation. One of the esters must not have any α-hydrogen atoms; that is, it cannot form an enolate. One ester must also be more susceptible to attack of a nucleophile at the carbonyl carbon atom than the second ester in the mixed Claisen condensation. Only then can the reaction give a good yield. For example, a mixed Claisen condensation occurs between methyl benzoate and methyl propanoate.



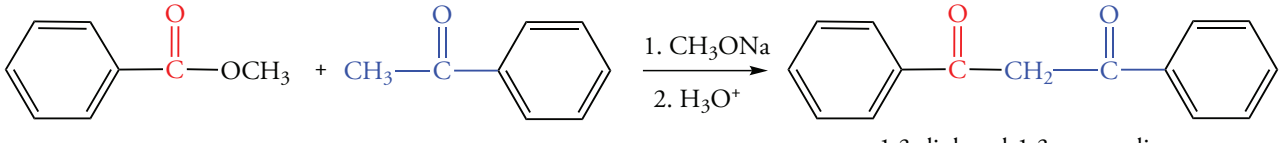
methyl 2-methyl-3-phenyl-3-oxopropanoate

Reaction between two methyl benzoate molecules cannot occur because it has no α-hydrogen atoms. Therefore, methyl benzoate is mixed with a base, and methyl propanoate is then slowly added. The reaction converts methyl propanoate to an ester enolate anion. The enolate of methyl propanoate reacts preferentially with methyl benzoate for two reasons.

1. Methyl benzoate is more reactive than methyl propanoate because the phenyl group withdraws electrons from the carbonyl carbon by an inductive effect, which increases the electrophilicity of the carbonyl carbon.
2. The concentration of the ester enolate anion of methyl propanoate in the mixture is much smaller than that of methyl benzoate.

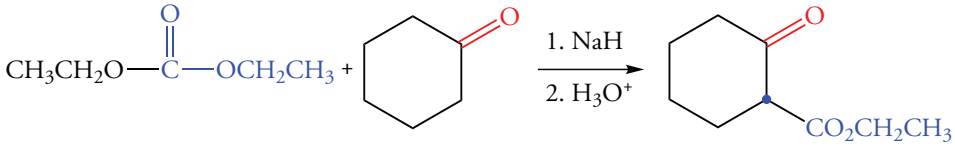
Acylation of Ketones with Esters

Nonenolizable esters can be used to acylate a ketone, yielding a β-diketone. For example, methyl benzoate can react with the enolate anion derived from acetophenone.



1,3-diphenyl-1,3-propandione

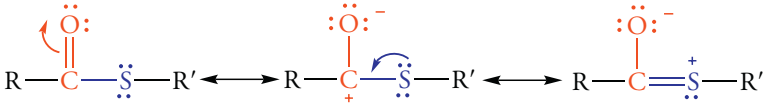
A useful variation of the acylation of a ketone with an ester uses diethyl carbonate as the ester with no α-hydrogens. Diethyl carbonate will react with the enolate anion of a ketone. The enolate displaces one of the two alkoxy groups of diethyl carbonate. The product of this Claisen-type condensation is a β-keto ester.

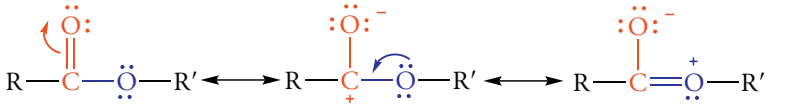


Claisen Condensation of Thioesters: A Biochemical Process

A variation on the Claisen condensation is an important biochemical reaction responsible for carbon–carbon bond formation in the biosynthesis of fatty acids. Also, a reverse Claisen condensation occurs in the catabolism of fatty acids. We have seen that the base-catalyzed condensation of two carboxylate esters occurs because the proton α to the carbonyl group is slightly acidic. The α-hydrogen atom in β-keto esters has a pK_a of about 10.5. This pK_a value is too high for β-keto esters to be of much use in biochemical reactions. At pH 7, the ratio of the conjugate base (the enolate anion) to the keto ester is less than 0.001.

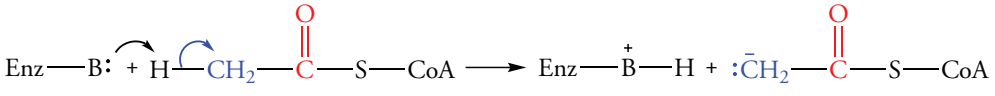
Claisen condensations in cells result from the condensation of thioesters. The sulfur atom of the thioester is part of a relatively large molecule called coenzyme A. The pK_a of an α-hydrogen atom of a thioester is about 8.5. It is a hundred times more acidic that the α-hydrogen of β-keto ester. The increased acidity of thioesters results from the ineffective resonance stabilization of the positive charge of the carbonyl carbon atom by sulfur compared to oxygen.



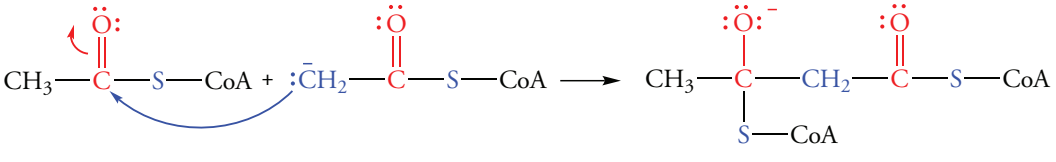


Because the 3p orbitals of sulfur do not effectively overlap with the 2p orbitals of carbon, the positive charge of the dipolar resonance form of a carbonyl group cannot be further delocalized. The higher positive charge of the carbonyl carbon atom of the thioester more strongly polarizes the C—H bond in the thioester, increasing its acidity.

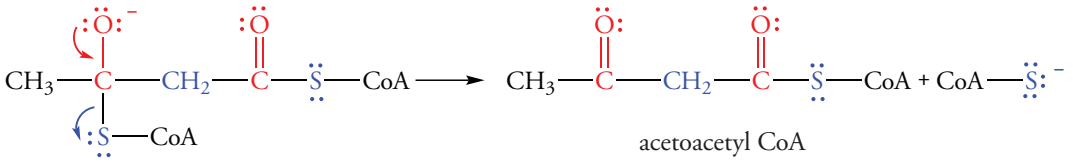
Enzymes called acyl CoA ligases catalyze the Claisen condensation of thioesters of acetyl coenzyme A. In the first step in the reaction, a basic residue in the enzyme (Enz—B:) abstracts the acidic α-hydrogen atom of acetyl coenzyme A to form a resonance-stabilized thioenolate anion.



This thioenolate anion is a nucleophile that attacks the electrophilic carbonyl carbon atom of a second acetyl CoA molecule to give a tetrahedral intermediate.



The tetrahedral intermediate undergoes an elimination reaction that produces the Claisen product, acetoacetyl CoA, plus the thiolate anion of coenzyme A (CoA—S⁻).



Problem 22. 25

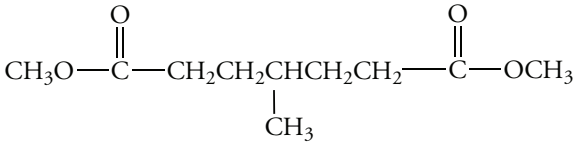
Which of the following esters cannot undergo a Claisen condensation?

(a) $CH_3CH_2CH_2CO_2CH_3$ (b) $CH_3CH_2CH_2CO_2CH_3$

(c) $(CH_3)_2CHCO_2CH_2CH_3$ (d) $C_6H_5CO_2CH_3$

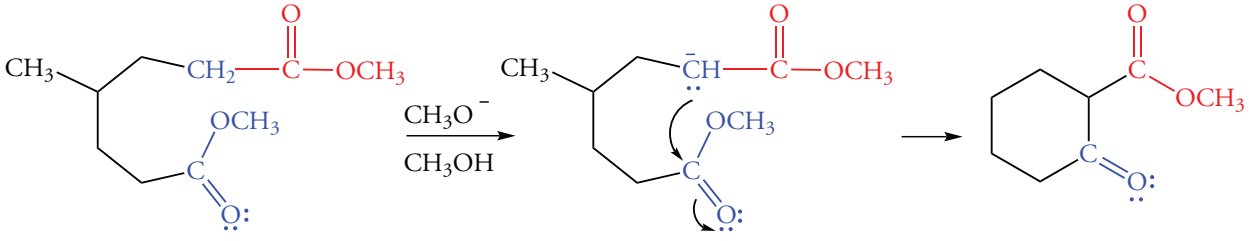
Problem 22. 26

Draw the structure of the product formed by a Dieckmann reaction of the following diester with sodium methoxide.



Sample Solution

The diester is symmetrical. Abstraction of a hydrogen ion from either of the two equivalent α-methylene groups gives an ester enolate that can attack a carbonyl carbon atom. There are four carbon atoms between the ester enolate and the carbonyl carbon atom. Thus, a six-membered ring forms in the Dieckmann condensation.

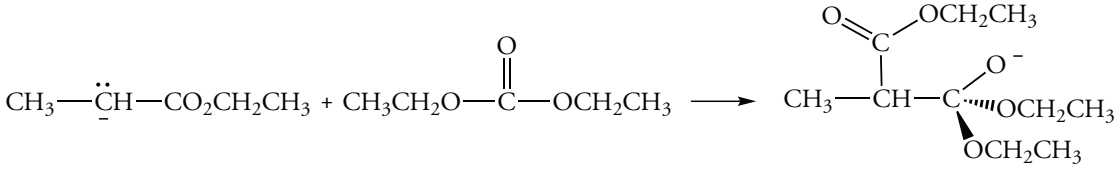


Problem 22. 27

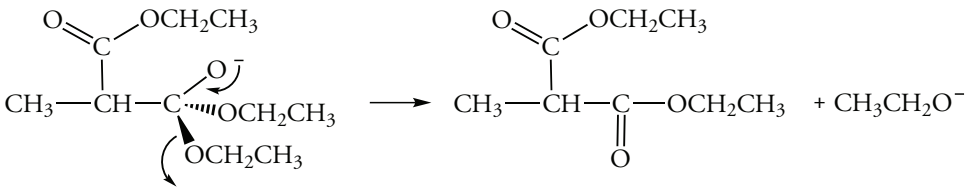
Write the structure of the product of a mixed Claisen reaction using ethyl propanoate and diethyl carbonate.

Sample Solution

Ethyl propanoate can form an enolate, but diethyl carbonate cannot. Thus, nucleophihc attack of the enolate of ethyl propanoate on the carbonyl carbon atom of diethyl carbonate can occur.

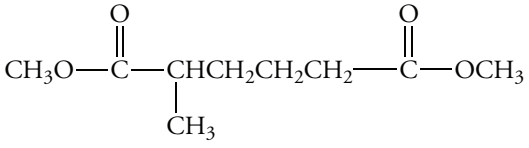


Loss of an ethoxide ion from the tetrahedral intermediate gives a methyl-substituted malonate ester.



Problem 22. 28

The dimethyl ester of 2-methyladipic acid is not symmetrical. However, a good yield of a single Dieckmann condensation product is possible. Explain why. Write the structure of the product.



Problem 22. 29

Draw the structure of the major product formed in the reaction of methyl formate and dimethyl succinate using a molar equivalent of sodium methoxide.

Problem 22. 30

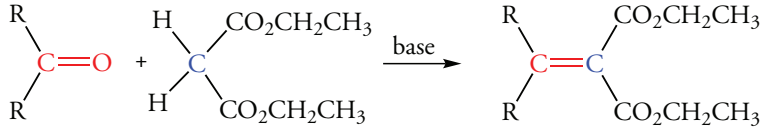
Ethyl 4-oxohexanoate forms a cyclic product when treated with a molar equivalent of sodium methoxide. Draw the structure of the product.

22.15 ALDOL-TYPE CONDENSATIONS OF ACID DERIVATIONS

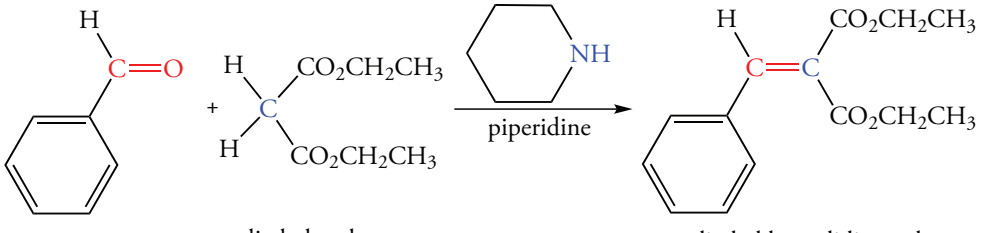
We recall that an aldol condensation occurs by attack of a carbanion derived from an aldehyde or ketone on the carbonyl carbon atom of a second molecule of an aldehyde or ketone. The product is a β-hydroxy carbonyl compound, or an α,β-unsaturated carbonyl dehydration product. Aldol-type condensations also occur when the carbanion is derived from carboxylic acid derivatives.

Knoevenagel Condensation

The Knoevenagel condensation reaction resembles a mixed aldol condensation. In this process, an enolate derived from an ester attacks the electrophilic carbon atom of an aldehyde or ketone. Dehydration occurs under the reaction conditions to give an α,β-unsaturated carbonyl compound.



The Knoevenagel condensation is restricted to compounds with α-hydrogen atoms that are relatively acidic, such as malonate esters or esters of acetoacetic acid. Piperidine, a saturated analog of pyridine, is often used as a base for the reaction.

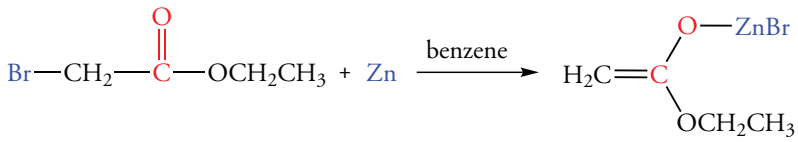


diethyl malonate

diethyl benzylidinemalonate

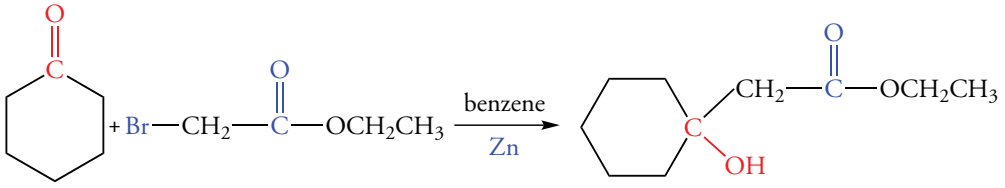
Reformatskii Reaction

The reaction of an α-halo ester with zinc gives an intermediate ester enolate coordinated to a zinc ion. This ester enolate resembles the enolate formed by deprotonation of an ester. Although the charge on an enolate is delocalized, the zinc is bonded to the oxygen atom, the site of most of the negative charge.



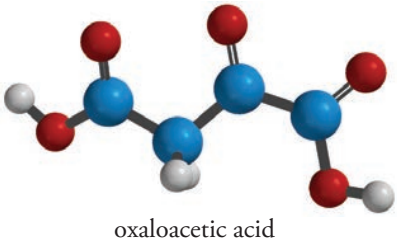
ethyl 2-bromoacetate — zinc enolate

The zinc enolate can potentially react with an electrophilic carbonyl carbon atom or at the oxygen atom of the enolate. However, we recall that similar reactions of enolates of aldehydes and ketones occur at carbon, thus retaining the very stable carbonyl group. The same considerations are important for the reactions of ester enolates, which also react at the carbonyl carbon.



ethyl 2-(1-hydroxycyclohexyl)acetate

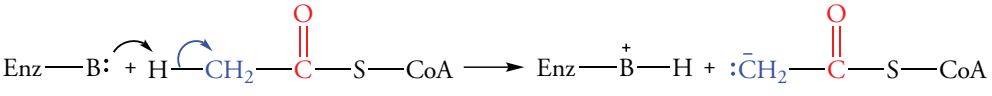
The Reformatskii reaction resembles an aldol reaction because a enolate anion attacks a carbonyl group to give an α-hydroxy carbonyl compound. In an aldol reaction, the enolate is derived from an aldehyde or ketone. In the Reformatskii reaction, the enolate is derived from an ester.



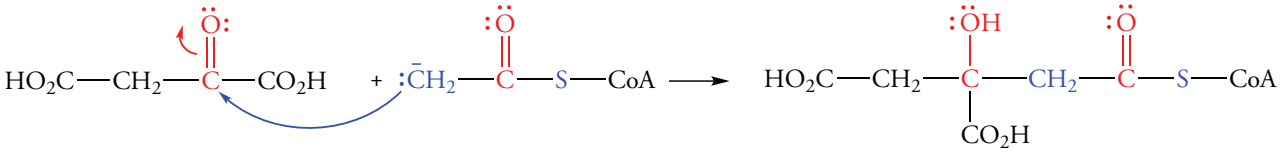
oxaloacetic acid

Biochemical Condensation Reactions

A condensation reaction between oxaloacetic acid, an α-ketoacid, and the thioester acetyl coenzyme A occurs in the citric acid cycle. As in the Claisen condensation of two acetyl CoA molecules, the first step is formation of a thioenolate ester.

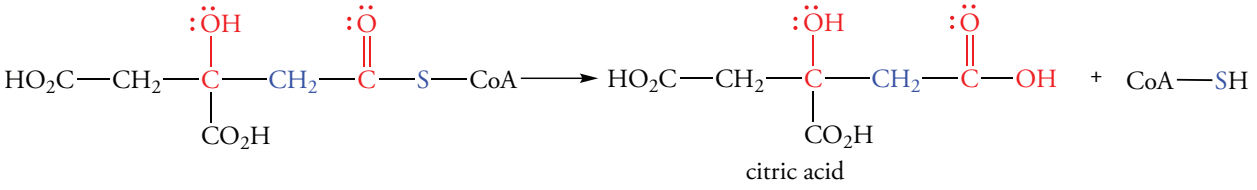


The α-carbon of acetyl coenzyme A forms a bond to the carbonyl carbon of oxaloacetic acid in a reaction that resembles an aldol condensation. The product is citryl CoA

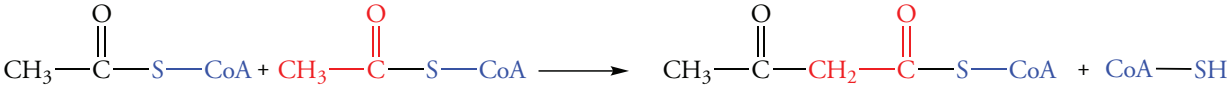


citryl CoA

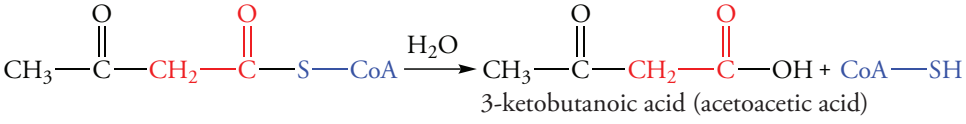
Hydrolysis of citryl CoA produces citric acid and releases CoA. This step provides the driving force for the biosynthesis of citric acid.



Acetyl CoA is produced by the catabolism of carbohydrates, fats, and certain amino acids. The catabolism of fatty acids predominates over the catabolism of carbohydrates in certain illnesses, such as diabetes. When there is not enough oxaloacetate to react with the available CoA, a Claisen condensation of two acetyl CoA molecules produces acetoacetyl CoA.



Hydrolysis of the thioester gives 3-ketobutanoic acid (acetoacetic acid). We recall that β-keto acids readily undergo decarboxylation. In this case, the decarboxylation product is acetone. And that is the source of the "acetone breath" of people suffering from severe episodes of diabetes.



Problem 22. 31

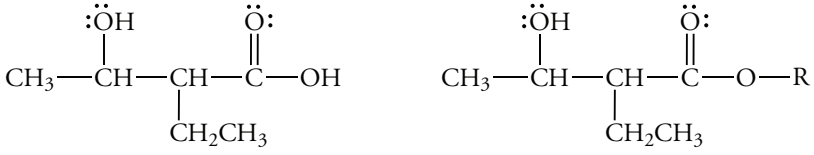
Draw the structure of the product formed in the reaction of ethyl acetoacetate and benzaldehyde catalyzed by piperidine.

Problem 22. 32

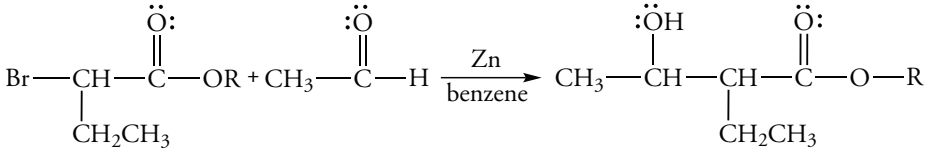
Outline a synthesis of 2-ethyl-2-butenoic acid using the Reformatskii reaction as one of the steps in the reaction sequence. Will a single product result from this reaction?

Sample Solution

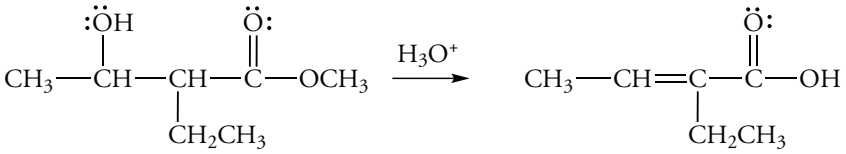
The product is an α,β-unsaturated carboxylic acid. It can be obtained by dehydration of a β-hydroxy acid.



The β-hydroxy ester is a typical product of a Reformatskii reaction, which forms by the reaction of a α-halo acid with an aldehyde or ketone.



The Reformatski reaction of the methyl ester of 2-bromobutanoic acid with acetaldehyde gives the β-hydroxy ester shown above. Hydrolysis of the ester simultaneously leads to loss of water to give the α,β-unsaturated acid. A mixture of (*E*) and (*Z*) isomers results.



Problem 22. 33

Outline a synthesis of 3-phenyl-2-butenoic acid using the Reformatskii reaction as one of the steps in the reaction sequence. Will a single product result from this reaction?

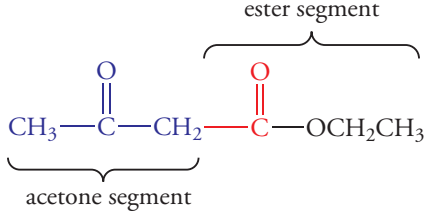
22.16 β-DICARBONYL COMPOUNDS IN SYNTHESIS

The alkylation of simple aldehydes, ketones, or esters is limited as a synthetic procedure. When a alkoxide is used as the base to form an enolate, a competing aldol condensation occurs in the case of aldehydes and ketones, and a Claisen condensation occurs in the case of esters. Strong bases, such as LDA, can be used to form alkylated compounds, but these very reactive reagents require special handling techniques.

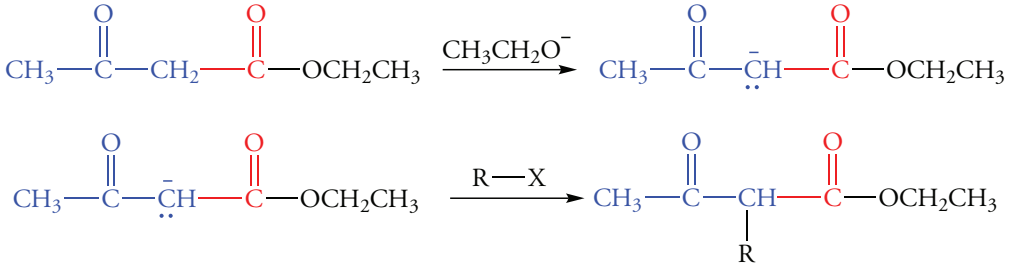
Alkylation at the α-position of a carbonyl compound can be carried out indirectly by using a β-dicarbonyl compound such as ethyl malonate or ethyl acetoacetate. Both compounds are readily deprotonated by alkoxide anions, and the resulting enolate is easily alkylated. β-Keto esters are valuable synthetic intermediate because they readily undergo decarboxylation. At the end of the synthesis, the β-keto ester is hydrolyzed to yield a β-keto acid. We recall that β-keto acids readily decarboxylate when heated (Section 19.8). Therefore, the final product is the same as that obtained by direct alkylation of simpler carbonyl compounds. The yields are high even though more steps are required. Furthermore, it is more convenient to use common bases such as alkoxides than the stronger bases required for direct alkylation of an ester. Finally, because the enolate of a β-dicarbonyl compound is a weaker base, both primary and secondary alkyl halides can be used as alkylating agents without competing elimination reactions.

Acetoacetate Ester Synthesis

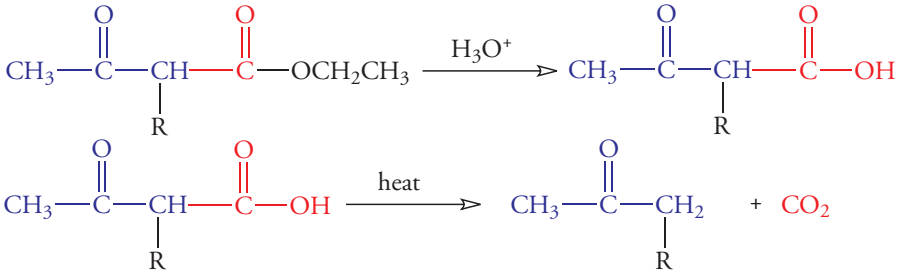
The Claisen condensation of ethyl acetate yields ethyl acetoacetate. This readily available compound and other β-keto esters formed by Claisen condensations are used as intermediates on the synthesis of alkyl derivatives of ketones. For example, ethyl acetoacetate is like an acetone molecule with an appended ester group.



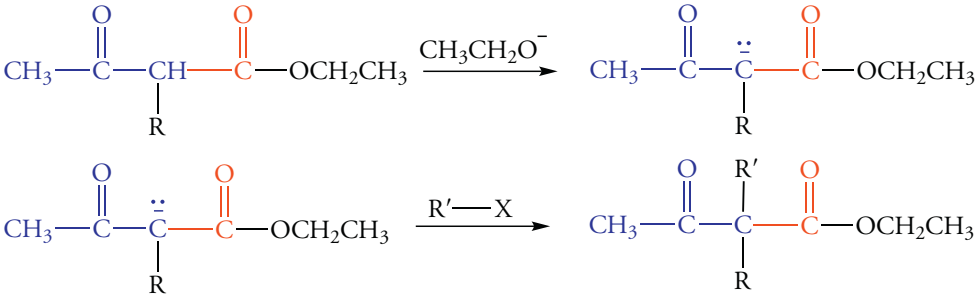
Sodium ethoxide is basic enough to extract a proton from the α-carbon atom. Treating the enolate anion with an alkyl halide gives an alkylated product.



Acid hydrolysis converts the β-keto ester to a β-keto acid that readily decarboxylates when heated.

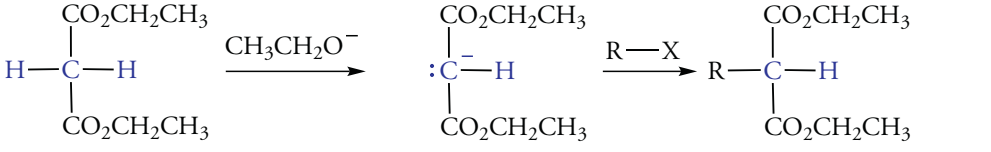


The net result of these reactions is the alkylation of acetone without competing side reactions. The above sequence of reactions can be repeated a second time to give a dialkylated acetone.

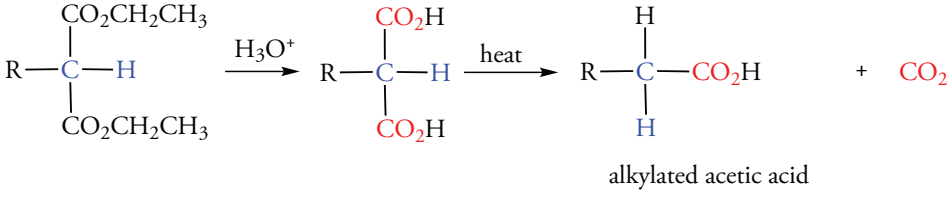


Malonate Ester Synthesis

The malonate ester synthesis resembles the acetoacetate ester synthesis. It is used to prepare alkylated derivatives of acetic acid and other carboxylic acids rather than derivatives of acetone or other ketones prepared by the acetoacetic ester synthesis. The α-hydrogen atom of diethyl malonate is sufficiently acidic to be deprotonated by ethoxide ion. Subsequent alkylation with a primary or secondary alkyl halide yields an alkylated malonate ester.

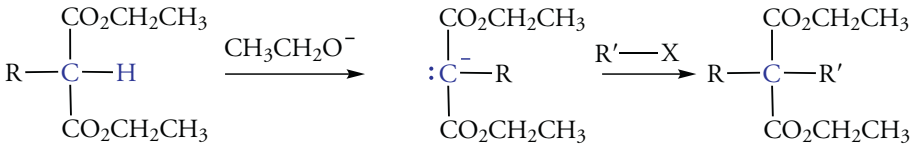


Acid-catalyzed hydrolysis of the alkylated product yields a malonic acid that decarboxylates when heated.

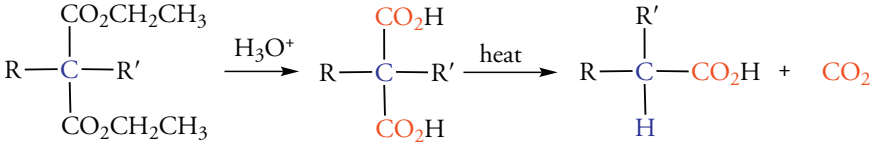


In summary, acetic acid has been alkylated by taking advantage of a "temporary" ester group, which enhances the acidity of the α-hydrogen atom and allows the alkylation of the α-carbon atom. Then the ester group is removed.

More complicated structures can be prepared by the malonate ester synthesis. It is possible to introduce a second alkyl group by repeating the steps outlined above using either the same alkyl group or a different one.



alkylated diethyl malonate | enolate ion | alkylated diethyl malonate



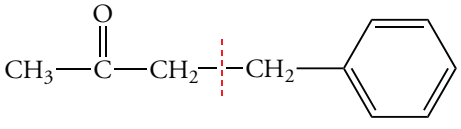
dialkylated acetic acid

Problem 22. 34

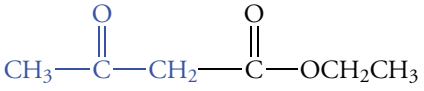
What reactants are required to prepare 4-phenyl-2-butanone using the acetoacetic ester method.

Sample Solution

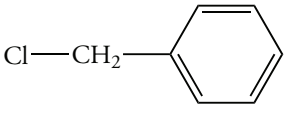
Identify the carbon–carbon bond that forms in the acetoacetic ester condensation. It is located between the α-carbon atom of an acetone unit and the alkylating group.



The acetone unit is derived from an acetoacetic ester such as ethyl acetoacetate. The alkylating group is available in the form of a halogen derivative such as benzyl chloride.

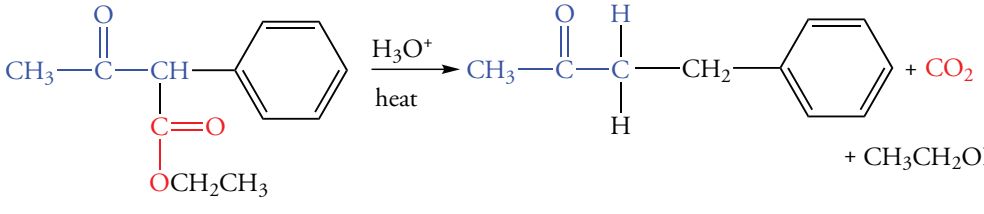


ethyl acetoacetate



benzyl chloride

Reaction of ethyl acetoacetate with sodium ethoxide followed by addition of benzyl chloride gives an alkylated acetoacetate ester. Subsequent acid-catalyzed hydrolysis with heat leads to decarboxylation of the β-keto acid.



Problem 22. 35

What alkylating agent is required to prepare 1-phenyl-1,4-pentanedione using ethyl acetoacetate as the other reactant?

Problem 22. 36

Ethyl acetoacetate can be doubly alkylated. Outline a multistep synthetic sequence to produce 3-propyl-5-hexen-2-one from ethyl acetoacetate as one of the starting materials.

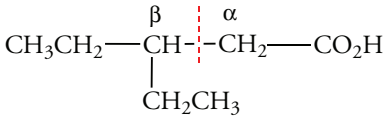
Problem 22. 37

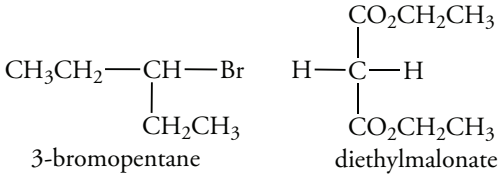
What reactants are required to prepare 3-ethylpentanoic acid by the malonate ester synthesis?

Sample Solution

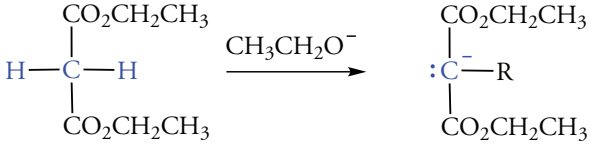
Identify the carbon–carbon bond between the α- and β-carbon atoms.

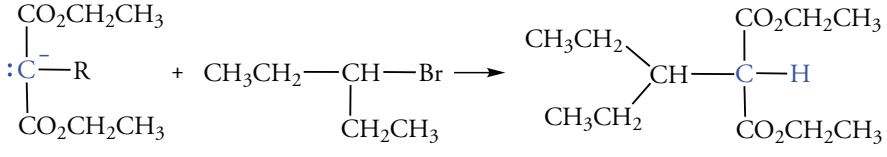
The acetic acid portion, which includes the methylene group and the carboxyl group, is derived from a malonate ester. The alkyl group is available as a haloalkane such as 3-bromopentane.

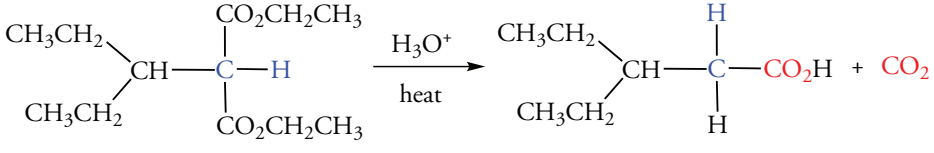




Reaction of diethyl malonate with sodium ethoxide followed by addition of 3-bromopentane gives an alkylated malonate ester. Subsequent acid-catalyzed hydrolysis with heat leads to decarboxylation of the dicarboxylic acid to give 3-ethylpentanoic acid.







Problem 22. 38

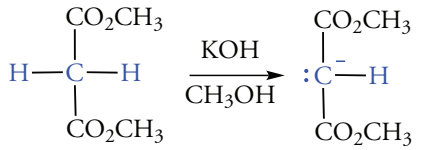
Explain why 3,3-dimethylpentanoic acid cannot be prepared by the malonate ester synthesis.

Problem 22. 39

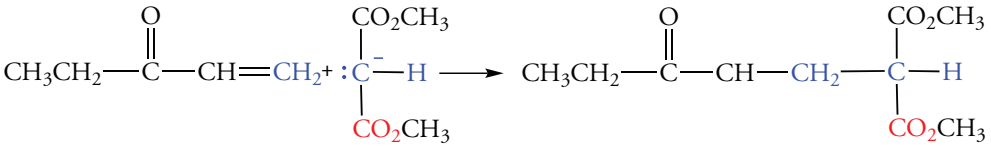
The reaction of diethyl malonate and 1,4-dibromobutane in the presence of two moles of sodium ethoxide followed by acidification and heat gives a compound $C_6H_{10}O_2$. What is the structure of the product?

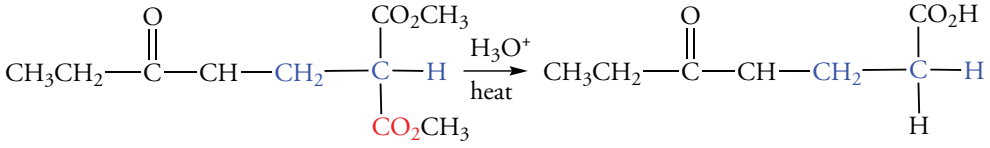
22.17 MICHAEL CONDENSATIONS OF ACID DERIVATIVES

In the Michael reaction, an enolate acts as a nucleophile and adds 1,4 to an α,β-unsaturated carbonyl compound (Section 22.12). 1,3-Dicarbonyl compounds frequently provide the enolate, called the Michael donor. Three α,β-unsaturated carbonyl compounds are commonly used as Michael acceptors 3-buten-2-one (methyl vinyl ketone), 2-propenal (acrolein), and methyl 2-propenoate (methyl acrylate). For example, dimethyl malonate reacts with 3-buten-2-one in a base-catalyzed reaction.



dimethyl malonate enolate ion





5-oxohexanoic acid

Hydrolysis of the ester functional groups of this Michael product followed by decarboxylation yields a 5-keto acid. In general, the Michael addition of 1,3-dicarbonyl donors to typical α,β-unsaturated carbonyl compounds (Michael acceptors) yields 1,5-dicarbonyl compounds.

Problem 22. 40

Draw the product of the Michael addition of methyl acetoacetate to 2-cyclohexenone. Draw the product obtained by hydrolyzing the adduct followed by heating to decarboxylate the intermediate acid.

Exercises

Acidity of α-Hydrogen Atoms

22.1 The pK_a of 2,4-pentanedione is 9. Calculate the equilibrium constant for the acid–base reaction of 2,4-pentanedione with sodium ethoxide. The pK_a of ethanol is 15.9.

22.2 The pK_a of acetonitrile, CH_3CN, is 25. Calculate the equilibrium constant for the acid–base reaction of acetonitrile with LDA. The pK_a of isopropylamide is 40.

22.3 The pK_a of acetophenone is 16. Calculate the equilibrium constant for the acid–base reaction of acetophenone with LDA.

22.4 The pK_a of nitromethane is 10.2. Calculate the equilibrium constant for the acid–base reaction of nitromethane with sodium ethoxide. The pK_a of ethanol is 15.9

22.5 The pK_a values of acetone and 3-pentanone as measured in DMSO are 26.5 and 27.1, respectively. Explain this order of values.

22.6 The pK_a values of acetone and 1-phenyl-2-propanone as measured in DMSO are 26.5 and 19.8, respectively. Explain this order of values.

Stability of Enols

22.7 Which ketone has the larger percent enol at equilibrium, cyclohexanone or cyclobutanone?

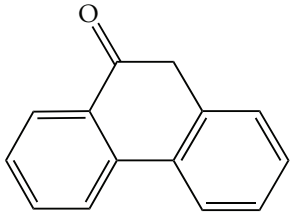
22.8 Which ketone has the larger percent enol at equilibrium, 1,3-cyclohexanedione or 1,4-cyclohexanedione?

22.9 Write the structures of the isomeric enols of 2,2-dimethyl-3-pentanone and rank them in order of their stability.

22.10 Write the structures of the isomeric enols of 2-methylcyclopentanone and rank them in order of relative stability.

22.11 Which ketone has the larger percent enol at equilibrium, 1,2-diphenylethanone or 1,3-dipheny1-3-propanone?

22.12 Write the structure for the enol tautomer of the following molecule. What structural features contribute to its stability?



Enolates

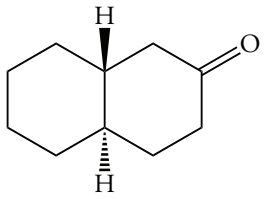
22.13 Write the resonance form with a negative charge on the oxygen atom for the enolates derived from each of the following compounds.
(a) 3,3-dimethyl-2-butanone (b) acetophenone (c) 2,2-dimethylcyclohexanone

22.14 Write the resonance form with a negative charge on the oxygen atom for all possible enolates derived from each of the following compounds. Which enolate is the most stable in each case?
(a) 2-pentanone (b) 1-phenyl-2-propanone (c) 1,3-cyclohexanedione

22.15 Write the contributing resonance forms of the conjugate base of acetonitrile (CH_3CN) and nitromethane (CH_3NO_2).

22.16 Write the contributing resonance forms for all possible conjugate bases of 3,6,6-trimethyl-2-cyclohexenone.

22.17 The following ketone gives a mixture of two enolates in approximately equal amounts (53:47). (a) Write the structures of the enolates and (b) explain why they are of comparable stability.

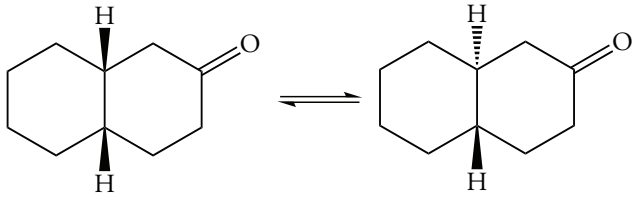


22.18 2-Methylcyclopentanone gives a mixture of two enolates in a 94:6 ratio. (a) Write their structures and (b) assign their relative stabilities.

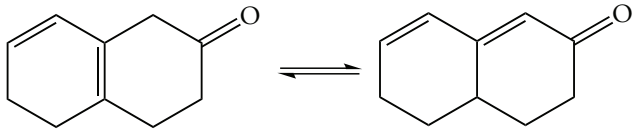
22.19 3-Pentanone gives a mixture of two enolates in a 84:16 ratio. (a) Write their structures and (b) assign their relative stabilities.

22.20 2,2-Dimethyl-3-pentanone gives a mixture of two enolates. Based on the data in Exercise 22.20, predict how the ratio of the amounts of the two enolates would differ from the ratio for 1-pentanone.

22.21 Write the mechanism for the following isomerization reaction, which occurs using sodium ethoxide in ethanol. Predict which isomer is more stable.



22.22 Write the mechanism for the following isomerization reaction, which occurs using sodium ethoxide in ethanol. Predict which isomer is more stable.



22.23 Write a mechanism for the base-catalyzed isomerization of 3-cyclohexenone to 2-cyclohexenone.

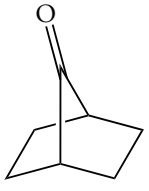
22.24 Write a mechanism for the base-catalyzed isomerization of 5-methyl-2-cyclopentenone to 2-methyl-2-cyclo pentenone. (Hint. A third isomeric unsaturated ketone is a required intermediate.)

22.25 Write a mechanism that explains why a solution of (*R*)-2-methyl-1-pheny1-1-pentanone in ethanol containing sodium ethoxide gradually loses optical activity, but a solution of (*R*)-3-methyl-1-phenyl-1-pentanone does not.

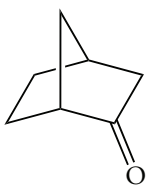
22.26 Predict the change in the optical activity of each of the following in a solution of sodium ethoxide in ethanol.
(a) (*R*)-2-methylcyclohexanone (b) (*R*)-3-methylcyclohexanone (c) (*R*)-2-methyl-2-ethylycyclohexanone.

Deuterium Exchange

22.27 Explain why 7-bicyclo[2 2 1]heptanone does not undergo an exchange reaction using sodium hydroxide in D_2O, but 2-bicyclo[2.2.1]heptanone readily reacts. Which hydrogen atoms are exchanged?

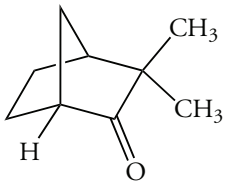


7-bicyclo[2.2.1]heptanone



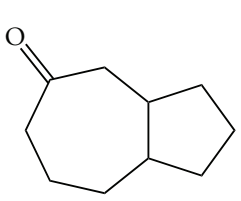
2-bicyclo[2.2.1]heptanone

22.28 Explain why 3,3-dimethyl-2-bicyclo[2.2.1]heptanone does not undergo an exchange reaction using sodium hydroxide in D_2O.

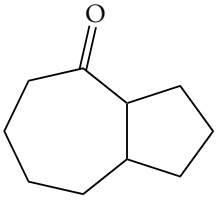


3,3-dimethyl-2-bicyclo[2.2.1]heptanone

22.29 Explain how the following isomeric ketones could be distinguished using the base-catalyzed exchange reaction with deuterium.



I



II

22.30 Explain how 2-pentanone and 3-pentanone could be distinguished using the base-catalyzed exchange reaction with deuterium.

22.31 3-Methyl-2,4-pentanedione rapidly exchanges one hydrogen using sodium hydroxide and D_2O. After a long time, a total of seven hydrogen atoms are eventually exchanged. Explain these observations.

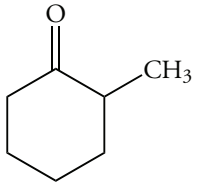
22.32 After a long time, 3-methyl-2-cyclohexenone exchanges a total of eight hydrogen atoms. (a) Identify the hydrogen atoms exchanged and (b) write a step showing the transfer of deuterium to an enolate that gives exchange at each of the required sites.

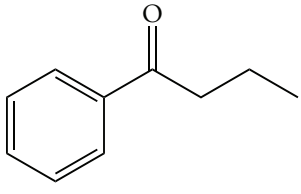
α-Halogenation Reactions

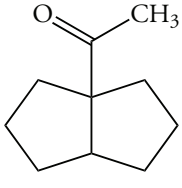
22.33 Reaction of 3-methyl-2,4-pentanedione with bromine under acidic conditions rapidly yields a monobromo derivative. (a) Write the structure of the product and (b) explain how it forms.

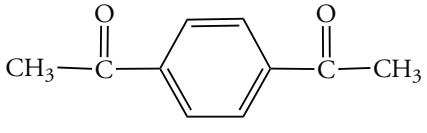
22.34 Reaction of 3-methyl-2-butanone with bromine under acidic conditions yields a mixture of two monobromo derivatives in a 95:5 ratio. (a) Write the structure of the products and (b) explain why the high ratio of isomers occurs.

22.35 Which of the following compounds will give a positive iodoform test when treated with iodine in a basic solution?

(a) 

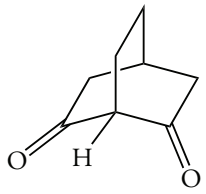
(b) 

(c) 

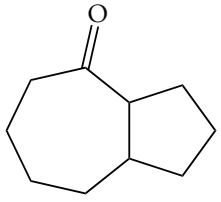
(d) 

22.36 Write the structure of a compound with molecular formula $C_8H_{14}O_2$ that gives adipic acid when reacted with excess bromine in a basic solution.

22.37 Explain why the indicated hydrogen atom at the bridgehead carbon of the following compound is not replaced by bromine in basic solution. What competing reactions may occur?

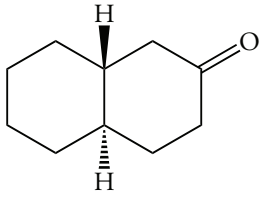


22.38 Predict the structure of the dibromo derivative obtained from the following ketone in basic solution.



22.39 Bromination of 4-*tert*-butylcyclohexanone under acidic conditions yields a mixture of two isomeric monobromo derivatives in approximately equal amounts. (a) Write the structures of the products and (b) explain why the ratio of the two compounds is approximately one.

22.40 Write the structures of the four isomeric monobromo products that could result from bromination of the following ketone in acidic solution.



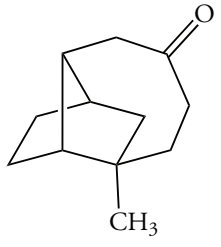
Reactions at the α-Carbon Atom

22.41 Write the structure of the product obtained by the reaction of 2,2-dimethyl-3-pentanone with sodium hydride followed by addition of 1-iodobutane.

22.42 Explain why reaction of cyclohexanone with LDA followed by the addition of 2-brompropane gives only the original ketone upon aqueous workup.

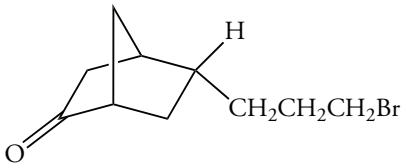
22.43 The enolate derived from reaction of LDA with 4-*tert*-butylcyclohexanone reacts with ethyl iodide to give a mixture of two monoalkylated products in approximately equal amounts. (a) Write the structures of the products and (b) explain why the ratio of the two compounds is approximately one.

22.44 Write the structures of the four isomeric monobromo products that could result from bromination of the following ketone in acidic solution.

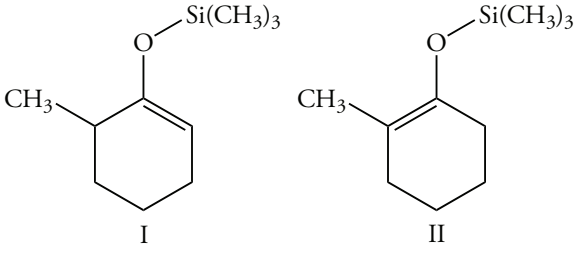


22.45 Reaction of 6-bromo-3,3-dimethy1-2-hexanone with LDA give a product with the molecular formula $C_8H_{14}O$. Write its structure.

22.46 Reaction of the following ketone with a sterically hindered strong base gives a product with the molecular formula $C_{10}H_{14}O$. Write its structure.

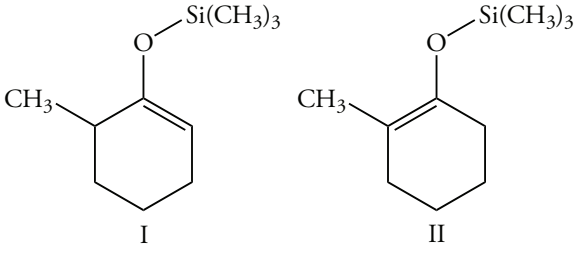


22.47 Trimethylchlorosilane, $(CH_3)_3SiCl$, reacts with enolates exclusively at the oxygen atom to give trimethylsilyl enol ethers. When heated with triethylamine and trimethylchlorosilane, the silyl ethers I and II derived from 2-methyl¬cyclohexanone occur in a 1:3 ratio. Which is more stable? Why is it more stable?.



22.48 Using the data in Exercise 22.47, predict the structure of the main product of the reaction of 2-pentanone with triethylamine and trimethylchlorosilane.

22.49 The reaction of 2-methylcyclohexanone with LDA in 1,2-dimethoxyethane at 0 °C yields a solution that, when subsequently reacted with trimethylchlorosilane and triethylamine, yields I and II in a 99:1 ratio. Explain why the indicated ratio occurs.

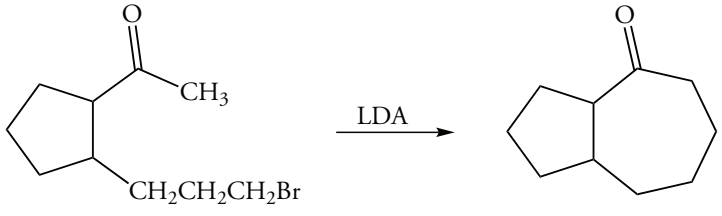


22.50 Based on the data in Exercise 22.49, predict the structure of the major product of the reaction of 2-pentanone with LDA in 1,2-dimethoxyethane at 0 °C followed by trimethylchlorosilane and triethylamine.

22.51 The reaction of 2-methylcyclohexanone with LDA in 1,2-dimethoxyethane at 0°C yields a solution that reacts with benzyl bromide to give 2-benzyl-6-methylcyclohexanone and 2-benzyl-2-methylcyclohexanone in a 12:1 ratio. Explain why the indicated ratio occurs.

22.52 What experimental conditions would favor formation of 2-benzyl-2-methylcyclohexanone by alkylation of 2-methylcyclohexanone with benzyl bromide?

22.53 Explain why the reaction of the following ketone with LDA in THE at –60 °C yields the indicated bicyclic ketone.

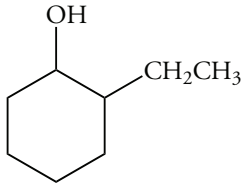


22.54 The ketone shown in Exercise 22.53 reacts with potassium *tert*-butoxide in *tert*-butyl alcohol to give a constitutional isomer of the bicyclic ketone shown above. (a) Write its structure and (b) explain its origin.

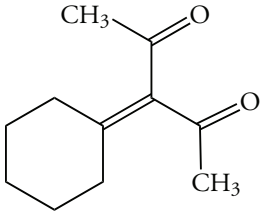
22.55 Draw the structure of the product of the self-condensation of each of the following aldehydes in the presence of a catalytic amount of sodium hydroxide.
(a) 2-methylpropanal (b) phenylethanal (c) octanal

22.56 What reactants are required to give the following compounds by a mixed aldol reaction?

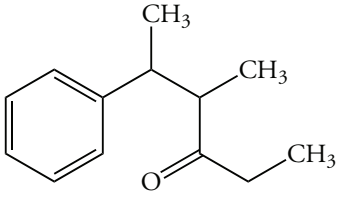
(a)



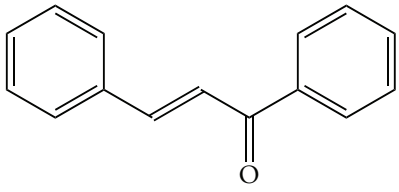
(b)



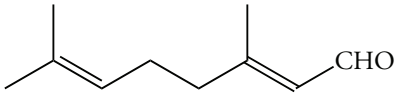
(c)



(d)



22.57 Pseudoionone, a component of some perfumes, has the molecular formula $C_{13}H_{20}O$. It can be prepared by a mixed aldol reaction of citral and acetone. Write the structure of pseudoionone.

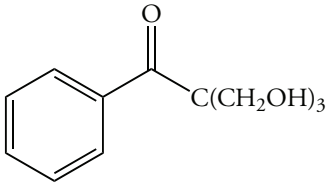


citral

22.58 A mixed aldol reaction between citral and 2-butanone yields two isomeric compounds. Write their structures.

22.59 2,2-Dimethyl-l,3-propanediol can be synthesized by reduction of a mixed aldol product using sodium borohydride. (a) What is the aldol and (b) what two carbonyl compounds are required to produce it?

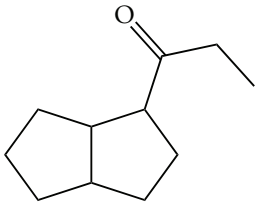
22.60 Suggest a synthesis of the following compound starting from acetophenone.



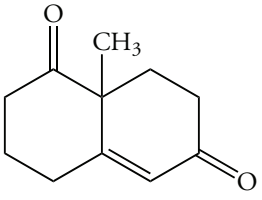
22.61 The favored products of the intramolecular aldol condensation of 2,5-hexanedione and 2,6-heptanedione are given in Section 22.9. (a) Write an alternative isomeric structure for each product and (b) explain why it is not formed.

22.62 The intramolecular aldol condensation of 2,6-octanedione could yield two possible six-membered unsaturated products. (a) Write their structures and (b) predict which isomer would be the major product.

22.63 What diketone will yield the following as a product of an intramolecular aldol condensation? What isomeric bicyclic compound could also form, but in smaller amount?



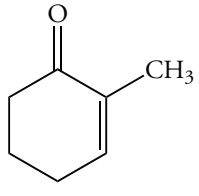
22.64 What reactant could yield the following product from an intramolecular aldol condensation?

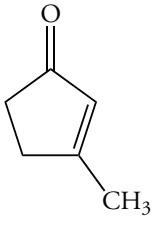


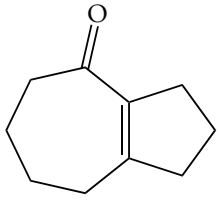
Conjugate Addition Reactions

22.65 Amines react with α,β-unsaturated ketones to give a conjugate addition products. Write the structure of the product for each of the following combinations of reactants.
(a) 2-cyclohexenone and $CH_3CH_2NH_2$
(b) 3-butenone and $(CH_3)_2NH$
(c) 4-methyl-3-penten-2-one and CH_3NH_2

22.66 The conjugate addition of HCN to α,β-unsaturated ketones can be done using diethylaluminum cyanide, $(C_2H_5)_2Al—CN$, followed by acid workup. Write the structure of the addition product for each of the following reactants.

(a)


(b)


(c)


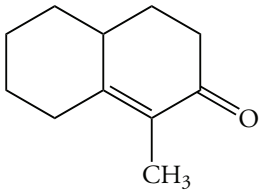
22.67 Write the structure of the addition product of 2-cyclohexenone with ethylmagnesium bromide after hydrolysis. Do the same for the addition product of 2-cyclohexenone with lithium diethylcuprate.

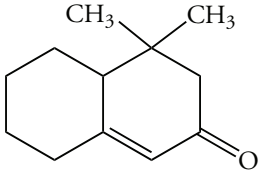
22.68 What combination of an α,β-unsaturated ketone and a Gilman reagent is required to synthesize each of the following compounds?
(a) 3-phenylcycloheptanone
(b) 2-hexanone
(c) 3-vinylcyclohexanone

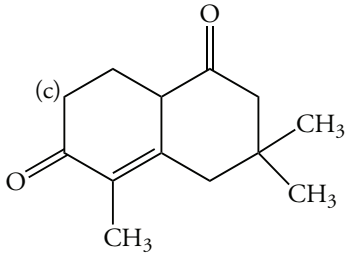
Michael Addition and Robinson Annulation Reactions

22.69 Write the structure of the product of the Michael addition reaction of 2-methyl-1,3-cyclopentanedione with 3-buten-2-one followed by Robinson annulation.

22.70 What combination of α,β-unsaturated ketone and a ketone is required to synthesize each of the following compounds by a Michael addition followed by Robinson annulation?

(a)


(b)


(c)


Acidity of α-Hydrogen Atom of Acid Derivatives

22.71 The cyano group is more deactivating in electrophilic aromatic substitution than a carboethoxy group. Which compound is more acidic, ethyl β-cyanoacetate or diethyl malonate?

22.72 The pK_a of nitromethane is 11. Which compound is more acidic, nitroacetone or ethyl acetoacetate?

22.73 The pK_a of malonitrile, $CH_2(CN)_2$, is 11. Calculate the equilibrium constant for the acid–base reaction of malonitrile with sodium ethoxide.

22.74 The equilibrium constant for the reaction of ethyl 2-cyanoacetate with sodium ethoxide is approximately 10^7. What is the pK_a of ethyl 2-cyanoacetate?

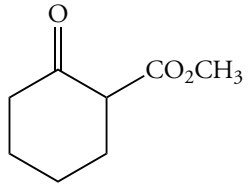
Enolates of Acid Derivatives

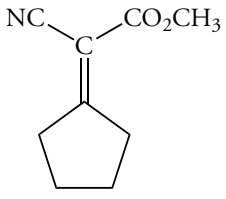
22.75 Write the resonance forms of the conjugate base of (a) malonitrile and (b) dinitromethane.

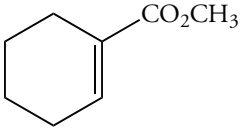
22.76 Write the resonance forms of the conjugate base of ethyl 2-cyanoacetate.

22.77 Ethyl acetoacetate reacts with two equivalents of LDA to give a dianion. Draw the structure of the dianion.

22.78 Draw the resonance contributors of the anion formed by deprotonation of the most acidic hydrogen atom of each of the following compounds.

(a) 

(b) 

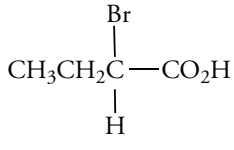
(c) 

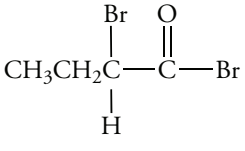
Reactions at the α-Carbon Atom

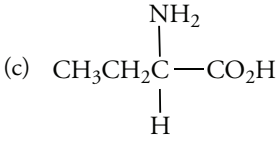
22.79 What products result from the reaction of each of the following isomeric esters with sodium ethoxide in CH_3CH_2OD?
(a) ethyl pentanoate
(b) ethyl 2-methylbutanoate
(c) ethyl 3-methylbutanoate

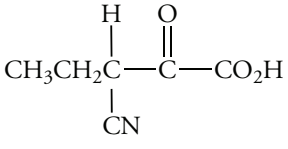
22.80 Ethyl acetoacetate reacts rapidly with sodium ethoxide in CH_3CH_2OD to give a product incorporating two deuterium atoms. After a longer period of time, an additional three deuterium atoms are incorporated. Explain why.

22.81 Write the equations for the synthesis of each of the following compounds starting from butanoic acid.

(a) 

(b) 

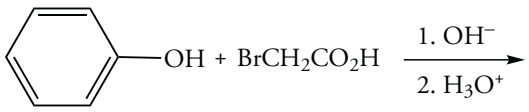
(c) 

(d) 

22.82 Draw the structure of the product of each of the following reactions.

(a) $CH_3CH_2CO_2H \xrightarrow{Br_2 / PBr_3} \xrightarrow{CH_3NH_2}$

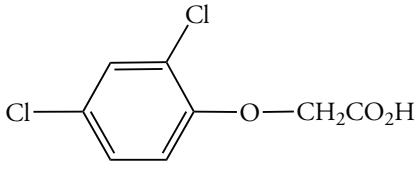
(b) $CH_3CO_2H \xrightarrow[PBr_3 / (1\ eq.)]{Br_2} \xrightarrow{CN^-}$

(c) 

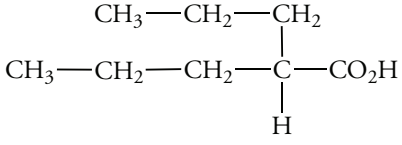
22.83 Draw the structure of the product resulting from reaction of each of the following esters with LDA followed by reaction of the enolate with the second reactant.
(a) *tert*-butyl-2-methylpropanoate and benzoyl chloride
(b) ethyl 2-methylpropanoate and ethyl iodide
(c) *tert*-butyl-2-methylpropanoate and one equivalent of 1-bromo-3-chloropropane

22.84 (a) Explain why diethyl 2-phenylmalonate cannot be prepared by arylation of diethyl malonate. (b) Suggest a method of synthesis starting from ethyl 2-phenylacetate.

22.85 Outline a synthesis of the herbicide 2,4-D using acetic acid as one of the reactants.



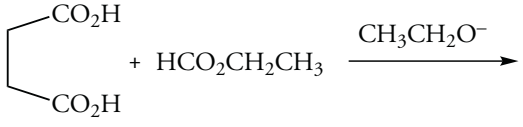
22.86 Outline a synthesis of valproic acid, a compound used in treatment of epilepsy, using ethyl acetate as one of the reactants.

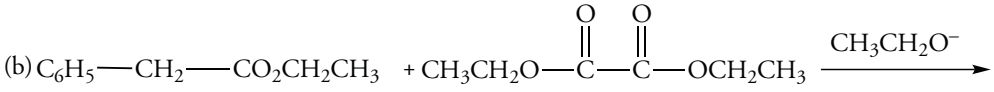


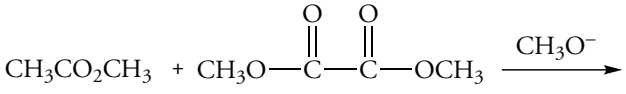
Claisen Condensations

22.87 Draw the structure of the product of the self-condensation of each of the following esters in the presence of a molar equivalent of sodium methoxide.
(a) methyl propanoate
(b) methyl 3-phenylbutanoate
(c) methyl 2-cyclohexylethanoate

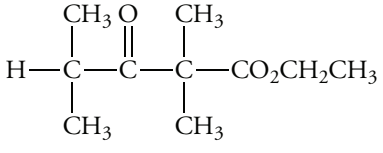
22.88 Draw the structure of the product of each of the following reactions.

(a) 

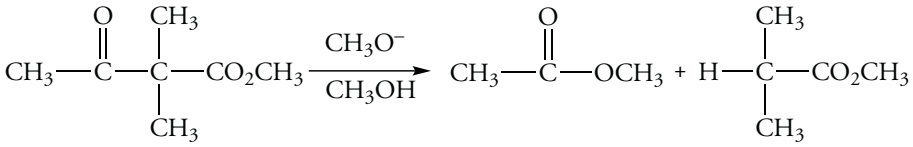
(b) 

(c) 

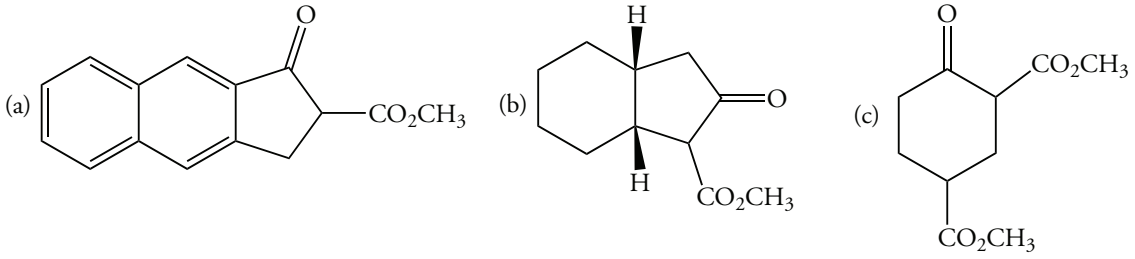
22.89 Explain why the following keto ester reacts with sodium ethoxide in ethanol to yield ethyl 2-methylpropanoate.



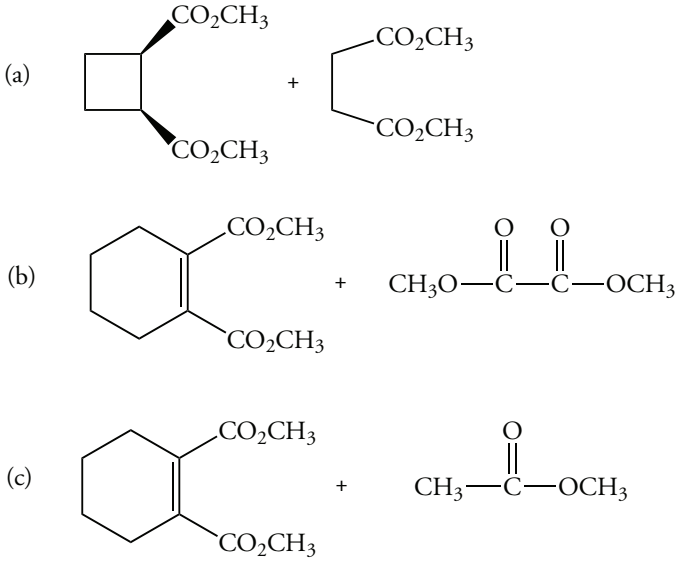
22.90 Explain why the equilibrium constant for the following reaction is greater than one.



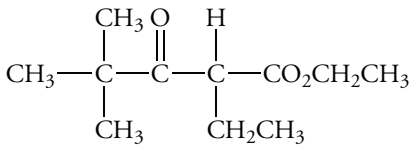
22.91 What reactant is required to synthesize each of the following structures using a Dieckmann condensation?

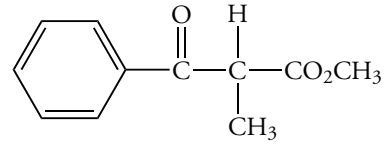


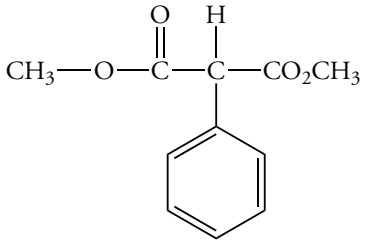
22.92 Each of the following pairs of compounds undergoes a "double" Claisen condensation in methanol and sodium methoxide to form a structure containing a second fused ring. Draw the structure of the product of each reaction.



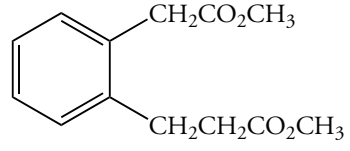
22.93 What esters are required to give the following mixed Claisen products?

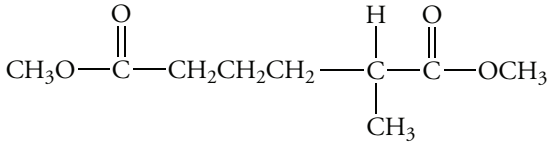
(a) 

(b) 

(c) 

22.94 There are two possible Dieckmann condensation products for each of the following compounds. Which product forms in each case?

(a) 

(b) 

22.95 2-Methylcyclohexanone is treated with one molar equivalent of LDA to form an enolate. Draw the structure of the product of the reaction of the enolate with diethyl oxalate.

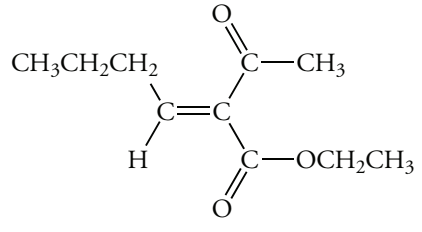
22.96 A mixture of cyclohexanone and diethyl carbonate is allowed to react in a solution of ethanol containing sodium ethoxide. Write the structure of the product.

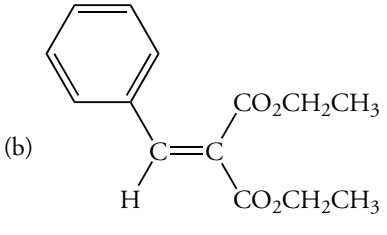
Aldol-Type Condensations

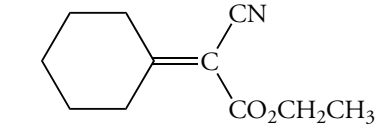
22.97 Draw the structure of the product of each of the following combinations of reagents in a reaction using one equivalent of sodium ethoxide.
(a) *p*-nitrobenzaldehyde and diethyl malonate
(b) cyclopentanone and ethyl acetoacetate
(c) cyclooctanone and diethyl succinate

22.98 Explain why the reaction of ethyl 2-bromopropanoate with zinc and acetophenone gives a pair of isomers.

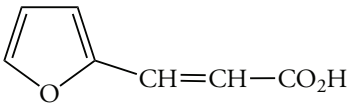
22.99 What reactants are required to prepare the following compounds using the Knoevenagel condensation?

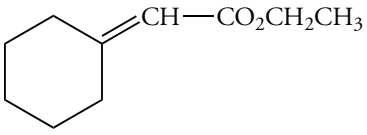
(a) 

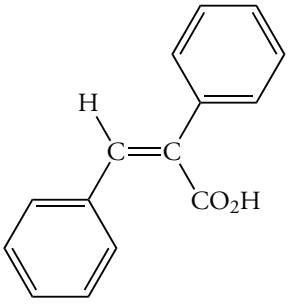
(b) 

(c) 

22.100 The product of a Reformatskii reaction can be dehydrated to give an α,β-unsaturated acid or ester. What reactants are required to synthesize each of the following products using the Reformatskii reaction as one of the steps?

(a) 

(b) 

(c) 

Synthesis Using β-Dicarbonyl Compounds

22.101 Outline the synthesis of each of the following compounds using diethyl malonate as one of the reactants.
(a) 2-methyl-4-pentenoic acid (b) 3-propylpentanoic acid (c) 2-benzylbutanoic acid
(d) 3-phenylpropanoic acid (e) 2-ethyl-4-pentynoic acid

22.102 Outline the synthesis of each of the following compounds using ethyl acetoacetate as one of the reactants.
(a) 4-phenyl-2-butanone
(b) 5-hexene-2-one
(c) 5-methyl-2-hexanone
(d) 3-propyl-5-hexene-2-one
(e) 4-cyclopentyl-3-methyl-2-butanone

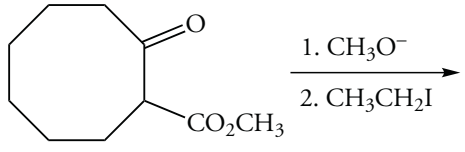
22.103 The malonic acid synthesis can be used to prepare cycloalkanecarboxylic acids by a double alkylation using a dihalide. Write the structure of the product of each of the steps in the following sequence.

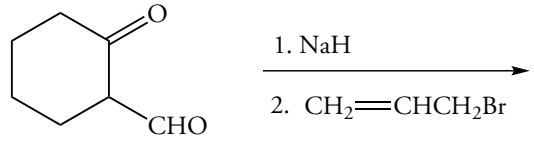


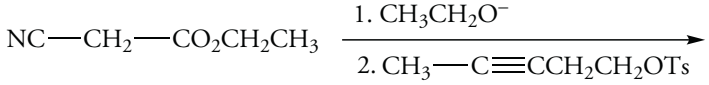
22.104 What is the product of a malonic acid synthesis if the final step uses aqueous hydroxide ion in a saponification reaction followed by careful neutralization with HCl rather than an acid-catalyzed hydrolysis reaction?

22.105 Ethyl acetoacetate reacts with one molar equivalent of sodium ethoxide followed by the addition of 2,2-dimethyloxirane to give a cyclic compound of molecular formula $C_8H_{12}O_3$. Draw its structure.

22.106 The malonic acid synthesis can be used to prepare cycloalkanecarboxylic acids by a double alkylation using a dihalide. Write the structure of the product of each of the steps in the following sequence.

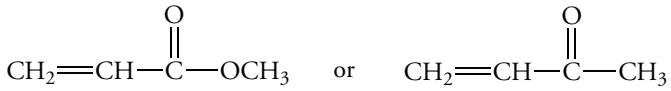
(a) 

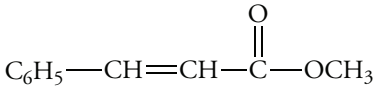
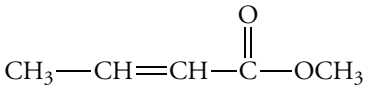
(b) 

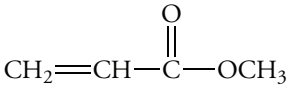
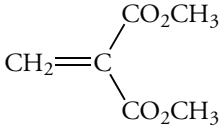
(c) 

Michael Addition Reactions

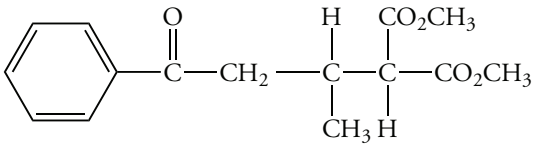
22.107 Which member of each of the following pairs is more reactive as an acceptor in the Michael addition reaction?

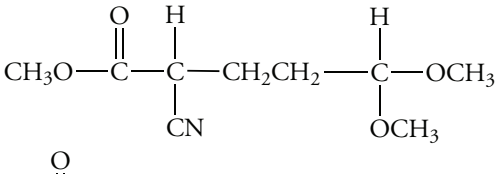
(a)  or

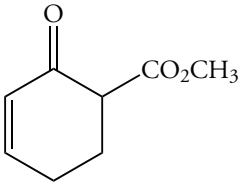
(b)  or 

(c)  or 

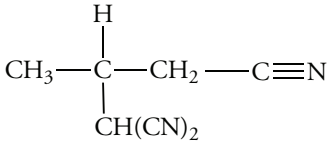
22.108 What reactants arc required to synthesize each of the following compounds using a Michael addition reaction in one of the steps?

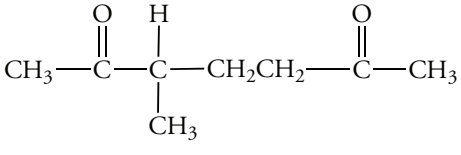
(a) 

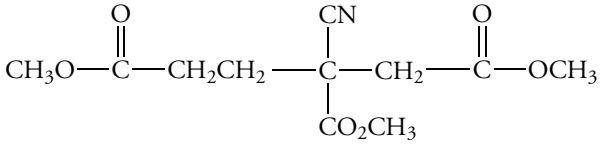
(b) 

(c) 

22.109 Write the reaction sequence required to synthesize the following structures using a Michael addition reaction as one of the steps.

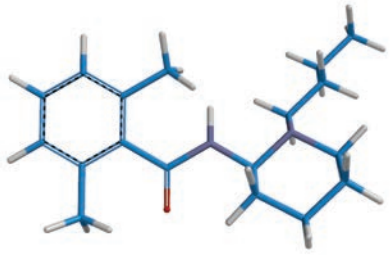
(a) 

(b) 

(c) 

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23 Amines and Amides

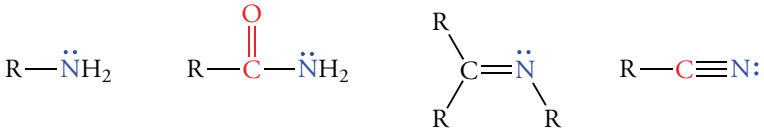


Bupivacaine (a local anaesthetic)

23.1 ORGANIC NITROGEN COMPOUNDS

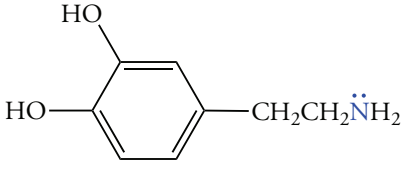
For most of this text we have concentrated on the compounds of carbon, hydrogen, and oxygen. We have paid less attention to compounds containing sulfur and nitrogen. Nitrogen is the fourth most common element in living systems after carbon, hydrogen, and oxygen. Organic compounds containing nitrogen not only are widely distributed in plants and animals but are necessary for life. Nitrogen is present in many vitamins and hormones. Nitrogen is essential in amino acids and proteins, in nucleotides and nucleic acids, and in scores of other cellular molecules. In addition, many nitrogen-containing compounds are important industrial products, including polymers such as nylon, many dyes, explosives, and pharmaceutical agents.

A nitrogen atom with five valence electrons forms a total of three covalent bonds to carbon or hydrogen atoms in neutral compounds. A nitrogen atom in a functional group can form single, double, or triple bonds. We have discussed all of these functional groups in previous chapters. In this chapter we will focus on amines and amides, but will also discuss the other functional groups that are either the reactants required to form amines and amides or the products of their reactions.

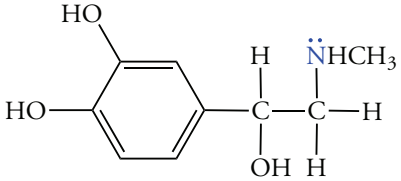


(an amine) (an amide) (an imine) (a nitrile)

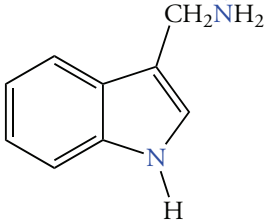
Many amines are physiologically active. They affect the brain, spinal cord, and nervous system. These compounds include the neurotransmitters: epinephrine, serotonin, and dopamine. Epinephrine, commonly called adrenaline, stimulates the conversion of glycogen into glucose. Serotonin is a hormone that causes sleep. Serotonin deficiency is implicated in some forms of mental depression. Parkinson's disease is accompanied by a low concentration of dopamine.



dopamine



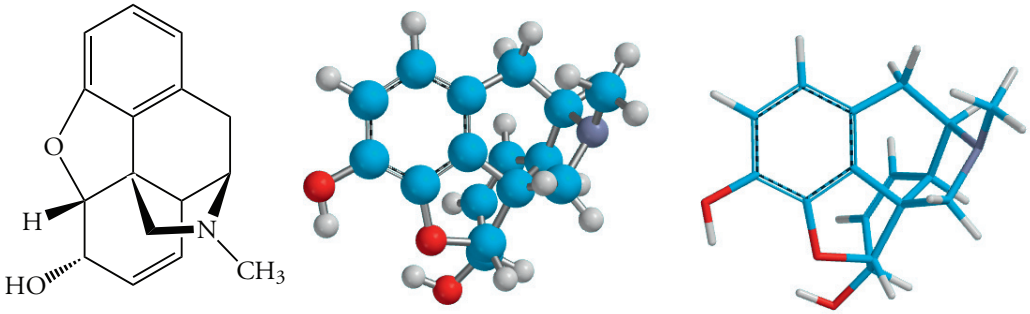
epinephrine



seratonin

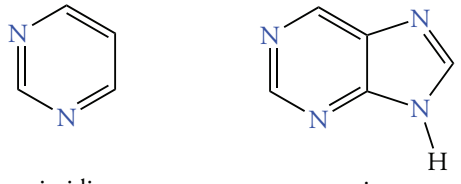
Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00023-1
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And morphine, a powerful opiate and analgesic, which takes its name from Morpheus, the Greek god of dreams, also contains an amine functional group that is essential for its biological activity.



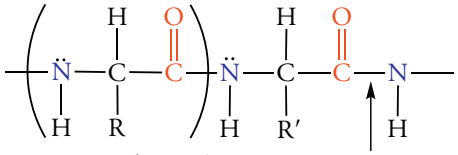
Three views of morphine

Compounds that have one or more atoms other than carbon in the ring are **heterocyclic**. Heterocyclic compounds containing two or more nitrogen atoms are required for the transmission of genetic information. DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) contain substituted pyrimidine and purine rings.



pyrimidine purine

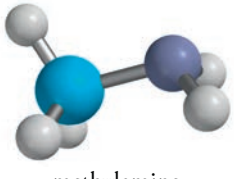
Proteins, among the most important and versatile biological compounds, consist of nitrogen-containing molecules called α-amino acids. In proteins, each amine functional group of one α-amino acid is bonded to the carbonyl carbon of another α-amino acid in a chain of amino acyl groups that contains many amide bonds or peptide bonds.



(an amino acyl group) (an amide bond or peptide bond)

23.2 BONDING AND STRUCTURE OF AMINES

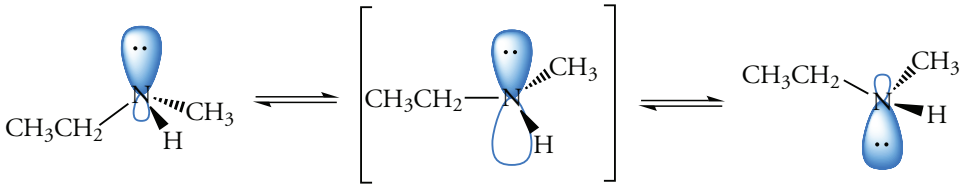
We discussed the bonding and structure of simple amines in Chapter 1 (Figure 1.18). In the simplest amine, methylamine (CH_3NH_2), a methyl group has replaced one hydrogen atom of ammonia. The C—N—H and H—N—H bond angles are approximately 112° and 106°, respectively, so methylamine has a pyramidal shape around the nitrogen atom. In methylamine and other amines, the nitrogen atom has five valence electrons in four sp^3 hybrid orbitals. As expected from VSEPR theory, these orbitals point to the corners of a tetrahedron. Three are half-filled. They form three covalent bonds. The fourth orbital contains a pair of nonbonded electrons.



methylamine

Nitrogen Inversion of Amines

If the pyramidal structure of acyclic amines were static, compounds with three different groups around the nitrogen atom would be chiral. However, the nonbonded electron pair on nitrogen, which we could regard as the fourth group required for a stereogenic center, does not remain in one place. Amines undergo nitrogen inversion by a process in which the three bonded groups temporarily occupy a common plane. We can think of this, perhaps somewhat whimsically, as analogous to an umbrella turning inside out in the wind.

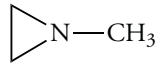


planar transition state

The planar form of the amine transition state resembles an S_N2 transition state in which an electron pair of one group attacks from one side of a plane while another group leaves with an electron pair from the other side. In nitrogen inversion, an electron lone pair pushes the three bonded groups from one side to the other and inverts the configuration. The process requires only 25 kJ mole^{-1}, so the rate of inversion is so fast that the enantiomers cannot be resolved. In effect, an amine with three different bonded groups is a racemic mixture.

Problem 23.1

Explain why the inversion barrier for *N*-methylaziridine (80 kJ mole^{-1}) is larger than the inversion barrier for trimethylamine (25 kJ mole^{-1}).



N-methylaziridine

Problem 23.2

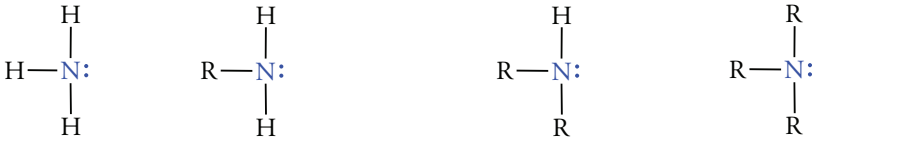
(a) Explain why the N—H bond of ammonia is shorter than the C—H bond in methane. (b) The C—N bond length of aniline is 140 pm. Give two reasons why this bond length is shorter than the 147 pm C—N bond length of alkylamines.

Sample Solution

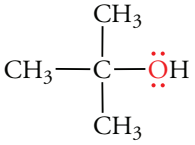
The C—N bond of aniline is formed with an sp^3 hybrid orbital of carbon compared to the sp^2 hybrid orbital of carbon in alkylamines. The greater s character decreases the resulting bond length because the bonding electron supplied from carbon is closer to the nucleus. The bond is also shorter because the nonbonding electrons of nitrogen can contribute to resonance forms in which the electrons are supplied to the aromatic ring. These resonance forms have a carbon–nitrogen double bond. These resonance forms contribute to the shorter carbon–nitrogen bond.

23.3 CLASSIFICATION AND NOMENCLATURE OF AMINES

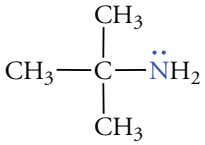
Just as we can regard alcohols and ethers as organic derivatives of water, we can regard amines as organic derivatives of ammonia. However, amines are *not* classified like alcohols. The classification of alcohols is based on the number of groups attached to the carbon atom bearing the hydroxyl group. Amines are classified by the number of alkyl (or aryl) groups attached to the nitrogen atom.



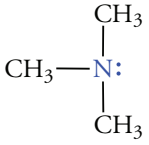
For example, *tert*-butylamine has a *tert*-butyl group attached to an —NH_2 group. However, the amine is primary because only one alkyl group is bonded to the nitrogen atom. In contrast, *tert*-butyl alcohol is a tertiary alcohol because the carbon atom bonded to the —OH group is bonded to three alkyl groups. Trimethylamine is a tertiary amine because the nitrogen atom is bonded to three alkyl groups.



tert-butyl alcohol
(a tertiary alcohol)

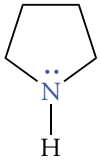


tert-butylamine
(a primary amine)

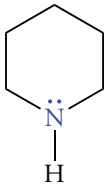


trimethylamine
(a tertiary amine)

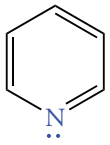
Amines in which a nitrogen atom is part of a ring are common in biological systems. For example, pyrrolidine and piperidine are five- and six-membered heterocyclic compounds that are secondary amines. Pyridine is an aromatic amine considered a tertiary amine since there are three bonds to nitrogen.



pyrrolidine
(a secondary amine)



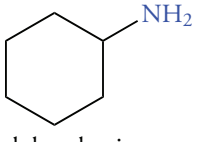
piperidine
(a secondary amine)



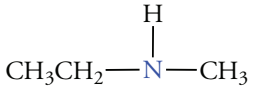
pyridine
(a tertiary amine)

Common Names of Amines

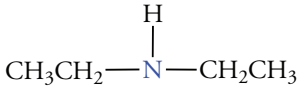
In common nomenclature, amines are described as *alkylamines*. The common name of a primary amine results from naming the alkyl group bonded to the amino group (—NH_2) and adding the suffix *-amine*. The entire name is written as one word. The common name for a secondary or tertiary amine is obtained by listing the alkyl groups alphabetically. When two or more identical alkyl groups are present, the prefixes di- and tri- are used.



cyclohexylamine

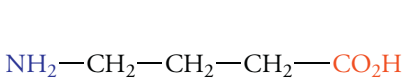


ethylmethylamine

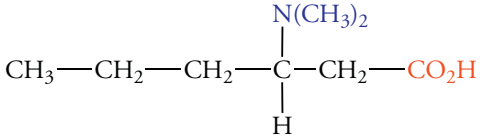


diethylamine

In more complex primary amines, the amino group is treated as a substituent. The nitrogen-containing substituent in complex secondary and tertiary amines is named as an *N*-alkylamino (—NHR) or *N,N*-dialkylamino (—NRR′) group. The capital *N*-indicates that the alkyl group is bonded to the nitrogen atom and not to the parent chain. The largest or most complicated group is used as the parent molecule.

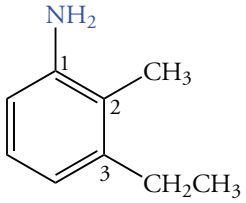


γ-aminobutryic acid

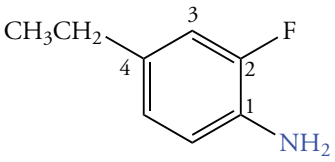


β-(*N,N*-dimethylamino)caproic acid

As we already know, amino-substituted benzene compounds are anilines. They are numbered starting at the carbon atom bearing the amino group if the other groups bonded to the ring have a lower priority for citation than the amino group. The direction of the numbering is based on the location of the second group using the first point of difference concept established with our early study of alkanes. Substituents are listed in alphabetical order.



3-ethyl-2-methylaniline

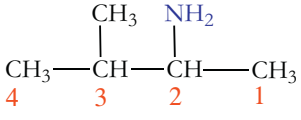


4-ethyl-2-fluorolaniline

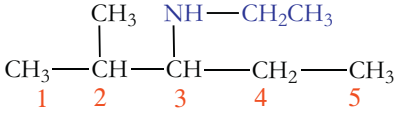
However, the priority for citation of an amino group is low. It ranks below all carbonyl compounds (acids, acid derivatives, aldehydes, ketones) and even the hydroxyl group. Thus, a benzene compound containing both a carboxylic acid group and an amino group is an amino-substituted benzoic acid, not a carboxylic acid-substituted aniline.

Systematic Names of Amines

The systematic nomenclature of amines was devised by the Chemical Abstracts Service (CAS) and has been adopted as one of two systematic methods accepted by IUPAC. Because the CAS system is based on the same system used for alcohols, we will use CAS names. The longest continuous chain to which the amino group is attached is the parent alkane. The *-e* ending of the alkane is changed to *-amine*. Substituents on the carbon chain, including the amino group, are designated by number. The prefix *N-* is used for each substituent on the nitrogen atom.

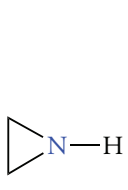


3-methyl-2-butanamine

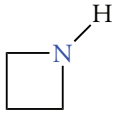


N-ethyl-2-methyl-3-pentanamine

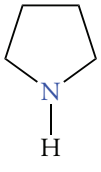
We developed the concepts for naming heterocyclic compounds containing oxygen in Chapter 16 when we discussed ether nomenclature. Similar concepts are used to name heterocyclic compounds containing nitrogen. Saturated three-, four-, five-, and six-membered rings containing one nitrogen atom are named aziridine, azetidine, pyrrolidine, and piperidine, respectively. The rings are numbered from the heteroatom.



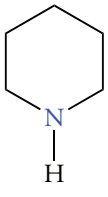
aziridine



azetidine

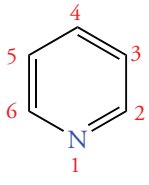


pyrrolidine

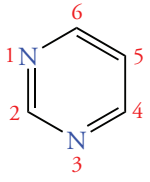


piperidine

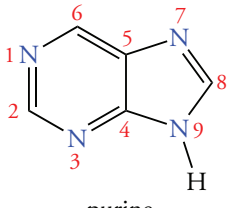
Amines in which the nitrogen atom is part of an aromatic ring are called **heterocyclic aromatic amines**. In these compounds, the positions of substituents are established by using the numbering system indicated below. A nitrogen atom is assigned the number 1, and the direction of numbering provides the lowest possible numbers if the ring has more than one nitrogen atom.



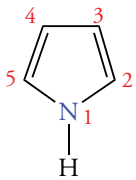
pyridine



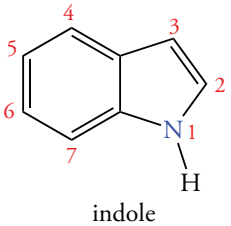
pyrimidine



purine



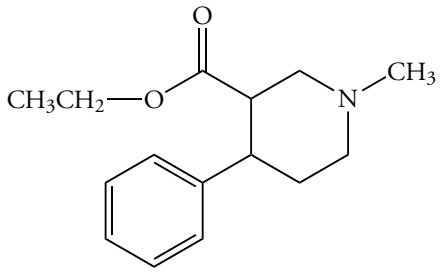
pyrrole



indole

Problem 23.4

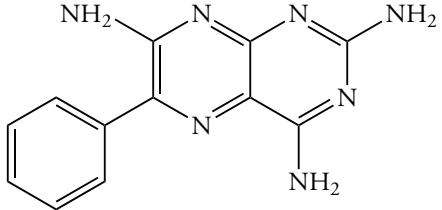
Classify Demerol, a synthetic narcotic analgesic, as a primary, secondary, or tertiary amine.



Demerol

Problem 23.5

The systematic name for Dyrenium, a diuretic, is 2,4,7-triamino-6-phenylpteridine. (a) Number the heterocyclic ring system. It is called pteridine. (b) Explain this choice of numbers.



Dyrenium

Problem 23.6

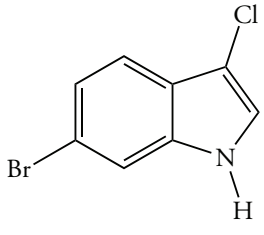
The thiosemicarbazide of 5-hydroxypyridine-2-carbaldehyde has some antitumor activity. Write the structure of the aldehyde and the thiosemicarbazide.

Problem 23.7

2-(3,4,5-Trimethoxyphenyl)ethanamine is the systematic name of mescaline, a hallucinogen. Write its structure.

Problem 23.8

Name the following compound, which is produced by the marine acorn worm.



23.4 PHYSICAL PROPERTIES OF AMINES

Melting Points and Boiling Points of Amines

Amines with low molecular weights are gases at room temperature, but amines with higher molecular weights are liquids or solids (Table 23.1). Amines have higher boiling points than alkanes of similar molecular weight, but lower boiling points than alcohols.

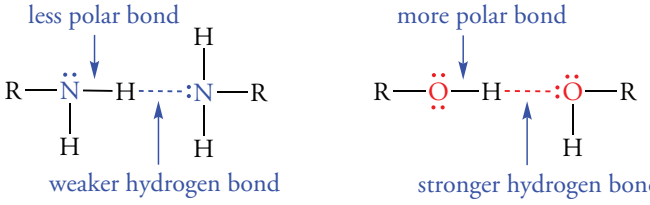
$CH_3—CH_2—CH_3$	$CH_3—CH_2—NH_2$	$CH_3—CH_2—OH$
bp –42 °C	bp 17 °C	bp 78 °C

Table 23.1
Boiling Points of Amines

Name	*Boiling Point, °C*
Methylamine	–7
Ethylamine	17
Propylamine	48
Isopropylamine	33
Butylamine	77
Isobutylamine	68
sec-butylamine	63
tert-butylamine	45
Cyclohexylamine	134
Dimethylamine	7
Ethylmethylamine	37
Diethylamine	56
Dipropylamine	111
Trimethylamine	3
Triethylamine	90
Tripropylamine	156

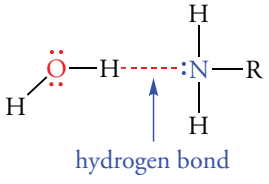
Amines have higher boiling points than hydrocarbons of comparable molecular weight because the C—N bond is more polar than a C—C bond. Also, primary and secondary amines can form intermolecular hydrogen bonds because they can act as both hydrogen bond donors and acceptors. Tertiary amines have no hydrogen atoms bonded to the nitrogen atom and therefore are not hydrogen bond donors. Thus, tertiary amines cannot form intermolecular hydrogen bonds. As a result, they have lower boiling points than primary and secondary amines of comparable molecular weight.

Amines have lower boiling points than alcohols because nitrogen is less electronegative than oxygen. As a result the N—H bond is less polar than the O—H bond, and the N—H---N hydrogen bond in amines is weaker than the O—H---O hydrogen bond in alcohols.



Solubility of Amines in Water

Amines with five or fewer carbon atoms are miscible with water. As we have seen for other types of compounds, the solubility of amines decreases with increasing molecular weight because the functional group is a less significant part of the structure. Primary and secondary amines are both hydrogen bond donors and acceptors, and they readily form hydrogen bonds with water. Even tertiary amines are soluble in water because the nonbonded electron pair of the nitrogen atom is a hydrogen bond acceptor of a hydrogen atom of water.



The solubilities of toluene (0.05 g/100 mL) and aniline (3.5 g/100 mL) illustrate the effect of hydrogen bonding on the solubilities of arylamines. Aniline forms hydrogen bonds with water and is slightly soluble in water. Toluene cannot form hydrogen bonds with water and is insoluble in water.

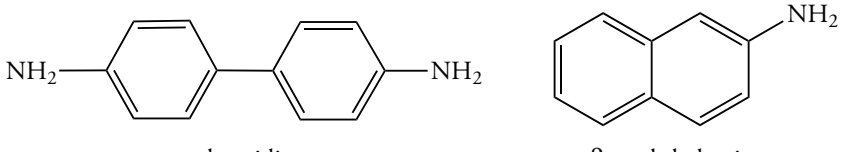
Odor and Toxicity of Amines

Amines with low molecular weights have sharp penetrating odors similar to ammonia. Amines with higher molecular weights smell like decaying fish. Two compounds responsible for the odor of decaying animal tissue have the common graphic names putrescine and cadaverine.

$NH_2CH_2CH_2CH_2CH_2NH_2$ putrescine

$NH_2CH_2CH_2CH_2CH_2NH_2$ cadaverine

Because many amines have high physiological activity, the ingestion of an amine not normally used by a living organism can cause poisoning and death. In addition, the skin absorbs arylamines, and they must be handled carefully. Some arylamines such as benzidine and β-naphthylamine are carcinogenic.



Problem 23.9

The boiling points of pyrrole and imidazole are 130 and 263 °C, respectively. Explain the large difference.



pyrrole imidazole

Sample Solution

Both pyrrole and imidazole are hydrogen bond donors. Only imidazole is a hydrogen bond acceptor because it has a nonbonded electron pair in an sp^2 hybrid orbital on a pyridine-like nitrogen atom. The valence electrons of the nitrogen atom of the N—H bonds in both pyrrole and imidazole are incorporated in the π system of an aromatic ring and are not available to form hydrogen bonds. Because imidazole forms intermolecular hydrogen bonds, it has a higher boiling point than pyrrole.

Problem 23.10

The dipole moments of pyridine (2.26 D) and piperidine (1.17 D) are both directed toward nitrogen. Explain why the pyridine has larger dipole moment than piperidine.

23.5 BASICITY OF AMINES

The basicity of an amine is usually listed as a pK_b, the negative logarithm of K_b. For an amine with $K_b = 10^{-4}$, the pK_b is 4. The pK_b values of strong bases are small. Thus, as pK_b increases, base strength decreases. It is also common practice to indicate the relative base strength of amines in terms of the pK_a values of their conjugate acids. (We recall that $pK_a = -\log K_a$.) If an amine has a small pK_b, its conjugate ammonium ion has a large pK_a. The values of pK_b and pK_a for a conjugate acid–base pair are related as follows.

$$pK_b + pK_a = 14$$

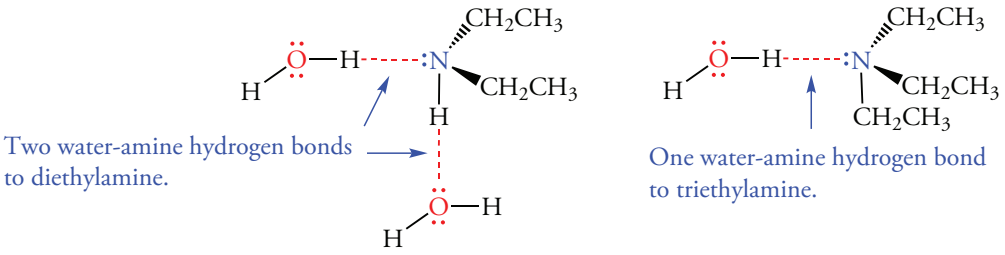
To understand the basicity of amines, we must consider the effect of a structural feature on both the amine and its conjugate acid. Any feature that stabilizes the amine relative to the ammonium ion makes the amine a weaker base. Any feature that stabilizes the ammonium ion relative to the amine makes the amine a stronger base.

Table 23.2 lists the base ionization constants for several amines. We know that alkyl groups donate electrons to carbocations, and that they donate electrons in electrophilic aromatic substitution reactions. We might expect alkyl-substituted amines to be slightly stronger bases than ammonia because the inductive donation of electrons to the nitrogen atom by alkyl groups makes the unshared pair of electrons more available to a proton. However, the order of basicities does not increase in a simple order.

	NH_3	$CH_3CH_2NH_2$	$(CH_3CH_2)_2NH$	$(CH_3CH_2)_3N$
pK_b	4.7	3.60	3.01	3.24

The reversal of the expected order for a secondary and a tertiary amine indicates that a second factor affects the basicity of amines. That factor operates in a direction opposite to the inductive effect of the alkyl groups. It is the difference in the degree of solvation of the ammonium ions and the resultant stabilization of that product. The dialkylammonium ion has two N—H bonds that can form hydrogen bonds with water. The trialkylammonium ion has only one N—H bond.

Thus, triethylamine is a weaker base than diethylamine because its conjugate acid is not as effectively solvated. Diethylamine is the strongest base of the series because it has the best balance of inductive electron donation by alkyl groups and stabilization by solvation of the conjugate acid.



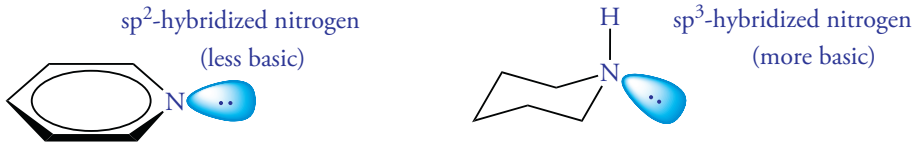
The formation of an enol in the rate-determining step is an acid-catalyzed reaction. Because the acid-catalyzed exchange of deuterium also occurs by way of an enol, the rate of deuterium exchange is identical to the rate of the acid-catalyzed halogenation. The addition of an electrophilic halogen atom to the double bond of the enol is analogous to the addition to alkenes we discussed in Chapter 7. However, the double bond of an enol is more reactive because the oxygen atom releases electron density by resonance.

Table 23.2
Basicity of Amines

Name	K_b	pK_b
Methylamine	4.3×10^{-4}	3.37
Ethylamine	4.4×10^{-4}	3.36
Propylamine	4.7×10^{-4}	3.33
Isopropylamine	4.0×10^{-4}	3.40
Butylamine	4.8×10^{-4}	3.22
Cyclohexylamine	4.7×10^{-4}	3.33
Dimethylamine	5.3×10^{-4}	3.28
Diethylamine	9.8×10^{-4}	3.01
Dipropylamine	1.0×10^{-3}	3.00
Trimethylamine	5.5×10^{-5}	4.26
Triethylamine	5.7×10^{-4}	3.24
Tripropylamine	4.5×10^{-4}	3.35

Heterocyclic Amines

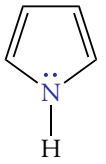
The basicity of heterocyclic amines varies over a wide range and reflects both the hybridization of the orbital of nitrogen containing the lone pair electrons and the effects of delocalization. Pyridine is a substantially weaker base than alkylamines such as piperidine. The electron pair of pyridine occupies an sp^2-hybridized orbital and lies closer to the nucleus than the electron pair in the sp^3-hybridized orbital of alkylamines. As a result, pyridine is a weaker base (larger pK_b) than an alkylamine.



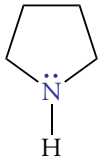
pyridine
pK_b 8.75

piperidine
pK_b 2.88

Pyrrole is an exceedingly weak base. The pair of electrons that might be protonated is not readily available because it is required to maintain the sextet of electrons in the ring required for aromaticity. Pyrrolidine, which is not aromatic, is a much stronger base.

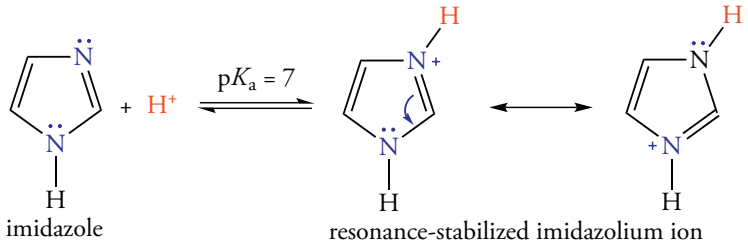


pyrrole
pK_b 15



pyrrolidine
pK_b 2.73

Imidazole is an important aromatic ring found in many proteins. It has two nitrogen atoms. One resembles pyrrole and is not basic. The second nitrogen is structurally similar to the nitrogen atom of pyridine. However, imidazole is about 100 times more basic than pyridine. The increased basicity results from resonance stabilization of the charge to both nitrogen atoms.

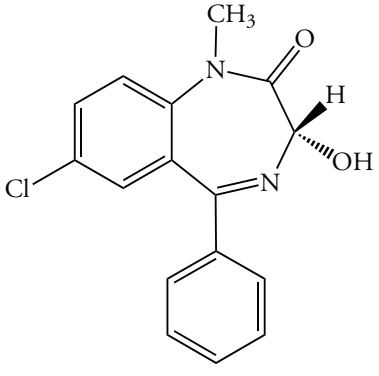


imidazole

resonance-stabilized imidazolium ion

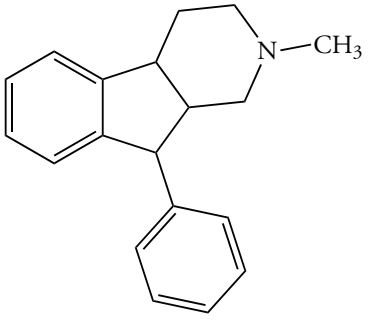
Problem 23.11

The pK_a of the conjugate acid of diazepam (Valium) is 3.3. What is its K_a? Calculate the K_b and pK_b of diazepam.



Problem 23.12

Based on the data in Table 23.2, estimate the pK_a of phenindamine, an antihistamine.



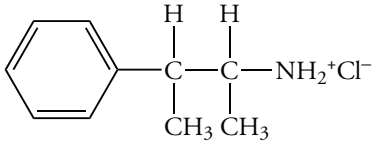
23.6 SOLUBILITY OF AMMONIUM SALTS

When an amine is added to a solution of a strong acid, such as hydrochloric acid, the amine nitrogen atom is protonated to produce an ammonium salt.

$$RNH_2 + HCl \rightleftharpoons RNH_3^+Cl^-$$

Ammonium salts of low molecular weight are soluble in water if the hydrocarbon portion of the amine is small. Because the nitrogen atom of an ammonium salt has a positive charge, ammonium salts are more water-soluble than amines. Drugs containing an amino group are often prepared as ammonium salts to improve their solubility in body fluids.

The ammonium salts of many drugs are more stable and less prone to oxidation than the amine itself. Also, ammonium salts have higher melting points and virtually no odor. For example, ephedrine melts at 79 °C and has a fishy odor. Its hydrochloride salt, used in cold and allergy medications, melts at 217 °C and is odorless.



ephedrine hydrochloride

Amines can be separated from other substances by converting them to ammonium salts. Consider, for example, the separation of 1-chlorooctane from 1-aminooctane. Both compounds are insoluble in water. Adding HCl to a solution containing both compounds converts the 1-aminooctane into its ammonium salt, whereas 1-chlorooctane is not affected.

$$CH_3(CH_2)_6CH_2NH_2 + HCl \longrightarrow CH_3(CH_2)_6CH_2NH_3^+Cl^-$$

(insoluble in water) (soluble in water)

$$CH_3(CH_2)_6CH_2Cl + HCl \not\longrightarrow \text{no reaction}$$

(insoluble in water)

The 1-chlorooctane is physically separated from the aqueous acid solution. Then the acid solution is neutralized with sodium hydroxide to form the free amine. The amine can then be physically separated from the aqueous solution.

$$CH_3(CH_2)_6CH_2NH_3^+ + OH^- \longrightarrow CH_3(CH_2)_6CH_2NH_2 + H_2O$$

(soluble in water) (insoluble in water)

23.7 SYNTHESIS OF AMINES BY SUBSTITUTION REACTIONS

In prior chapters we have already discussed many general methods to synthesize amines. In this section we consider substitution reactions of alkyl halides with ammonia or an amine, and a variation on this method that improves yields.

Alkylation of Amines by Alkyl Halides

The nucleophilic substitution reaction of ammonia with an alkyl halide yields a mixture of products in which successive alkylated products continue to react, yielding a complex mixture of alkyl ammonium ions.

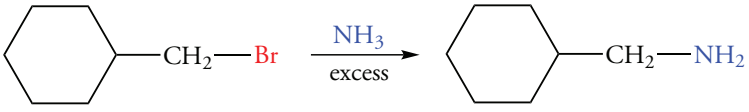
$$CH_3I + NH_3 \longrightarrow CH_3NH_3^+I^- \longrightarrow (CH_3)_2NH_2^+I^- \longrightarrow (CH_3)_3NH^+I^- \longrightarrow (CH_3)_4N^+I^-$$

$$CH_3I + NH_3 \longrightarrow CH_3NH_3^+I^-$$

$$CH_3NH_3^+I^- + NH_3 \rightleftharpoons CH_3NH_2 + NH_4^+I^-$$

$$CH_3NH_2 + CH_3I \longrightarrow (CH_3)_2NH_2^+I^-$$

Continued deprotonation of the ammonium ion product in equilibrium reactions, followed by alkylation, eventually leads to products with all possible degrees of alkylation. The exact amounts of the products depend on the relative amounts of the starting materials and on the reaction conditions. Selecting the proper reaction conditions can diminish chances for multiple alkylation. For example, if an alkyl halide reacts with ammonia in the presence of excess ammonia, the reaction can convert an alkyl halide to a primary amine. When the concentration of ammonia is greater than the concentration of the primary amine product, the probability decreases that the primary amine will react with the alkyl halide.

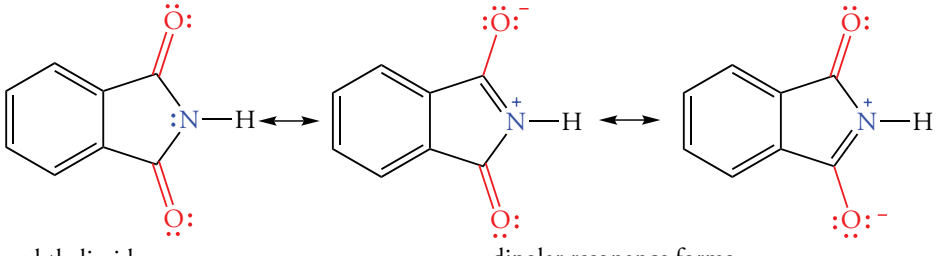


By analogy, we expect that secondary amines could be prepared by reaction of an alkyl halide with an excess of a primary amine. In general, this reaction is not used because the excess amine, which is more expensive than the ammonia used to pre-pare primary amines, is wasted.

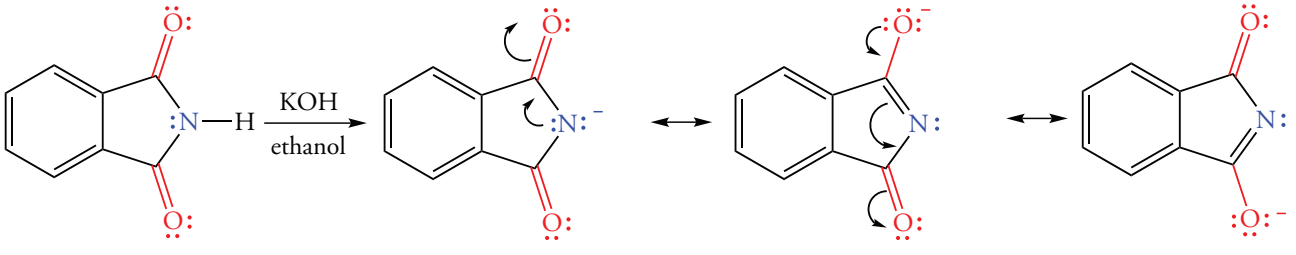
In general, the preparation of amines by nucleophilic displacement is restricted to inexpensive alkyl halides and to easily separated amines. Separation by distillation using efficient fractionating columns makes possible the industrial preparation of some simple amines by substitution reactions.

Gabriel Synthesis

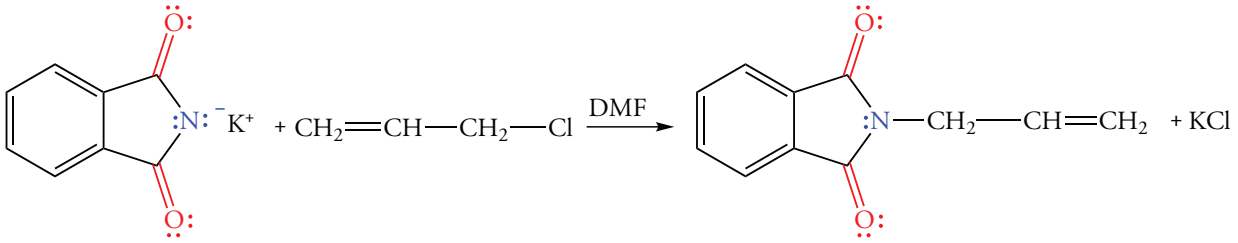
We can bypass the problem of multiple alkylation of nitrogen in the preparation of primary amines by protecting the nitrogen atom of the nucleophile so that can react only once with an alkylating agent. An example of a compound that contains a protected nitrogen atom with a single N—H bond is phthalimide. Not only is there no possibility for multiple alkylation, but the carbonyl groups modify the reactivity of the nitrogen. The dipolar resonance forms decrease the nucleophilicity of nitrogen.



The pK_a of the N—H bond of phthalimide is 8.3. The enhanced acidity of the N—H bond results from both an inductive effect and a resonance effect. The inductive effect of two carbonyl groups increases the acidity of the N—H bond. The more important effect is resonance stabilization of the conjugate base by delocalization of the electrons of nitrogen with the carbonyl groups.

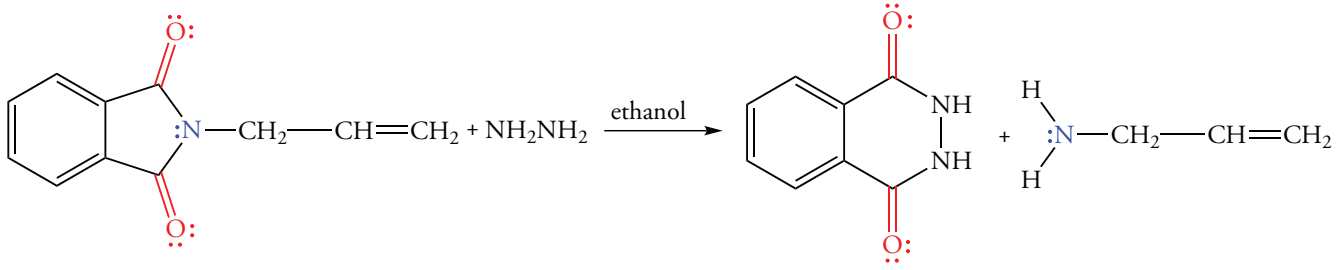


The negatively charged nitrogen atom of the salt of phthalimide is a good nucleophile. It displaces halides from primary alkyl halides and tosylate groups from primary tosylates to yield an N-alkylated phthalimide. This reaction, with its related workup procedures, is called the **Gabriel synthesis**.



The product is a diacyl derivative of an amine. Thus, the lone pair electrons of nitrogen are so effectively delocalized that they cannot displace a halide even from a compound as reactive as allyl chloride. Thus, only a single substitution reaction occurs.

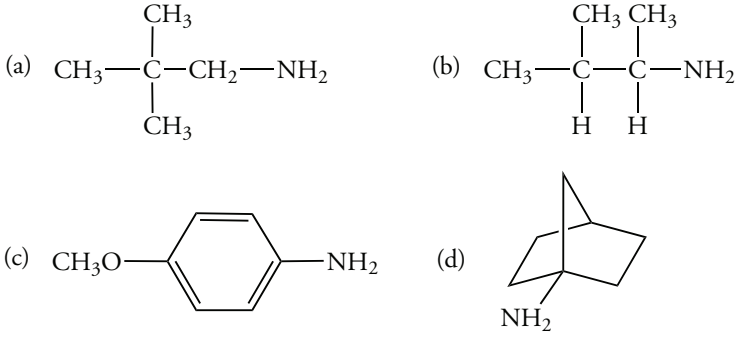
The N-alkyl phthalimide product can be hydrolyzed with either aqueous acid or base to form phthalic acid and liberate the amine. However, it is difficult to hydrolyze amides (Section 21.5). A more effective method uses hydrazine to form a phthalyl hydrazide by acyl transfer.



The Gabriel synthesis is limited to the formation of primary amines because secondary and tertiary alkyl halides undergo competitive elimination reactions. Aryl halides cannot be used because they do not undergo nucleophilic substitution under these reaction conditions.

Problem 23.13

Consider the possible synthesis of each of the following amines using the Gabriel synthesis. What limitations are there in each case?



Problem 23.14

4-Aminobutanoic acid, commonly known as γ-aminobutyric acid or GABA, is a neurotransmitter. Explain why it cannot be synthesized by a Gabriel synthesis using 4-chlorobutanoic acid. What alternate chlorinated acid derivative might be used.

Sample Solution

Only one of the two α carbon atoms has bonded hydrogen atoms. Removing a proton from the methyl group of acetophenone by KH gives a resonance-stabilized enolate anion.

Sample Solution

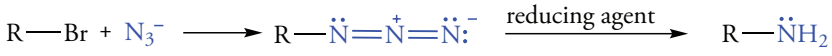
The carboxylic acid is sufficiently acidic to rapidly protonate the salt of the phthalimide prior to the S_N2 displacement of the chloride ion. The related ester and nitrile are possible alternative reactants. However, the imide salt would displace an alkoxide of the ester and form an amide. The nitrile, 4-chlorobutanenitrile, is a better choice. The product, 4-aminobutanenitrile, can be hydrolyzed to the corresponding carboxylic acid.

23.8 SYNTHESIS OF AMINES BY REDUCTION

Amines are the most reduced form of nitrogen in organic compounds. Thus, almost any functional group containing nitrogen in a higher oxidation state or with multiple bonds to nitrogen can be reduced to an amine.

Reduction of Azides

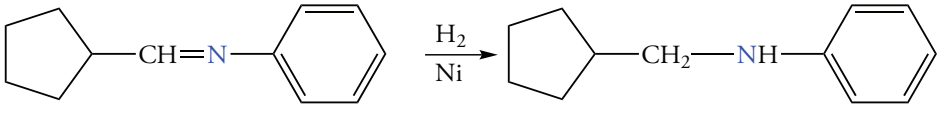
Alkyl azides are unstable compounds, but they can be easily prepared by nucleophilic substitution of a halide by the very nucleophilic azide ion, (N_3^-). Reduction of azides yields amines.

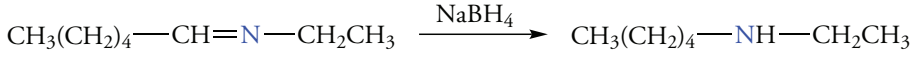


Catalytic hydrogenation using hydrogen and platinum may be used, but lithium aluminum hydride in an ether solvent is the more common reducing agent.

Reduction of Imines

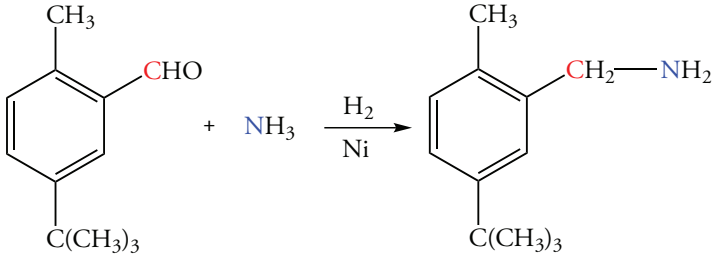
We recall that the carbonyl group of aldehydes or ketones is reduced to an alcohol by either catalytic hydrogenation or metal hydrides. Imines are the nitrogen analogs of carbonyl compounds, and they are also reduced by the same reagents.



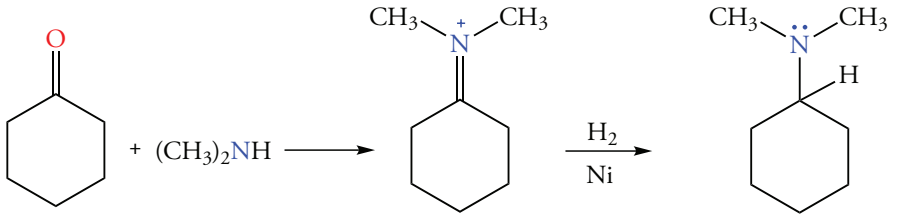


Imines are less stable than carbonyl compounds, and the reaction conditions must be selected to drive the equilibrium reaction of a carbonyl compound with an amine toward an imine (Section 18.10). Only imines of aromatic amines are easily prepared and isolated.

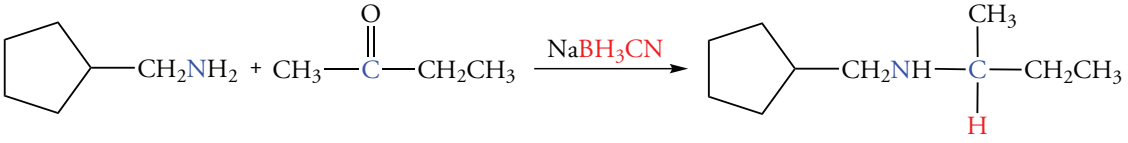
Imines do not have to be separately prepared and isolated for subsequent reduction. A mixture of a carbonyl compound and ammonia or the appropriate amine reacts in the presence of hydrogen gas and a metal catalyst. An imine forms initially, and it is reduced to an amine. The overall process is called **reductive amination**. Primary amines are prepared using ammonia as the nitrogen source.



Secondary amines are prepared by reductive amination using a primary amine as the nitrogen source. Condensation of an aldehyde or ketone with a secondary amine gives an iminium salt, which is subsequently reduced to a tertiary amine.

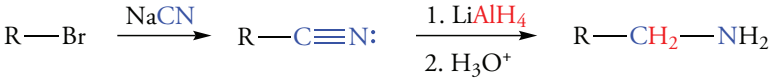


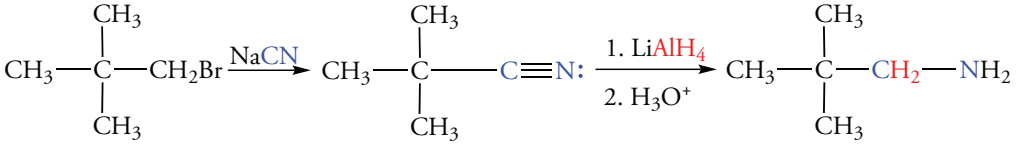
Reductive amination can also be accomplished by using a modified borohydride called sodium cyanoborohydride. This reagent reduces the intermediate imine functional group, but not the carbonyl group of the reactant.



Reduction of Nitriles

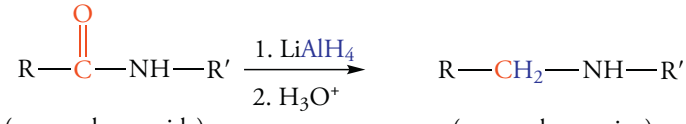
Nitriles can be prepared from primary alkyl halides by a direct S_N2 reaction using sodium cyanide as the nucleophile. The nitrile is then reduced to a primary amine with lithium aluminum hydride.



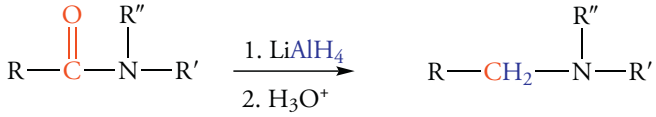


Reduction of Amides

Reduction of amides is one of the most frequently used methods of preparing amines. The method is very versatile because primary, secondary, and tertiary amines are easily prepared from the corresponding classes of amide. Amides are prepared by acylation of amines using activated acyl derivatives such as acid chlorides or acid anhydrides (Section 21.7).



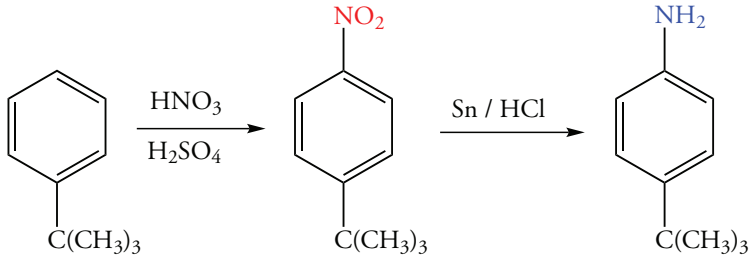
(a secondary amide) (a secondary amine)



(a tertiary amide) (a tertiary amine)

Reduction of Nitro Compounds

There is no synthetic procedure to introduce an amino group onto an aromatic ring in one step. However, it is possible to substitute an amino group onto an aromatic ring in two steps. First, the ring is nitrated. Then, the nitro group is reduced to an amino group.

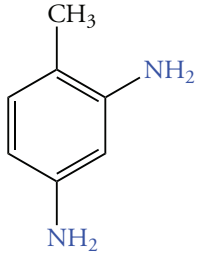


Problem 23.15

Outline three synthetic methods to prepare 2-phenylethylamine using a reductive step.

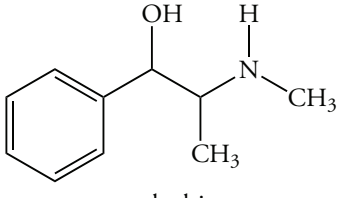
Problem 23.16

Outline a synthesis of the following diamine starting from toluene.



Problem 23.17

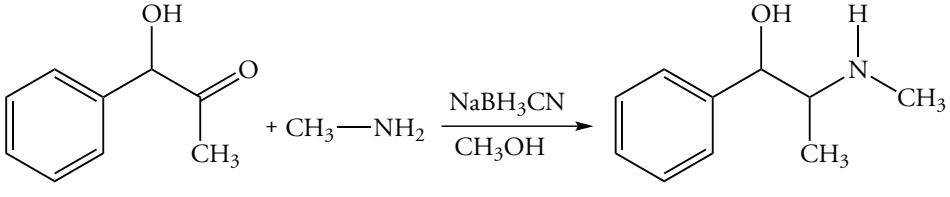
Ephedrine is used in the treatment of bronchial asthma. What reactants are required to synthesize this compound using a reductive amination step.



ephedrine

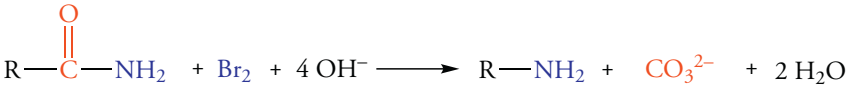
Sample Solution

There are two possible combinations of reactants because either of the two carbon atoms bonded to nitrogen could be derived from a carbonyl carbon atom. Either of the remaining carbon atoms in each case could be bonded to a nitrogen atom of an amine. The required carbonyl compound using methylamine as the reactant is 1-hydroxy-l-phenyl-2-propanone.



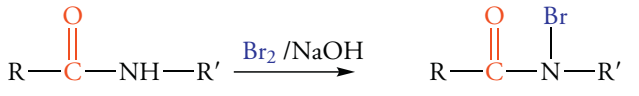
23.9 THE HOFMANN REARRANGEMENT

Primary amides can be converted into amines containing one less carbon atom by the **Hofmann rearrangement**.



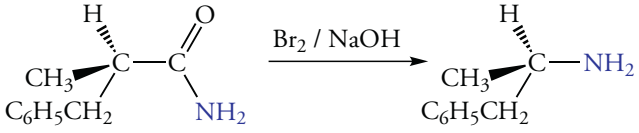
The structural change corresponds to removing the carbonyl group and attaching the amino group to the α carbon atom. A rearrangement occurs by a migration of the R group from the carbonyl carbon atom to the nitrogen atom. The following experimental observations form the basis of the mechanism.

1. The nitrogen atom must have two protons attached to it. Thus, only primary amides react to give the amine.
2. Under the reaction conditions, secondary amides yield *N*-bromoamides.



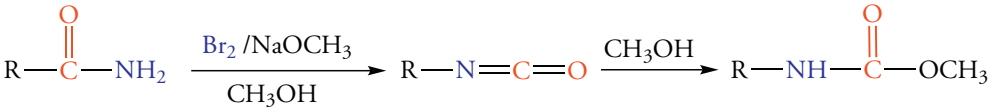
(a secondary amide) (an *N*-bromoamide)

3. The reaction occurs with retention of configuration at the α carbon atom.



(*R*)-2-methyl-3-phenylpropanamide (*R*)-1-phenyl-2-propanamine

4. An intermediate isocyanate (R—N=C=O) forms under the reaction conditions. The existence of the isocyanate is shown by "trapping" it using methanol as solvent. Under these conditions, a carbamate forms.



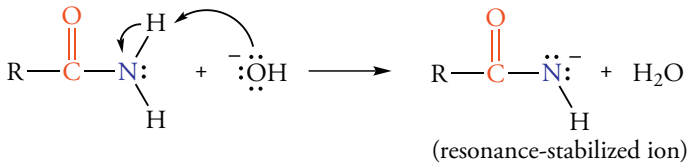
(an isocyanate) a methyl *N*-alkylcarbamate

Mechanism of the Hofmann Rearrangement

The Hofmann rearrangement is somewhat complicated. For convenience we will divide its mechanism into three stages, each having two steps.

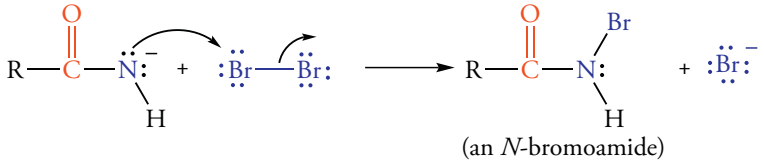
Stage I. Conversion of the amide to an *N*-bromoamide .

Step 1.



(resonance-stabilized ion)

Step 2.

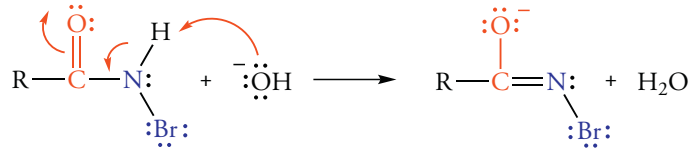


(an *N*-bromoamide)

Stage II. The *N*-bromoamide is converted into an isocyanate in two steps.

Step 1. Hydroxide ion extracts a hydrogen atom of the *N*-bromoamide, which is even more acidic than the original amide because bromine withdraws electron density from the nitrogen.

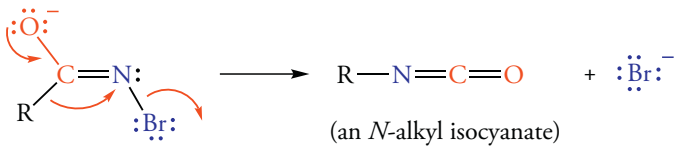
Step 1.



(conjugate base of an *N*-bromoamide)

Stage II. Step 2. The *N*-bromoamide undergoes a rearrangement reaction in which the R group migrates from the carbonyl carbon atom to the nitrogen atom. A bromide ion simultaneously leaves. As the bromide ion departs, the nitrogen atom develops some cationic character, which provides the driving force for the reaction. Thus, the migration of the alkyl group resembles that of alkyl groups in carbocation rearrangement.

Step 2.

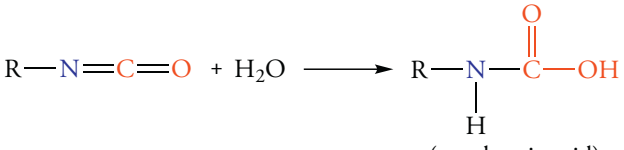


(an *N*-alkyl isocyanate)

Stage III. Step 1. The isocyanate hydrolyzes in a base-catalyzed reaction to give an *N*-alkylcarbamic acid.

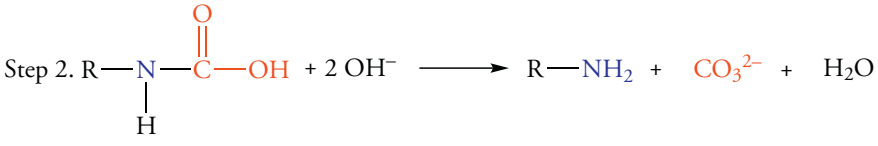
Step 2. The carbamic acid continues to react to give the final product.

Step 1.



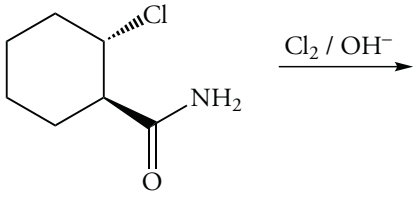
(a carbamic acid)

Step 2.



Problem 23.18

Draw the product of the following reaction.



23.10 OVERVIEW OF AMINE REACTIONS

In Chapter 15, we analyzed the reactions of alcohols based on the number and type of bonds broken. Let's do the same thing for amines and compare the chemistry of amines and alcohols. As we will shortly see, the substitution of the nitrogen atom of Group 5 for the oxygen atom of Group 6 causes amine chemistry to differ dramatically from that of alcohols.

Acid and Base Properties

Alcohols are weak acids, pK_a 16–18, but their conjugate bases form easily. We have seen that the reaction of alkoxides as nucleophiles is an important feature of the chemistry of alcohols. In contrast, amines are very weak acids, pK_a 35. The difference in acidities of alcohols and amines agrees with the periodic trends for CH_4NH_2 and H_2O. Because amines are very weak acids, the chemistry of their conjugate bases is quite limited. In fact, the conjugate bases of amines such as lithium diisopropylamide are used only to form conjugate bases of compounds such as enolates of carbonyl compounds.

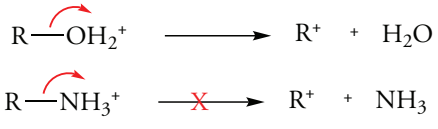
Also based on periodic trends, we know that amines are stronger bases than alcohols. Alcohols are very weak bases and are protonated only in strong acid solutions. Amines are used to neutralize acids generated in reactions, such as the HCl generated in the reaction of an acid chloride with an alcohol. They are also used to catalyze reactions such as the Knoevenagel reaction.

Nucleophilicity

We recall that within the same period, nucleophilicity and basicity parallel each other (Section 9.1). Thus, ammonia is a better nucleophile than water, and amines are better nucleophiles than alcohols. Most of the reactions of amines result from the nonbonding electron pair on nitrogen. We recall that a nonbonding electron pair of an alcohol is only weakly nucleophilic. For example, it is usually only available to displace leaving groups, such as a halide ion in S_N2 reactions, when the alcohol is converted to the more nucleophilic alkoxide ion. As we saw in Section 23.8, the nonbonding electron pair of the neutral amine can displace a halide ion from alkyl halides. Both alkylation and acylation of an amine result directly from the nucleophilicity of the nonbonding electron pair. The alkyl or acyl group replaces a hydrogen atom of an N—H bond. However, the hydrogen atom leaves in a subsequent step of the reaction after the nonbonding electron pair attacks an electrophilic center.

Substitution Reactions

Many reactions of alcohols break the C—O bond, as in the replacement by a halogen atom in nucleophilic substitution reactions by either an S_N2 or an S_N1 mechanism. However, we recall that the leaving group tendencies within a group are inversely related to their basicity (Section 9.3). Thus, hydroxide ion is a poor leaving group, and it is necessary to protonate the hydroxyl group to generate water as a leaving group. Because NH_2^- is a much stronger base than OH^-, the C—N bond of amines does not break in S_N1 or S_N2 reactions. Even if an amine is protonated to provide ammonia as a leaving group, neither S_N1 nor S_N2 reactions occur.



Elimination Reactions

We recall that in some reactions of alcohols in which either the C—O or the O—H bond breaks, a C—H bond also breaks. If this bond is on the carbon atom adjacent to the carbon atom bearing the hydroxyl group, the reaction is a β-elimination. The corresponding reaction of the N—H and C—H bonds of amines is relatively unimportant.

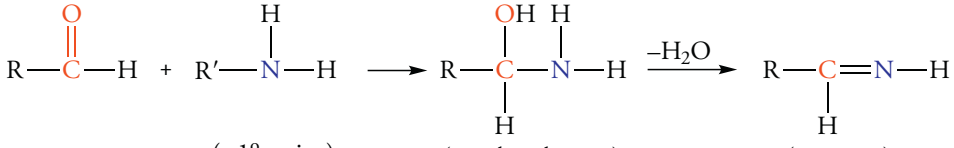
As in the case of substitution reactions, the basicity of the leaving group is important in β-elimination reactions. Consequently, amines do not undergo β-elimination reactions because both NH_2^- and NH_3 are poor leaving groups. However, one specialized reaction in which an amine is converted into a quaternary ammonium ion is an E2 elimination. We will discuss this process, known as the Hofmann elimination, in Section 23.15.

Oxidation Reactions

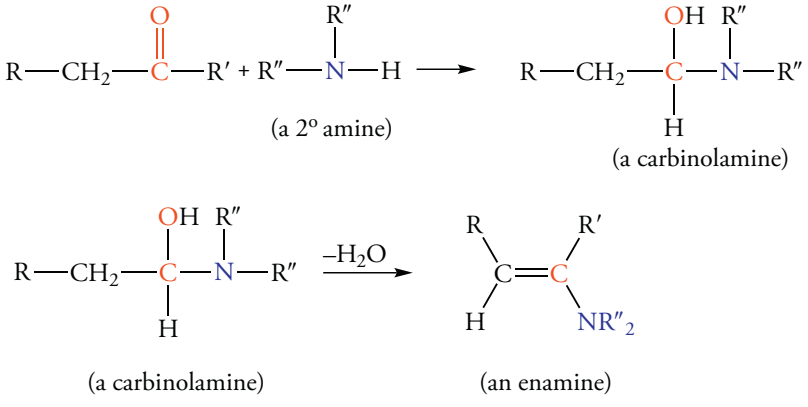
We recall that breaking both the O—H bond of an alcohol and the C—H bond at the carbon atom bearing the hydroxyl group is an oxidation reaction or an α-elimination reaction. Amines can be similarly oxidized, but the products are sensitive to reaction conditions, and synthetic applications of this chemistry are limited. We recall, for example, that imines are very reactive. In this chapter, we consider only one type of reaction that can be termed an oxidation. Nitrous acid (HNO_2) is a mild oxidizing agent that generates intermediates that are oxidized relative to an amine. We have already seen some of this chemistry in the conversion of aromatic amines into aromatic diazonium ions (Section 13.8). We will expand on this reaction and related chemistry in this chapter for alkylamines.

23.11 ENAMINES

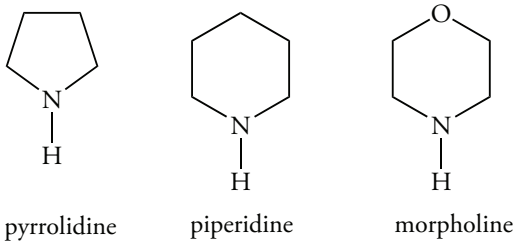
In Section 18.10 we described the addition–elimination reaction of primary amines with carbonyl compounds. An amine adds to the electrophilic carbonyl carbon atom to give a tetrahedral intermediate. This carbinolamine is unstable, and it loses water to form an imine.



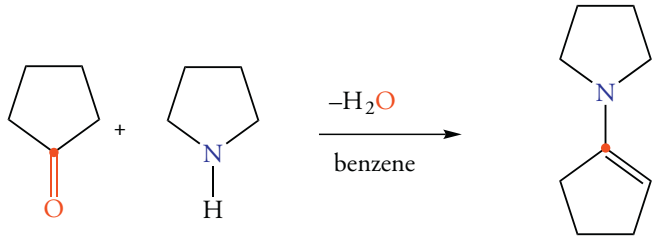
Secondary amines also react with aldehydes or ketones to form carbinolamines, but this intermediate cannot dehydrate to give an imine. However, the carbinolamine derived from a secondary amine can lose water to give a carbon–carbon double bond in a compound called an enamine (pronounced "ene amine"). The water is removed by azeotropic distillation with benzene.



Pyrrolidine, piperidine, and morpholine are the most common secondary amines used to prepare enamines.



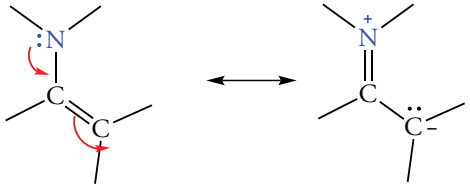
For example, cyclopentanone reacts with pyrrolidine to give an enamine.



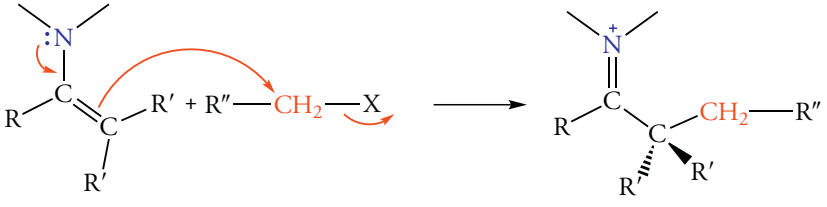
pyrrolidine *N*-(1-cyclopentenyl)pyrrolidine

Alkylation of Enamines

Enamines are used as intermediates to form carbon–carbon bonds in reactions that parallel those of carbonyl compounds. The carbon–carbon double bond is nucleophilic because the lone pair electrons of nitrogen can be released to the carbon atom that was the α carbon atom of the original carbonyl compound.



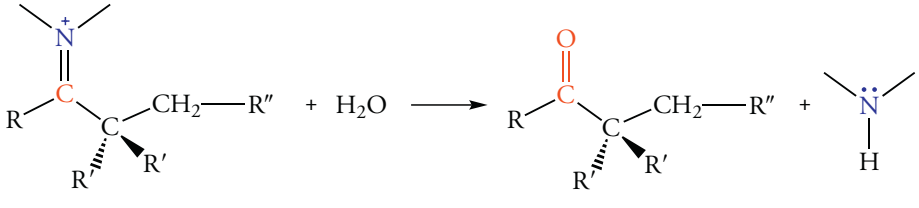
Enamines resemble enols because both have an increased electron density at a structurally related α carbon atom. The electron density at the α carbon atom in enamines is greater than that in enols because nitrogen is less electronegative than oxygen and releases an electron pair more readily. As a result, enamines are more nucleophilic than enols, and they are useful intermediates in alkylation reactions. We recall that enolate anions react with alkyl halides to give α-alkylated carbonyl compounds (Section 23.6), but uncharged enols are not sufficiently nucleophilic to be alkylated. Alkylation of the more nucleophilic enamine produces an iminium ion.



(an enamine) (an alkyl halide) (an alkylated enamine)

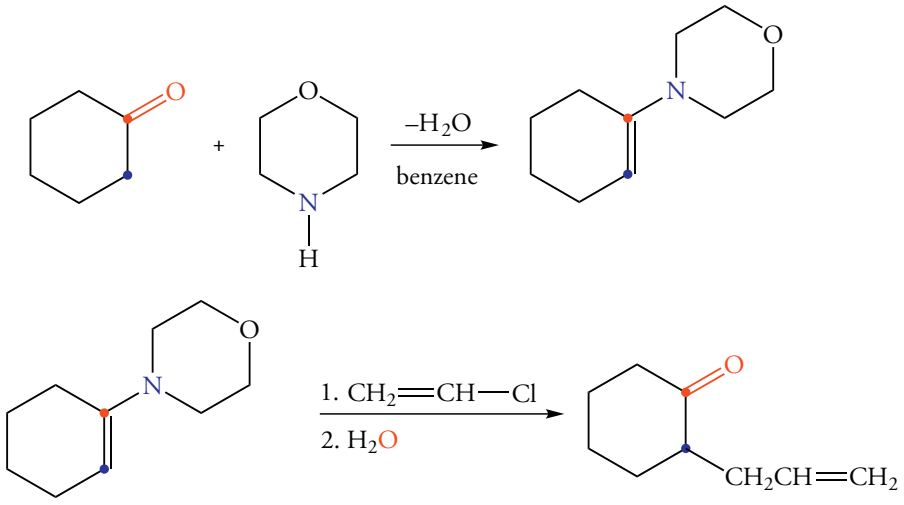
The S_N2 displacement reaction by the electron pair of an enamine occurs for primary alkyl halides, α-halo carbonyl compounds, and α-halo ethers.

Like imines, the iminium ion hydrolyzes readily to give an alkylated carbonyl compound.

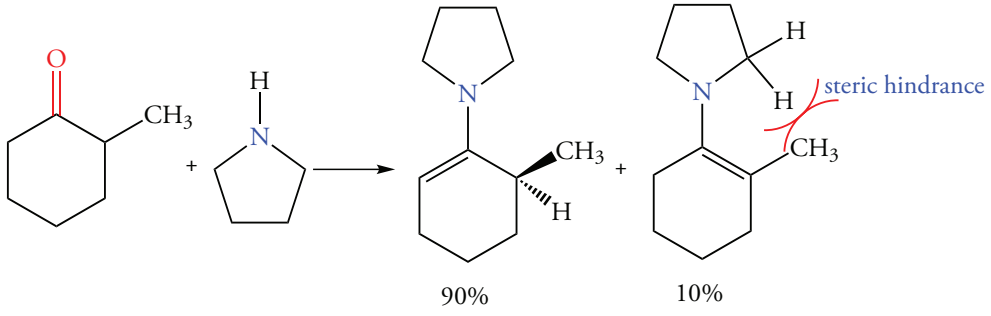


The use of enamines to alkylate carbonyl compounds at the α-position rather than the direct alkylation of the carbonyl compound has two major advantages.

1. First, no strong base is present, so side reactions with the alkyl halide such as substitution and elimination do not occur.
2. Second, because alkylation of the enamine gives an iminium ion, the derivative is no longer nucleophilic. As a result, monoalkylation occurs in good yield. This result contrasts with the alkylation of enolates, where proton transfer between alkylated product and reactant leads to multiple alkylation steps (Section 21.6).



Two isomeric enamines can form with unsymmetrical ketones. The major isomer is the one with the less substituted double bond, as shown for 2-methylcyclohexanone.



This distribution results from resonance stabilization and steric effects. The enamine is stabilized by overlap of the orbital of nitrogen containing the nonbonded electrons with the π electrons of the double bond. For maximum overlap, the groups bonded to nitrogen and two carbon atoms of the double bond must be coplanar. In the minor isomer, there is an unfavorable steric interaction with the methyl group and a methylene unit of the pyrrolidine ring that resembles that of *cis* alkenes. Although the same interaction may appear to exist in the major isomer, it is less severe. The methyl group of this isomer is bonded to an sp^3-hybridized carbon atom and is not in the same plane as the pyrrolidine ring.

Problem 23.19

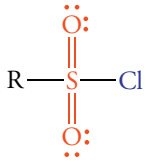
(a) Draw the structure of the enamine formed from cyclopentanone and piperidine. (b) Draw the structure of the product of reaction between this enamine and benzyl chloride.

Problem 23.20

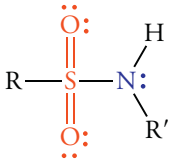
Enamines act as Michael donors in conjugate addition reactions (Section 21.12). Draw the structure of the product formed by reaction of the enamine of cyclohexanone and pyrrolidine with methyl vinyl ketone.

23.12 SULFONAMIDES

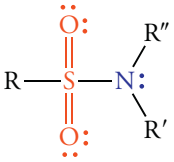
Sulfonyl chlorides are the acid chlorides of sulfonic acids. Like acid chlorides, sulfonyl chlorides react with amines to form amides called sulfonamides. These compounds are crystalline solids with high melting points.



a sulfonyl chloride

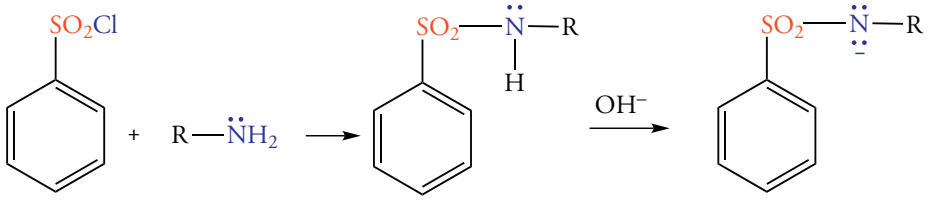


sulfonamide of a 1° amine



sulfonamide of a 2° amine

The properties of sulfonamides differ from those of amides. Because the sulfonyl group withdraws electrons more strongly than an acyl group, the N—H bond of the sulfonamide of a primary amine is acidic. Thus, reaction of a primary amine with benzenesulfonyl chloride yields a sulfonamide that is soluble in sodium hydroxide.

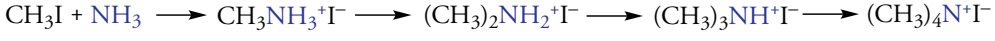


Secondary amines also react with benzenesulfonyl chloride to give sulfonamides. They are insoluble in base because there is no acidic N—H bond. Tertiary amines do not form stable compounds with benzenesulfonyl chloride because they have no hydrogen atom on the nitrogen atom of the amine.

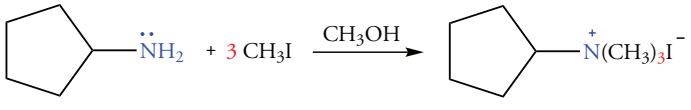
A classical method of distinguishing between the types of amines is based on the difference in the reactivity of amines with benzenesulfonyl chloride followed by reaction with sodium hydroxide. The procedure is called the Hinsberg test. First, benzenesulfonyl chloride is shaken with a mixture of an amine and aqueous base. Then, the reaction mixture is examined to determine which of three possible events occurred. If the amine was tertiary, no precipitate appears, and there is no evidence of any reaction. If the amine was secondary, a water-insoluble sulfonamide forms and appears as a precipitate. Primary amines also give no evidence of a reaction because the sulfonamide is soluble in the base, but if the solution is neutralized with an acid, the neutral water-insoluble sulfonamide precipitates. Thus, the experimental results are unique for each class of amine. Infrared spectroscopy and NMR allow us to identify classes of amines (Section 23.14).

23.13 QUATERNARY AMMONIUM SALTS

In Section 23.7 we described nucleophilic substitution reactions of primary amines with alkyl halides, which give secondary amines, tertiary amines, and eventually quaternary ammonium salts.

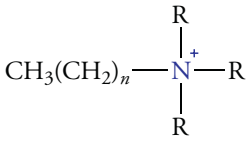


Methyl iodide reacts so readily with nucleophiles that primary amines are completely converted to quaternary ammonium salts by a process called **exhaustive methylation**.



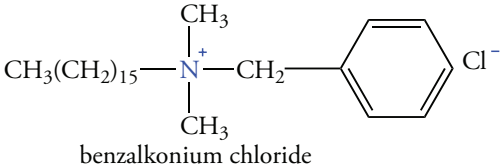
Invert Soaps

Some quaternary ammonium salts containing a long carbon chain are invert soaps. Invert soaps differ from soaps and detergents because the polar end of the ion is positive rather than negative. As with soaps, the long hydrocarbon tail associates with nonpolar substances, and the polar head dissolves in water. Thus, invert soaps act by the same cleansing mechanism described in Section 20.5 for soaps and detergents.

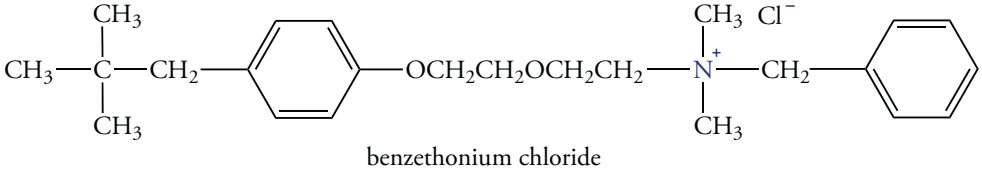


(an invert soap)

Invert soaps are widely used in hospitals, but for their bactericidal properties rather than their cleansing properties. They are active against bacteria, fungi, and protozoans, but they are not effective against spore-forming microorganisms. One type of invert soap is the family of benzalkonium chlorides. The alkyl groups of these compounds contain from 8 to 16 carbon atoms. These compounds are effective at concentrations of 1:750 to 1:20,000. The more complex benzethonium chloride is also an effective antiseptic.



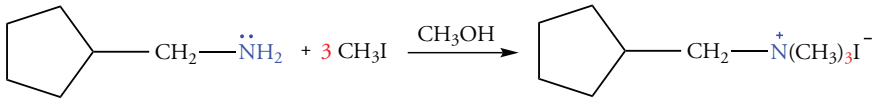
benzalkonium chloride



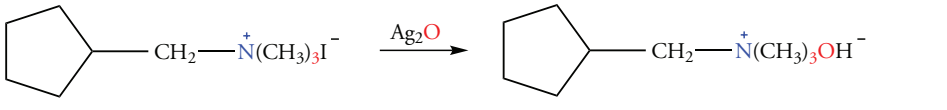
benzethonium chloride

The Hofmann Elimination

Quaternary ammonium iodides, prepared by the exhaustive methylation of primary amines, are converted to quaternary ammonium hydroxides by treatment with silver oxide.

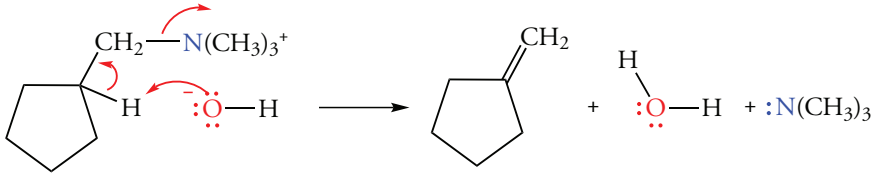


(cyclopentylmethyl)trimethylammonium iodide

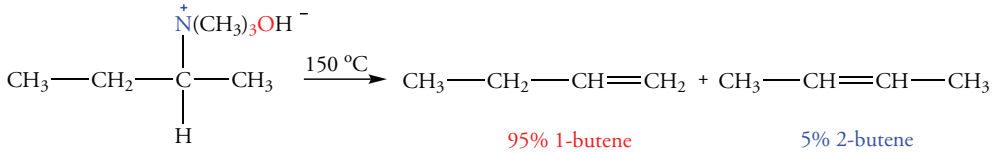


(cyclopentylmethyl)trimethylammonium hydroxide

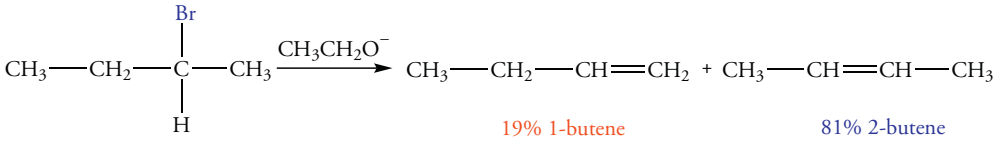
Quaternary ammonium hydroxides undergo β-elimination to form an alkene and trimethylamine when heated. This reaction is called the **Hofmann elimination**.



In the above example, only one elimination product can form. The Hofmann elimination of quaternary ammonium salts is regioselective. This E2 elimination occurs to give the less substituted alkene by removal of the less sterically hindered β hydrogen atom by base. Hence, methyl groups lose a proton in the elimination reaction in preference to loss of a proton from a methylene group. The less substituted alkene, which forms preferentially, is termed the Hofmann product.



We recall that the β-elimination of bromoalkanes with ethoxide as the base gives the more substituted alkene, called the Zaitsev product. The Zaitsev product results from the greater stability of the developing double bond in the alkene generated in the transition state.



The regioselectivity of the Hofmann elimination reaction is controlled by two major factors:

1. The regioselectivity results in part from the acidity of the C—H bond β to the positively charged trimethylammonium group $(CH_3)_3N^+$. The acidity of the C—H bond decreases in the order 1° > 2° > 3°, reflecting carbanion stability.
2. The regioselectivity also results from steric effects in the transition state for the E2 elimination. A $(CH_3)_3N^+$ group has approximately the same van der Waals radius as a *tert*-butyl group. A *trans* periplanar arrangement of the proton to be eliminated and the $(CH_3)_3N^+$ group is required for an E2 elimination reaction of the quaternary ammonium salt to take place.

In the transition state required to form 1-butene, no steric repulsions occur because the $(CH_3)_3N^+$ group is gauche to two hydrogen atoms (Figure 23.1). In the transition states leading to the two isomeric 2-butenes, the $(CH_3)_3N^+$ group is gauche to a methyl group. As a consequence, the transition state energy required for an E2 elimination to give 2-butene is higher, and these products form more slowly. The *cis* isomer forms in a smaller amount than the *trans* isomer because the two methyl groups are gauche in the conformation required for the E2 elimination.

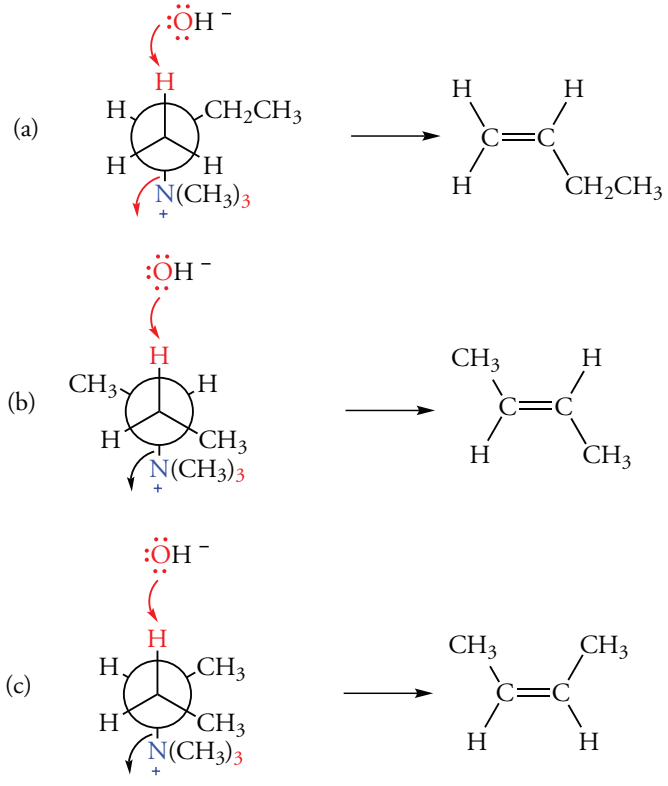


Figure 23.1
The Hofmann Elimination
(a) The abstraction of a hydrogen atom at C-1 occurs from a conformation that has no steric crowding of the trimethylammonium group.

(b) The abstraction of a hydrogen atom at C-2 occurs from a conformation in which the C-4 methyl group and the trimethylammonium ion are gauche. The product is *trans*-2-butene.

(c) In this conformation the C-4 methyl group and the trimethylammonium ion are gauche. However, the C-4 and C-1 methyl groups are also gauche. The *cis*-2-butene product is formed in smaller amount than the *trans*-2-butene derived from (b).

Problem 23.21

Two isomeric alkenes form in a 10:1 ratio when the quaternary ammonium hydroxide derived from 1-methylcyclohexylamine and methyl iodide is heated. (a) Draw the structures of the isomers. (b) Which one forms in the larger amount?

Problem 23.22

Explain why benzylic and allylic C—H bonds are more easily eliminated in the Hofmann reaction than other alkyl C—H bonds.

Problem 23.23

Explain why iodoethane cannot be used in place of iodomethane in the exhaustive alkylation of amines for the Hofmann elimination reaction.

23.14 SPECTROSCOPY OF AMINES

Infrared Spectroscopy

The C—N stretching absorption occurs in the 1050–1250 cm^{-1} region. This is an area of the infrared spectrum that contains many other absorptions. As in the case of the C—O stretching absorptions of alcohols, the identification of an amine is not usually based on identification of the C—N stretching absorption. The N—H absorptions that occur in the 3200–3380 cm^{-1} region are diagnostic for amines. Primary amines have two absorptions in this region (Figure 23.2). Secondary amines have a single absorption (Figure 23.3). Tertiary amines have no absorption in the 3200–3380 cm^{-1} because they lack an N—H bond. Because amines form hydrogen bonds, the absorption for N—H stretching is broadened by the presence of a variety of species. However, because amines are not as strongly hydrogen bonded as alcohols, this broadening is less than that of alcohols.

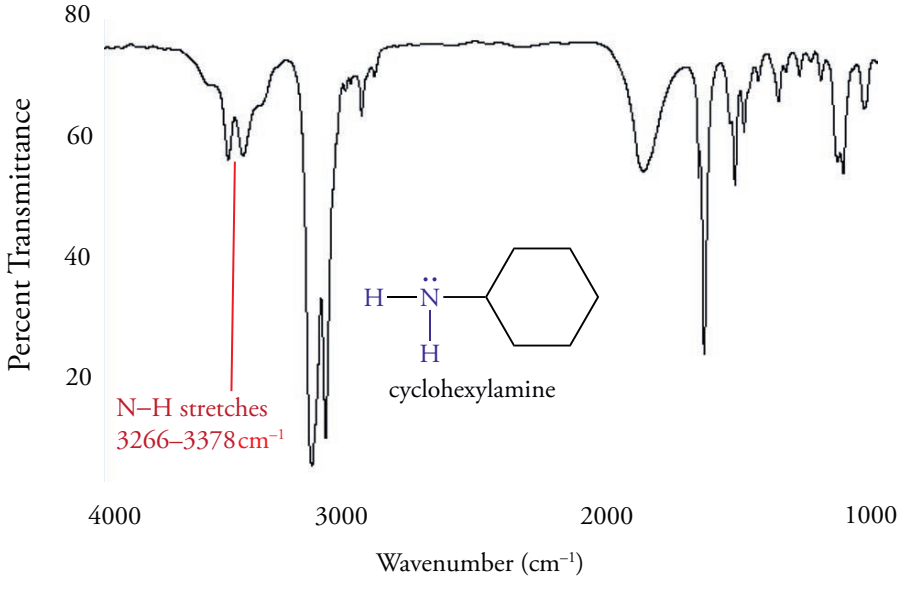


Figure 23.2 Infrared Spectrum of a Primary Amine
Primary amines have two absorptions in the IR in the 3200–3380 cm^{-1} region, as shown for cyclohexylamine.

NMR Spectroscopy

Like the O—H hydrogen atom of an alcohol, the chemical shift of the N—H hydrogen atom of amines is concentration dependent because hydrogen bonding is less extensive in amines than in alcohols. Also, because nitrogen is less electronegative than oxygen, the hydrogen resonance of the N—H hydrogen is at higher field than that of the O—H hydrogen atom. Simple alkylamines have an N—H resonance of about 1 δ. This chemical shift is at lower field for arylamines as a result of deshielding by the aromatic π electrons (Section 13.13).

The N—H hydrogen atoms of amines undergo rapid exchange with solvent, and their resonance is not split by neighboring C—H hydrogen atoms. When D_2O is added, hydrogen–deuterium exchange occurs and the resonance of the N—H hydrogen is eliminated.

The C—H resonance of the groups directly attached to the nitrogen atom is shifted to lower field as a result of the inductive effect of the nitrogen atom. The resonances of hydrogen atoms on carbon atoms further removed from the nitrogen atom are essentially the same as those of structurally similar alkanes, as shown for diethylamine in Figure 23.4.

Figure 23.3
Infrared Spectrum of a Secondary Amine

Secondary amines have one absorption in the IR in the 3200–3380 cm^{-1} region, as shown for diethylamine.

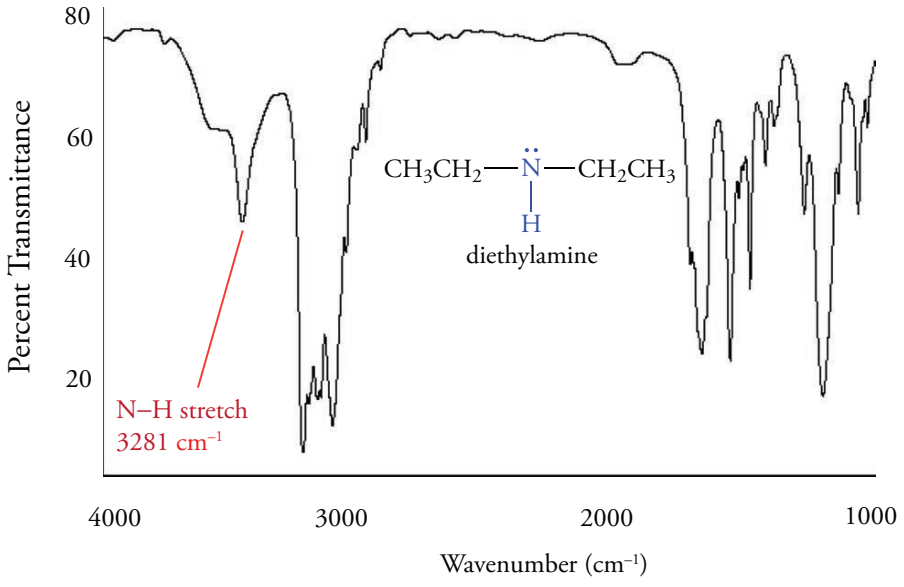
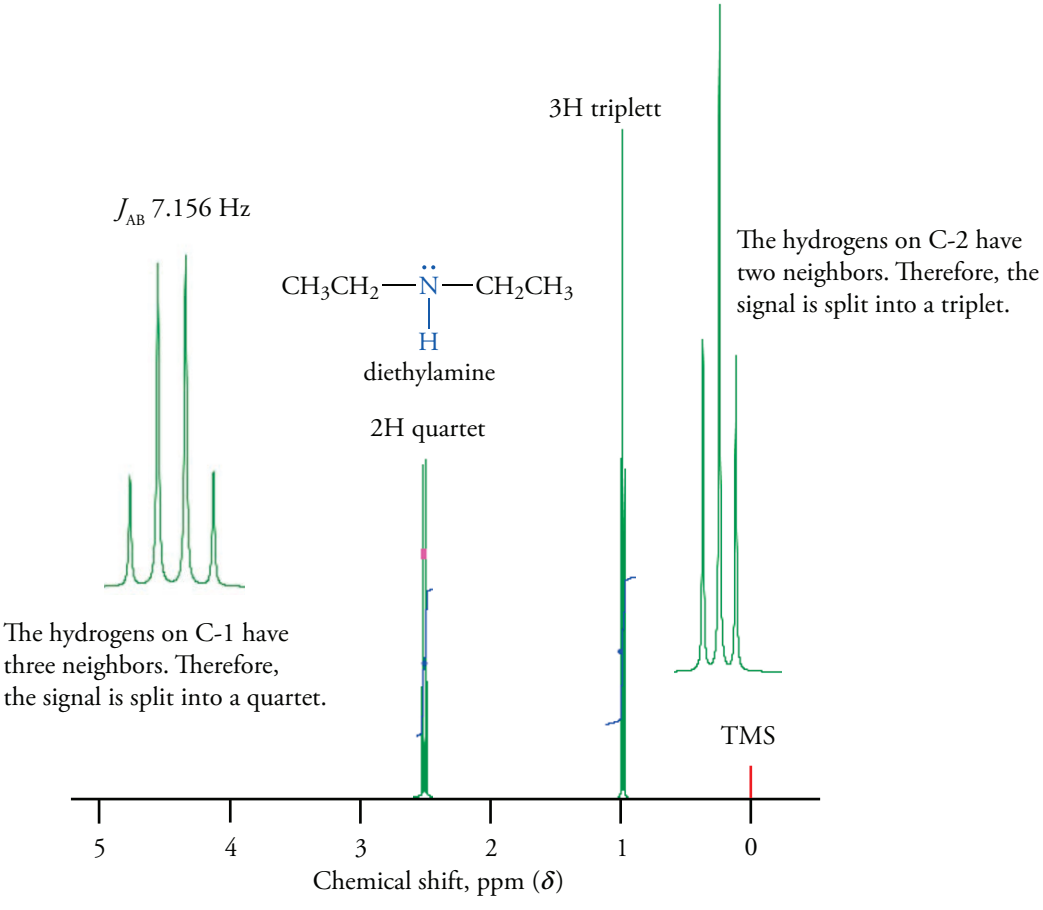
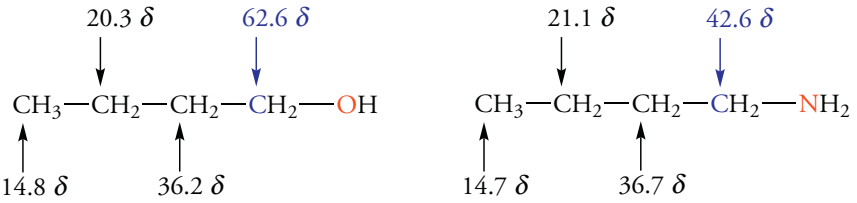


Figure 23.4 NMR Spectrum of Diethylamine

The alkyl hydrogens of primary amines have about the same chemical shifts as those of alkanes. When a small amount of D_2O is added to the sample, the N—H hydrogen exchanges with D_2O, and the N—H resonance disappears.



The carbon-13 NMR of amines is characterized by the deshielding of the carbon atom bonded directly to the nitrogen atom; other carbon atoms are less affected. The carbon absorptions of the N—C unit are in the 30–50 δ range. Thus, the deshielding of carbon by nitrogen is less than the deshielding of carbon by the more electronegative oxygen atom, as illustrated by the ^{13}C chemical shifts *n*-butyl alcohol and *n*-butylamine.



Problem 23.24

Write the structures of all compounds with molecular formula $C_5H_{13}N$ that have no absorption in the 3200–3400 cm^{-1} region.

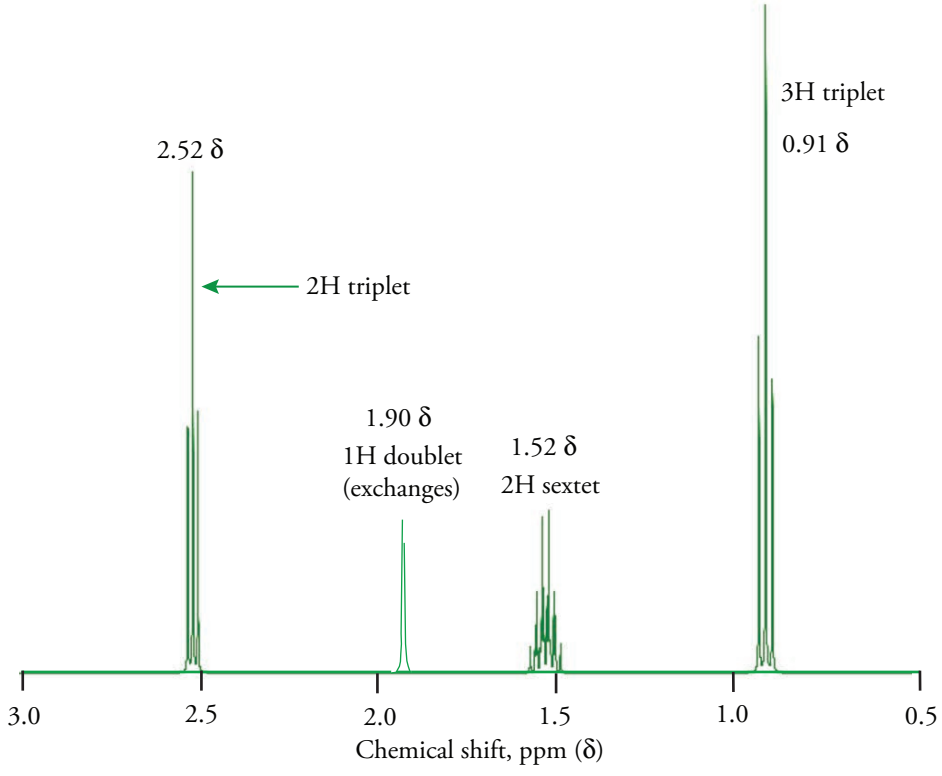
Problem 23.25

Deduce the structure of a compound with molecular formula $C_8H_{19}N$ that has the following absorptions in its hydrogen NMR spectrum, all of which are singlets. The N—H resonance at 1.28 δ is eliminated by exchange with D_2O. The number of hydrogen atoms in indicated within parentheses.

1.02 δ (9H), 1.17 δ (6H), 1.44 δ (2H), 1.34 δ (2H, exchanges)

Problem 23.26

Deduce the structure of a compound with molecular formula $C_6H_{15}N$ that has the following proton NMR.



EXERCISES

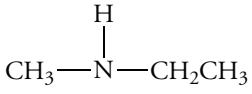
Bonding and Structure

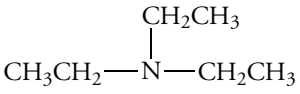
23.1 Which compound has the greater N—H bond length, pyrrole or pyrrolidine?

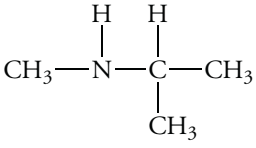
23.2 Which compound has the larger activation energy for the nitrogen inversion, *tert*-butyldimethylamine or trimethylamine?

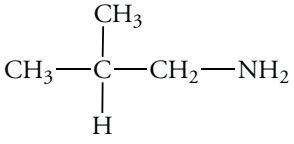
Classification of Amines

23.3 Classify each of the following amines.

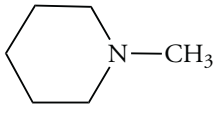
(a) 

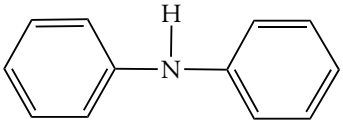
(b) 

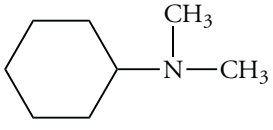
(c) 

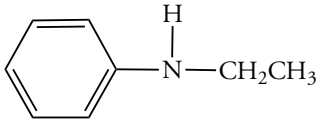
(d) 

23.4 Classify each of the following amines.

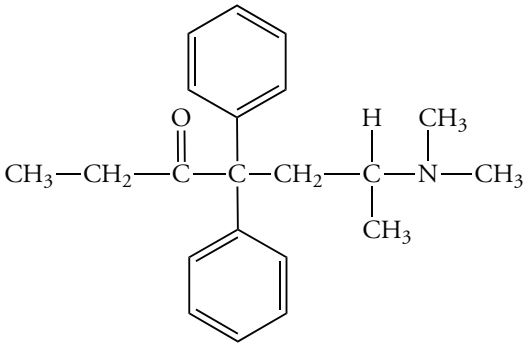
(a) 

(b) 

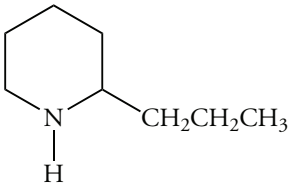
(c) 

(d) 

23.5 Classify the nitrogen-containing functional group in each of the following structures.
(a) methadone, a heroin substitute used in treating addicts

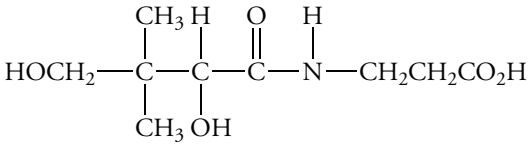


(b) coniine, the hemlock poison that was used to execute Socrates



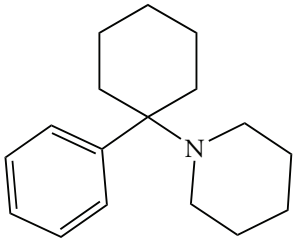
coniine

(c) pantothenic acid, vitamin B_5



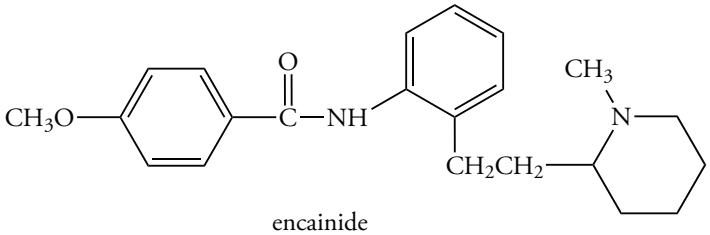
pantothenic acid, vitamin B_5

23.6 Classify the nitrogen-containing functional group in each of the following structures.
(a) phencyclidine, a hallucinogen



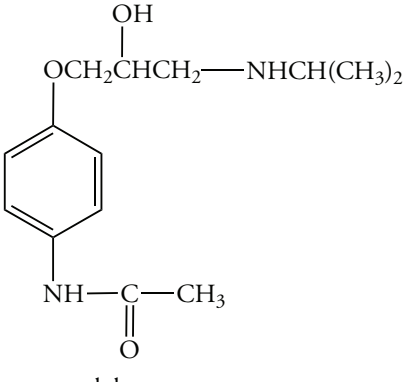
phencyclidine

(b) encainide, an antiarrhythmic drug



encainide

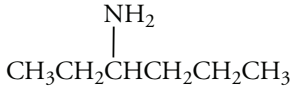
(c) practolol, an antihypertensive drug

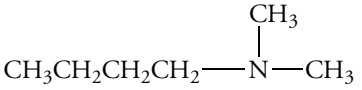


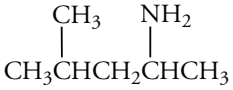
practolol

Nomenclature

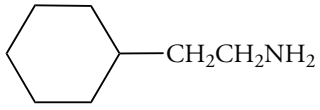
23.7 Give the IUPAC name for each of the following compounds.

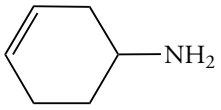
(a) 

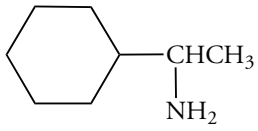
(b) 

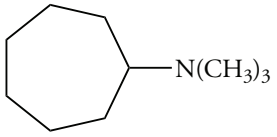
(c) 

23.8 Give the IUPAC name for each of the following compounds.

(a) 

(b) 

(c) 

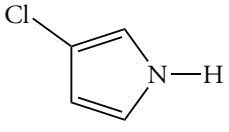
(d) 

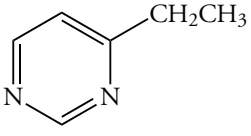
23.9 An antidepressant drug is named *trans*-2-phenylcyclopropylamine. Draw its structure.

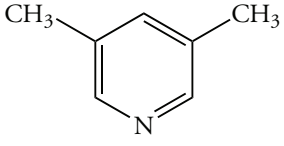
23.10 Tranexamic acid is a drug that aids blood clotting. Its IUPAC name is *trans*-4-(aminomethyl)cyclohexanecarboxylic acid. Draw its structure.

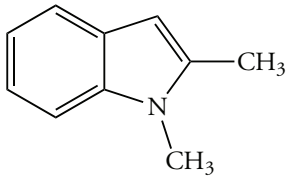
23.11 Draw the structure of each of the following compounds.
(a) 2-ethylpyrrole (b) 3-bromopyridine (c) 2,5-dimethylpyrimidine (d) 2,6,8-trimethylpurine

23.12 Name each of the following compounds.

(a) 

(b) 

(c) 

(d) 

Molecular Formulas of Amines

23.13 (a) What is the general molecular formula for a saturated amine? (b) What is the general molecular formula for a saturated cyclic amine?

23.14 How many isomers are possible for each of the following molecular formulas?
(a) C_2H_7N (b) C_3H_9N (c) C_3H_7N

23.15 Draw the isomers of the primary amines with molecular formula $C_4H_{11}N$.

23.16 Draw the isomers of the tertiary amines with molecular formula $C_5H_{13}N$.

Properties of Amines

23.17 The boiling points of the isomeric compounds propylamine and trimethylamine are 49 and 3.5 °C, respectively. Explain this large difference.

23.18 The boiling point of 1,2-diaminoethane is 116 °C. Explain why this compound boils at a much higher temperature than propylamine (49 °C).

23.19 The difference between the boiling points of pentane (36 °C) and 1-butanamine (78 °C) is 42 °C. Explain why the difference between the boiling points of nonane (151 °C) and dibutylamine (159 °C) is smaller.

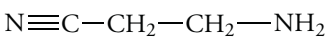
23.20 Explain why the boiling points of tertiary amines are close to the boiling points of the structurally related alkanes.

Basicity of Amines

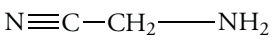
23.21 The pK_a values for cyclohexylamine and triethylamine are 3.34 and 2.99, respectively. Which compound is the stronger base?

23.22 The K_a values for dimethylamine and diethylamine are 4.7×10^{-4} and 3.1×10^{-4}, respectively. Which compound is the stronger base?

23.23 Explain the difference between the pK_a values of the conjugate acids of the following bases.

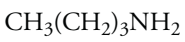


I (pK_a 7.8)



II (pK_a 5.3)

23.24 Explain the difference between the pK_a values of the conjugate acids of the following bases.



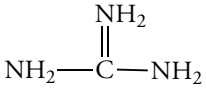
I (pK_a 10.6)



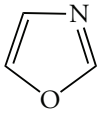
II (pK_a 9.9)

23.25 Explain the order of acidity of the following generalized structures. Why is the difference between the pK_a values of the conjugate acids of an imine and a nitrile twice the difference between those of the conjugate acids of an amine and an imine?

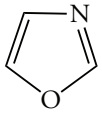
23.26 Explain why the basicity of guanidine is comparable to that of an alkoxide ion. Where does protonation occur?



23.27 Explain why oxazole is a weaker base than thiazole.

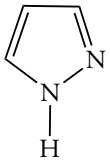


oxazole

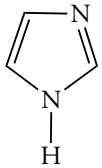


thiazole

23.28 Explain why pyrazole is a weaker base than imidazole.



pyrazole



imidazole

Synthesis of Amines

23.29 Write the steps required for the synthesis of each of the following compounds starting from 1-pentanol.
(a) 1-butanamine (b) 1-pentanamine (c) 1-hexanamine

23.30 Write the steps required for the synthesis of each of the following compounds starting from 3-methyl-l-butanol.
(a) 2-methyl-l-propanamine (b) 3-methyl-1-butanamine (c) 4-methyl-1-pentanamin

23.31 Suggest a synthesis of *cis*-4-methylcyclohexylamine starting from each of the following compounds.
(a) *trans*-4-methylcyclohexanol (b) *cis*-4-methylcyclohexanecarboxylic acid
(c) *trans*-4-bromomethylcyclohexane (d) *cis*-4-methylcyclohexanol

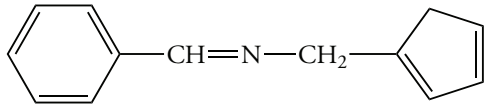
23.32 Outline the steps required to convert each reactant into the indicated product.
(a) benzoic acid into *N*-ethylbenzylamine
(b) benzyl chloride into 2-phenylethanamine
(c) 1,4-dibromobutane into 1,6-diaminohexane

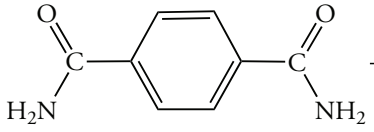
23.33 Reaction of (R)-2-butyl tosylate with azide ion gives an alkyl azide. Subsequent reduction by lithium aluminum hydride gives an amine. Write the structure of the product.

23.34 Cyclohexene oxide reacts with azide ion to give an azido alcohol. Subsequent reduction by lithium aluminum hydride gives an amino alcohol. Write the structure of the product showing its stereochemistry.

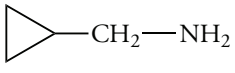
23.35 Write the structure of the product of each of the following reactions.

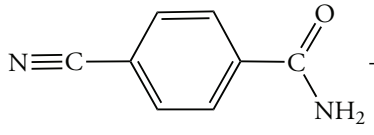
(a) $CH_3-\overset{\overset{O}{\|}}{C}-CH_2-CH_3 + CH_3-CH_2-NH_2 \xrightarrow{NaBH_3CN}$

(b)  $\xrightarrow{LiAlH_4}$

(c)  $\xrightarrow{LiAlH_4}$

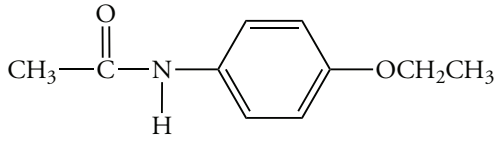
23.36 Write the structure of the product of each of the following reactions.

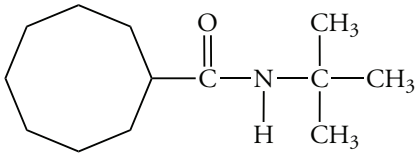
(a) $CH_3-\overset{\overset{O}{\|}}{C}-CH_2CH_2CH_3 +$  $\xrightarrow{NaBH_3CN}$

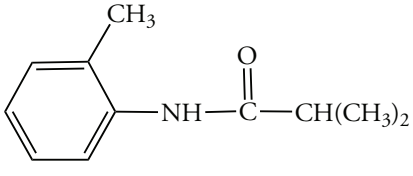
(b)  $\xrightarrow{LiAlH_4}$

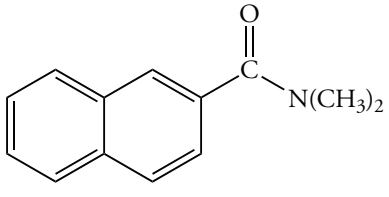
(c) $CH_3-\overset{\overset{O}{\|}}{C}-CH_2CH_2CH_3 + CH_3-NH_2 \xrightarrow{Ni\ /\ H_2}$

23.37 Write the product of reduction of each of the following compounds by lithium aluminum hydride.

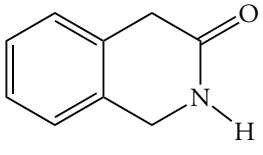
(a) 

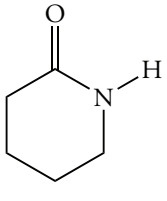
(b) 

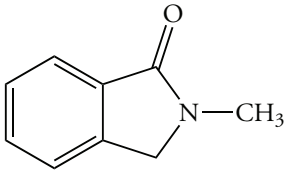
(c) 

(d) 

23.38 Write the product of reduction of each of the following lactams by lithium aluminum hydride.

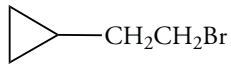
(a) 

(b) 

(c) 

23.39 Write the structure of the final product of each of the following sequences of reactions.

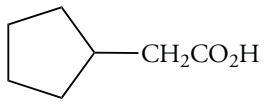
(a) $CH_3(CH_2)_4CO_2H \xrightarrow[2.\ NH_3]{1.\ SOCl_2} \xrightarrow{LiAlH_4}$

(b)  $\xrightarrow{CN^-} \xrightarrow{LiAlH_4}$

(c) $CH_3(CH_2)_4CO_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4} \xrightarrow[2.\ NH_3\ (excess)]{1.\ PBr_3}$

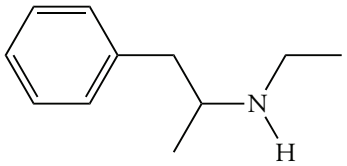
23.40 Write the structure of the final product of each of the following sequences of reactions.

(a) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_2CH_3 \xrightarrow{PCC} \xrightarrow[2.\ CH_3NH_2]{1.\ Ni\ /\ H_2}$

(b)  $\xrightarrow[2.\ NH_3]{1.\ SOCl_2} \xrightarrow{LiAlH_4}$

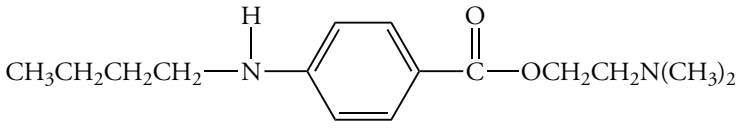
(c) $HOCH_2(CH_2)_4CH_2OH \xrightarrow[(excess)]{HBr} \xrightarrow[(excess)]{CN^-} \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4\ (excess)}$

23.41 Devise a synthesis of Apetinil, an appetite suppressant, from each of the following starting materials.
(a) 1-phenyl-2-bromopropane (b) 1-phenyl-2-propanone
(c) 1-phenyl-2-propanamine (d) 2-methyl-3-phenylpropanoic acid



Apetinil

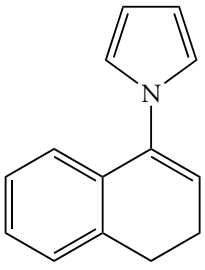
23.42 Devise a synthesis of tetracaine, a spinal anesthetic, from *p*-nitrobenzoic acid.

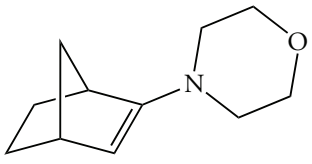


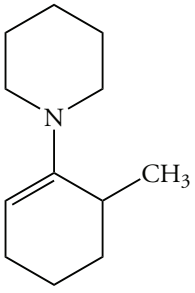
Tetracaine

Enamines

23.43 Identify the compounds used to prepare each of the following enamines.

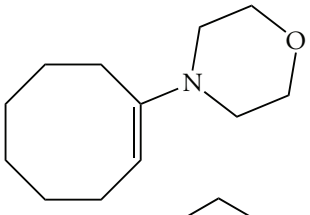
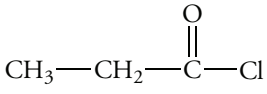
(a) 

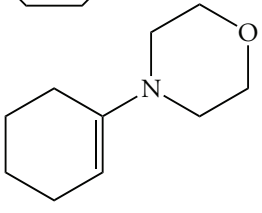
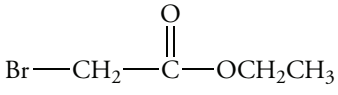
(b) 

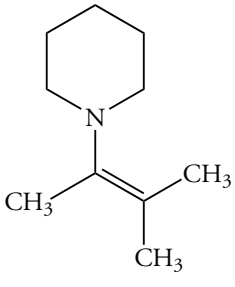
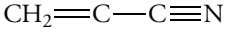
(c) 

23.44 Draw the structure of the enamine prepared from each of the following combinations of reagents.
(a) cyclooctanone and piperidine (b) 2-pentanone and pyrrolidine (c) butanal and morpholine

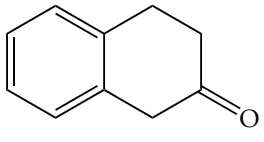
23.45 Draw the structure of the product obtained in the reaction of each of the following combination of reactants.

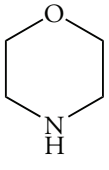
(a)  and 

(b)  and 

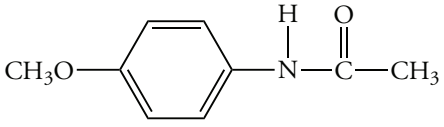
(c)  and 

23.46 (a) Explain why a single enamine forms from the following combination of reactants. (b) Draw its structure. (c) Draw the structure of the product of the reaction of this enamine and allyl bromide.

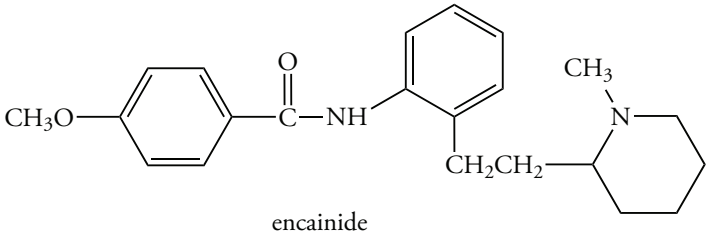




23.47 What amine and acid derivative are required to form the amides contained in each of the following compounds?
(a) acetaminophen, an analgesic

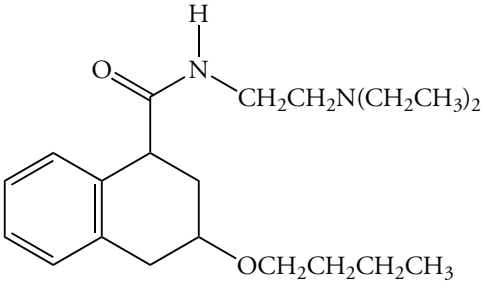


(b) encainide, an antiarrhythmic drug

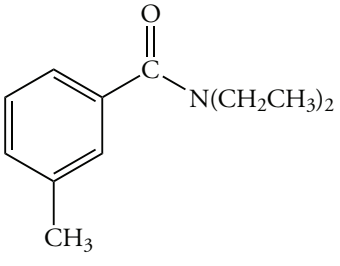


encainide

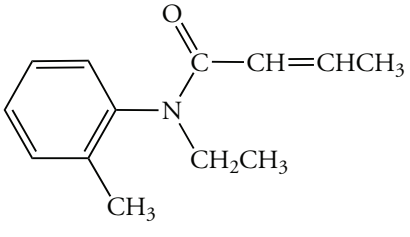
(c) dibucaine, a local anesthetic



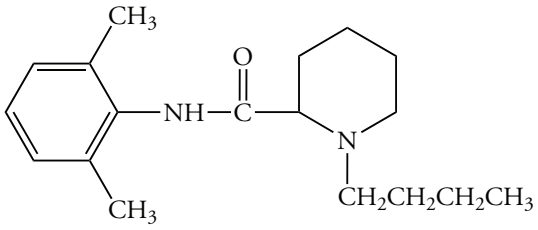
23.48 What amine and acid derivative are required to form the amides contained in each of the following compounds?
(a) DEET, an insect repellent.



(b) crotamiton, used to treat scabies

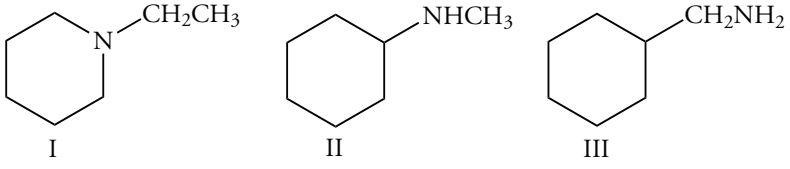


(c) bupivacaine, a local anesthetic

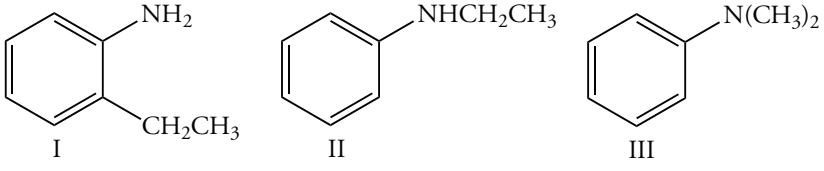


Sulfonamides

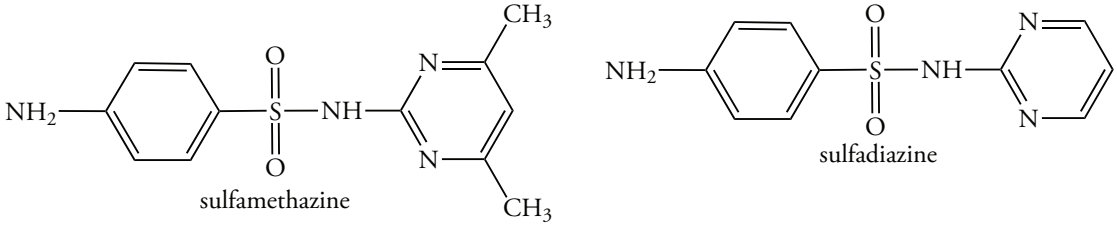
23.49 Explain how the following isomeric amines can be distinguished by the Hinsberg test.



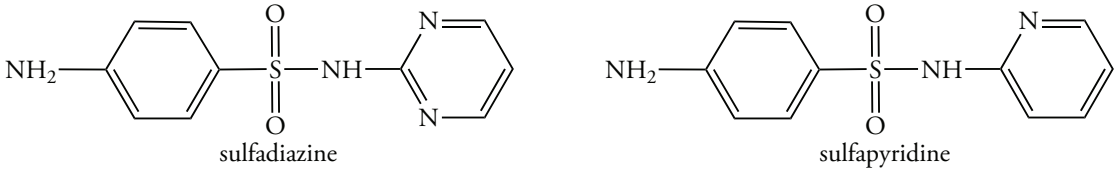
23.50 What observations would be made for the Hinsberg test for each of the following amines?



23.51 Explain why sulfamethazine is a weaker acid than sulfadiazine.

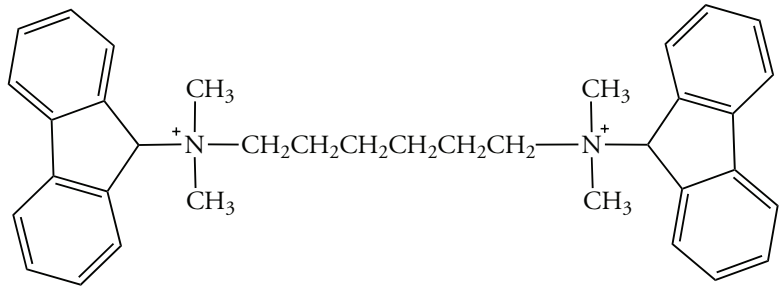


23.52 Explain why sulfadiazine is a stronger acid than sulfapyridine.

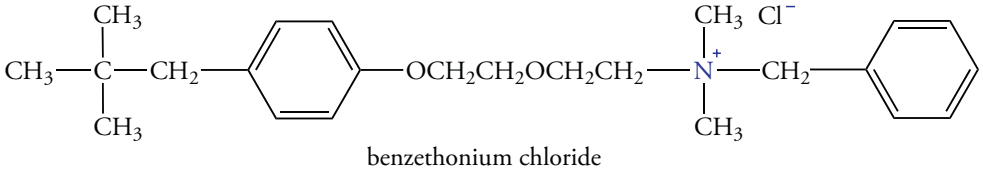


Quaternary Ammonium Salts

23.53 Propose a synthesis of hexafluorenium bromide, a neuromuscular blocking agent, using 1,6-dibromohexane.



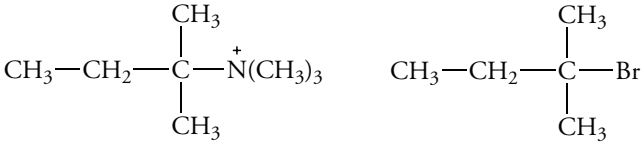
23.54 Draw the structure of the primary amine required to synthesize benzethonium chloride, an antimicrobial agent in first aid antiseptics.



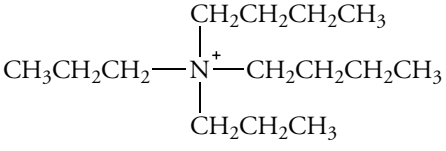
benzethonium chloride

Hofmann Elimination

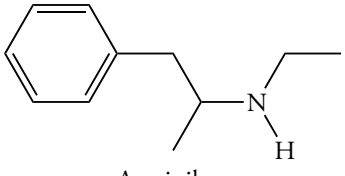
23.55 The following quaternary ammonium ion undergoes a Hofmann elimination to give a mixture of two products. The structurally related bromoalkane reacts with sodium ethoxide to give a mixture of the same two products. One of the two reactants gives a 6:4 ratio of the two alkenes. The other gives a 1:12 ratio of the same two alkenes. What are the structures of the two alkenes, and which product ratio corresponds to each reactant?



23.56 Explain why the following quaternary ammonium ion undergoes a Hofmann elimination to give propene and 1-butene in a 2:1 ratio.

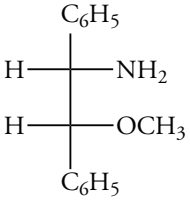


23.57 Exhaustive methylation of Apetinil, the ingredient of a "diet pill," followed by the Hofmann elimination reaction gives a mixture of alkenes. (a) Draw their structures. (b) Which alkene is the major product?

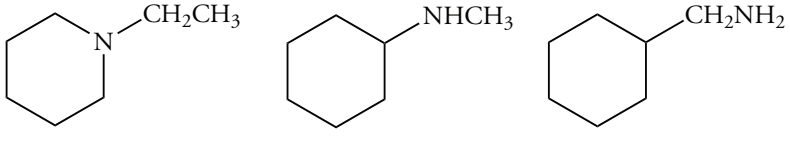


Apetinil

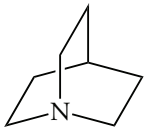
23.58 Draw the structure of the product, indicating the stereochemistry around the double bond, when the following undergoes exhaustive methylation and subsequent Hofmann elimination.



23.59 What unsaturated compound is obtained by exhaustive methylation of each of the following amines followed by a Hofmann elimination?

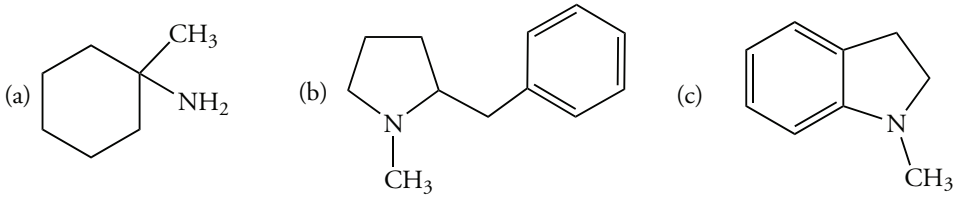


23.60 Draw the structure of the unsaturated compound obtained by exhaustive methylation followed by Hofmann elimination for quinuclidine.

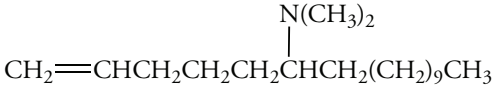


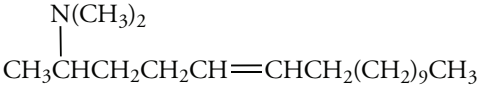
quinuclidine

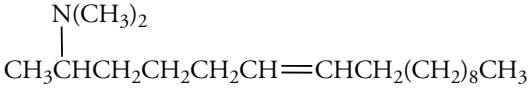
23.61 What unsaturated compound is obtained by exhaustive methylation of each of the following amines followed by Hofmann elimination?



23.62 A compound found in the venom of the red fire ant has the molecular formula $C_{17}H_{35}N$. It undergoes exhaustive methylation and Hoffman elimination to give the following mixture of products. Draw the structure of original amine.

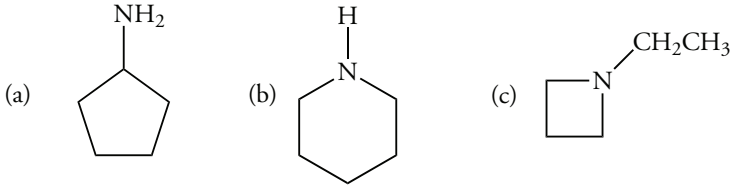






Spectroscopy of Amines

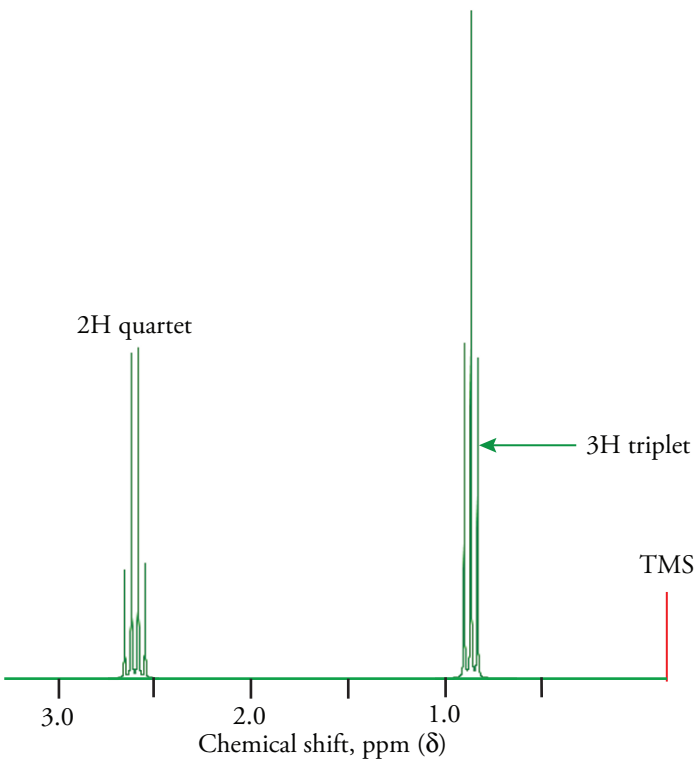
23.63 How can the following amines be distinguished using infrared spectroscopy?



23.64 Which of the isomeric compounds with molecular formula $C_4H_{11}N$ have the following characteristics in their infrared spectrum?
(a) no absorption in the 3200–3400 cm^{-1} region
(b) a single absorption in the 3200–3400 cm^{-1} region
(c) two absorptions in the 3200–3400 cm^{-1} region

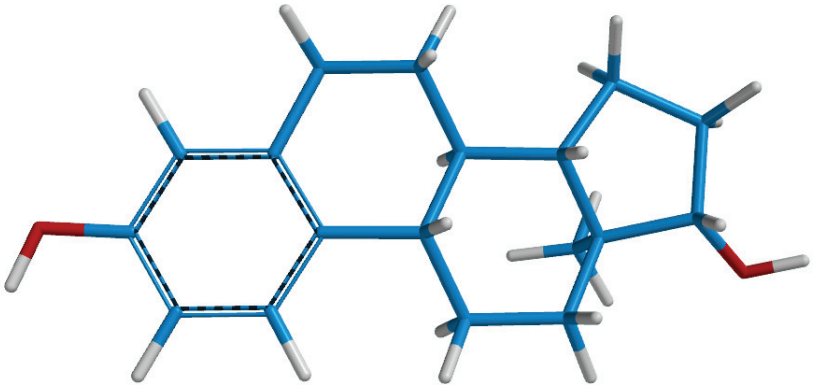
23.65 Deduce the structure of isomeric amines with molecular formula $C_6H_{15}N$ that have the following hydrogen NMR spectra.

(a)



23.66 Deduce the structure of each of the following diamines with the indicated molecular formulas and proton NMR spectra. The number of hydrogen atoms and the multiplicity of each resonance are given within parentheses.
(a) $C_5H_{14}N_2$; 2.25 δ (12H singlet), 2.7 δ (2H singlet)
(b) $C_3H_{10}N_2$; 1.1 δ (4H singlet), 1.6 δ (2H singlet), 2.75 δ (4H singlet)
(c) $C_4H_{12}N_2$; 1.2 δ (4H singlet), 1.1 δ (6H singlet), 2.5 δ (2H singlet)

24 Aryl Halides, Phenols, and Anilines



ESTRADIOL: The hydroxyl group on the left, is bonded to a benzene ring; it is a phenol; the hydroxyl group on the right is a secondary alcohol.

24.1 PROPERTIES OF AROMATIC COMPOUNDS

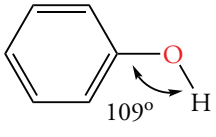
In Chapter 9, we considered alcohols and haloalkanes. The chemistry of these compounds, which includes nucleophilic substitution and elimination reactions, is governed by a C—O or C—X bond of an sp^3-hybridized carbon atom. In Chapter 22, we discussed the chemistry of alkylamines. These compounds undergo substitution reactions at the nitrogen atom rather than the carbon atom. They undergo elimination reactions with difficulty.

Substituents, such as a halogen atom, hydroxyl group, or amino group bonded to an sp^2-hybridized carbon atom, have very different chemistry than they do in alkyl halides, alcohols, and alkylamines. We recall that nonbonded electron pairs of electronegative atoms bonded directly to aromatic rings affect the rate of electrophilic aromatic substitution reactions (Section 13.5). The second period elements nitrogen and oxygen can donate nonbonded electron pairs to the aromatic ring. Chlorine, a third-period element, is a far less effective donor of electrons by resonance. And so, if we now change our focus from the aromatic ring to the substituent itself, we should expect to see some modification of the properties of C—X, C—O, and C—N bonds. In this chapter, we examine the special chemical reactivity that results from bonding between an aryl carbon atom and a halogen atom, hydroxyl group, or amino group.

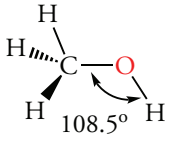
Bonding and Structure

The carbon–halogen bond of an aryl halide is slightly shorter than the carbon–halogen bond of an alkyl halide. This decrease in bond length results from a larger percent s character in the sp^2 hybrid orbital of the aryl carbon atom compared to the sp^3 hybrid orbital of an alkyl carbon atom. The aryl-chlorine bond dissociation energy (407 kJ $mole^{-1}$ for carbon-chlorine) is substantially larger than the bond dissociation energy for a typical alkyl-chlorine bond (340 kJ $mole^{-1}$). This very high bond energy accounts in part for the different reactivities of aryl and alkyl halides.

The carbon–oxygen bond lengths of phenols and alcohols are 136 and 142 pm, respectively. Again, the C—O bond of a phenol is shorter because of the increased s character of the sp^2-hybridized carbon atom, which draws electrons closer to the carbon nucleus. The geometry around the oxygen atom of phenols is essentially the same as that in alcohols. The C—O—H angle has the tetrahedral angle of 109°.



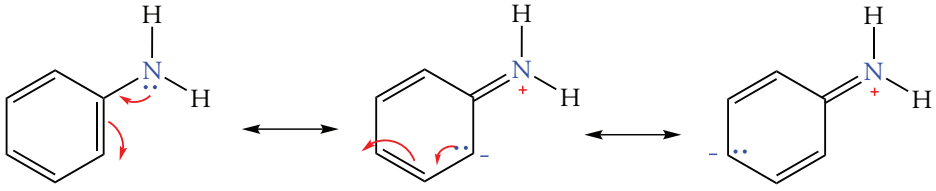
phenol



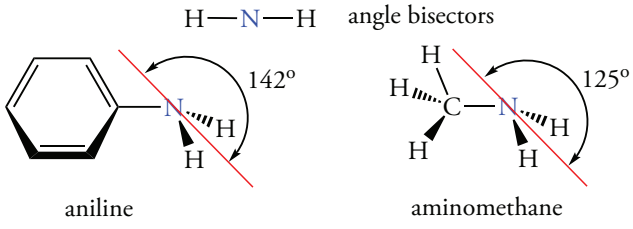
methanol

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00024-3
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The groups around nitrogen in arylamines form a shallower pyramid than the groups in alkylamines. Also, the carbon–nitrogen bond in arylamines (140 pm) is shorter than in alkylamines (147 pm). The shortened bond length results from the double bond character of the carbon–nitrogen bond, shown in the resonance forms of aniline. In these resonance forms, the lone pair electrons of nitrogen are delocalized into the benzene ring.



In aniline two opposing forces balance, producing a stable structural compromise. The most effective overlap between the nitrogen orbital and those of the aromatic ring would occur if the lone pair electrons occupied an unhybridized 2p orbital. This would maximize resonance stabilization. The bonded pairs would then occupy sp^2 hybrid orbitals, and all atoms bonded to the nitrogen atom would be in a plane. However, nitrogen would pay a price to adopt this hybridization. If the lone pair electrons were in a 2p orbital, they would move farther from the nitrogen nucleus as a result of resonance stabilization. Nitrogen is very electronegative, and it attracts electrons toward its nucleus most effectively by using an sp^3 hybrid orbital, but this would diminish resonance stabilization. The compromise is a hybridization for the nitrogen orbital with somewhat more p character than the 75% of an sp^3 hybrid orbital. The angle between the C—N bond and a line bisecting the H—N—H bond angle provides evidence of this compromise.



Bond Polarity

The bond polarities of aryl–halogen and aryl–oxygen bonds compared to those in alkyl halides and alcohols provide a measure of the effect of the sp^2 hybrid orbital on the σ bond and of the resonance interactions between the nonbonded electrons of the substituent and the aromatic ring. The dipole moment of chlorobenzene is smaller than the dipole moment of chlorocyclohexane.

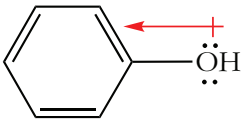


chlorobenzene (1.7 D)

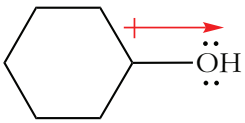
chlorocyclohexane (2.2 D)

This difference indicates that electron density in the σ bond is not "pulled" as strongly toward the chlorine atom in chlorobenzene as in chlorocyclohexane. The higher s character of the sp^2-hybridized carbon atom of chlorobenzene makes it more electron attracting than an sp^3-hybridized carbon atom. Thus, the electronegativity difference between carbon and chlorine is smaller for an sp^2-hybridized carbon atom than for an sp^3-hybridized carbon atom.

The *magnitude* of the dipole moment of phenol is also slightly less than that of cyclohexanol, its cycloalkyl counterpart, but in the *opposite* direction. The oxygen atom is the positive end of the dipole in phenol.



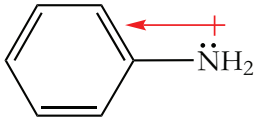
phenol
(1.5 D)



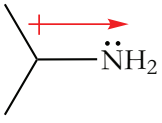
cyclohexanol
(1.7 D)

The sp^2-hybridized carbon atom of a phenol also pulls the bonding electrons of the C—O bond toward the ring, an effect similar to that which accounts for the decreased polarity of chlorobenzene compared to chlorocyclohexane. However, the reversal of net polarity results from donation of nonbonded electrons of oxygen by resonance to the aromatic ring.

The dipole moments of alkylamines are in the expected direction. That is, the negative end of the dipole is toward the more electronegative nitrogen atom. However, again as in the case of phenols, the dipole moments of arylamines are opposite in direction. The nitrogen atom is the positive end of the dipole in aniline.



aniline
(1.3 D)



isopropylamine
(1.3 D)

Problem 24.1

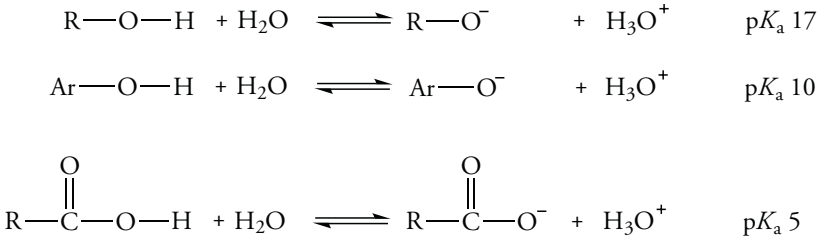
The dipole moment of toluene is 0.4 D. Predict the direction of this dipole. The dipole moment of *p*-fluorotoluene is 2.0 D. Predict the direction of dipole moment of fluorobenzene.

24.2 ACID-BASE PROPERTIES OF PHENOLS AND ANILINES

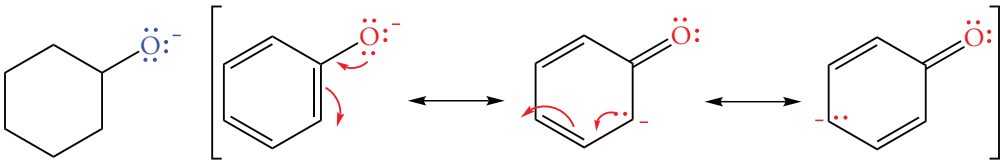
We have discussed the effect of structure on the acidity of alcohols and on the basicity of amines. The acid–base properties of their aromatic cousins, phenols and anilines, are affected by the aromatic ring. Both the pK_a values of phenols and the pK_b values of anilines illustrate this effect.

Phenols

Phenols have pK_a values between those of alcohols and carboxylic acids. The pK_a value of phenol is 10. The pK_a value of a typical alcohol is in the neighborhood of 17. However, phenols are not nearly as acidic as carboxylic acids, whose pK_a values are around 5.



Phenol is more acidic than cyclohexanol and acyclic alcohols because the phenoxide ion is more stable than the alkoxide ion. In an alkoxide ion, the negative charge is localized at the oxygen atom. But in a phenoxide ion, the negative charge is delocalized over the benzene ring. Phenoxide ion is therefore resonance stabilized.



localized
negative charge

delocalized resonance contributing structures

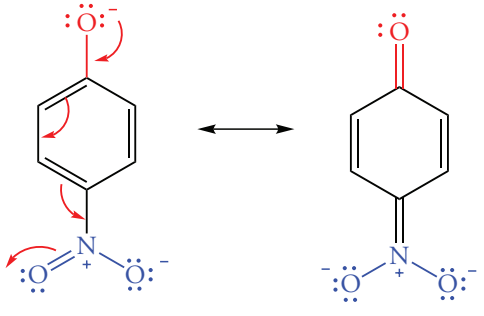
Phenols are weaker acids than carboxylic acids even though there is delocalization of charge over the aromatic ring of the phenoxide ion. The carboxylate ion is more stabilized relative to the phenoxide ion because the negative charge is located on the oxygen atoms of the carboxylate ion. In the phenoxide ion, some of the charge is located on the less electronegative carbon atom. Therefore, the resonance stabilization of a carboxylate ion is more effective, and carboxylic acids are stronger acids than phenols.

The pK_a values of substituted phenols are listed in Table 24.1. Although the pK_a values increase for electron-donating groups such as *p*-methyl or *p*-methoxy, the decrease in acidity is less than a factor of 2 in pK_a. Electron-withdrawing groups cause a substantial increase in the K_a of phenols.

Table 24.1
pK_a Values of Phenols

Substituent	*ortho*	*meta*	*para*
H	10	10	10
Bromo	8.42	8.87	9.26
Chloro	8.48	9.02	9.38
Cyano			7.95
Methoxy	9.08	9.65	10.21
Methyl	10.29	10.09	10.26
Nitro	7.22	8.39	7.15

The nitro group causes the largest increase in K_a. *p*-Nitrophenol is almost 1000 times more acidic than phenol. The acidity increases because delocalization of the negative charge onto the oxygen atoms of the nitro group stabilizes the conjugate base.



Anilines

Aryl-substituted amines are much weaker bases than ammonia and alkyl-substituted amines. Their K_b values are less than 10^{-9}. For example, the K_b value of aniline is 10^{-6} times smaller than the K_b value for cyclohexylamine. Aryl-substituted amines are weaker bases than ammonia because the unshared pair of electrons of the nitrogen atom is resonance delocalized over the π orbital system of the benzene ring. As a result, the unshared electron pair of nitrogen is less available for bonding with a proton. Table 24.2 lists the pK_b values of some substituted anilines.

Table 24.2
pK_b Values of Anilines

Substituent	*ortho*	*meta*	*para*
H	9.40	9.40	9.40
Bromo	11.47	10.42	10.14
Chloro	11.35	10.48	10.02
Cyano	13.05	11.25	12.26
Methoxy	9.48	9.77	8.66
Methyl	9.56	9.28	8.90
Nitro	14.26	11.53	13.00
Trifluoromethyl		10.80	11.25

Electron-donating groups increase the basicity of aniline by a small amount. Electron-withdrawing groups, such as nitro and cyano, decrease the basicity by substantially larger amounts because the lone pair electrons of the amine can be delocalized into the substituent group.

Problem 24. 2

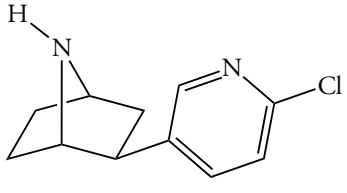
Explain why *m*-nitrophenol is a weaker acid than *p*-nitrophenol, but is still a stronger acid than phenol.

Sample Solution

As a result of the formal positive charge of the nitrogen atom, the nitro group is inductively electron withdrawing. In the *meta* position, the nitro group stabilizes the phenoxide ion by withdrawal of electron density. Stabilizing the conjugate base increases the acidity of the phenol. Although located at a greater distance, the *para* nitro group is even more effective in stabilizing the conjugate base, but not as a result of an inductive effect. In the *para* position, the nitro group can delocalize the negative charge of the phenoxide ion to the two oxygen atoms. Resonance stabilization of the phenoxide ion by a meta nitro group is not possible.

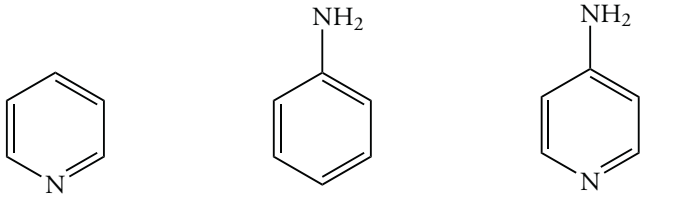
Problem 24.3

Estimate the pK_a values for each basic site in the following compound, which is a poison secreted by an Ecuadoran frog.



Problem 24.4

The pK_a values of pyridine and aniline are similar, but the pK_a of 4-aminopyridine is much smaller. Which of the two nitrogen atoms of 4-aminopyridine is more basic? Why is it more basic than the corresponding site in one of the reference compounds?



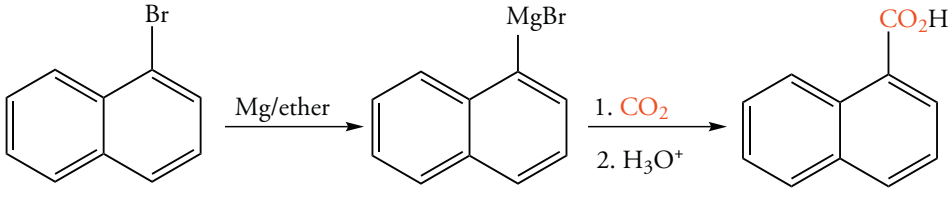
pyridine
$pK_b = 8.7$

aniline
$pK_b = 9.4$

4-aminopyridine
$pK_b = 4.9$

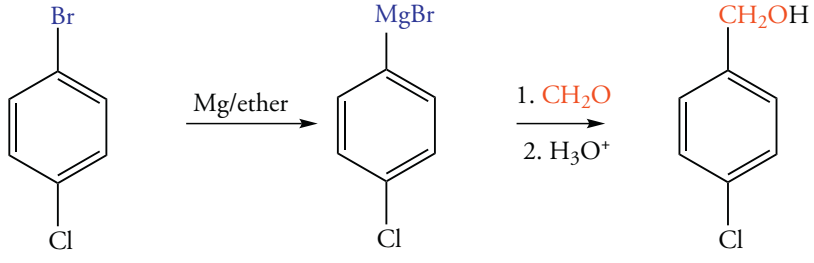
24.3 CONVERTING ARYL HALIDES TO GRIGNARD REAGENTS AND ORGANOLITHIUM REAGENTS

In Chapter 17, we saw that the Suzuki coupling reaction, the Heck, reaction and the Sonogashira reaction can be used to couple aryl halides. Aryl bromides also react with magnesium to form Grignard reagents, which undergo the same reactions with carbonyl compound as alkyl Grignard reagents.



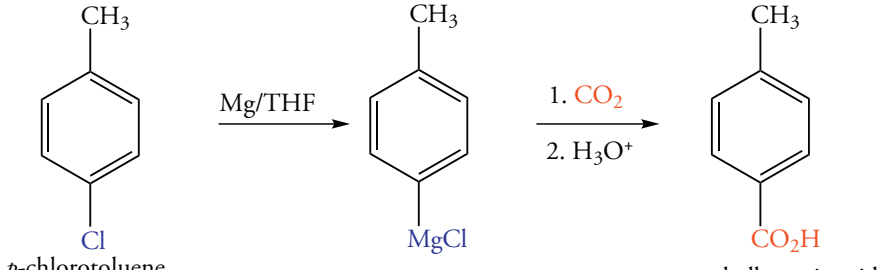
1-bromonaphthalene — 1-naphthoic acid

Aryl chlorides do not form Grignard reagents when ether is the solvent. As a result, an aromatic compound substituted with both bromine and chlorine can be selectively converted into a Grignard reagent at the site of the bromine atom.



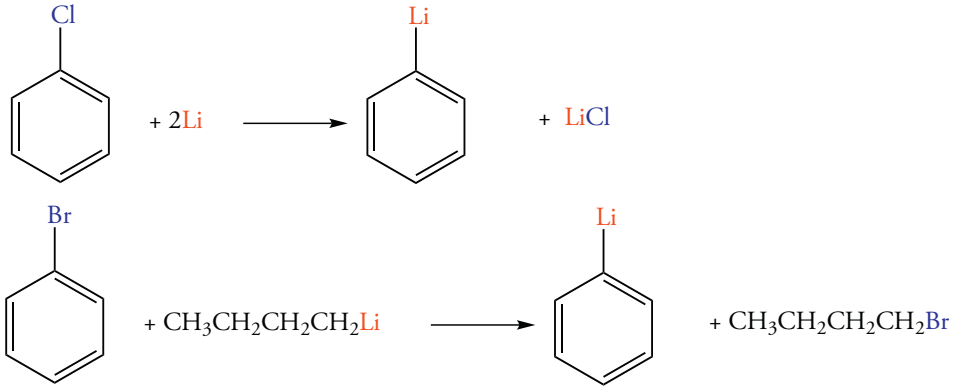
1-bromo-4-chlorobenzene — 4-chlorobenzyl alcohol

Aryl chlorides do form Grignard reagents when tetrahydrofuran is the solvent. Once formed, they undergo the same reactions as other Grignard reactions.



p-chlorotoluene — *p*-methylbenzoic acid

Aryl lithium reagents can be prepared by direct reaction of an aryl chloride or bromide with lithium metal. These reagents can also be prepared by a transmetallation reaction of an aryl halide with an alkyllithium reagent such as butyl lithium.



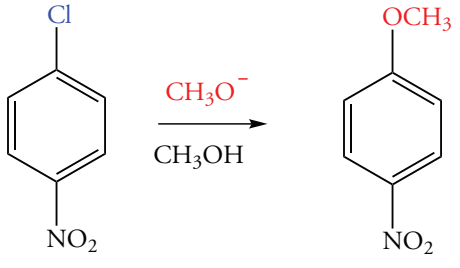
We saw in Chapter 17 that organolithium compounds reaction with Cu(I) to give Gilman reagents. Thus organolithium compounds are important synthetic intermediates.

24.4 NUCLEOPHILIC AROMATIC SUBSTITUTION

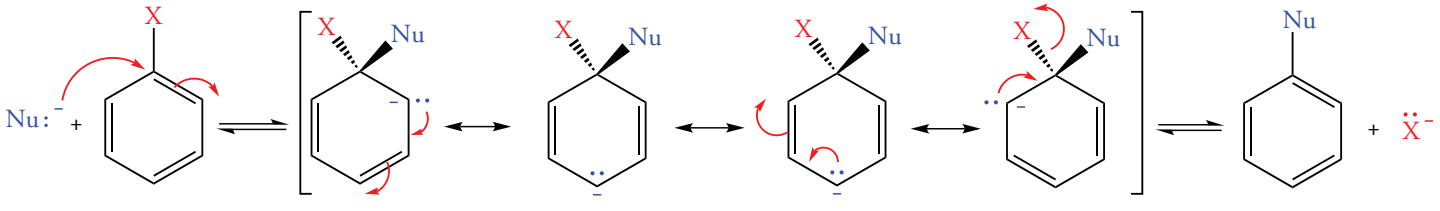
We recall that nucleophilic substitution reactions at sp^3-hybridized centers are easily classified using S_N2 and S_N1 mechanisms. These two mechanisms encompass a wide range of substrate structures, nucleophiles, and leaving groups. Nucleophilic substitution of aryl halides can occur, but only on a limited number of aromatic compounds. Also, neither S_N2 nor S_N1 mechanisms account for the characteristics of the reactions. An S_N2 process does not occur because the aromatic ring prevents the approach of a nucleophile from the side opposite that of the carbon–halogen bond. An S_N1 mechanism is not favored because the formation of an sp^2-hybridized carbocation requires more energy than formation of an sp^3-hybridized carbocation. Nucleophilic substitution of aromatic compounds occurs by two different, multiple-step mechanisms, termed **addition–elimination** and **elimination–addition**. Although similarly named, the mechanisms are different and result from different reactant structures and reaction conditions.

Addition–Elimination

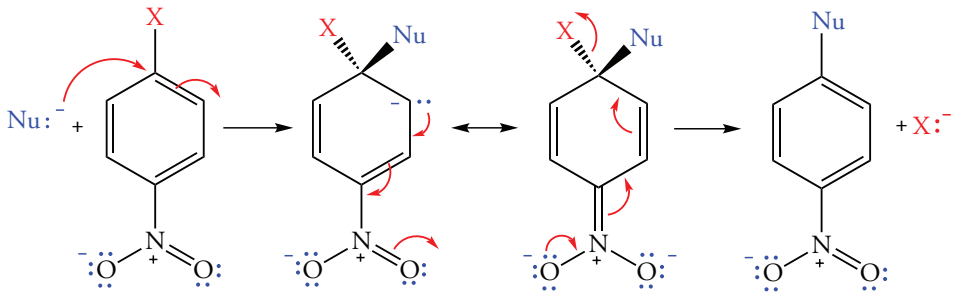
Aryl halides with a strong electron-attracting group *ortho* or *para* to the halogen are substituted by nucleophiles such as hydroxide, alkoxides, ammonia, and amines. Suitable groups that facilitate the reaction are nitro > cyano > carbonyl. The reactions occur under relatively mild conditions.



The mechanism is similar to the addition–elimination mechanism of acyl derivatives in which a tetrahedral intermediate forms. The addition step is a nucleophilic attack that yields a resonance-stabilized cyclohexadienyl anion. The anion can then eject the nucleophile or a leaving group in the elimination step.



The initial addition step occurs only if the ring has a substituent that can stabilize the negative charge of the intermediate. The substituent must be *ortho* or *para* to the site of the reaction. For example, a *p*-nitro group is effective because the negative charge can be distributed to its two oxygen atoms.



Because the electron-withdrawing nitro group anion stabilizes the anion intermediate, the nitro group activates the aromatic ring toward nucleophilic aromatic substitution. This statement may appear inconsistent with the properties of the nitro group in electrophilic aromatic substitution. We recall that the nitro group deactivates the aromatic ring toward attack by electrophiles. The characteristics of the nitro group have not changed. It attracts electrons from the aromatic ring in both reactions. However, its effect on the stability of the resonance-stabilized intermediate depends on the charge of the intermediate. In nucleophilic aromatic substitution, a negatively charged intermediate forms, so the nitro group stabilizes the charge. In electrophilic aromatic substitution, a positively charged intermediate forms, and the nitro group destabilizes it. These two examples remind us that the terms "activating group" or "deactivating group" cannot be attributed to a substituent without reference to the reaction type.

Figure 24.1 shows the reaction rate profile for the addition–elimination mechanism. The first step is rate determining. This fact is established by the order of reactivity of p-halonitrobenzenes: F > Cl > Br > I. We recall that the order of leaving group abilities of the halide ions is $I^- > Br^- > Cl^- > F^-$. Therefore, the second step, in which the halide ion is a leaving group, cannot be rate determining. In the elimination step, the carbon–halogen bond breaks. This step is faster than the rate-determining first step in which addition occurs.

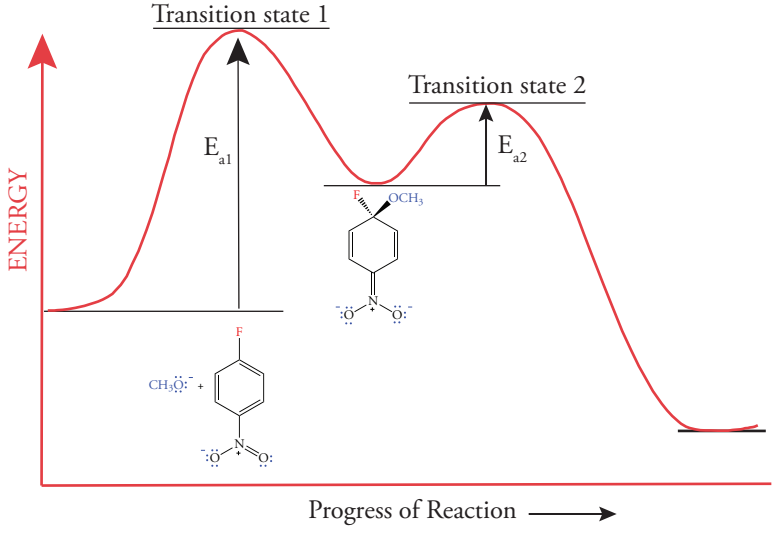
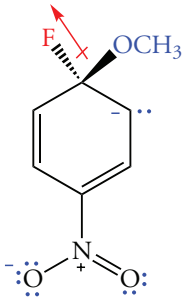


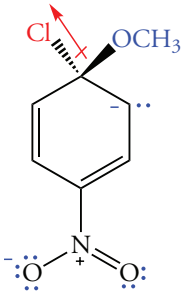
Figure 24.1
Addition–Elimination Reaction
The rate-determining step is the addition of the nucleophile to give a tetrahedral intermediate that then reacts in a faster second step to eliminate the leaving group.

The effect of the halogen atom on the first step of the addition–elimination reaction reflects the stability of the cyclohexadienyl anion intermediate. The electronegativity of the halogen atom explains the order of reactivity of the halogen compounds. Fluorine is the most electronegative halogen, and it is most effective in stabilizing the cyclohexadienyl anion by inductive electron withdrawal.

Fluorine is very effective in withdrawing electrons.



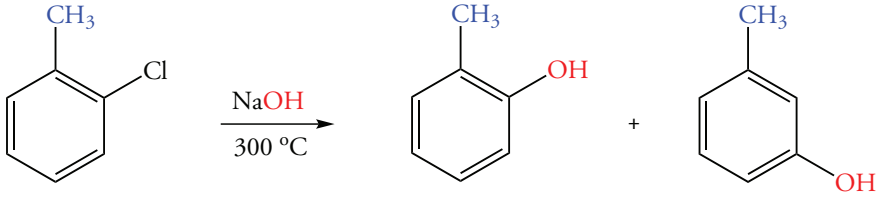
Chlorine is less effective in withdrawing electrons.



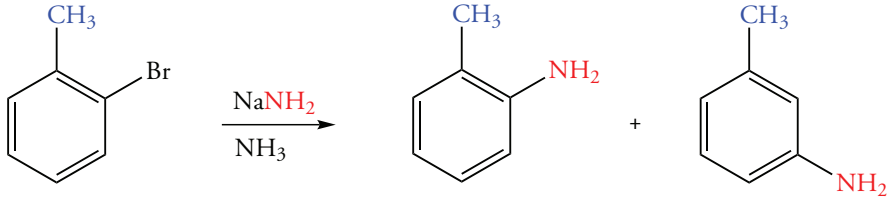
Stabilized cyclohexadienyl anion

Elimination–Addition

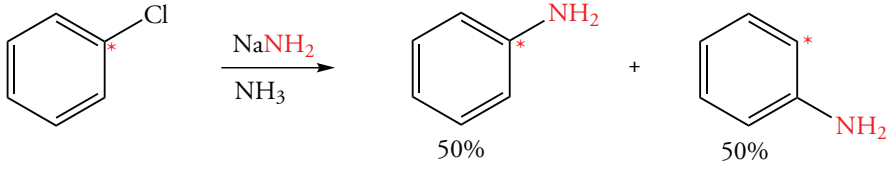
Aryl halides without strongly electron-withdrawing ring substituents undergo substitution reactions. However, the mechanism is an elimination–addition process that occurs only at high temperatures or if the nucleophile is a very strong base. For example, *o*-chlorotoluene reacts with sodium hydroxide at temperatures of about 300 °C to yield a mixture of equal amounts of *o*- and *m*-methylphenols.



Under milder conditions, a strong amide base in liquid ammonia at –33 °C yields similar products. The entering group substitutes at the position originally occupied by the halogen and at the adjacent ring position.

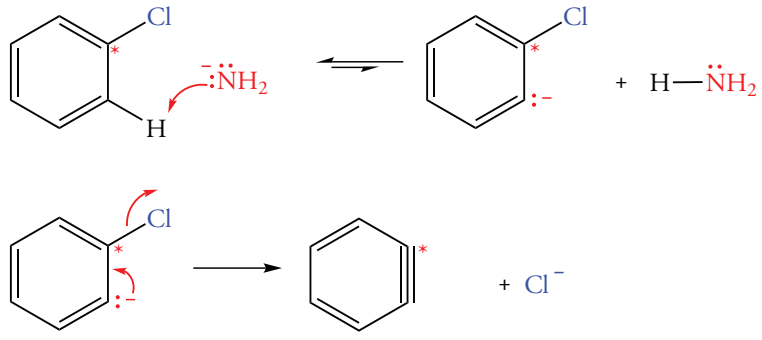


An intermediate known as **benzyne**, which has a triple bond, accounts for the equivalence of two carbon atoms toward the nucleophile. This intermediate was proposed on the basis of isotopic labeling studies using chlorobenzene labeled with ^{14}C at C-1. Reaction with amide ion gives a mixture of two differently labeled anilines in equal amounts. The following equation shows location of the ^{14}C with an asterisk.



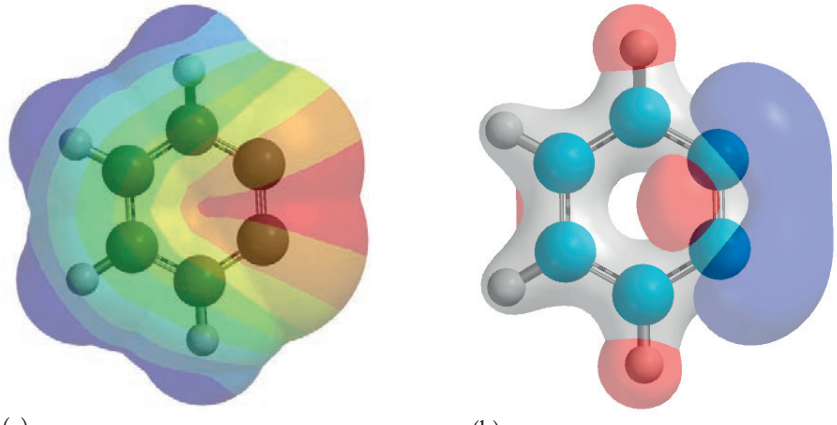
Half of the product has the radioactive isotope at the same carbon atom substituted in the original reactant. The other half of the product has the radioactive isotope at the carbon adjacent to the substituted carbon atom of the reactant. To account for this distribution of products, C-1 and C-2 must be equivalent in the reaction intermediate.

The first two steps in the elimination–addition mechanism generate benzyne by deprotonation followed by loss of chloride ion. The two steps constitute the elimination part of the mechanism.



The base removes a proton from C—H bond at a position adjacent to the C—X bond because the electronegative atom slightly increases the acidity at that site by inductive withdrawal of electrons.

Benzyne is a very reactive intermediate because the "triple bond" is strained (Figure 24.2). The two atoms of an ordinary alkyne, as well as the directly bonded atoms, should be colinear. This is geometrically impossible for benzyne. The bonding in benzyne cannot be described by classical Lewis structures. Molecular orbital calculations show that there is an electron-rich region in the plane of the ring. We can imagine that this results from side-by-side overlap of two sp^2 hybrid orbitals that are in the same plane as the benzene ring. The orbitals that contribute this "π bond" are not parallel, so less overlap exists in this bond than in the overlap of 2p atomic orbitals of most π bonds.

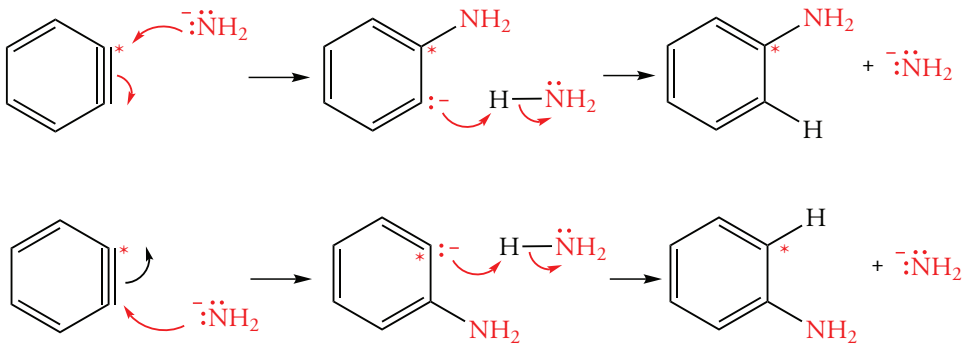


(a) (b)

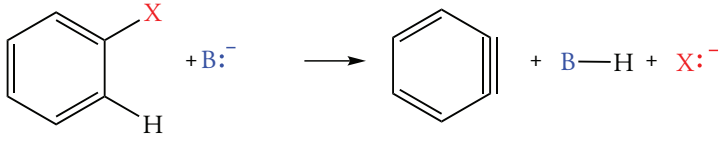
Figure 24.2
Structure of Benzyne

The overlap of two sp2 hybrid orbitals to form a "π bond" is not as efficient as the overlap of two p orbitals because the orbitals are not parallel. (a) Electrostatic potential map. The bright red region lying outside of the ring and in the plane of the ring atoms results from the "triple bond" in the Lewis structure of benzyne. (b) Highest occupied molecular orbital of benzyne, shown in red and blue, is superimposed on the bond density (shown in grey). The electron density in this image lies in the plane of the benzyne ring.

Because of the overlap of the sp^2 orbitals in the second π bond of benzyne, the bond is very reactive toward nucleophiles. Attack of a nucleophile such as amide ion can occur at either carbon atom of the triple bond. Subsequent protonation of both of the two possible anions yields the product mixture. These two steps constitute the addition portion of the mechanism.



The elimination–addition mechanism accounts for the substantial difference in the rates of reaction for hydroxide ion compared to amide ion. The reaction with hydroxide ion requires a very high temperature. The reaction with amide ion occurs at the temperature of liquid ammonia. The amide ion is a better nucleophile than hydroxide ion. However, the difference in nucleophilicities cannot explain the very large difference between their rates. The difference between the basicities of the amide ion and hydroxide ion accounts for the different rates. (The pK_a values of NH_3 and H_2O are 35 and 15.7, respectively.) The rate of the reaction therefore depends on the elimination step.



When the C—H bonds *ortho* to the halogen are nonequivalent, two isomeric benzyne structures form. In general, the formation of the benzynes is not regioselective. However, there may be a small preference for formation of the benzyne that results from deprotonation of the more acidic C—H bond. Note that the acidity of these bonds is affected only by the inductive effect of substituents. The electron pair of the anion occupies an sp^2 hybrid orbital. The pair cannot be delocalized in the π system because it is perpendicular to the 2p orbitals that form the aromatic system.

Once it has formed, a benzyne reacts very rapidly, and with very little regioselectivity, to give a 50:50 mixture of the two possible addition products. We can see why this occurs when we look at the potential energy surface shown in Figure 24.2b, which shows at the electron density is the same at both "ends" of the benzyne triple bond. The only structural feature that may give a small regioselectivity is the relative stability of the two possible anions. For example, inductive electron-withdrawing substituents can stabilize the charge.

Problem 24. 5

3,4-Dichloronitrobenzene reacts with only one equivalent of sodium methoxide to give an anisole derivative. What is the structure of the product? Explain why only one equivalent of sodium methoxide readily reacts.

Sample Solution

Only the 4-chloro group is replaced because the negative charge of the intermediate formed by addition of methoxide ion can be delocalized to the oxygen atoms of the nitro group. No such stabilization is possible if attack occurs at the meta position. Thus, the 3-chloro group cannot be displaced in an addition–elimination mechanism. The product is 2-chloro-4-nitroanisole.

Problem 24.6

p-Bromotoluene reacts with sodium amide in liquid ammonia to give a mixture of two aniline derivatives. Draw their structures and explain the origin of the two products. Estimate the relative amounts of the two products formed.

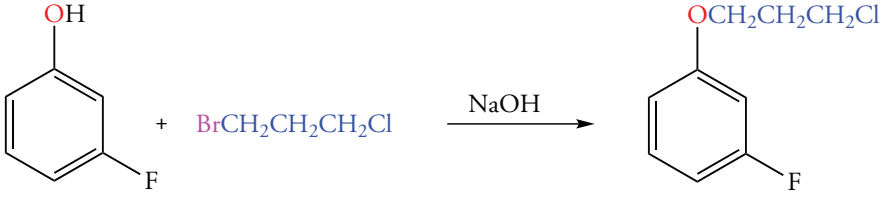
24.5 AN OVERVIEW OF PHENOL REACTIONS

Reaction of phenols can be separated into those at the hydroxyl oxygen and those at the carbon atoms of the aromatic ring. For reactions at the oxygen atom, phenols act as nucleophiles and react with electrophiles. Reactions at the carbon atoms of the aromatic ring also involve electrophiles, but the mechanism for electrophilic aromatic substitution differs from substitution reactions at oxygen.

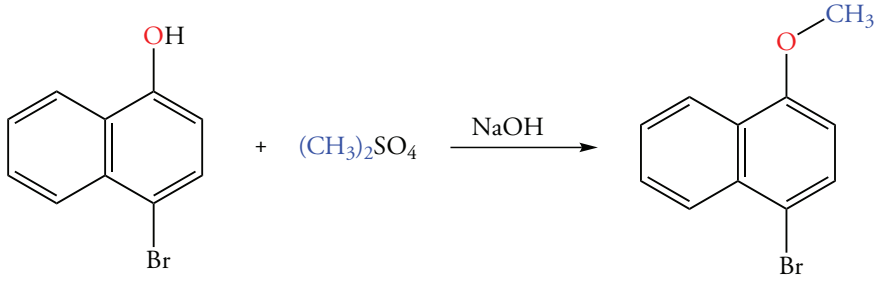
Ether Synthesis

Alkyl phenyl ethers are prepared by the Williamson synthesis (Section 16.6). In these reactions a phenoxide ion displaces a halide ion from a primary haloalkane. Because alcohols are weak acids, an alkoxide ion must be prepared using a strong base such as sodium hydride. However, phenols are much more acidic than alcohols, so phenoxides can be obtained by adding hydroxide ion to the phenol.

We recall that the Williamson method works best with primary alkyl halides. Secondary and especially tertiary alkyl halides undergo elimination reactions rather than the S_N2 reaction that gives the ether. The reaction may be carried out in protic solvents such ethyl alcohol or aprotic solvents such as acetone or dimethylformamide.



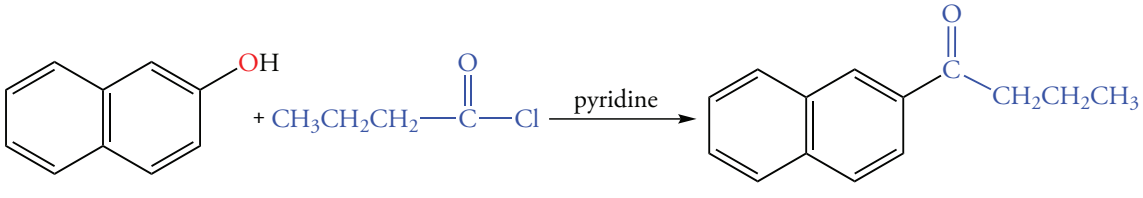
Aryl methyl ethers can be prepared using methyl iodide, but dimethyl sulfate is also widely used.



Ester Synthesis

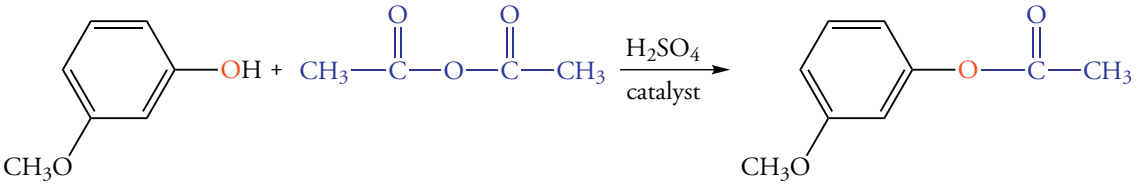
Phenols cannot be converted to esters by the Fischer esterification method because the position of equilibrium is not as favorable as for alcohols. The enthalpy of reaction for ester formation from a phenol and a carboxylic acid is positive.

Esters of phenols are synthesized with acyl halides using the same reaction conditions required to prepare esters of alcohols.



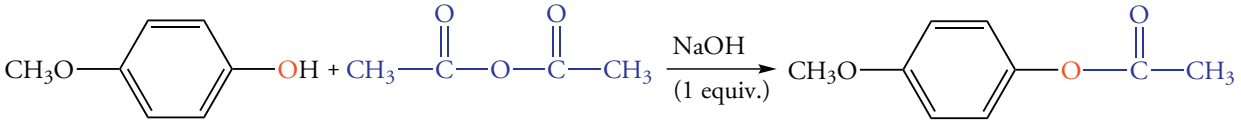
2-naphthol 2-napthyl butanoate

When available, acid anhydrides can also be used to form esters of phenols. Acetic anhydride is a readily available, inexpensive reagent that is used to prepare acetate esters. The reaction can be done using a catalytic quantity of sulfuric acid to protonate the carbonyl oxygen atom of the anhydride. The reaction can also be carried out by adding a stoichiometric amount of base to convert the phenol to the more nucleophilic phenoxide ion.



m-methoxyphenol

m-methoxyphenyl ethanoate

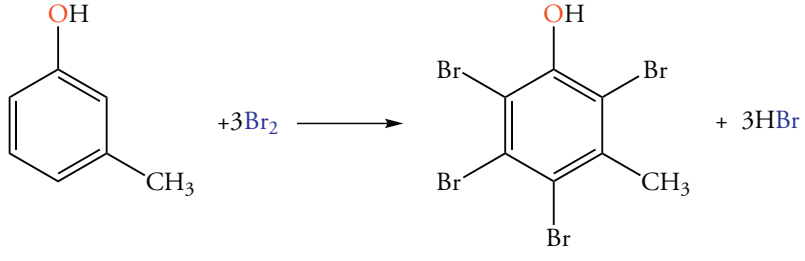


p-methoxyphenol

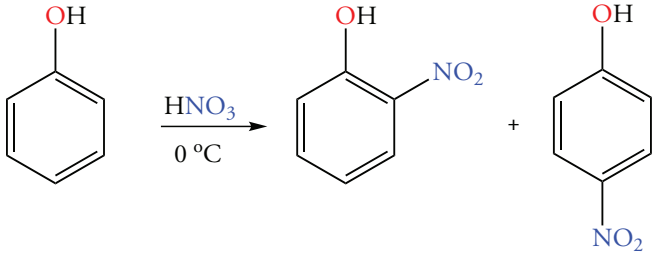
p-methoxyphenyl ethanoate

Electrophilic Substitution

The phenol hydroxyl group is a strongly activating group. Therefore, substitution reactions with many electrophiles occur so rapidly that it is sometimes difficult to avoid multiple substitution by the electrophile. Bromination is one such reaction.



Reactions that introduce a deactivating group decrease the reactivity of the product so that only monosubstituted products form. For example, the nitration of phenol using dilute nitric acid at room temperature illustrates both the activating influence of the hydroxyl group and the deactivation by a nitro group that permits the formation of a mononitrated product.

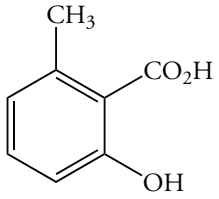


Problem 24. 7

2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) is a herbicide. Propose a synthesis of 2,4,5-T using the Williamson ether synthesis.

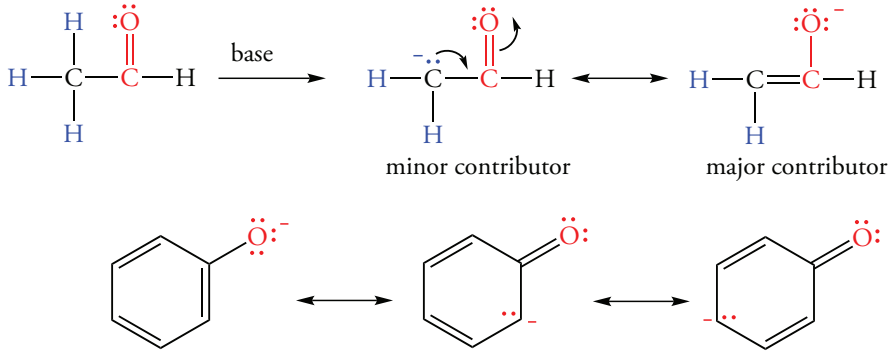
Problem 24.8

The structure of 6-methylsalicylic acid is shown below. What ring carbon atom is selected as C-1 to give this name? What is the structure of the dibrominated product of 6-methyl-salicylic acid?



24.6 REACTIONS OF PHENOXIDE IONS

Phenoxide ions are structurally related to enolates. In both ions, the negative charge is largely located on the oxygen atom, although we have seen that the phenoxide anion is resonance stabilized.



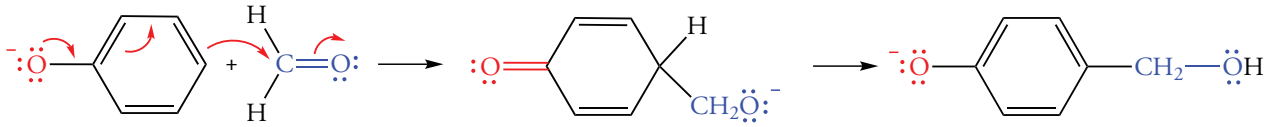
However, we have seen that the reaction enolates with electrophiles occurs at carbon rather than oxygen. Therefore, enolates most often behave as carbanions.



This feature explains several reactions of phenolates. For example, in basic solution phenols react rapidly with bromine. The reaction resembles the bromination of ketones under basic conditions. We recall that multiple bromination of ketones occurs under basic conditions because the enol form of the product is more acidic than the starting ketone. For much the same reason, multiple bromination of phenols occurs in basic solution at all available *ortho* and *para* positions.

Addition to Formaldehyde

We recall that enolates undergo condensation reactions with the carbonyl carbon atom of aldehydes (Section 21.7). Enolates tend to react to give alkylation at carbon. A similar reaction occurs between the phenolate ion and formaldehyde. Because both C-2 and C-4 are nucleophilic, two possible condensation products may result. The following reaction shows condensation at C-4, producing a conjugation-extended enolate. Subsequent tautomerization generates the enol form, which is a phenol. Solvent-mediated proton transfer also occurs, giving a phenoxide rather than the more basic (and less stable) alkoxide ion.

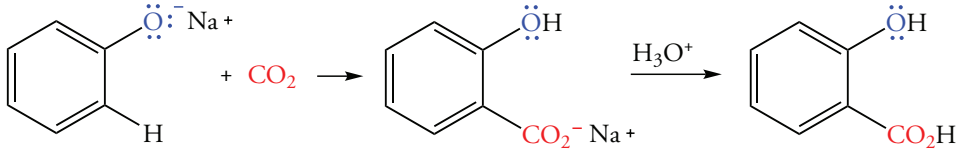


Like the aldol condensation product, the product of condensation of phenol with formaldehyde easily dehydrates. Dehydration is shown for the *para* condensation product. An isomeric condensation product at the *ortho* position can also form.



The Kolbe Synthesis

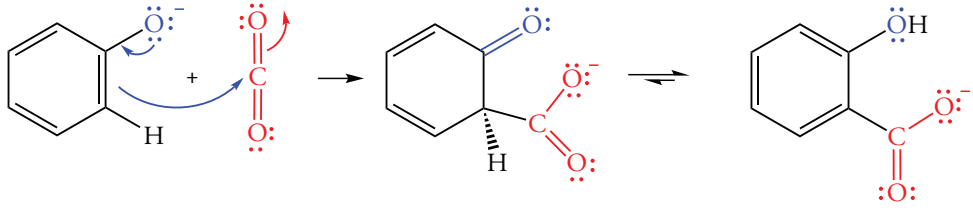
The phenolate ion can react with carbon dioxide to form carboxylic acids. This reaction is one of the steps in the synthesis of acetylsalicylic acid (aspirin).



sodium salicylate salicylic acid

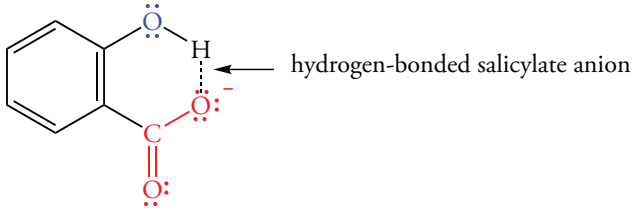
The reaction, which is carried out under 100 atm. pressure of carbon dioxide, is called the **Kolbe reaction**. It is named after the German chemist H. Kolbe, who developed the process.

The Kolbe reaction is mechanistically similar to the reaction of Grignard reagents with carbon dioxide. The increased electron density at C-2 or C-4 in the phenolate ion allows either carbon atom to act as a nucleophile and attack the carbon atom of carbon dioxide. Reaction at the position *ortho* to the oxygen atom is shown. Tautomerization of the cyclohexadienone gives the phenol.



cylhexadienone intermediate salicylate anion

The *para* isomer can also form. However, the Kolbe reaction is reversible. Thermodynamic control favors the more stable ortho isomer. The stability of the ortho isomer may result from intramolecular hydrogen bonding.



hydrogen-bonded salicylate anion

Problem 24. 9

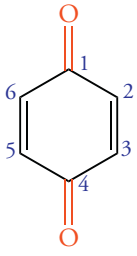
Draw the structure of the addition product of formaldehyde with phenol at the ortho position. Draw the structure of the Michael product of this compound with phenol at the ortho position.

Problem 24.10

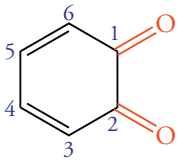
Draw the structure of the product obtained by the Kolbe reaction of *p*-methylphenol (*p*-cresol).

24.7 QUINONES

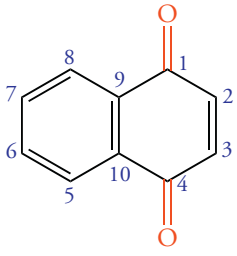
Quinones are cyclohexadienediones whose carbonyl groups can be either 1,2 or 1,4 to each other.



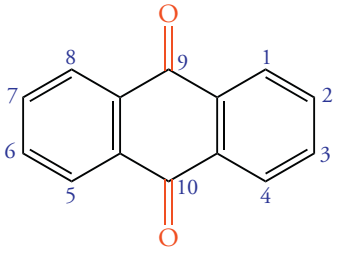
p-benzoquinone



o-benzoquinone

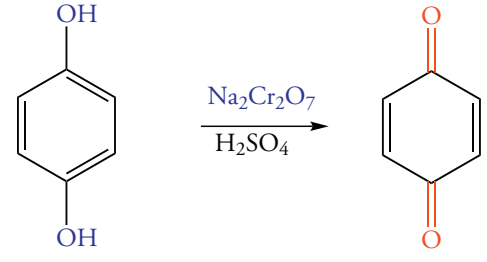


1,4-naphthaquinone

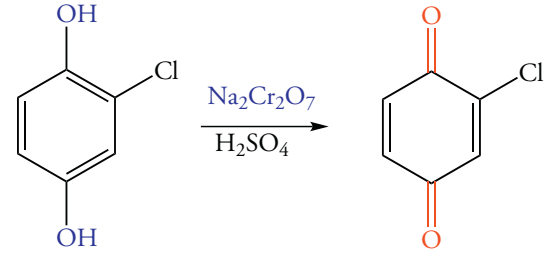


9,10-phenanthraquinone

Quinones can be prepared by the oxidation of phenols or anilines, although generally in poor yield. However, appropriately disubstituted phenols or anilines are easily oxidized to give better yields of quinones.



hydroquinone — *p*-benzoquinone (quinone)



hydroquinone — 2-chloro-1,4-benzoquinone

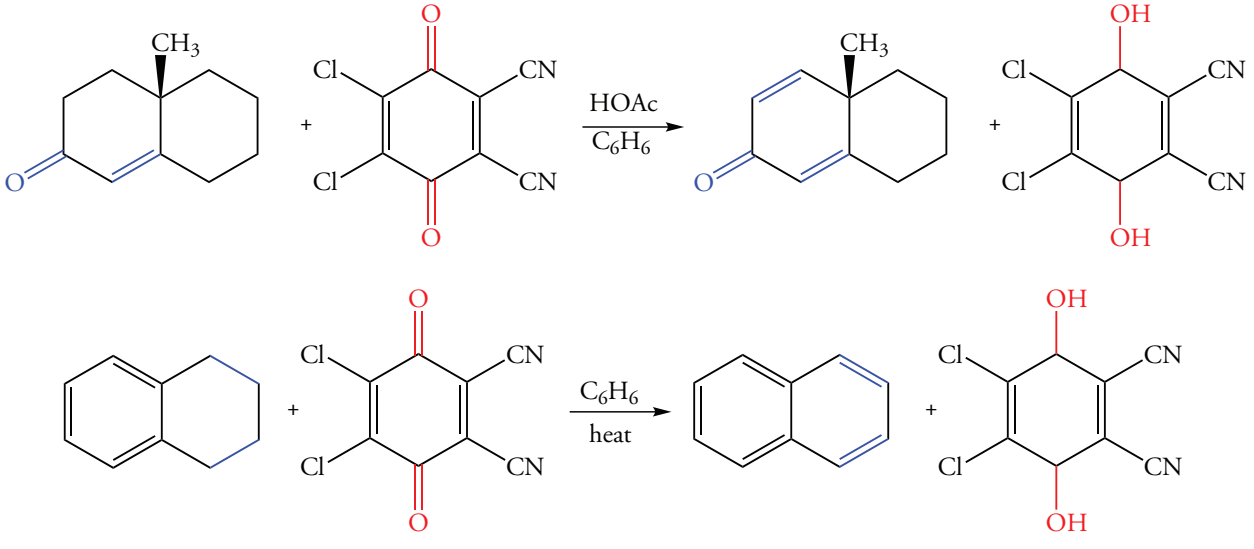
1,4-Quinones are more easily prepared and are substantially more stable than 1,2-quinones. Milder oxidizing agents are required to prevent further oxidation of 1,2-quinones.

Quinones are easily reduced to regenerate the aromatic ring of a hydroquinone. Table 24.3 lists the standard reduction potentials, E_o, for quinones. We recall from general chemistry that as the standard reduction potential increases, the ease of reduction, and thus E_o, increases. Note that electron-attracting groups increase the reduction potential. This trend is reasonable because reduction occurs by transfer of electrons to the substrate.

Table 24.3
Reduction Potentials of Quinones

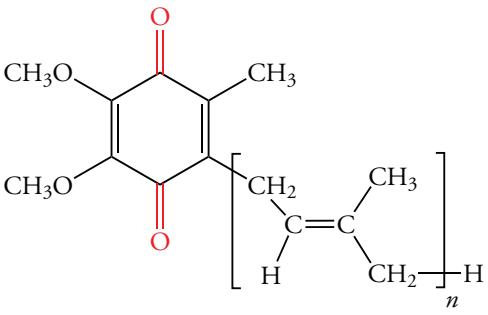
Quinone	*Reduction Potential* $E_o(v)$
1,4-Benzoquinone	0.699
2-Methyl-1,4-benzoquinone	0.645
2-Hydroxyl-1,4-benzoquinone	0.590
2-Bromo-1,4-benzoquinone	0.715
2-Chloro-1,4-benzoquinone	0.713
1,4-Naphthaquinone	0.47
1,2-Naphthaquinone	0.56
9,10-Anthraquinone	0.13
9,10-Phenanthraquinone	0.44

Quinones can be used as mild oxidizing agents. Because the standard potential for quinones varies with the substituent, it is possible to selectively oxidize substrates with specific quinones. Quinones with several electron-withdrawing groups are sufficiently strong oxidizing agents to dehydrogenate hydrocarbons in which a conjugated product can form. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) can oxidize ketones to give α,β-unsaturated ketones. It can also oxidize some nonaromatic hydrocarbons to aromatic hydrocarbons.

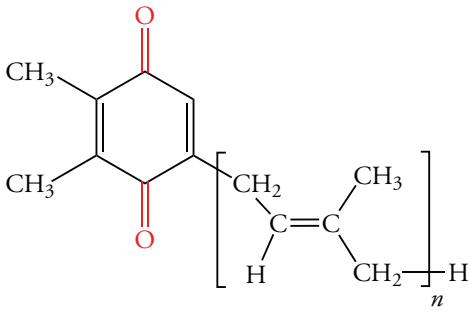


Coenzyme Q: The Ubiquitous Quinone

Quinones of various types play important roles in cells. One of these quinones is coenzyme Q (CoQ). It is synthesized by most organisms, including humans. Coenzyme Q is also called ubiquinone a pun on its apparently ubiquitous occurrence in nature. Ubiquinone is a 1,4-quinone. Its ring contains two methoxy groups, a methyl group and a polyisoprene moiety. The polyisoprene group contains 6–10 isoprenyl units—6 in bacteria and 10 in mammals. Plants synthesize similar molecules that are called plastoquinones because they are found in chloroplasts. Plastoquinones usually contain nine isoprene units.



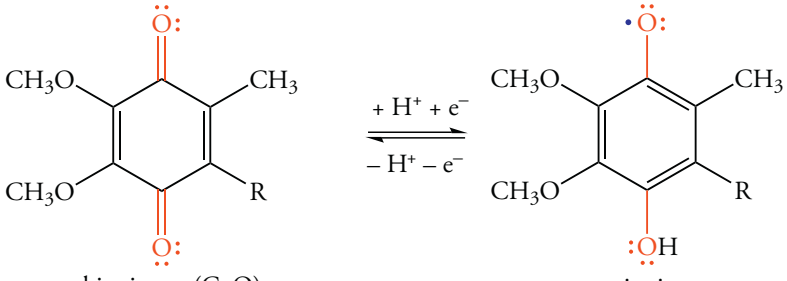
ubiquinone (CoQ)



plastoquinone

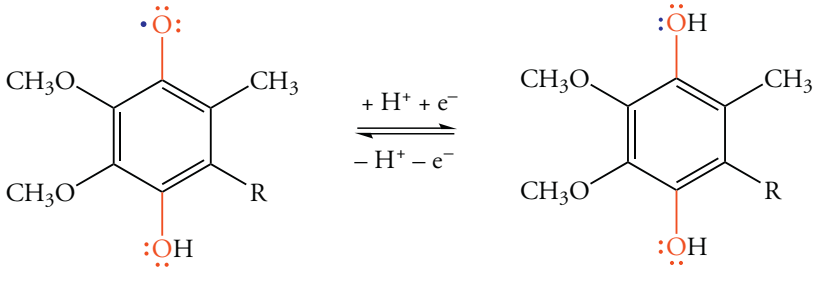
Coenzyme Q participates in redox reactions in the respiratory electron transport chain. It undergoes facile one-electron transfer reactions with free radical intermediates. Free radicals are often unstable, but the one generated by addition of an electron to ubiquinone is resonance stabilized, and also stabilized by electron-releasing substituents on the ring. The reduced form is ubiquinol (QH_2).

Ubiquinone is reduced in two successive one-electron transfer steps. The product of the first electron transfer, called a semiquinone, is a resonance-stabilized free radical.



ubiquinone (CoQ)

semiquinone
(extensively delocalized free radical)



ubiquinol (QH_2)

Ubiquinone accepts electrons from NADH in a reaction in the respiratory electron transport chain catalyzed by the mitochondrial enzyme complex NADH ubiquinone reductase. This enzyme complex in the yeast *Pichia pastoris* contains 41 polypeptide chains.

$$NADH + H^+ + Q \rightleftharpoons NAD^+ + QH_2$$

Many proteins and another coenzyme called flavin mononucleotide participate in this process, which involves five redox reactions. These redox reactions generate many resonance-stabilized free radicals.

The reduced form of ubiquinone, called ubiquinol, subsequently transfers electrons one at a time to an Fe_3^+ ion in the heme group of a protein called cytochrome *c*.

$$QH_2 + \text{cycochrome } c\ (Fe_3^{3+}) \rightleftharpoons \text{cycochrome } c\ (Fe_3^{2+}) + Q + 2H^+$$

The enzyme ubiquinone–cytochrome *c* reductase catalyzes this very complicated reaction. The enzyme is another gigantic protein complex with a molecular mass of about 500,000. Three different cytochromes and a protein containing an iron–sulfur complex are components of ubiquinone–cytochrome *c* reductase.

The processes in which ubiquinone participates occur in the inner mitochondrial membrane of eukaryotic cells and in the plasma membrane of bacterial cells. Ubiquinone and ubiquinol are soluble in the membrane, and they act as shuttles to transport electrons and protons from one multiprotein complex to another. Similar processes occur in the photoelectron transport chain in plants with plastiquinones as coenzymes.

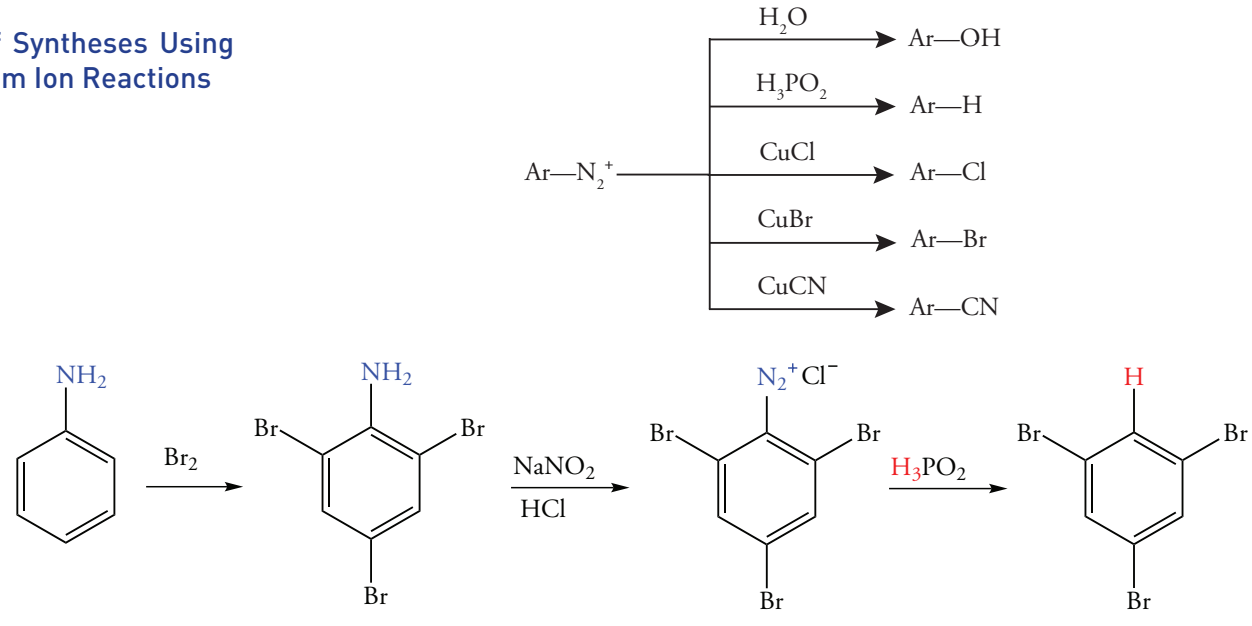
24.8 SUBSTITUTION REACTIONS OF ARYLDIAZONIUM SALTS

Reactions of Aryldiazonium Ions

We recall that primary alkylamines form unstable diazonium ion salts (Section 23.6). However, the carbon atom of the C—N bond of aryldiazonium ions is sp^2 hybridized rather than sp^3 hybridized as it is in alkyldiazonium ions. Homolytic cleavage of the bond to give an aryl cation and nitrogen therefore occurs at a slower rate than for formation of an alkyl cation from an alkyldiazonium ion. Aryldiazonium ions can be prepared in solution and reacted with a variety of reagents that replace nitrogen in regiospecific reactions. Figure 24.3 summarizes these reactions, first presented in Section 13.8.

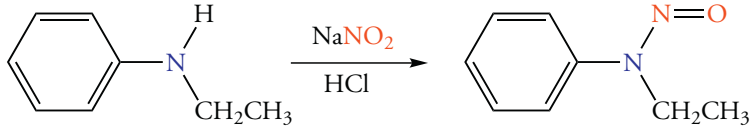
Aryldiazonium ions are important synthetic intermediates because they provide a means of modifying substituents already located at specific positions on the ring. The synthesis of an aryldiazonium ion on a multiply substituted aromatic ring allows us to make compounds that sequential electrophilic aromatic substitution could not produce. For example, bromination of aniline yields tribromoaniline. Diazotization of the product followed by treatment with hypophosphorous acid removes the amino group. The three bromine groups are located *meta* to one another. Direct bromination of benzene would not produce this compound because bromine is an *ortho–para* director.

Figure 24.3
Summary of Syntheses Using Aryldiazonium Ion Reactions



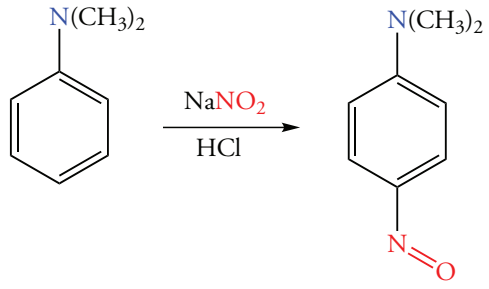
Nitrosation of Arylamines

N-Alkylarylamines are secondary amines that react by direct electrophilic attack of the nitrosonium ion on the electron pair of the amine to give *N*-nitrosoamines.



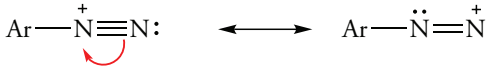
N-ethylaniline — *N*-ethyl-*N*-nitrosoaniline

The nitrosation of tertiary alkylamines does not give an isolable product. However, a tertiary arylamine such as *N*,*N*-dialkylarylamine undergoes an alternative reaction. The nitrosonium ion is a weak electrophile, but is reactive enough to nitrosate the activated aromatic ring.

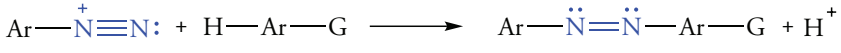


24.9 AZO COMPOUNDS

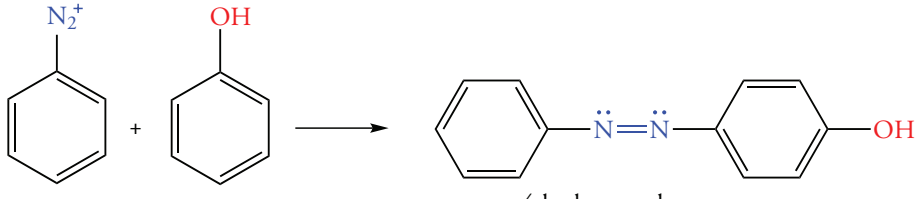
The diazonium ion portion of an aryldiazonium ion has two contributing resonance structures. The more important contributor has Lewis octets at both nitrogen atoms. The second form is electron deficient at the terminal nitrogen atom.



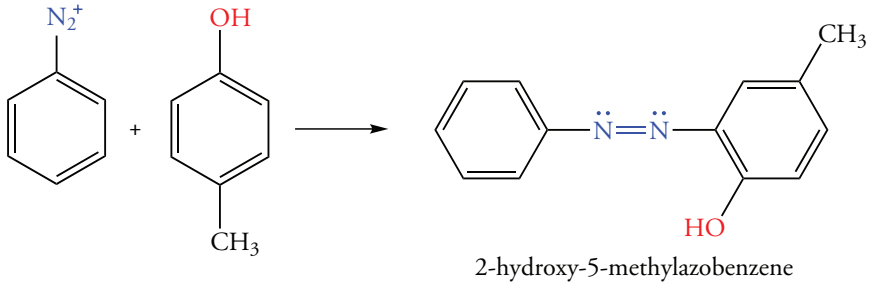
The terminal nitrogen atom in the second resonance form is electron deficient. Thus, we understand why the aryldiazonium ion is electrophilic and reacts with nucleophilic centers at the terminal nitrogen atom. For example, aryldiazonium ions can attack aromatic rings to give substitution reactions. However, the aryl diazonium ions are weak electrophiles, and therefore they react only with very activated aromatic compounds, such as phenols or dimethylanilines. Substitution produces an—N=N—functional group called the **azo group**. In the following equation, G represents a group that supplies electrons by resonance. The π electrons of the azo group form part of a conjugated system between the two aromatic rings.



Substitution of the activated aromatic ring by the electrophilic aryldiazonium ion occurs principally at the *para* position. However, if the *para* position is blocked by a substituent, substitution occurs at the *ortho* position.



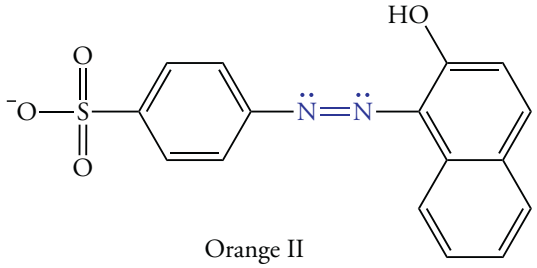
4-hydroxyazobenzene



2-hydroxy-5-methylazobenzene

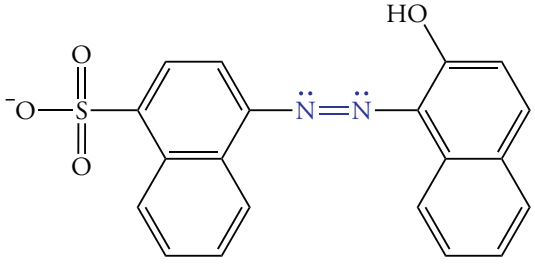
Extended conjugation occurs between aromatic rings linked by an azo group. These compounds are colored because the λ_{max} values of aromatic azo compounds are in the visible region. They are widely used as dyes for both food products and fabrics. Those used for fabric dyes usually contain one or more sulfonic acid groups both to increase water solubility and to provide binding sites between the dye and the surface of the fabric. Because sulfonic acids are strong acids, they exist as sulfonate ions at pH 7.

Variations in structure that affect the color of the azo compounds may involve both the aromatic rings and their substituents. Using naphthalene rings for both the diazonium ion and the activated ring produces compounds with different colors. For example, the product of azo coupling of the *para* sulfonic acid–substituted benzenediazonium ion with 2-naphthol is orange, whereas the product obtained using a similarly substituted naphthalenediazonium ion with 2-naphthol is red.



Orange II

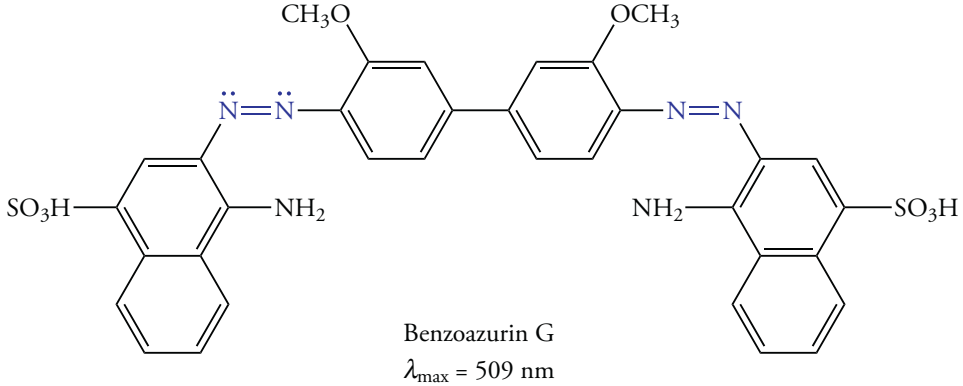
λ_{max} = 484 nm



Fast Red A

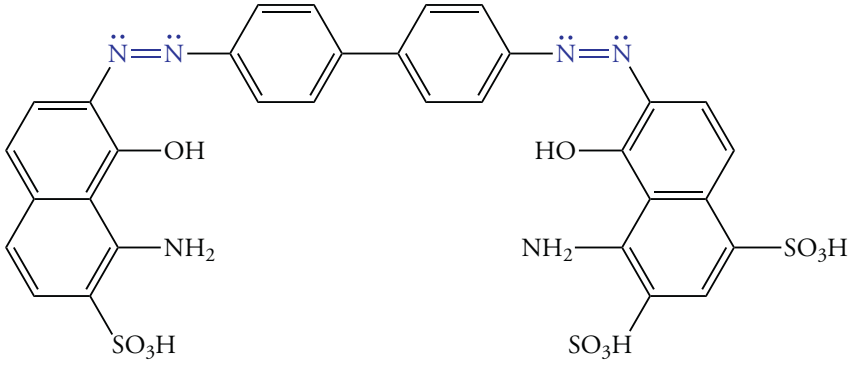
λ_{max} = 505 nm

Substituents change the max values of azo compounds and the corresponding colors. For example, adding hydroxy and sulfonic acid groups to Benzoazurin G changes the color, producing Sky Blue 6B.



Benzoazurin G

λ_{max} = 509 nm

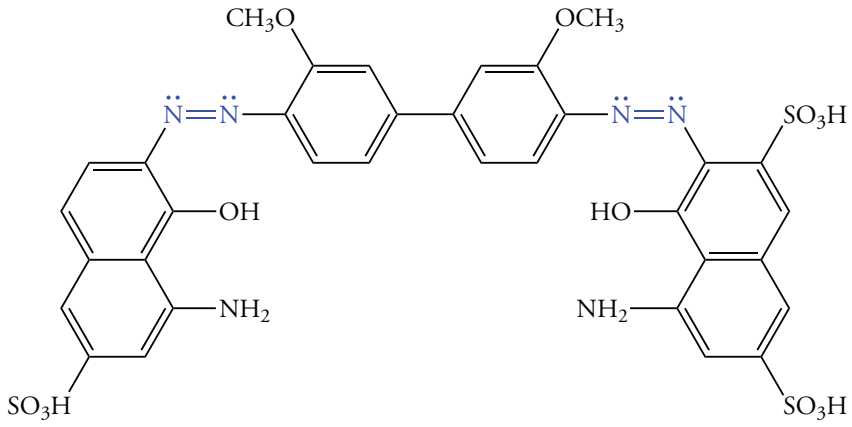


Sky blue 6B

λ_{max} = 627 nm

Problem 24. 11

Draw the structure of the amine needed to form the diazonium ion required to synthesize Direct Blue 2B.



Direct Blue 2B

Exercises

Properties of Aromatic Compounds

24.1 The boiling points of the 1,2-, 1,3-, and 1,4-benzenediols are 245, 276, and 285 °C, respectively. Explain why the boiling point of the *ortho* isomer is significantly lower than those of the other two isomers.

24.2 The boiling points of the three isomeric hydroxyanisoles are 205, 243, and 244 °C, respectively. What is the structure of the compound corresponding to the lowest boiling point?

24.3 The dipole moments of toluene and chlorobenzene are 0.4 and 1.7 D, respectively. Predict the dipole moment of *p*-chlorotoluene.

24.4 The dipole moments of toluene and phenol are 0.4 and 1.5 D, respectively. Predict the dipole moment of *p*-methylphenol.

24.5 The dipole moments of two of the isomeric dichlorobenzenes are 1.72 and 2.50 D. Assign a structure to each value.

24.6 The dipole moments of chlorobenzene and phenol are 1.7 and 1.5 D, respectively. Predict the dipole moment of *p*-chlorophenol.

24.7 Which compound has the longer C—N bond length, *p*-methoxyaniline or *p*-cyanoaniline?

24.8 Which compound has the larger activation energy for the nitrogen inversion, cyclohexylamine or aniline?

24.9 The dipole moment of pyrrolidine is 1.57 D, and the negative end of the dipole is directed toward nitrogen. The dipole moment of pyrrole is 1.80 D, but the dipole is opposite that of pyrrolidine. Explain why.

24.10 The dipole moments of aniline, *p*-(trifluoromethyl)aniline, and (trifluoromethyl)benzene are 1.3, 4.3, and 2.9 D, respectively. Explain how these data are used to deduce the direction of the dipole moment of aniline.

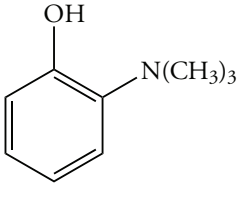
Acid–Base Properties

24.11 Explain why *p*-hydroxybenzaldehyde (pK_a = 7.62) is a substantially stronger acid than phenol.

24.12 Explain why 2,4-dinitrophenol (pK_a = 3.96) is a stronger acid than 3,5-dinitrophenol (pK_a = 6.73).

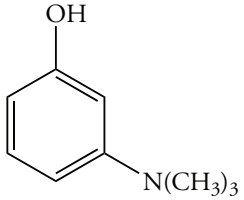
24.13 Based on resonance structures, explain why I-naphthol (pK_a = 9.31) is a stronger acid than II-naphthol (pK_a = 9.55). A review of Section 13.10 may be helpful.

24.14 Which of the following isomeric phenols is the more acidic?



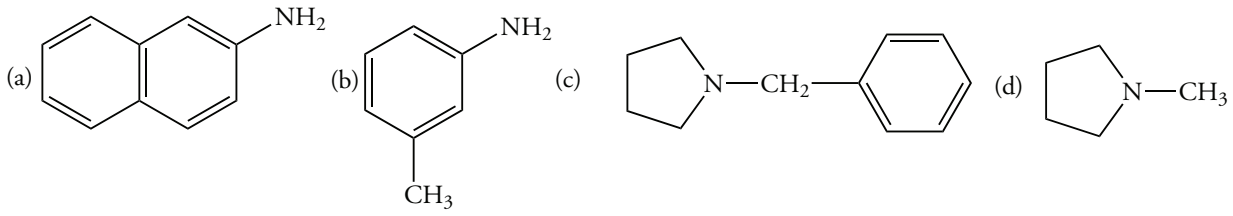
I

or

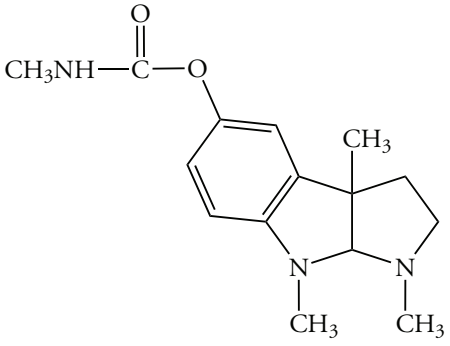


II

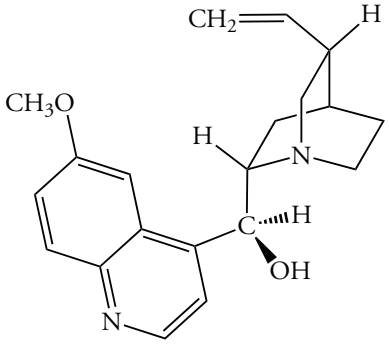
24.15 Estimate K_b in each of the following compounds.



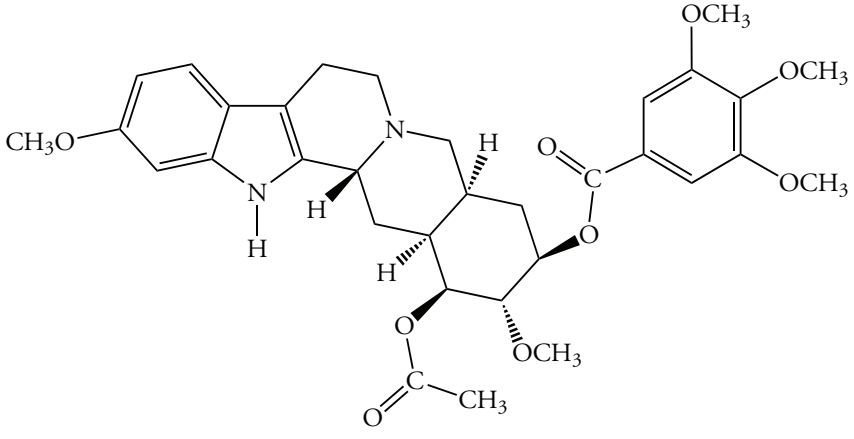
24.16 Physostigmine is used in 0.1–1.0% solutions to decrease the intraocular pressure in treatment of glaucoma. Rank the three nitrogen atoms in the molecule in order of increasing basicity.



24.17 Quinine is an antimalarial drug, and reserpine is an antihypertensive drug. Estimate the pK_b values of both nitrogen atoms in each drug.



quinine

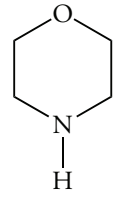


reserpine

24.18 Explain why the pK_a values of the anilinium ions of *m*-cyanoaniline and *p*-cyanoaniline are 2.75 and 1.74, respectively.

24.19 Explain why the pK_a values of the anilinium ions of *m*-methoxyaniline and *p*-methoxyaniline are 4.2 and 5.3, respectively.

24.20 Explain why morpholine (pK_b = 5.67) is a weaker base than piperidine (pK_b = 2.88).

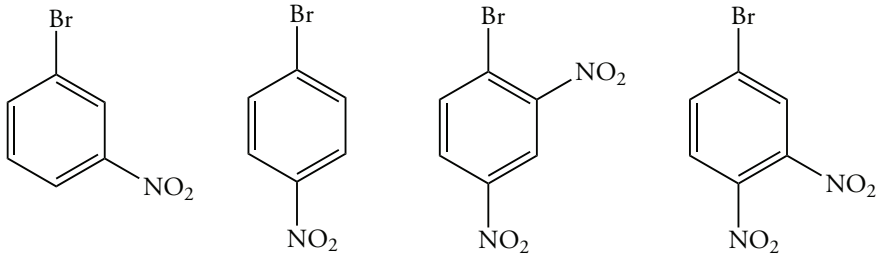


morpholine

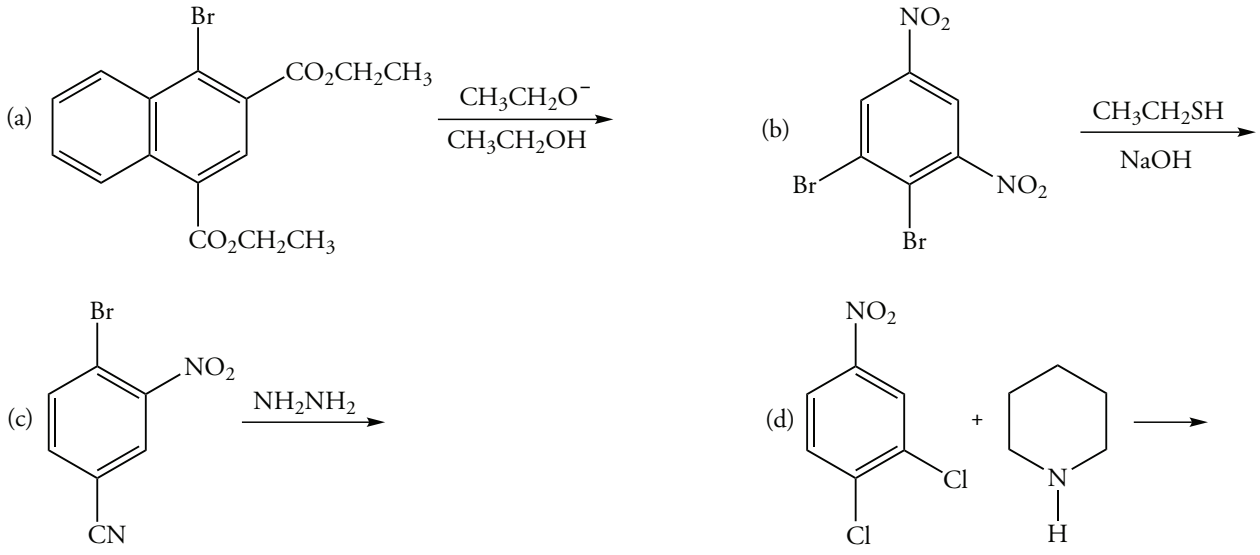
24.21 The acidities of benzoic acid and of acetic acid differ by a factor of about 4, whereas the acidities of the anilinium ion and of the methylammonium ion differ by about a factor of 10^6. Why does the aromatic ring have so little effect on the acidity of carboxylic acids and a large effect on the acidity of ammonium ions?

Nucleophilic Aromatic Substitution

24.22 Rank the following compounds in order of increasing reactivity toward sodium methoxide in methanol.



24.23 Draw the product of each of the following reactions.



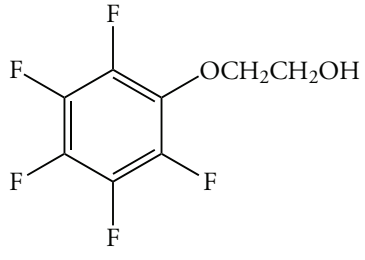
24.24 Explain why 4-chloropyridine reacts with methoxide to give 4-methoxypyridine under conditions where 3-chloropyridine is unreactive.

24.25 At one time 2,4-dinitrofluorobenzene was used to form derivatives of peptides at the N-terminal amino acid. Write a general structure of this type of derivative. Explain why the reaction readily occurs.

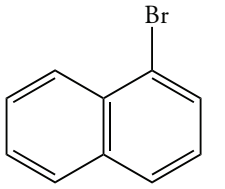
24.26 Explain why hexafluorobenzene readily reacts with sodium methoxide in methanol at 75 °C to yield 2,3,4,5,pentafluoroanisole.

24.27 2,3,4,5,6-Pentafluoronitrobenzene reacts with sodium methoxide in methanol at 25 °C to yield a mixture of two isomeric products with the molecular formula $C_7H_3F_4NO_3$. Draw their structures.

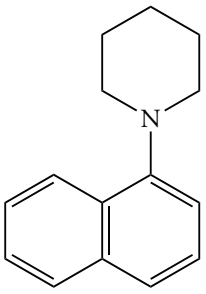
24.28 The following compound reacts in basic solution to give a product with the molecular formula $C_8H_4F_4O_2$. Suggest a structure for this product.



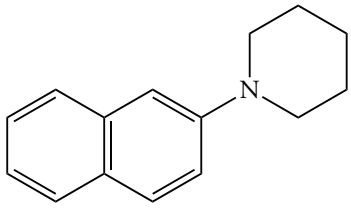
24.29 1-Bromonaphthalene reacts slowly with piperidine at 230 °C to give compound I. The addition of sodium amide accelerates the reaction, which then occurs at 100 °C to give compounds I and II. (a) Explain the difference in the two reaction conditions. (b) Explain the product distribution.



1-bromonaphthalene



I

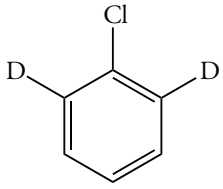


II

24.30 The two benzyne intermediates derived from reaction of sodium amide and 3-chlorotoluene are formed in approximately equal amounts. Calculate the composition of the mixture of aniline isomers formed in this reaction.

24.31 The reaction of 3-chloro(trifluoromethyl)benzene with sodium amide is regioselective. Which of the two possible isomeric benzynes is formed? Suggest a reason why the reaction is regioselective.

24.32 Draw the structures of the products formed in the reaction of the following deuterated chlorobenzene with sodium amide in liquid ammonia.

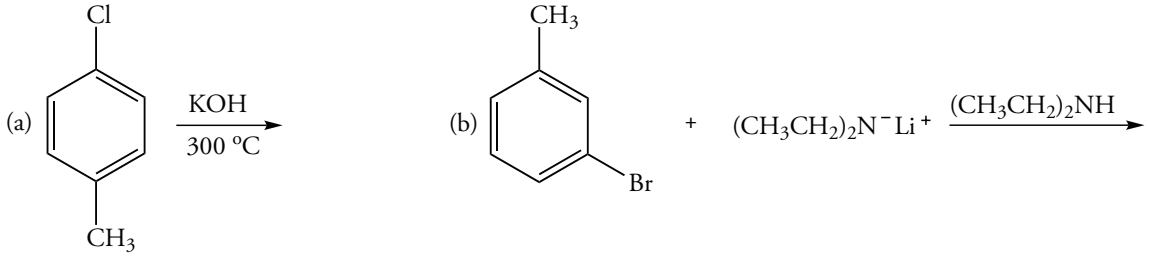


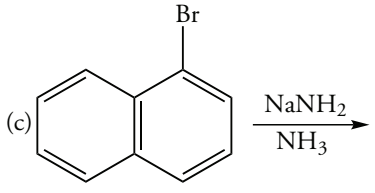
24.33 Reaction of 2-bromoanisole with sodium amide in liquid ammonia gives a high yield of 3-aminoanisole. Explain why the reaction of the benzyne intermediate is regioselective.

24.34 Reaction of *o*-bromofluorobenzene with magnesium in tetrahydrofuran gives an intermediate that decomposes to yield benzyne. Write the mechanism of this reaction.

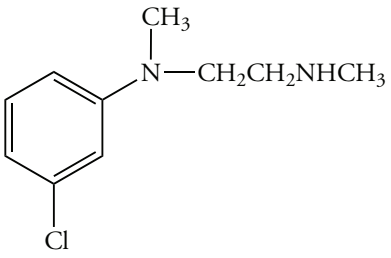
24.35 Reaction of 2-aminobenzoic acid with nitrous acid yields an intermediate that decomposes to yield benzyne. Write the mechanism of this reaction.

24.36 Draw the structures of the products formed in the reaction of the following deuterated chlorobenzene with sodium amide in liquid ammonia.



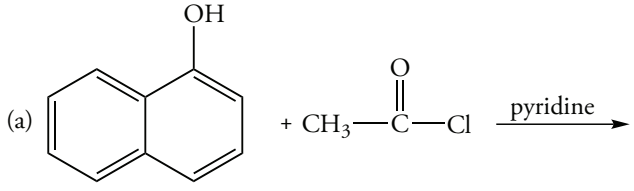


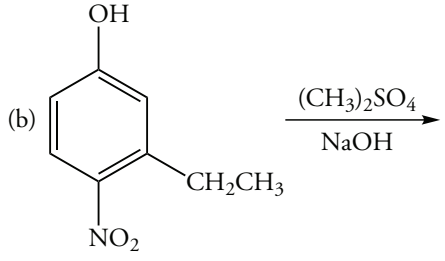
24.37 The following compound reacts with sodium amide in ether to give a product with the molecular formula $C_{10}H_{14}N_2$. Suggest a structure for this product.

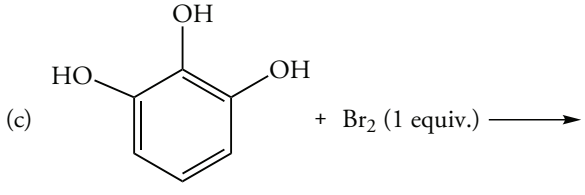


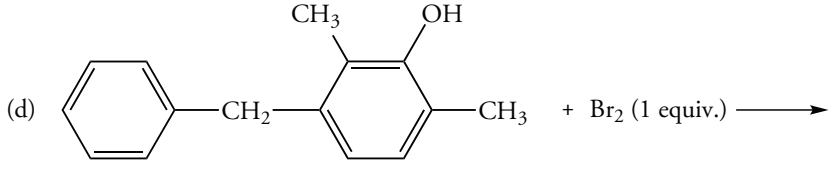
Reactions of Phenols

24.38 Draw the product of each of the following reactions.

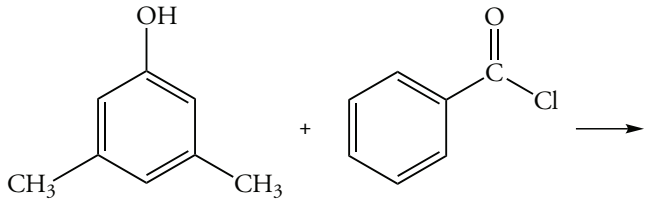
(a) 

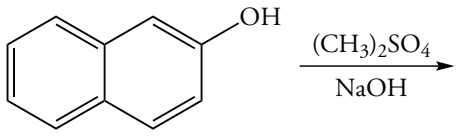
(b) 

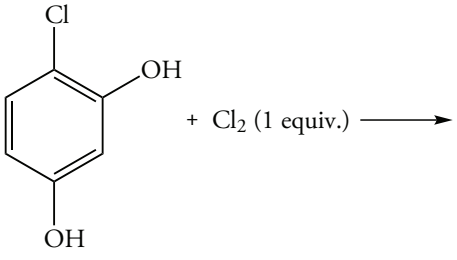
(c) 

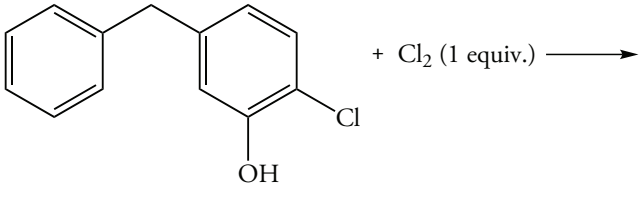
(d) 

24.39 Draw the product of each of the following reactions.

(a) 

(b) 

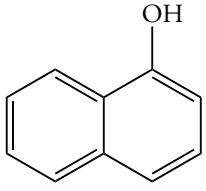
(c) 

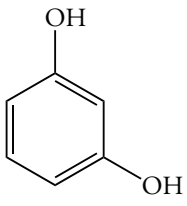
(d) 

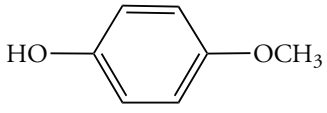
Reactions of Phenolate Ions

24.40 Could a polymer result from the reaction of phenolate ion with acetone?

24.41 Draw the structure of the product of the reaction of CO_2 with the phenolate ion of each of the following compounds.

(a) 

(b) 

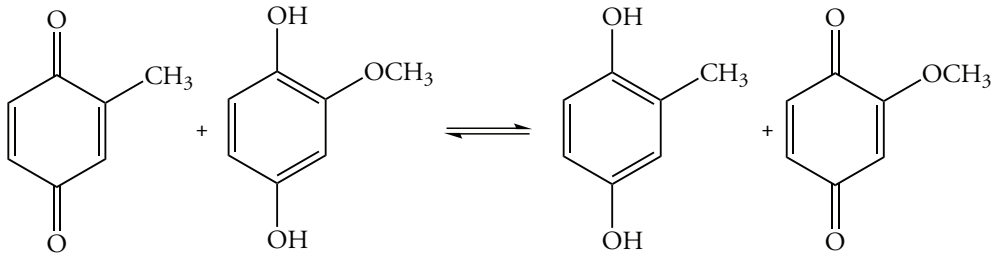
(c) 

Quinones

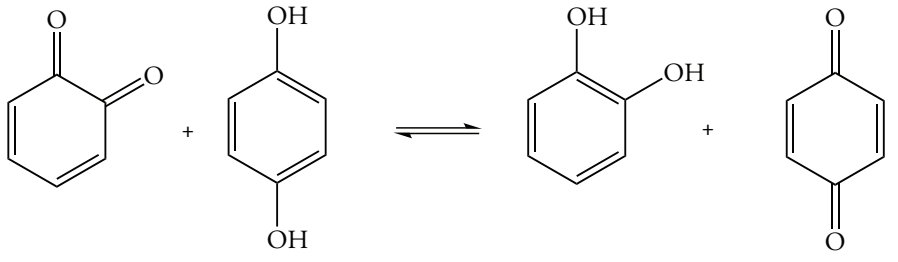
24.42 Based on the structures of ubiquinone and plastoquinone, which compound has the larger reduction potential?

24.43 Phenanthrene can be directly oxidized by vanadium(V) oxide to 9,10-phenanthraquinone. Based on the resonance forms of phenanthrene, explain why the central ring is oxidized rather than the other rings.

24.44 Predict whether the following reaction has an equilibrium constant greater or less than 1.



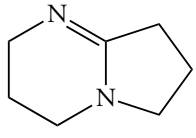
24.45 The E_o of the following reaction is 0.08 V. What is the reduction potential for 1,2-benzoquinone?



Quinones

24.46 Select the better nucleophile from each of the following pairs of amines.
(a) aniline and cyclohexylamine
(b) *p*-nitroaniline and *p*-methoxyaniline
(c) aniline and *N*,*N*-dimethylaniline

24.47 The amidine group (—N—C=N—) is a stronger base than amines. Determine the site of protonation in 1,5-Diazabicyclo[4.3.0]non-5-ene, DBN, a base used in organic reactions. Explain why DBN is a stronger base than an amine.

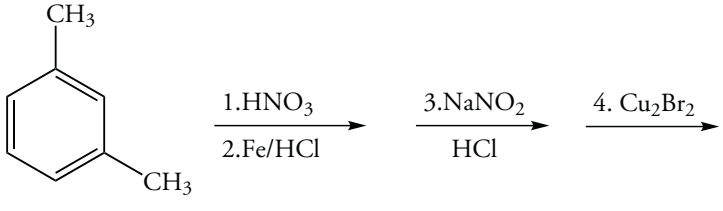


DBN

Synthesis Using Diazonium Compounds

24.48 Write a series of reactions required to prepare 2-bromo-4-methylphenol from toluene.

24.49 Starting from *m*-dimethylbenzene, write the products formed in each step of the following reaction sequence.



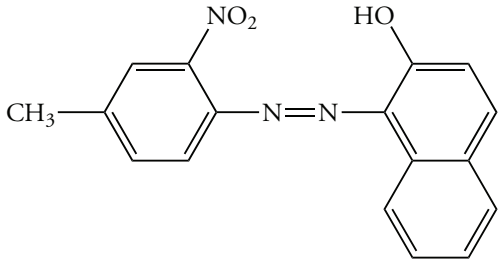
Azo Compounds

24.50 Explain why the *p*-nitrobenzenediazonium ion reacts faster than benzenediazonium ion with 2-naphthol.

24.51 Which member of each of the following pairs of aromatic compounds reacts faster with benzenediazonium chloride?
(a) aniline and *o*-bromoaniline
(b) *p*-methylphenol and *p*-methylphenoxide
(c) anisole and *N*,*N*-dimethylaniline

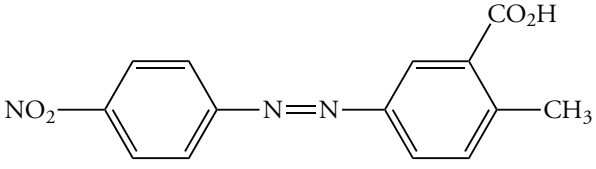
24.52 When *o*-aminobenzoic acid (anthranilic acid) is treated with $NaNO_2$ and HCl followed by addition of *N*,*N*-dimethylaniline to the solution, a dye called methyl red is formed. Draw its structure.

24.53 The following compound is a red dye used in some plastics. Write the structure of the amine needed to form the diazonium ion required to produce the compound. Outline a synthesis of this amine starting from toluene.



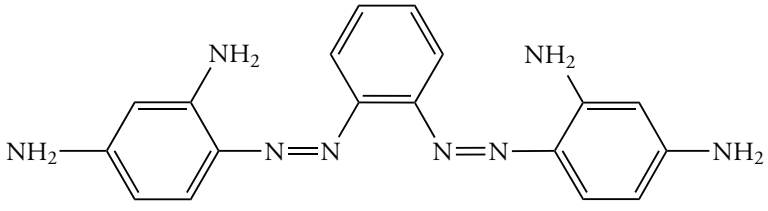
24.54 What compounds are required to synthesize each of the following dyes?

(a)



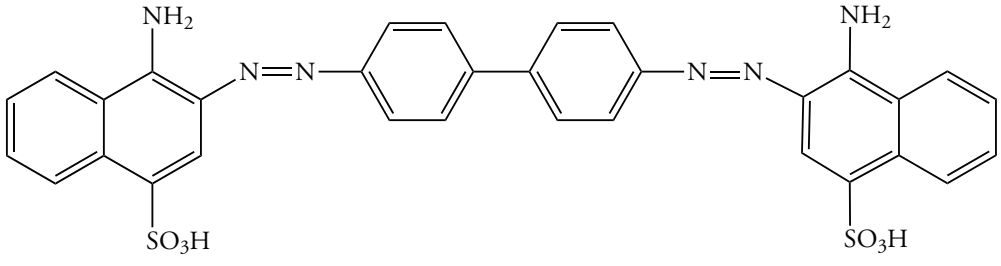
Alizarin Yellow R

(b)

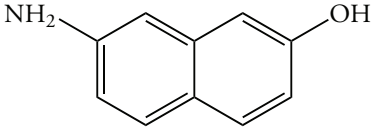


Bismark Brown B

(c)

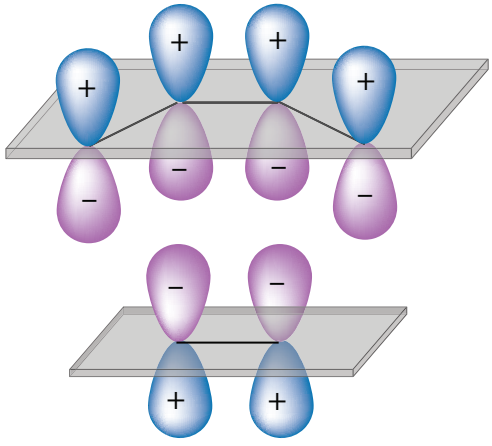


24.55 Reaction of 7-amino-2-naphthol with benzenediazonium ion at pH 9 results in substitution ortho to the hydroxyl group. At pH 5 the substitution occurs *ortho* to the amino group. Explain how the pH determines the ring in which substitution occurs. Remember that an amino group is a stronger *ortho–para* director than a hydroxyl group.



7-amino-2-naphthol

25 Pericyclic Reactions



25.1 CONCERTED REACTIONS

Many chemical reactions occur by multistep mechanisms that are described in terms of electrophiles and nucleophiles. We have also seen that some organic reactions occur by concerted S_N2 and E2 mechanisms in which bond making and bond breaking occur simultaneously. These reactions are usually stereoselective. They often require catalysts, such as acid or base, and their transition states have charged sites, so solvent polarity also affects these reactions.

In this chapter we examine three classes of **pericyclic reactions**. These reactions are concerted, but have very different characteristics from the concerted reactions we have studied up to this point. Pericyclic reactions depend upon the interactions of π orbitals and upon their symmetries.

Pericyclic reactions (Greek *peri*, around) are concerted reactions in which changes in the positions of π and σ bonds occur via cyclic transition states. In simplest terms, pericyclic reactions occur by a cyclic shift of electrons to give a transition state that is transformed to product. No intermediate forms. These reactions require no catalysts, and solvent polarity has no effect on the stereochemistry of the products or the rate of the reaction.

Pericyclic reactions require an energy source, which can be either thermal or photochemical. Pericyclic reactions are **thermal** if they only require heat for the conversion of one or more reactants into product. The temperature need not be high; some thermal pericyclic reactions occur at room temperature. The common feature of thermal pericyclic reactions is the transformation of ground state molecular orbitals of the reactant into the ground state molecular orbitals of the product. Pericyclic reactions are **photochemical** if they require light for the conversion of one or more reactants into product. Photochemical pericyclic reactions occur when a reactant absorbs light to form an electronically excited state. Thus, the mechanisms of thermal and photochemical pericyclic reactions differ because they involve different molecular orbitals as well as different energy sources.

At first glance these reactions might seem quite esoteric. We will see, however, that some important biochemical reactions are also pericyclic reactions. Some are photochemical, and others are thermal. Perhaps we should not be surprised by this. After all, many of the earth's creatures are bathed in light at least part of the time, and all require thermal energy to survive.

25.2 CLASSIFICATION OF PERICYCLIC REACTIONS

Pericyclic reactions are divided into three classes:

1. Electrocyclic reactions
2. Cycloaddition reactions
3. Sigmatropic rearrangements

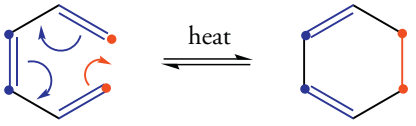
Within each class, we will consider the number of electrons in π molecular orbitals in the transition state. Pericyclic reactions may involve either $4n$ or $4n + 2$ electrons, where n is an integer. This distinction is important because the symmetry of the molecular orbitals in thermal or photochemical reactions depends on the number of π electrons in the transition state. The stereochemistry of the products of pericyclic reactions depends on the symmetry of these molecular orbitals. We will see that the stereochemistry of a product of a pericyclic reaction derived from a $4n$ π electron system differs from that of a $4n + 2$ π electron system. Thus, the concepts of orbital symmetry and Hückle systems that we considered in Chapter 11 and in particular the **highest occupied molecular orbital** (**HOMO**) and **lowest unoccupied molecular orbital** (**LUMO**) will play a central role in our discussions of pericyclic reactions.

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Electrocyclic Reactions

An electrocyclic reaction is an intramolecular process in which a polyene reacts to yield an isomeric cyclic product with one less double bond than the reactant. In this process, the two ends of the π system become linked by a σ bond and the positions of the double bonds change. The reverse of this reaction, in which a cyclic system opens to give an isomeric polyene, is also an electrocyclic reaction.

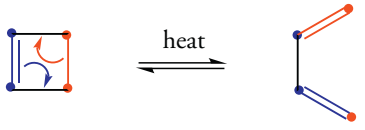
The thermal cyclization of *cis*-l,3,5-hexatriene to yield 1,3-cyclohexadiene is an example of an electrocyclic reaction. C-1 and C-6 of the original polyene are linked by a σ bond in the cyclic product. This reaction is known as the **Cope rearrangement**.



$\Delta H^{\circ}_{\text{reaction}} = -60 \text{ kJ mole}^{-1}$

The Cope rearrangement is exothermic, as we would expect from the change in the number and type of carbon–carbon bonds. The number of single bonds increases by two and the number of double bonds decreases by one.

The reverse of the cyclization of a polyene is also an electrocyclic reaction. For example, when cyclobutene is heated, it rearranges to 1,3-butadiene.



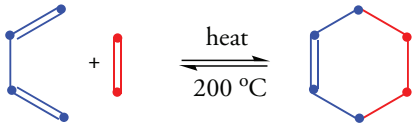
$\Delta H^{\circ}_{\text{reaction}} = -41 \text{ kJ mole}^{-1}$

The changes that occur in this reaction are the reverse of those for the cyclization of 1,3,5-cyclohexatriene. So we might expect the reaction to be endothermic. However, the reaction is actually exothermic. We recall that the cyclobutane ring is strained. Therefore, releasing the strain energy of the cyclobutene ring, which is larger than that of cyclobutane, drives the ring-opening reaction.

We will discuss both cyclization and ring-opening reactions and the stereochemistry of these reactions as it relates to the number of π electrons in Section 28.4. *cis*-1,3,5-Hexatriene has six π electrons. It is an example of a $4n + 2$ π electron system, where $n = 1$. 1,3-Butadiene is a $4n$ π electron system, where $n = 1$.

Cycloaddition Reactions

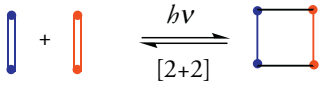
Two unsaturated molecules combine to form a ring in a cycloaddition reaction. The earliest studied example of a cycloaddition reaction is the Diels–Alder reaction, which we discussed earlier in terms of its value as a synthetic reaction (Section 11.8). It occurs between a conjugated diene and an alkene (or alkyne). The alkene is called a **dienophile**.



In the Diels–Alder reaction, the terminal carbon atoms of the diene form a σ bond to the carbon atoms of the alkene double bond. For geometric reasons, the diene must have a-*cis* configuration or adopt an s-*cis* conformation.

The Diels–Alder reaction requires six π electrons: four in the diene and two in the alkene (the dienophile). It is a **[4 + 2] cycloaddition**. In the Diels–Alder reaction, the transition state contains six π electrons.

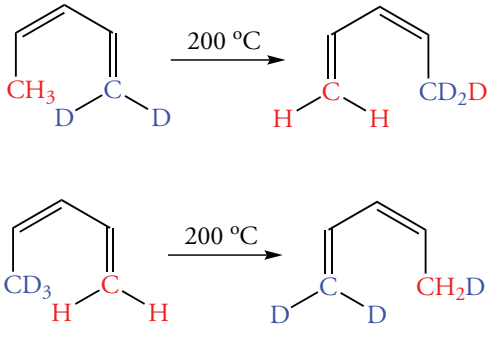
The reaction of two alkene molecules to give a cyclobutane ring has four π electrons in the transition state. It is an example of a $4n$ π system. Since each molecule contributes two π electrons to the transition state, it is a [2 + 2] cycloaddition. A [2+2] cycloaddition occurs photochemically, not thermally.



The entropy change (ΔS°_{rxn}) for a cycloaddition reaction is negative because two moles of reactant are converted into one mole of product. The approximate ΔS°_{rxn} value for a decrease of one mole of product in a reaction is –125 J mole^{-1} degree^{-1}. This unfavorable entropy change for cycloaddition is opposed by a very favorable enthalpy term. Therefore, the standard free energy change is negative, and the reaction is spontaneous. In both the Diels–Alder reaction and the [2 + 2] cycloaddition reaction, two double bonds are "lost" as the product forms and four single bonds form. Both types of cycloaddition reactions are therefore exothermic. However, the formation of cyclobutane is less exothermic than the formation of cyclohexene because the cyclobutene ring is much more strained than the cyclohexene ring.

Sigmatropic Rearrangements

Sigmatropic rearrangements are *intramolecular* reactions in which one atom or group of atoms linked by a σ bond migrates from one end of a π system to the other. In the process, the positions of single and double bonds simultaneously shift. Examples of one type of sigmatropic rearrangement are the isomerizations of the following deuterated 1,3-pentadienes.

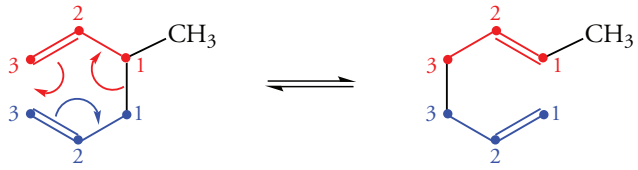


In these two rearrangements, a hydrogen (or deuterium) atom that is a bonded at an sp³-hybridized carbon atom moves from one end of a five-carbon-atom system to the other end. In the process, the locations of the alternating single and double bonds and the hybridization of the terminal atoms change. The rearrangement could not be detected without deuterium-labeled compounds because the reactant and product would be identical.

Sigmatropic rearrangements are identified by two numbers separated by a comma and enclosed within brackets. The two numbers refer to the number of atoms in the two groups connected by a σ bond. The numbers are also related to the orbitals in each piece of the original molecule that are involved in the rearrangement. The rearrangement of the 1,3-pentadiene occurs by a shift of a hydrogen atom across a five-carbon-atom system and is therefore a **[1,5] sigmatropic rearrangement**. The number "1" refers to the orbital of the hydrogen atom, which is bonded to one end of the system that rearranges. The number "5" refers to the five carbon 2p orbitals of the reacting system. Four of the orbitals are in the π system. The remaining carbon orbital is involved in bonding to the migrating hydrogen atom.

Studies of more complex compounds that undergo [1,5] sigmatropic shifts have shown that the reaction is stereospecific. The group that leaves from the sp³-hybridized site is transferred to the second site by a path along one side of the π system.

When groups of atoms migrate from one site to another, the σ-bonded atom that leaves one site is different than the one that forms a σ bond at the second site. In such reactions, both "ends" of a σ bond migrate. For example, in the rearrangement of 3-methyl-1,5-hexadiene, atom 3 of the three-atom migrating group eventually bonds to atom 3 of the second part of the molecule.



This is a [3,3] sigmatropic rearrangement. The ΔH°_{rxn} for the [1,5] sigmatropic rearrangements of the various deuterated 1,3-pentadienes are all approximately zero. The difference in the C—H and C—D bond energies is small, and the number and types of bonds in both reactant and product are the same. Also, because the molecules are structurally equivalent except for the position of deuterium labeling, the entropy of both product and reactant are the same, and ΔS°_{rxn} is zero.

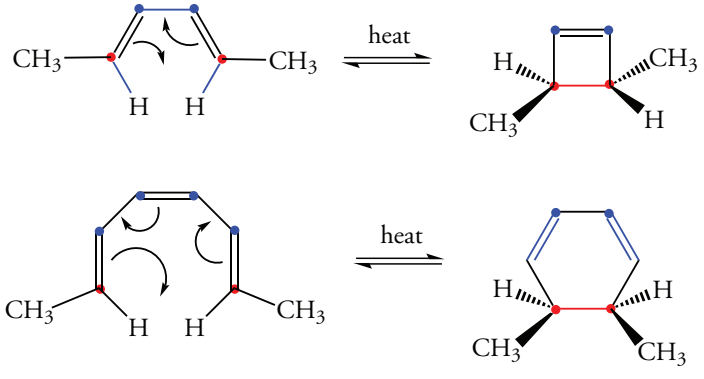
The ΔH°_{rxn} for the [3,3] sigmatropic rearrangement of 3-methyl-1,5-hexadiene is slightly negative. The number and types of bonds in both reactant and product are the same. However, the double bonds in the reactant are monosubstituted, whereas the product has a monosubstituted and a disubstituted double bond. The more stable disubstituted double bond increases the stability of the product. The ΔS°_{rxn} is approximately zero because the reactant and products are structurally similar and have the same degree of conformational mobility.

General Features of Pericyclic Reactions

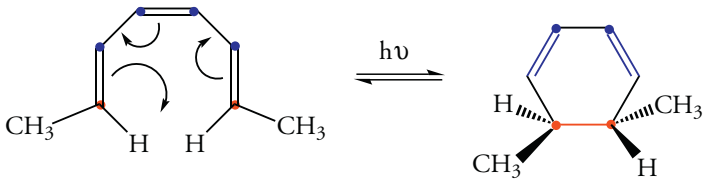
We must consider three factors when we analyze pericyclic reactions.

1. First, determine the number of π electrons in the transition state.
2. Second, determine whether the reaction occurs thermally or photochemically.
3. Third, determine the stereochemical course of the reaction.

We will find that the stereochemical results of pericyclic reactions depend upon the conditions under which the reaction occurs; that is, whether it is a thermal or a photochemical reaction. And these in turn are directly related to the number of π electrons in the transition state. Thus, our three "factors" are completely interrelated. Each provides facts that must be accommodated by the mechanisms of pericyclic reactions. In the thermal reactions shown below, the products have different stereochemistry for 6π and 4π electron systems.

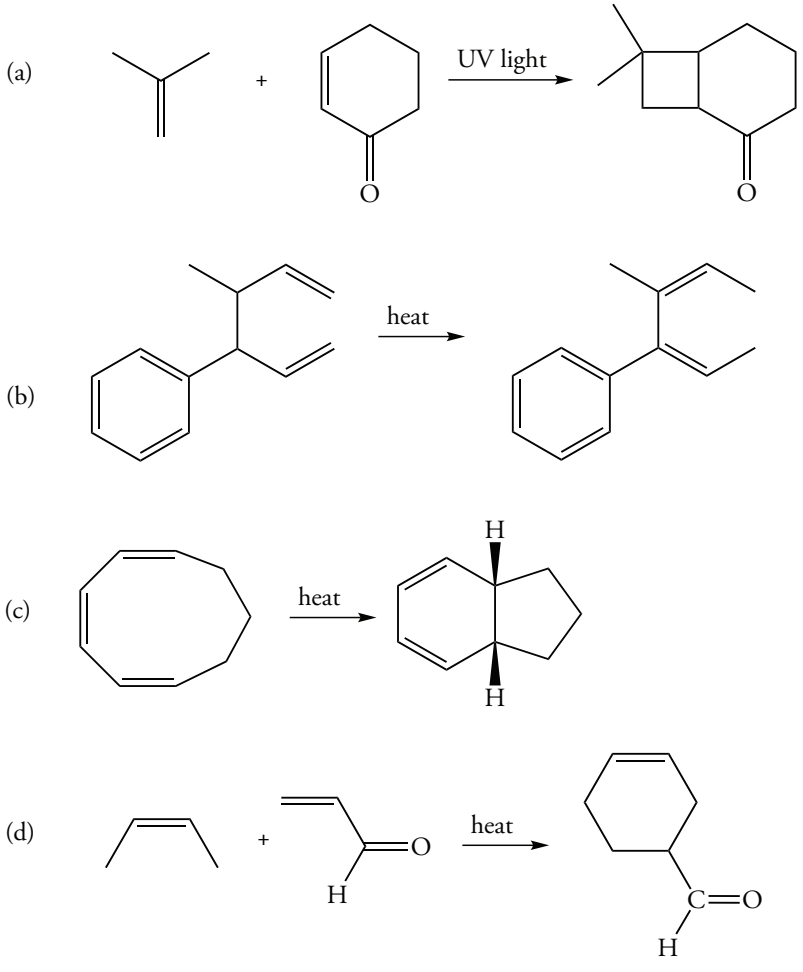


The effect of the number of π electrons upon the stereochemistry of a reaction is illustrated by the cyclization of a diene system compared to a triene system, as shown above. Although the methyl groups in both compounds have the *E* configuration, the products have different stereochemistry. Although both reactions are thermal, only the *trans* isomer results from the diene and only the *cis* isomer results from the triene. Thermal electrocyclic reactions of systems with $4n$ π electrons have the opposite stereochemistry to structurally related systems with $4n + 2$ π electrons. Furthermore, the stereochemistry of the thermal and photochemical pericyclic reactions is opposite. Photochemically initiated cyclization of the triene gives the *trans* isomer, whereas the *cis* isomer forms in the thermal cyclization.



Problem 25.1

Classify each of the following pericyclic reactions as an electrocyclic reaction, a cycloaddition, or a sigmatropic shift.



25.3 MOLECULAR ORBITALS IN PERICYCLIC REACTIONS

For a long time no general theory explained the three classes of pericyclic reactions. However, in 1965, R. B. Woodward and R. Hoffman showed that the course of a pericyclic reaction depends on the symmetry of the molecular orbitals of the reactants, and the changes required to generate the molecular orbitals of the product. The stereochemistry of pericyclic reactions requires the **conservation of orbital symmetry**.

In our discussions of pericyclic reactions, we will consider only simple polyene units and their molecular orbitals. Substituents bonded to the sp^2-hybridized carbon atoms may affect the energy of a molecular orbital slightly, but do not alter its symmetry. However, the locations of the substituents allow us to identify the changes in the molecular orbitals. The substituents move in a concerted way to generate a single stereoisomer as π molecular orbitals are transformed.

We can predict the outcome of pericyclic reactions by considering the symmetry of the molecular orbitals of the system. The Woodward–Hoffman method requires an analysis of the symmetry of all π molecular orbitals as they are transformed from those in the reactants to those in the products. We will use a similar, but simpler **frontier orbital method** developed by K. Fukui of Kyoto University. Fukui's method considers only the orbital symmetry of the highest occupied

molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). These are the "frontier orbitals," so-called because they lie on the energy boundary between bonding and antibonding orbitals.

The importance of the HOMO and LUMO in explaining pericyclic reactions is analogous to the way in which we explain the chemistry of the elements. The HOMO of a polyene resembles the outermost-shell electrons of an atom. Similarly, the electrons of the HOMO have the highest energy, and they can participate in chemical reactions with the lowest expenditure of energy. If more electrons are added to the HOMO of a π system, they go to the lowest unoccupied molecular orbital, the LUMO.

Symmetry-Allowed Reactions

The frontier molecular orbital approach considers only the symmetry of the HOMO and LUMO. A pericyclic reaction occurs *only* if the symmetry of the reactant molecular orbitals is the same as the symmetry of the product molecular orbitals. When this symmetry restriction is *allowed*, the lobes of molecular orbitals at atoms where bonding occurs have the same algebraic sign. The signs of the orbitals must be the same to allow constructive overlap for bonding overlap to occur in the transition state.

If the symmetries of the orbitals of the reactants and products match, a concerted **symmetry-allowed** reaction occurs. If the symmetries of the reactants and products do not match, the reaction is **symmetry forbidden** (or sometimes, "symmetry disallowed"). Symmetry-allowed reactions occur under reasonably mild conditions because the molecular orbitals can be smoothly transformed from reactant to product. Symmetry-forbidden reactions may actually occur, but they require much higher energies than symmetry-allowed reactions, and they occur by a different mechanism. They are not concerted, usually generate intermediates in multistep reactions, and are not stereospecific.

Brief Review of Molecular Orbitals

We introduced the molecular orbital theory of polyenes in Chapter 11. In this chapter, we will restrict our discussion to the symmetry of the molecular orbitals. The symmetric or antisymmetric character of a molecular orbital is described with respect to a vertical mirror plane through the center of the molecule and perpendicular to the plane of the molecule. If the signs of the lobes on the two sides of the mirror plane are the same, the molecular orbital is symmetric. If the signs are not the same, the orbital is antisymmetric. For example, π_1 of ethene, the bonding molecular orbital is symmetric; π_2, the antibonding molecular orbital is antisymmetric (Figure 25.1).

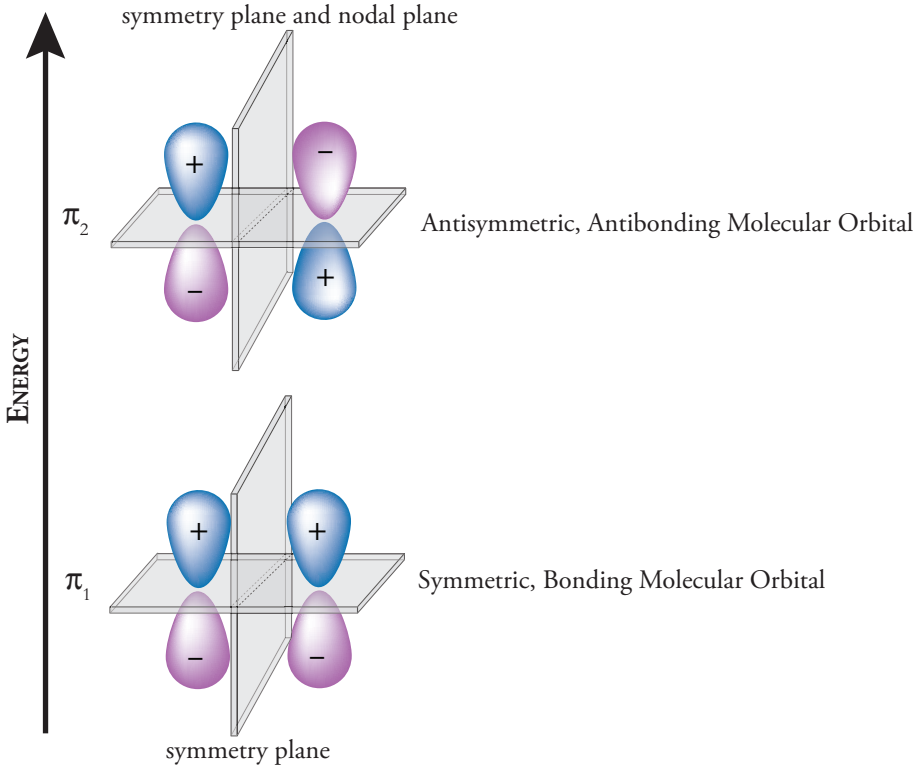


Figure 25.1 Symmetries of the π Molecular Orbitals of Ethene
The π_1 molecular orbital is symmetric with respect to a vertical plane that bisects the molecule. The π_2 molecular orbital is antisymmetric with respect to this vertical plane. This symmetry plane is therefore also a nodal plane.

Figure 25.2 shows the bonding and antibonding molecular orbitals of 1,3- butadiene. The molecular orbitals are also shown in an s-*cis* conformation rather than in the linear arrangement we used in Chapter 11 because the molecule must be in this conformation for electrocyclic reactions and cycloaddition reactions to occur.

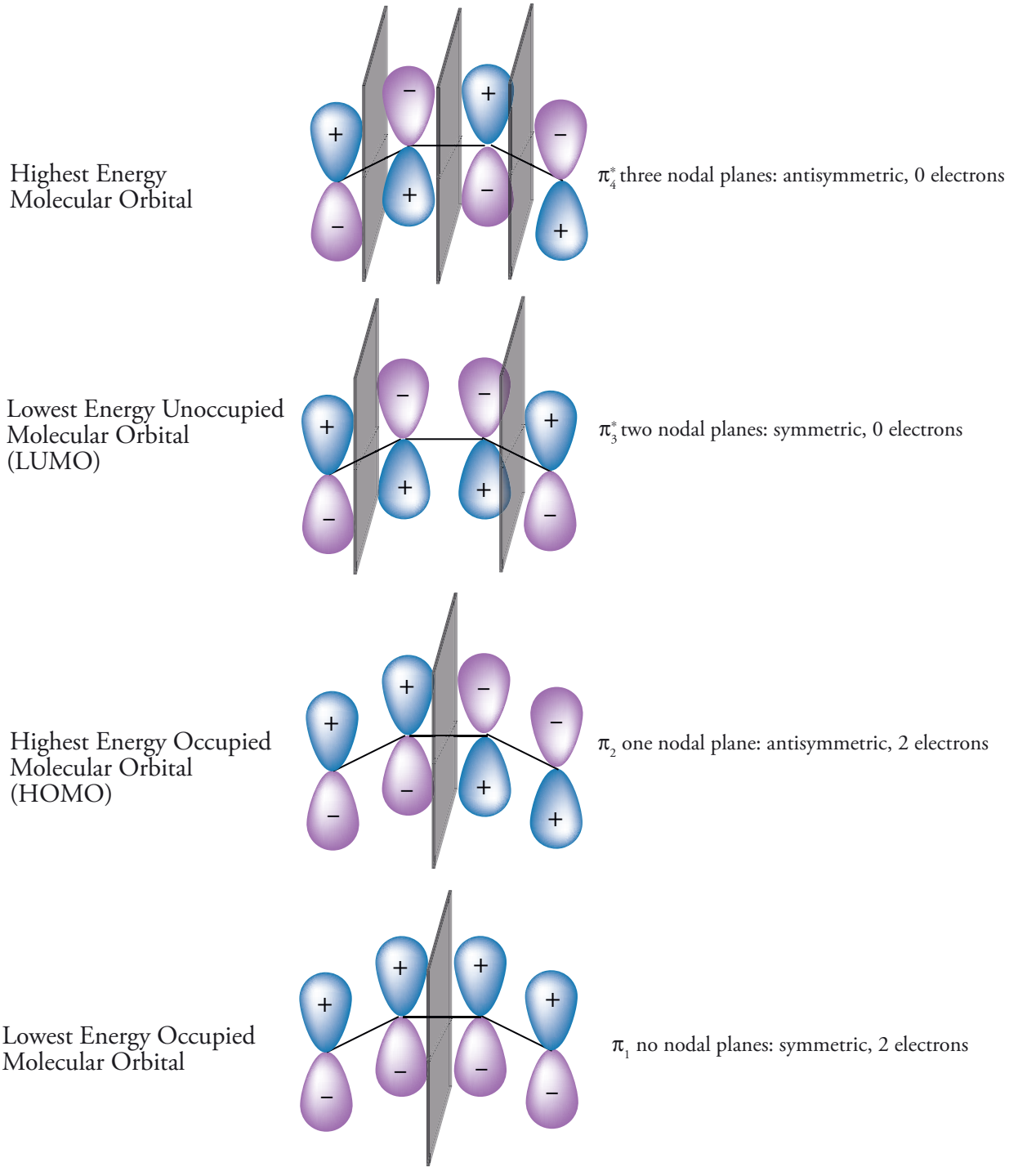


Figure 25.2 Molecular Orbitals of 1,3-Butadiene

The symmetry of the π molecular orbitals always changes in the following order: symmetric–antisymmetric–symmetric, etc. Thus, π_1 is symmetric, and π_2 is antisymmetric. The highest energy occupied molecular orbital (HOMO) of 1,3-butadiene is antisymmetric. The lowest energy unoccupied molecular orbital, LUMO, π_3, is symmetric.

Frontier molecular orbital theory considers only the signs of the wave functions at the terminal carbon atoms of the HOMO and LUMO. The HOMO of 1,3-butadiene is π_2. It is antisymmetric. As we noted earlier, this means that the signs of the wave functions of the contributing terminal 2p atomic orbitals are reversed on opposite sides of the reference vertical plane. In all cases, MOs are either symmetric or antisymmetric with respect to this plane. The LUMO of 1,3-butadiene is π_3. It is antisymmetric.

To explain the pericyclic reaction of 1,3,5-hexatriene by frontier molecular orbital theory, we need only consider the symmetry of π_3 and π_4. The HOMO is π_3; it is symmetric. The LUMO is π_4; it is antisymmetric. Note that this order of symmetry is opposite to that of 1,3-butadiene. The symmetry of the HOMO alternates with each additional double bond. The difference in the chemistry of polyenes noted earlier in this chapter for $4n$ π and $4n + 2$ π systems results from this difference in symmetry for the highest energy occupied molecular orbital involved in the reaction (Figure 25.3).

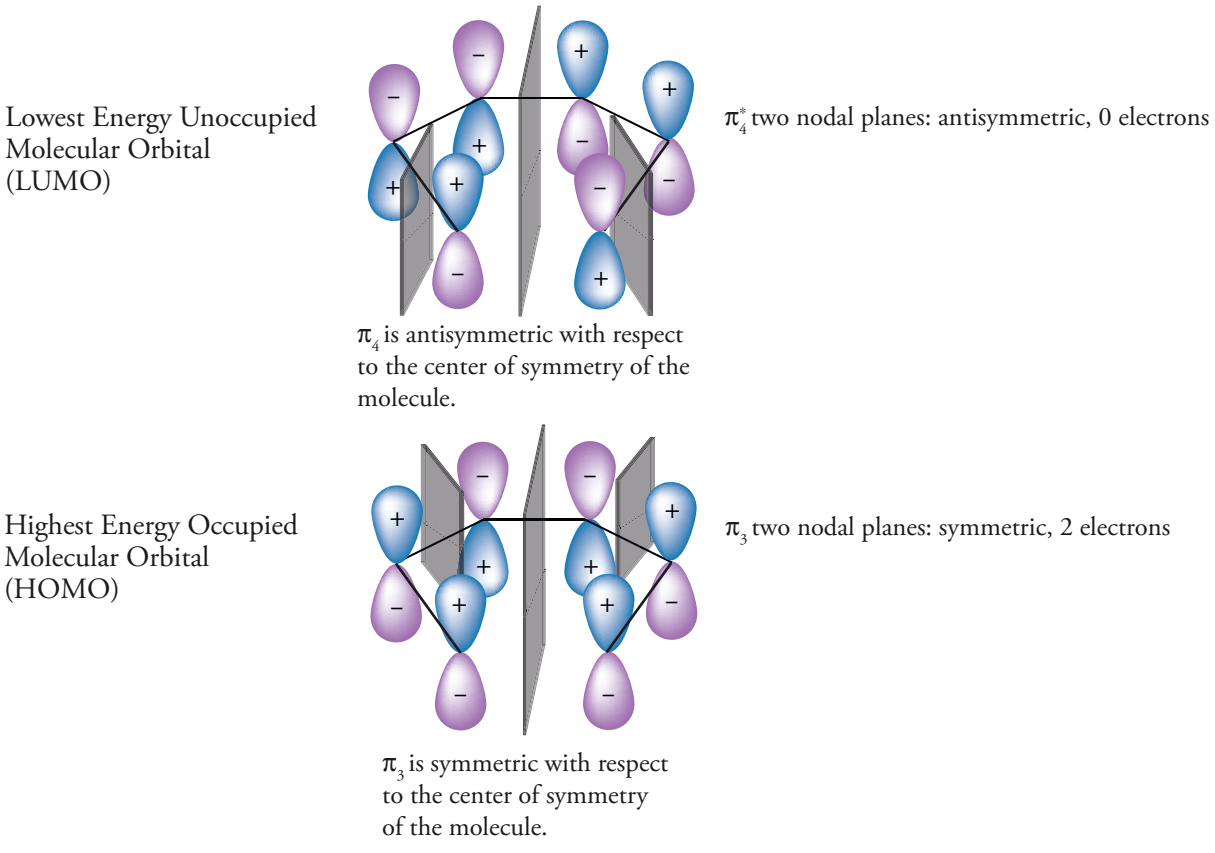


Figure 25.3 HOMO and LUMO for of 1,3,5-Hexatriene
The HOMO of 1,3-5-hexatriene, π_3, is antisymmetric with respect to the plane that passes through the center of symmetry. The HOMO has two nodal planes. The LUMO of 1,3-5-hexatriene, π_4, is antisymmetric with respect to this plane. The LUMO has three nodal planes.

25.4 ELECTROCYCLIC REACTIONS

In an electrocyclic reaction, a ring is closed and a σ bond forms by bonding the carbon atoms at each end of a conjugated π system. The 2p orbitals of the terminal carbon atoms of the π system of the HOMO must rotate in a concerted motion to overlap to form a σ bond. The rotation must occur so that a favorable bonding overlap occurs between lobes of like sign. If the terminal 2p orbitals have the positively signed lobes on the opposite "sides" of the molecule, the two orbitals must rotate in the same direction to form a σ bond. This situation occurs if π_3 of 1,3-butadiene is the frontier molecular orbital (Figure 25.4a). Both rotations shown are clockwise. If both rotated counterclockwise, a bonding interaction would also result. Because the two rotations are in the same direction, they are said to be **conrotatory**.

Now let's consider the motion required for bond formation if the terminal 2p orbitals have the positively signed lobes on the same "side" of the molecule. To form a bond, the two orbitals must rotate in opposite directions. That is, one moves in a clockwise direction and the other in a counterclockwise direction. This situation occurs if π_3 of 1,3-butadiene is the frontier molecular orbital involved in a reaction (Figure 25.4b). The combination of clockwise and counterclockwise motions of two orbitals is called **disrotatory**. As in the case of conrotatory motion, there are two possible disrotatory motions. The difference between these two processes can only be seen when substituents are bonded to the polyene system.

Now let's compare the motions required for the HOMO and LUMO of 1,3,5- hexatriene with the corresponding molecular orbitals of 1,3-butadiene. The HOMO of 1,3,5-hexatriene is symmetric, and therefore a disrotatory motion is required to form a σ bond (Figure 25.5a). This result is the opposite of that for 1,3-butadiene. The LUMO of 1,3,5-hexatriene is antisymmetric. Therefore, a conrotatory motion is required to form a σ bond (Figure 25.5b). This result is again the opposite of that observed for 1,3-butadiene.

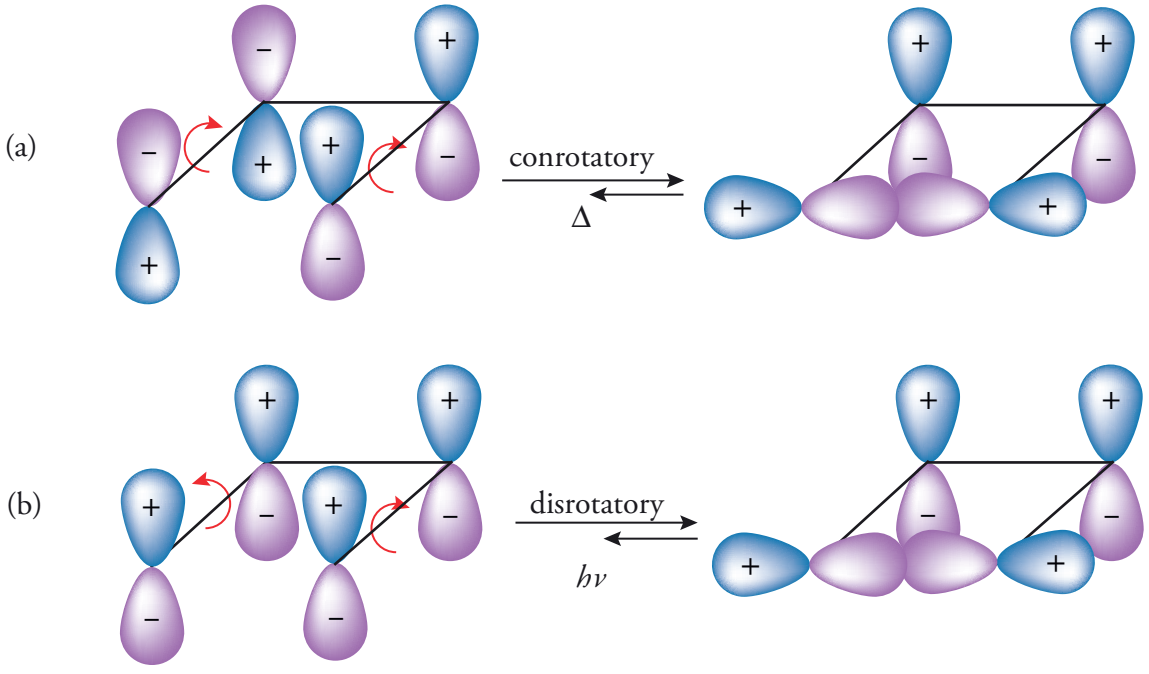


Figure 25.4 Conrotatory and Disrotatory Motion for a Diene

(a) A conrotatory motion is required for an electrocyclic reaction involving an antisymmetric orbital. The directions of rotation viewed along the C-1 to C-2 bond and along the C-4 to C-3 are both clockwise.

(b) A disrotatory motion is required for an electrocyclic reaction involving a symmetric orbital. The directions of rotation viewed along the C-1 to C-2 bond and along the C-4 to C-3 are in opposite directions, one is clockwise and the other is counterclockwise.

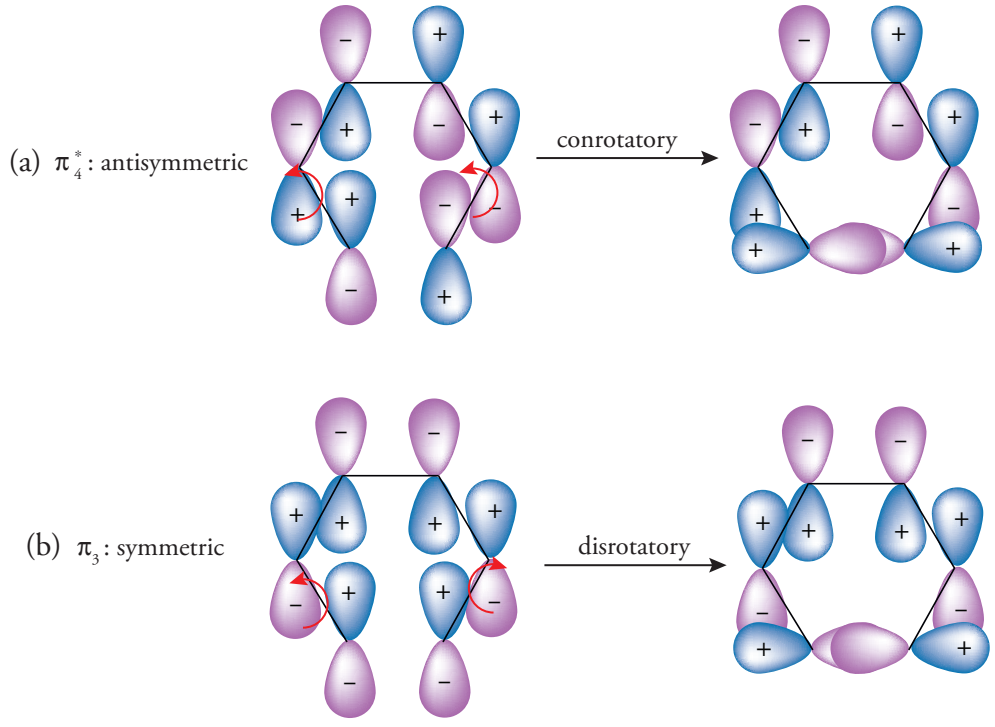


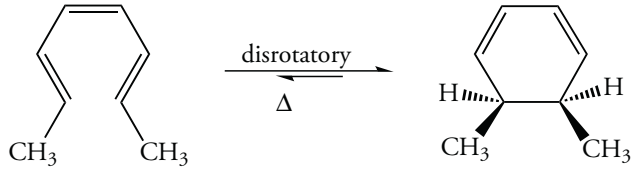
Figure 25.5 Conrotatory and Disrotatory Motion for a Triene
(a) A conrotatory motion is required for an electrocyclic reaction involving an antisymmetric orbital. The directions of rotation viewed along the C-1 to C-2 bond and along the C-4 to C-3 are both clockwise.
(b) A disrotatory motion is required for an electrocyclic reaction involving a symmetric orbital. The directions of rotation viewed along the C-1 to C-2 bond and along the C-4 to C-3 are in opposite directions.

Analysis of 1,3,5-hexatriene (a $4n + 2$ π system) and of 1,3-butadiene (a $4n$ π system) allows us to conclude that the difference in the stereochemistry of the product as a result of conrotatory or disrotatory motion depends on the number of electrons in the π system. The motion of the orbitals that occur in symmetry-allowed reactions of $4n$ π systems is the opposite of that of $4n + 2$ π systems.

Thermal Cyclization of $4n + 2$ π Systems

The type of motion the orbital of the terminal carbon undergoes in an electrocyclic reaction can be detected only if substituents are bonded to these atoms. Substituents move as orbitals move. The thermal cyclization of (2*E*,4*Z*,6*E*)-octatriene provides an example of this effect. We consider π_3 because it is the HOMO. It contains the highest energy electrons, so it is the frontier molecular orbital. As outlined above, disrotatory motion is required for a σ bond to form at the ends of a conjugated triene. Disrotatory motion of the terminal 2p orbitals causes simultaneous disrotatory motion of the C-1 and C-8 methyl groups and yields *cis*-5,6-dimethy1-1,3-cyclohexadiene (Figure 25.6a).

In this process, the hybridizations of the original C-2 and C-7 carbon atoms change, and the positions of the single and double bonds are interchanged.



(2*E*,4*Z*,6*E*)-octatrienet *cis*-5,6-dimethyl-1,3-cyclohexadiene

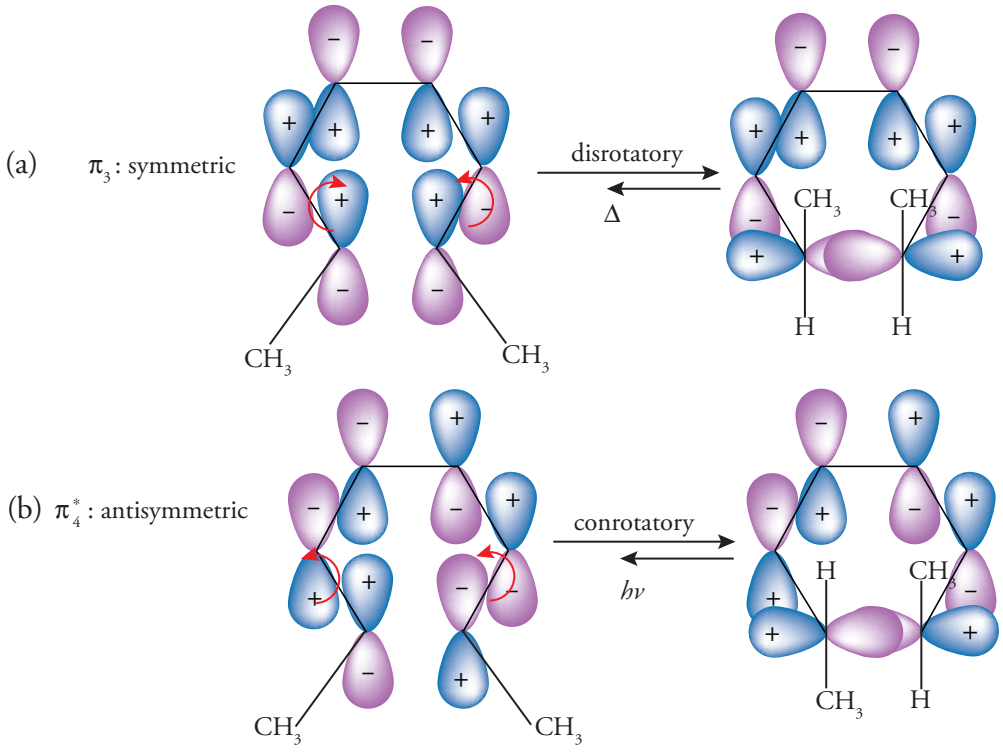
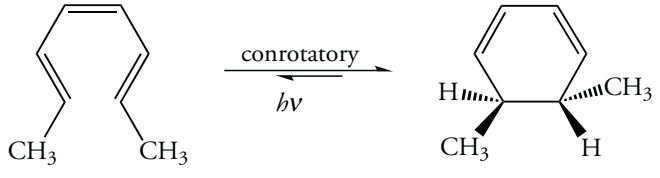


Figure 25.6 Electrocyclic Reactions of Trienes
(a) The frontier molecular orbital for the thermal reaction is π_3, which is symmetric. A disrotatory motion is required for a symmetry-allowed reaction.
(b) The frontier molecular orbital for the photochemical reaction is π_4, which is antisymmetric. A conrotatory motion is required for a symmetry-allowed reaction.

Photochemical Cyclization of $4n + 2$ π Systems

The product of the photochemical cyclization of a polyene has a different stereochemistry from the product of the thermal cyclization process. This difference results from the motion of the terminal 2p orbitals of a different frontier molecular orbital. Ultraviolet radiation promotes an electron from the HOMO to the LUMO of the molecule. The LUMO of a 1,3,5-hexatriene is π_4; it is antisymmetric. Because the signs of the terminal 2p orbitals on the same side of the molecule are opposite, the required motion of a bond formation is conrotatory. Let's compare the result of this motion for (2*E*,4*Z*,6*E*)-octatriene with the thermal reaction. Conrotatory motion of the orbitals causes simultaneous conrotatory motion of the C-1 and C-8 methyl groups and yields *trans*-5,6-dimethy1-1,3-cyclohexadiene (Figure 25.6b).

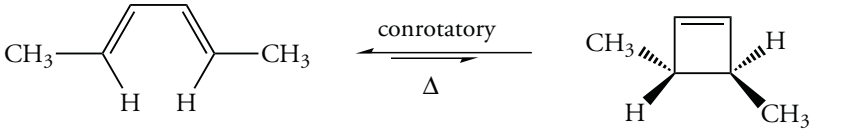


(2*E*,4*Z*,6*E*)-octatriene *trans*-5,6-dimethyl-1,3-cyclohexadiene

Thermal Cyclization of 4*n* π Systems

We will examine the thermal cyclization of 1,3-butadiene as an example of a 4*n* π system. We account for this cyclization using the HOMO, π_2. This molecular orbital is antisymmetric. Because the signs of the contributing terminal 2p carbon orbitals on one side of the molecule are opposite, formation of a bond between atoms 1 and 4 of the π system requires a conrotatory motion. Let's examine the result of this motion for (2*E*,4*E*)-hexadiene. Conrotatory motion of the orbitals causes simultaneous conrotatory motion of the C-1 and C-6 methyl groups to yield *trans*-3,4-dimethylcyclobutene (Figure 25.7a).

The cyclization of (2*E*,4*E*)-hexadiene has a very small equilibrium constant because *trans*-3,4-dimethylcyclobutene is the thermodynamically unstable isomer. Therefore, the reverse ring-opening reaction of a cyclobutene to a 1,3-butadiene is favored and is the observed reaction. The symmetry rules must apply in both directions based on the principle of microscopic reversibility, which states that *the mechanism for a forward and reverse reaction must be the same*. Thus, since the ring-closing reaction is a conrotatory process, ring opening must also occur in a conrotatory manner.



(2*E*,4*E*)-hexadiene *trans*-3,4-dimethylcyclobutene

The frontier molecular orbitals control the motions of the atoms in an electrocyclic reaction independent of the equilibrium constant for the reaction. The position of an equilibrium is controlled by $\Delta G^\circ_{\text{reaction}}$. Both a conjugated diene and a triene can undergo thermal electrocyclic reactions. In both cases, the cyclic compounds have more σ bonds and fewer π bonds. However, $\Delta G^\circ_{\text{reaction}}$ is favorable only for the triene. The strain of the four-membered ring of the diene effectively reverses the relative stability of the reactants and products in the cyclization of the diene.

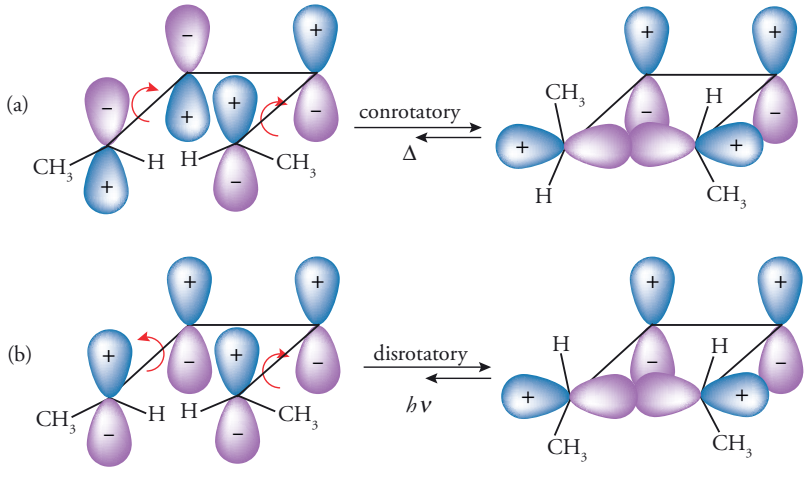
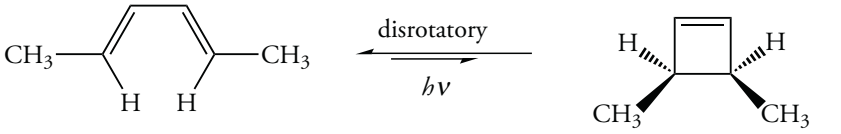


Figure 25.7 Electrocyclic Reactions of Dienes
(a) The frontier molecular orbital for the thermal reaction is π_3, which is antisymmetric. A conrotatory motion is required for a symmetry-allowed reaction.
(b) The frontier molecular orbital for the photochemical reaction is π_2, which is symmetric. A disrotatory motion is required for a symmetry-allowed reaction.

Photochemical Cyclization of $4n$ π Systems

As noted above, the product of the photochemical cyclization of polyenes with $4n + 2$ π electrons has a different stereochemistry from the product of the thermal cyclization process. The same reversal of stereochemistry is observed for $4n$ π electron systems. Ultraviolet radiation of a 1,3-butadiene system results in promotion of an electron from π_2, the HOMO, to π_3, the LUMO. In 1,3-butadiene, π_3 is symmetric. Because the signs of the terminal 2p orbitals on the same side of molecule are the same, the required motion to form a σ bond is disrotatory. For example, the photochemical cyclization of (2*E*,4*E*)-hexadiene occurs by a disrotatory motion of the C-1 and C-6 methyl groups and yields *cis*-3,4-dimethylbutene (Figure 25.7b).

This reaction converts the thermodynamically stable diene into the less stable cyclic cyclobutene product. This is a common result for photochemical reactions. However, no thermodynamic principles are violated. The reverse thermal reaction does not occur because at the low temperature used for the photochemical reaction, such thermal processes are very slow. Only the diene absorbs the ultraviolet radiation because λ_{max} of the cyclobutene is out of the range of the light source used. Thus, the energy of the light used to promote an electron from a HOMO to a LUMO drives the reaction "uphill" to yield the thermodynamically less stable isomer. The cyclobutene cannot absorb light. After it forms, cyclobutene is "trapped," and it cannot revert to the diene. In other words, equilibrium cannot be achieved under the photochemical reaction conditions.



(2*E*,4*E*)-hexadiene *cis*-3,4-dimethylcyclobutene

Summary of Electrocyclic Reactions

Two simple rules allows us to predict the stereochemical result of electrocyclic reactions.

1. Thermal reactions of $4n$ and $4n + 2$ π systems occur via the HOMO. The HOMO for $4n$ π systems is antisymmetric, and the HOMO for $4n + 2$ π systems is symmetric.
2. Photochemical reactions of both $4n$ and $4n + 2$ π systems occur via the LUMO. In $4n$ π systems, the LUMO is symmetric. In $4n + 2$ π systems it is antisymmetric.

From these generalizations, we can predict the outcome of any symmetry-allowed electrocyclic reaction. Table 25.1 lists the selection rules that correlate the number of π electrons, the type of reaction, and the allowed stereochemistry.

Table 25.1
Selection Rules for Electrocyclic Reactions

Number of π Electrons	*Type of Reaction*	*Stereochemistry*
$4n$	Thermal	Conrotatory
$4n$	Photochemical	Disrotatory
$4n + 2$	Thermal	Disrotatory
$4n + 2$	Photochemical	Conrotatory

Problem 25.2

Assume that a thermal cyclization occurs in a tetraene to give a cyclic triene. What is the frontier molecular orbital, and what is its symmetry? What type of orbital motion leads to cyclization?

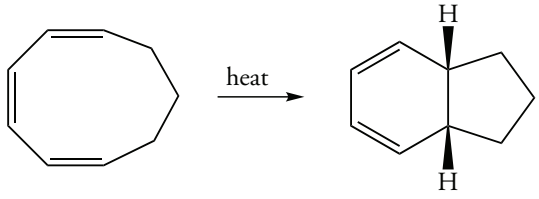
Sample Solution

The highest occupied molecular orbital of a tetraene is π_4 because the eight electrons are distributed starting at π_1, and two electrons are added to each molecular orbital until π_4 is filled. The symmetry of molecular orbitals in an array of molecular orbitals alternates between adjacent orbitals. The π_1 molecular orbital of any linear polyene is symmetric. Thus, π_4 is antisymmetric.

The terminal 2p orbitals of an antisymmetric molecular orbital have the positively signed lobes on the opposite sides of the molecule. Thus, the orbitals must rotate in the same direction to form a σ bond. The rotation is conrotatory.

Problem 25.3
Draw the product of the photochemical cyclization of 1,3-cycloheptadiene.

Problem 25.4
Is the following thermal cyclization reaction of 1,3,5-cyclononatriene symmetry allowed or forbidden?



1,3,5-cyclononatriene

25.5 CYCLOADDITION REACTIONS

In a cycloaddition reaction, the 2p orbitals of the terminal atoms of one π system overlap with the 2p orbitals of the terminal atoms of a second π system. This orbital overlap can occur only if the orbitals have the proper symmetry. The signs of each individual set of 2p orbitals that overlap to form a σ bond must be the same.

Cycloaddition reactions are classified with respect to the two planes of the reacting molecules and the stereochemistry of their interaction. Two π systems can interact in two ways. In **suprafacial** cycloaddition reactions, an overlap occurs between the terminal atoms of one π system and the terminal atoms of the other π system on the same face. Such an arrangement is shown for a [4 + 2] cycloaddition reaction in Figure 25.8.

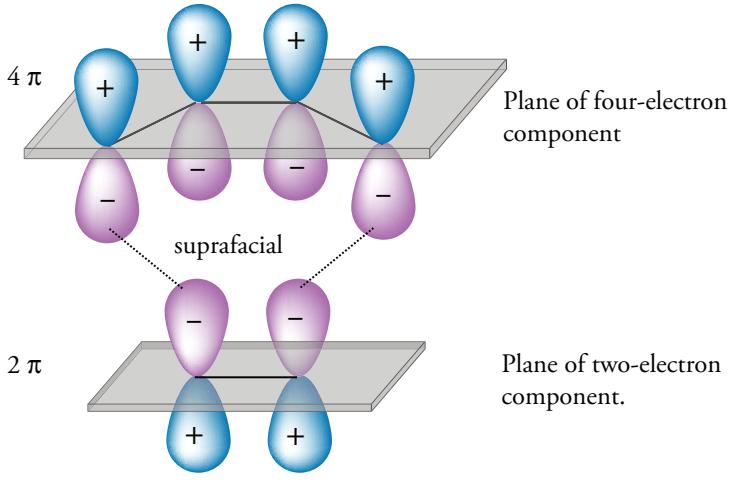


Figure 25.8 Suprafacial Addition of a 4*n* + 2 π System
A bonding interaction is required between the terminal orbitals of both π systems. If the bonding occurs across the same face, the addition is suprafacial.

If one of the interacting molecular orbitals for a cycloaddition reaction is symmetric, then the other must also be symmetric for a suprafacial process. If one of the interacting molecular orbitals is antisymmetric, then the other must also be antisymmetric.

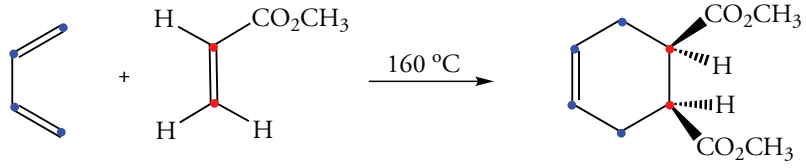
If a cycloaddition reactions results in bridging between *opposite* faces of the two π systems, the process is **antarafacial**. Antarafacial addition is symmetry allowed if one molecular orbital is symmetric and the other is antisymmetric. However, this type of cycloaddition has geometric constraints. A bridge that contains many atoms is required to permit simultaneous bonding to the opposite sides of a π system. So, antarafacial additions are rare.

The two modes of addition and the associated stereochemistry resemble other addition reactions we studied earlier. The suprafacial addition is a concerted *syn* addition to one of the π systems. The antarafacial addition corresponds to a concerted *anti* addition. Although *anti* addition reactions are common in the chemistry of alkenes, the two groups that add to the alkene are not bonded to each other in the transition state. In cycloaddition reactions, both atoms of the molecule that bond to the terminal atoms of the second molecule are also connected to each other. Thus, only if the number of atoms in each of the two molecules is quite large can one molecule add to the other in an antarafacial process.

Stereochemistry of Cycloaddition Reactions

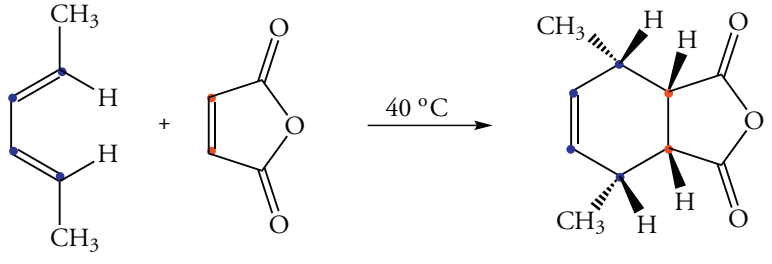
The Diels–Alder reaction has been studied for many years. The simplest Diels–Alder reaction converts 1,3-butadiene and ethylene into cyclohexene. However, the reaction occurs readily only at temperatures above 200 °C, and it has a low yield. Substituted dienes and dienophiles react at much lower temperatures with better yields. The best combination of reactants is a diene substituted with electron-donating groups and a dienophile substituted with electron-withdrawing groups.

Diels–Alder reactions occur with retention of stereochemistry in each component. For example, when dimethyl maleate reacts with 1,3-butadiene, the *cis* arrangement of the carbomethoxy groups of the reactant remains in the product.



1,3-butadiene dimethyl maleate

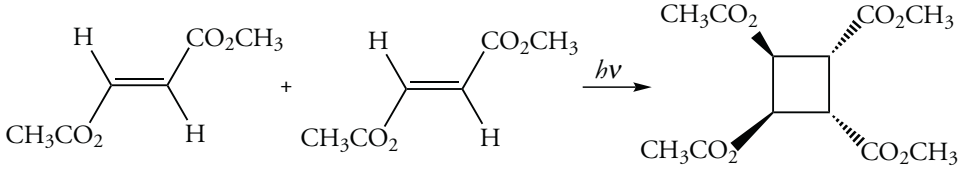
Retention of stereochemistry also occurs for the diene. For example, (2*E*,4*E*)-hexadiene reacts with maleic anhydride to give a product with *cis* methyl groups. Many examples of this type lead to the conclusion that the Diels–Alder and other [4 + 2] cycloaddition reactions occur suprafacially on each component.



(2*E*,4*E*)-hexadiene maleic anhydride

Thermal [2 + 2] cycloaddition reactions, which are rare, do not occur by a concerted mechanism. These reactions occur by a stepwise, radical mechanism. As a consequence, the reactions are not stereospecific. Because these reactions are not concerted, the rules of orbital symmetry do not apply.

Photochemical [2 + 2] cycloaddition reactions do occur. The process is useful as a method to produce cyclobutanes. An important biochemical reaction that cross-links bases on the same strand of DNA by formation of thymine dimers also occurs by a photochemical [2 + 2] cycloaddition. We will consider this reaction at the end of this section. From stereochemical studies, we conclude that the reaction occurs suprafacially.



Molecular Orbitals in Cycloaddition Reactions

To explain the stereochemistry of cycloaddition reactions using molecular orbitals, we must first determine which molecular orbitals in each reactant are involved in the transition state. The reaction can be thought of as a Lewis acid–Lewis base process in which one reactant donates an electron pair to the second reactant. We will arbitrarily assign the role of electron pair donor to one of the two reactants. This reactant provides electrons from the HOMO. The second reactant is the electron pair acceptor. It uses its LUMO in the reaction. The assignment of roles of electron donor and electron acceptor is arbitrary because the same stereochemical result is predicted if the roles are reversed. We recall that the symmetry of adjacent molecular orbitals in an array of molecular orbitals alternates. Thus, the reversal of HOMO and LUMO in one reactant results in a change of symmetry. However,

the reversal of the LUMO and HOMO of the second reactant also leads to a change of symmetry, so there is no net change.

For the Diels–Alder reaction, we will select the HOMO of the diene and the LUMO of the alkene. Therefore, π_2 in the diene supplies the electrons. To accommodate the electron pair, the alkene uses π_2. Both orbitals are antisymmetric, and the bonding of the terminal lobes occurs if the two molecules are arranged with suprafacial geometry (Figure 25.9). Note that we have to consider the signs of the wave functions only at the terminal lobes.

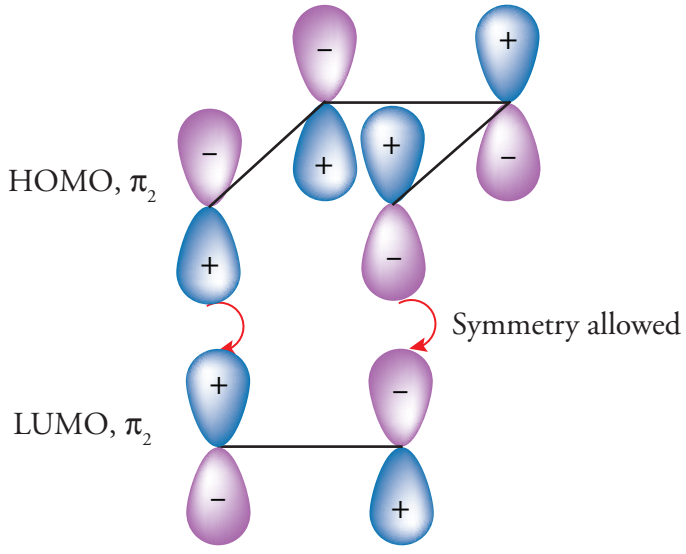


Figure 25.9 Molecular Orbitals for the Diels–Alder Reaction
The HOMO of the diene, π_2, which is antisymmetric, interacts with the LUMO of the dienophile, π_2, which is also antisymmetric. The process is suprafacial.

Now let's consider the possibility of a thermal [2 + 2] cycloaddition of two alkenes. The HOMO of one alkene is symmetric, and the LUMO of the other alkene is antisymmetric (Figure 25.10). Constructive overlap of one set of 2p orbitals is shown in a suprafacial arrangement. The overlap of the second set of 2p orbitals would be destructive. To achieve a constructive overlap of these 2p orbitals, an antarafacial arrangement would be required. However, geometric constraints prevent an antarafacial addition.

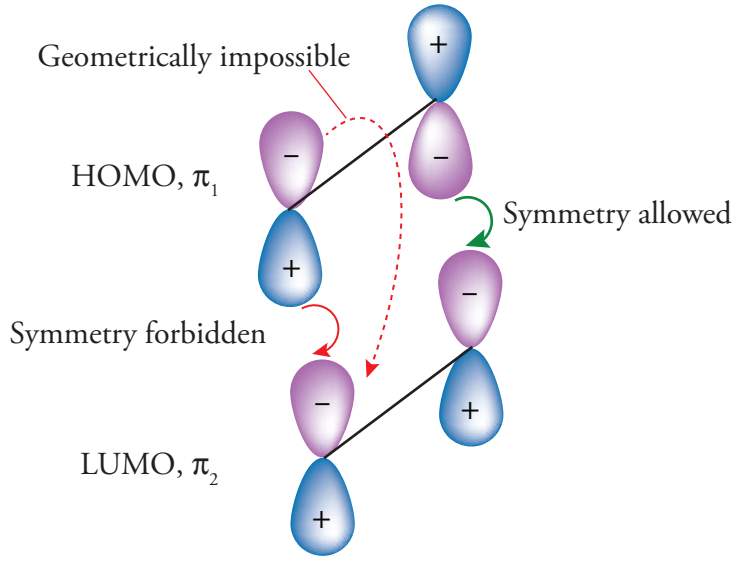
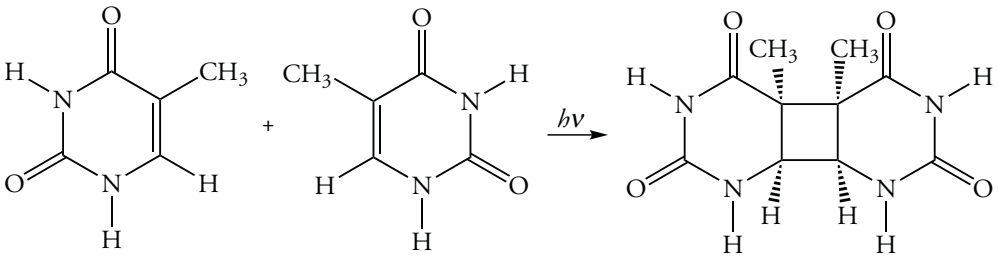


Figure 25.10 Symmetry-Forbidden Thermal (2 + 2) Addition Reaction
The HOMO of one alkene cannot interact with the LUMO of another alkene in a thermal reaction. Bonding is possible only at one set of carbon atoms for a suprafacial addition. An antarafacial addition of the positively signed lobes of the carbon atoms on the left of each alkene is geometrically impossible.

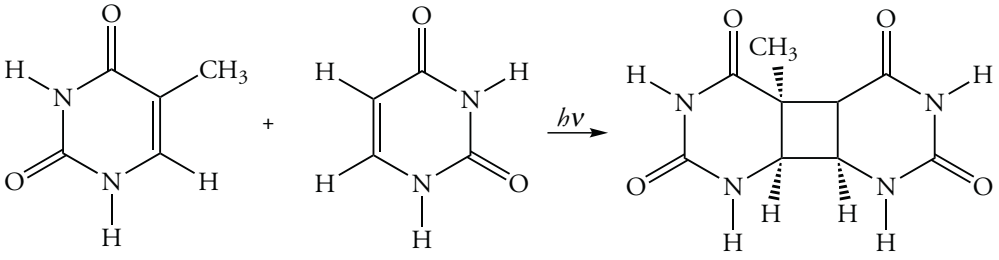
Formation of Thymine Dimers: A [2 + 2] Photochemical Cycloaddition Reaction

Ultraviolet light, which is necessary in small doses for the activation of vitamin D (Section 25.6), is devastating in high doses because it causes a [2 + 2] photocycloaddition reaction to occur in DNA between two stacked thymine bases, or between thymine and cytosine. The result is a cyclobutane ring between the two bases. If this dimer forms in a gene that controls cell growth such as Src protein kinase or the tumor suppressor p53, the mutation can result in cancer. This mutation occurs at a rate of 50–100 dimers per second, so it is by no means rare. And that is why people who are out in the sun should always use sunscreen.



thymine

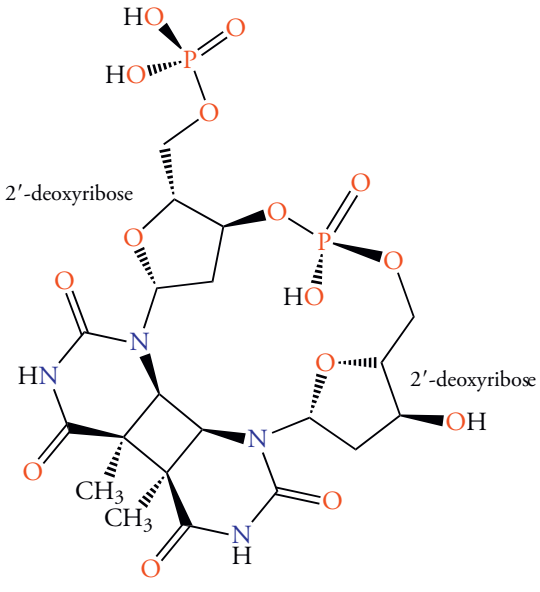
thymine dimer



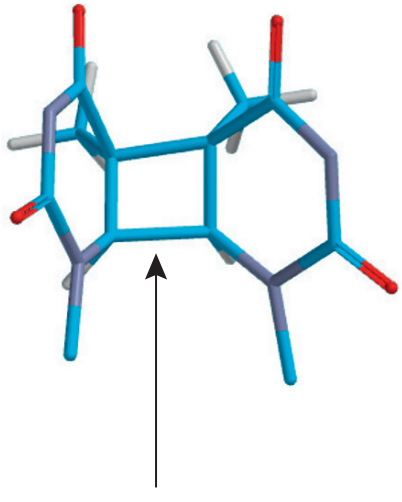
thymine

cytosine

thymine–cytosine dimer



Thymine dimer



Cyclobutane ring in thymine dimer

Table 25.2 summarizes the stereochemistry of cycloaddition reactions based on orbital symmetry rules. Again we note that geometric constraints prevent antarafacial reactions even though the reacting molecular orbitals have the proper symmetry relationship. Inadequate chain length as well as severe twisting of the molecules may make the transition state energy so high that no reaction occurs.

Table 25.2
Selection Rules for Cycloaddition Reactions

Number of π Electrons	*Type of Reaction*	*Stereochemistry*
$4n$	Thermal	Antarafacial
$4n$	Photochemical	Suprafacial
$4n + 2$	Thermal	Suprafacial
$4n + 2$	Photochemical	Antarafacial

Problem 25.5

What type of reaction would be required for two molecules of 1,3-butadiene to undergo a thermal [4 + 4] cycloaddition to yield 1,5-cyclooctadiene?

Sample Solution

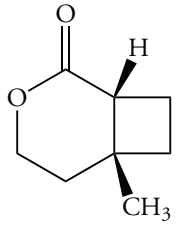
The HOMO of the diene that "donates" electrons in a cycloaddition reaction is π_2, which is antisymmetric. The LUMO of the diene that "accepts" electrons in a cycloaddition reaction is π_3, which is symmetric. In a suprafacial arrangement, the overlap of one set of orbitals at terminal atoms can be constructive. However, overlap of the second set of orbitals would be destructive, and suprafacial addition is forbidden. Only the alternate antarafacial addition could provide constructive overlap of orbitals at both ends of the two π systems.

Problem 25.6

Two molecules of 1,3-butadiene react in a thermal [4 + 2] cycloaddition reaction. Draw the structure of the product.

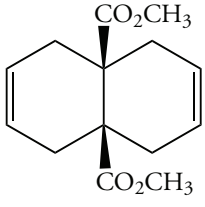
Problem 25.7

What type of reaction and reactants are required to synthesize the following compound using a cycloaddition reaction?



Problem 25.8

What type of reaction and reactants are required to synthesize the following compound using a cycloaddition reaction?



25. 6 SIGMATROPIC REARRANGEMENTS

The migration of a group from one site of a π system is called a sigmatropic rearrangement. This migration can occur in two ways.

1. Migration across the same face is a suprafacial rearrangement.
2. Migration from one face to the other face is an antarafacial rearrangement.

Therefore, sigmatropic rearrangements are controlled by the same orbital symmetry considerations as cycloaddition reactions. Table 25.3 lists the rules for thermal and photochemical sigmatropic rearrangements.

Table 25.3
Selection Rules for Sigmatropic Rearrangements

Number of π Electrons	*Type of Reaction*	*Stereochemistry*
$4n$	Thermal	Antarafacial
$4n$	Photochemical	Suprafacial
$4n + 2$	Thermal	Suprafacial
$4n + 2$	Photochemical	Antarafacial

Molecular Orbitals in Sigmatropic Rearrangements

To analyze sigmatropic rearrangements, it is convenient to consider a homolytic cleavage of the σ bond the migrating groups. Two radical fragments result from homolytic cleavage, and we can then examine the symmetry of their individual molecular orbitals. The reaction does *not* occur by this mechanism, but the stereochemical consequences are the same if the "radicals" are not allowed to move out of contact with each other. Because we will consider the allyl system to explain [3,3] sigmatropic rearrangements and the pentadienyl system to explain [1,5] sigmatropic rearrangements, we will first examine the molecular orbitals for these two systems.

We discussed the molecular orbitals for allyl radicals and their orbital symmetry in Chapter 11. Figure 25.11 shows the three π orbitals of the allyl system. The lowest energy MO is bonding over all three atoms and is symmetric. The MO-labeled π_3 is antibonding, has two nodes, and is symmetric. The MO-labeled π_2 is nonbonding. Because there are three atoms, the single nodal plane of this MO must contain the center carbon atom. This MO, which is antisymmetric, is the one that participates in [3,3] sigmatropic rearrangements.

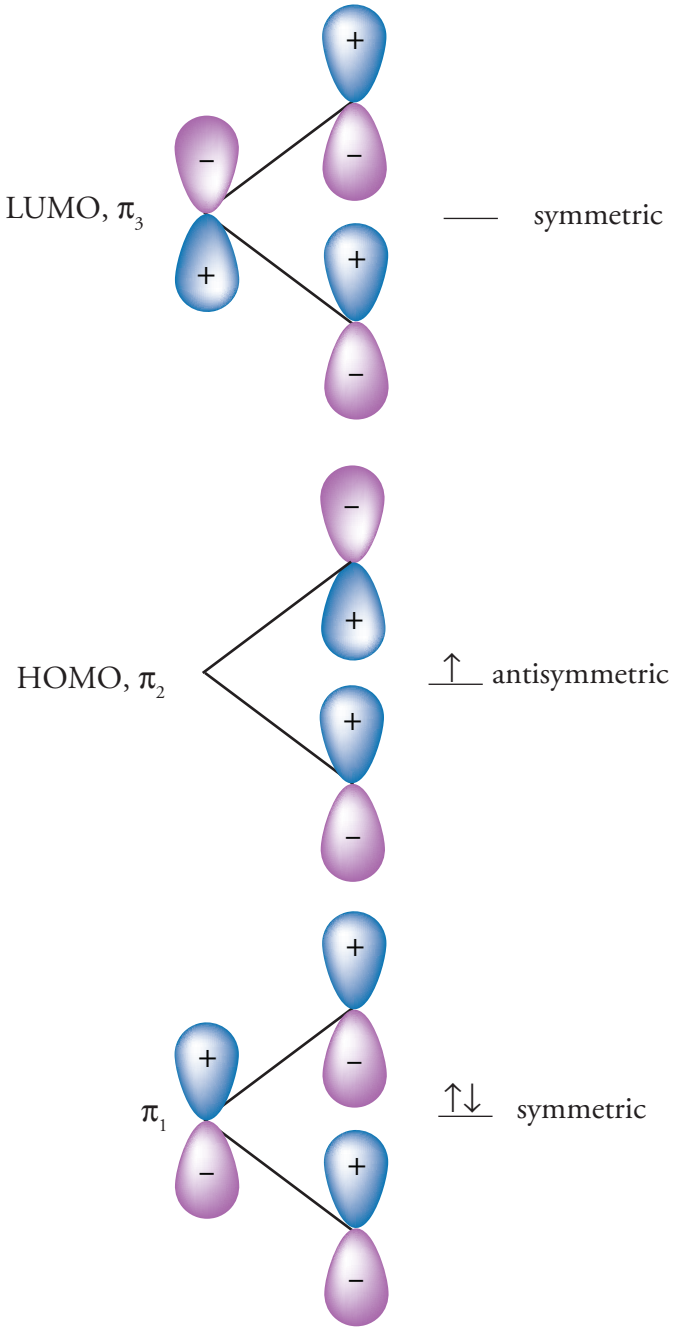
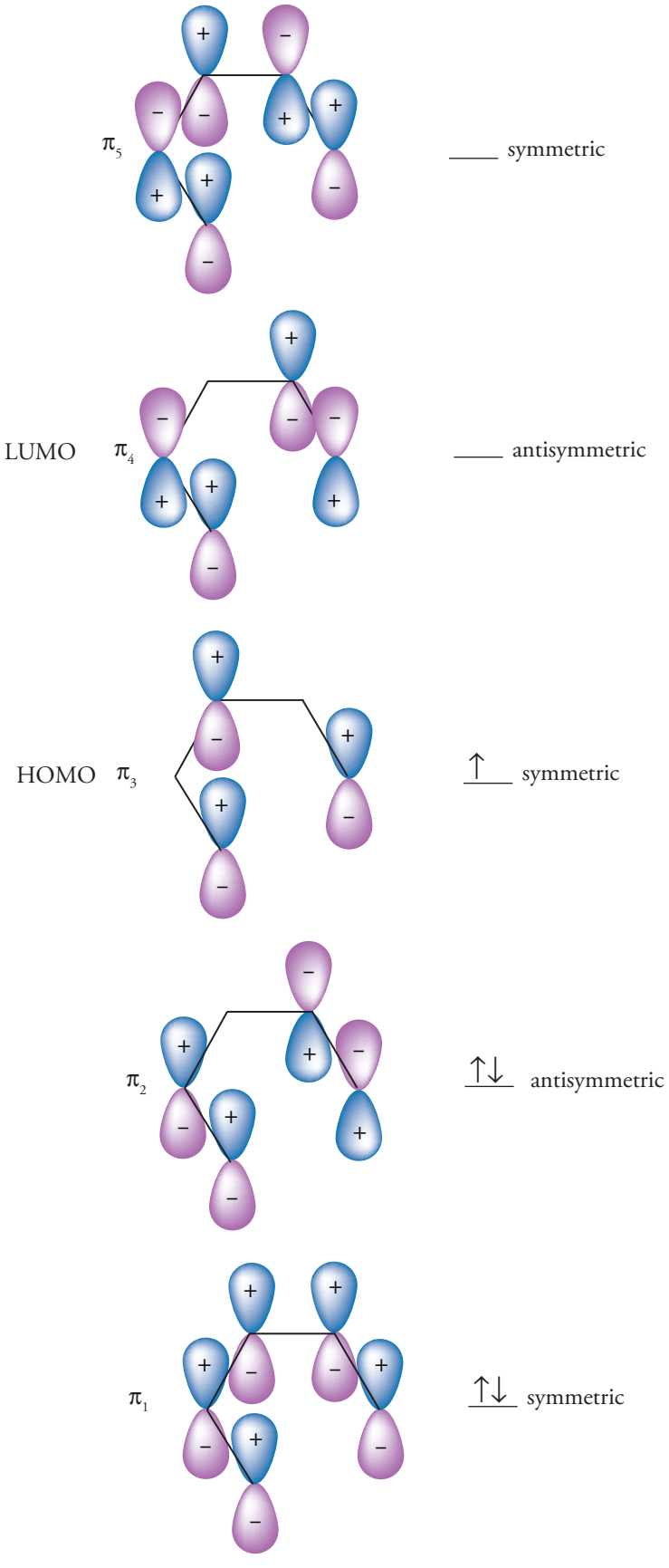


Figure 25.11 Molecular Orbitals of an Allyl Radical
The HOMO of the allyl radical is π_2. If we view the allyl radical as perpendicular to the plane of the page and bisected at C-2 by the page, we see that the HOMO is antisymmetric.

Figure 25.12 shows the five π orbitals of the pentadienyl system. The lowest energy MO is bonding over all five atoms and is symmetric. The symmetry of each succeeding MO of higher energy alternates. The MO required to explain [1,5] sigmatropic rearrangements is π_3. It is symmetric.

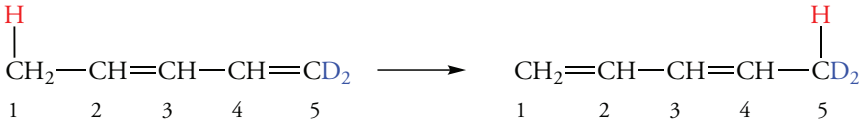
Figure 25.12 Molecular Orbitals of a Pentadienyl Radical

There are five π molecular orbitals for a pentadienyl radical. The HOMO is π_3. It is symmetric with respect to a plane perpendicular to the plane of the radical and bisecting C-3.

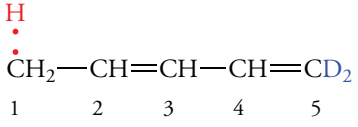


[1,5] Sigmatropic Rearrangements

The migration of a hydrogen atom over a pentadienyl system is the most common example of a [1,5] sigmatropic rearrangement.



If we *imagine* a homolytic cleavage of a C—H bond, the result is a hydrogen atom and a pentadienyl radical.



The pentadienyl radical has five π electrons that must be accommodated in the lowest energy molecular orbitals. Two electrons are located in the π_1 and π_2 molecular orbitals. The fifth electron is located in π_3, which is thus the HOMO. This molecular orbital is involved in the transfer of the migrating hydrogen atom. Because π_3 is symmetric, the terminal 2p orbitals have the same signs of the wave function on one side of the plane. As a result, the hydrogen atom moves across the surface of this orbital between C-1 and C-5 in a suprafacial process (Figure 25.13).

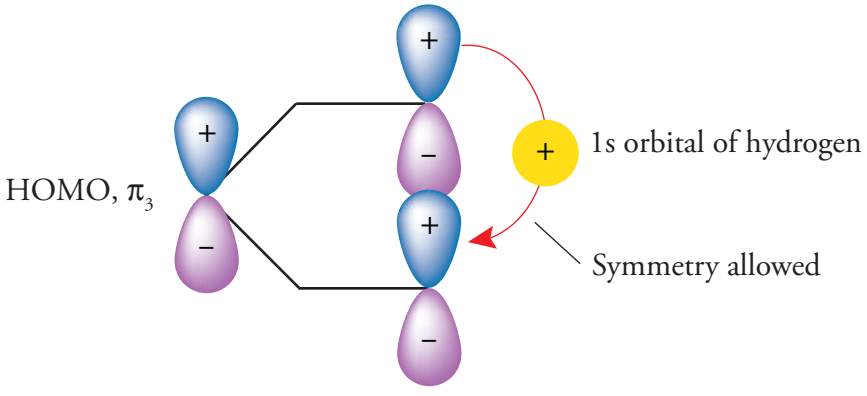
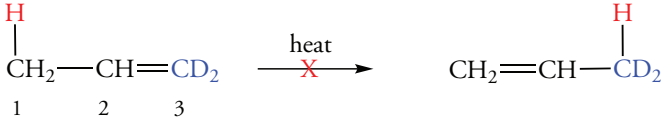
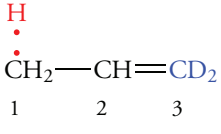


Figure 25.13 Molecular Orbitals and a [1,5] Sigmatropic Rearrangement
The HOMO of a pentadienyl radical, which is π_3, is symmetric. A [1,5] sigmatropic rearrangement can occur in a suprafacial process.

Sigmatropic rearrangements of a [1,3] type do not occur thermally. When we examine the molecular orbitals that would have to be involved in such a process, we can see why the model predicts that the reaction should not occur.



To visualize the reaction, we consider the homolytic cleavage of the C—H bond of the allyl system. Although the reaction does not occur this way, the orbitals involved in the concerted reactions have the same symmetry as those in the separate radical fragments. Thus, we consider the allyl radical and a hydrogen atom.



Two π electrons occupy π_1 and one occupies the π_2 molecular orbital. Thus, the HOMO is π_2, which is antisymmetric. Migration of a hydrogen atom suprafacially is geometrically possible, but it is *not* allowed by orbital symmetry. The hydrogen atom cannot leave C-1 and bond to C-3 because the symmetries of the orbitals are different (Figure 25.14).

Two π electrons occupy π_1 and one occupies the π_2 molecular orbital. Thus, the HOMO is π_2, which is antisymmetric. Migration of a hydrogen atom suprafacially is geometrically possible, but it is *not* allowed by orbital symmetry. The hydrogen atom cannot leave C-1 and bond to C-3 because the symmetries of the orbitals are different (Figure 25.14).

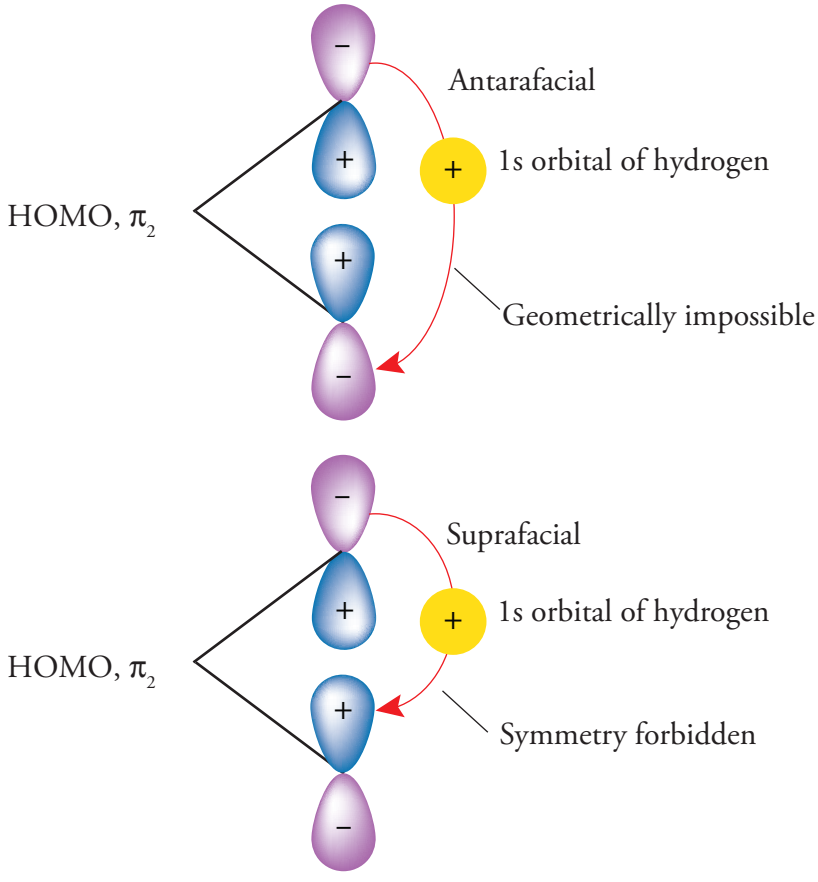


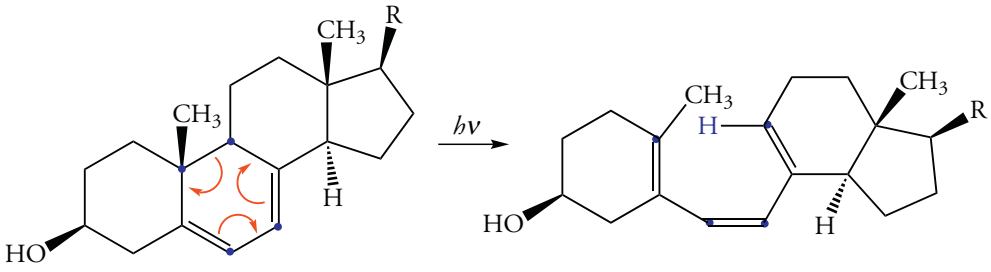
Figure 25.14 Molecular Orbitals of a [1,3] Sigmatropic Rearrangement
The HOMO of an allyl radical is antisymmetric. A [1,3] sigmatropic rearrangement cannot occur in a suprafacial process. An antarafacial rearrangement is symmetry allowed, but cannot occur because of geometric restrictions.

Photoactivation of Vitamin D: A [1,7] Suprafacial Reaction

We noted above that small amounts of ultraviolet light are required for the activation of vitamin D. This interesting reaction occurs by a [1,7] suprafacial rearrangement. Vitamin D is a necessary part of the human diet for bone growth. Inadequate amounts of this vitamin result in inadequate calcification of bones. This condition in children is called *rickets*. The disease in adults is called *osteomalacia*. In spite of a dietary vitamin D deficiency, it is known that an individual may generate vitamin D since sunlight can activate a Vitamin D precursor. But in northern climates where the days are short in the winter, and one's skin is covered, it is not possible to produce enough vitamin D to make up for dietary deficiencies.

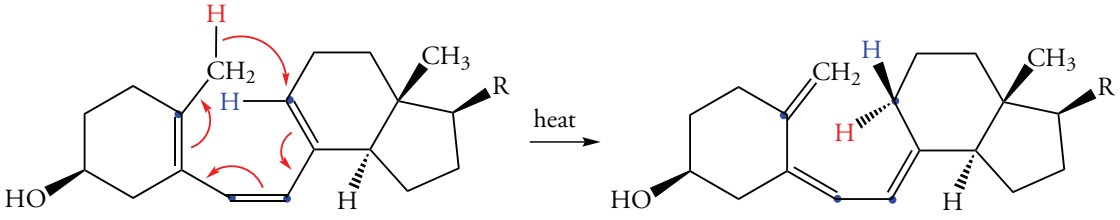
Several structurally related compounds are called vitamin D. The differences are denoted by subscripts as in vitamin D_2 or D_3. All of these vitamins come from steroid precursors and differ in the identity of the alkyl group bonded to the five-membered ring.

Vitamin D_2 is produced by two pericyclic reactions. One of them is photochemically initiated; the second thermally initiated. The first step is a photochemical electrocyclic reaction in which a cyclohexadiene of the B ring is isomerized to a triene. The reaction involves six π electrons and is the reverse of the photochemical cyclization reaction discussed in Section 28.4. Thus, by the principle of microscopic reversibility, this photochemically allowed ring opening involving a $4n$ +2 π system must occur by a conrotatory process.



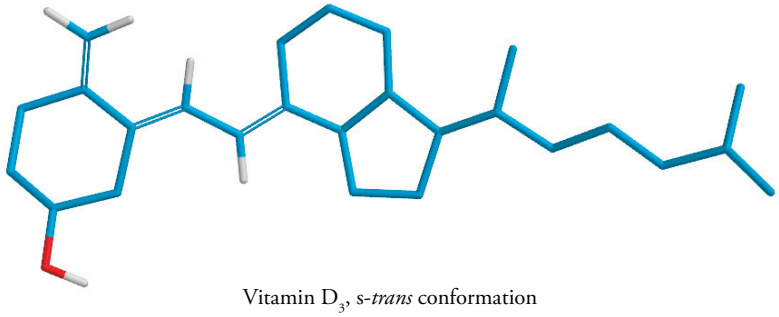
7-dehydrocholesterol previtamin D_3

The second step, which yields vitamin D_3, is a thermal [1,7] sigmatropic shift of a hydrogen atom. Based on the symmetry of the HOMO of a heptatrienyl system, the transfer of the hydrogen must occur antarafacially. Both the number of single bonds and the number of atoms provide sufficient flexibility for this reaction to occur.

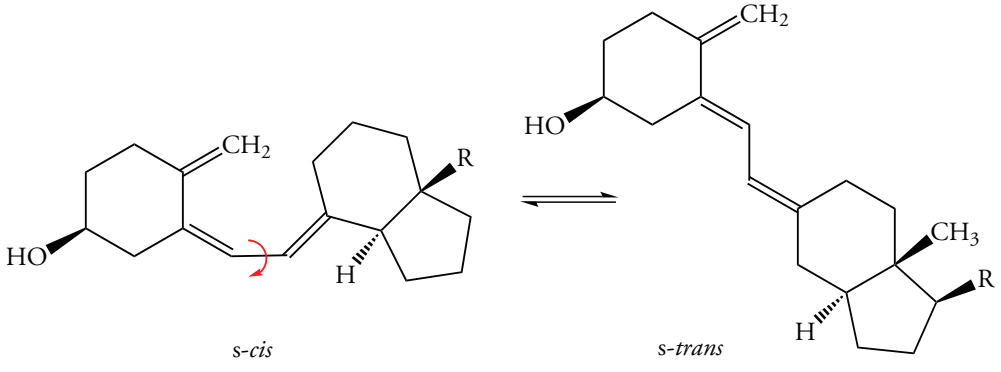


previtamin D_3 vitamin D_3

The thermal [1,7] sigmatropic shift is slow at body temperature, and it takes several days to "use up" the previtamin D_3 originally produced by exposure to sunlight. Vitamin D_3 exists in an equilibrium between an s-*cis*-conformation and a more stable s-*trans* conformation that results from rotation around the σ bond located between the two rings.

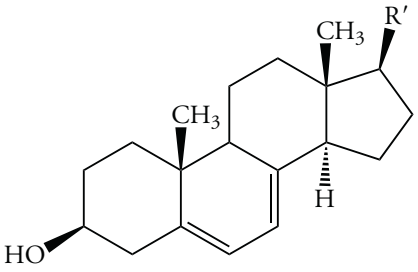


Vitamin D_3, s-*trans* conformation



s-*cis* s-*trans*

Another form, called vitamin D_2, is commonly added to milk. It is derived from ergosterol, which differs from 7-dehydrocholesterol by an additional methyl group and a double bond in the side chain bonded to the D ring of the cholesterol ring system. Ergosterol is irradiated to give a previtamin D_2 by a photochemically allowed, conrotatory ring-opening reaction. A subsequent thermal [1,7] sigmatropic shift occurs to give vitamin D_3. Because of labeling laws, milk that contains vitamin D_2 is indicated by the term *irradiated ergosterol*.



ergosterol

[3,3] Sigmatropic Rearrangements

A [3,3] sigmatropic rearrangement such as the Cope rearrangement of 1,5-hexadiene can be thought of as a process in which two three-carbon radical fragments form and then bond again in a different position. Again, as we noted previously, the reaction does not proceed by free radical intermediates. However, the same orbitals are involved in the concerted process. So we can explain the experimental results using this model (Figure 25.15). The resonance forms of the two allyl radicals used as models for the reactions are shown as a transition state in the following equation.

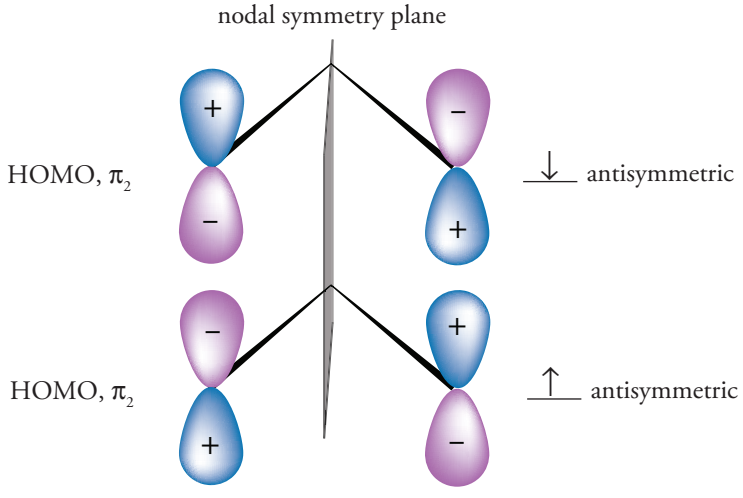
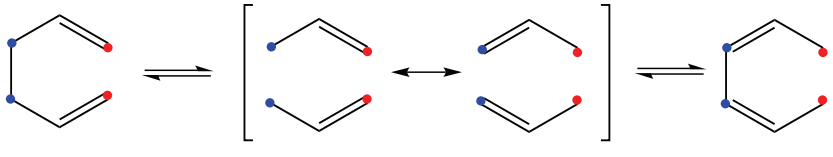


Figure 25.15 Molecular Orbitals of a [3,3] Sigmatropic Rearrangement
The HOMO of an allyl radical is antisymmetric. A [3,3] sigmatropic rearrangement cannot occur in a suprafacial process.

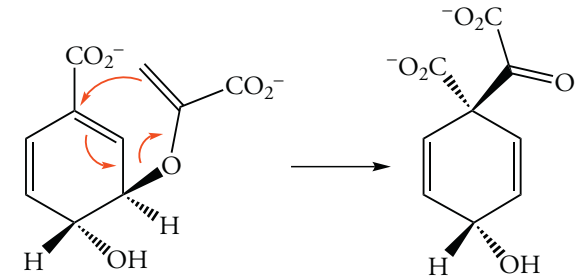
The resonance forms of the two allyl radicals used as models for the reactions are shown as a transition state in the following equation.



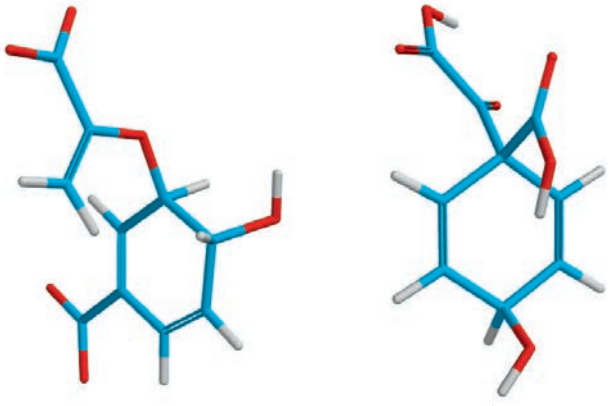
The resonance forms of the two allyl radicals used as models for the reactions are shown as a transition state in the following equation. An allyl radical contains three π electrons, two in π_1 and one in the π_2 molecular orbital. Therefore, the frontier molecular orbital is π_2. It is antisymmetric. The bond that is broken must generate 2p atomic orbitals with lobes of the same sign directed toward each other. The bond to be formed must occur between 2p atomic orbitals with lobes of the same sign directed toward each other. This can be accomplished using the HOMO of one radical to form a σ bond with the HOMO of the other radical.

A Biochemical [3,3] Sigmatropic Rearrangement: The Claisen Rearrangement

One of the metabolic reactions in the biosynthesis of the amino acid phenylalanine occurs by a [3,3] sigmatropic shift in a reaction called a **Claisen rearrangement**. In this reaction, chorismate, a vinyl ether, rearranges to prephenate.



chorismate prephenate



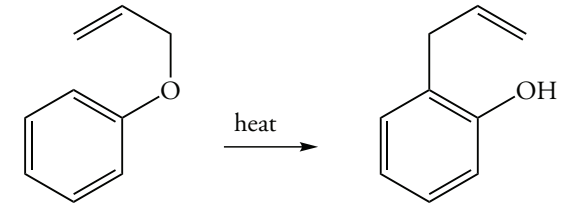
chorismate prephenate

The driving force for this exergonic reaction is the generation of the carbonyl bond. The metabolic reaction is catalyzed by chorismate mutase. The enzyme increases the rate by a factor of a million. The enzyme mechanism has been extensively studied, and it appears that the enzyme stabilizes the transition state in the conformation required for catalysis. Thus, it might well be that the enzyme increases the reaction rate mostly by an entropy effect.

The Claisen rearrangement of chorismate shows yet again how apparently esoteric organic reactions find their way into the biological world.

Problem 25.9

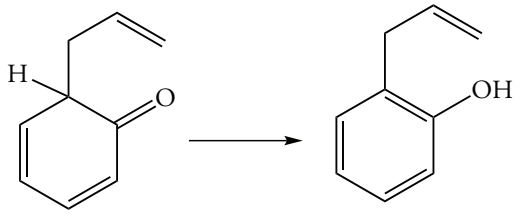
The Claisen rearrangement of allyl aryl ethers to give *o*-allylphenols is an example of a [3,3] sigmatropic shift. The initial product is an isomer of the *o*-allylphenol, which undergoes a familiar isomerization reaction. Draw the structure of the initial product. What is the subsequent isomerization reaction?



allyl phenyl ether o-allylphenol

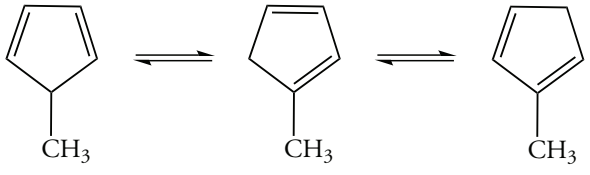
Sample Solution

A [3,3] sigmatropic rearrangement gives a ketone that lacks the resonance stabilization of an aromatic ring. However, tautomerization gives the enol form, which is a phenol and contains an aromatic ring.



Problem 25.10

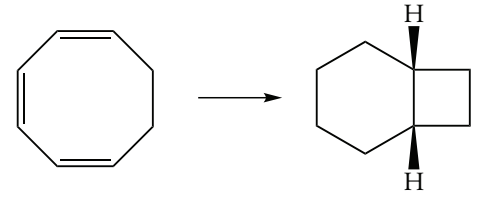
5-Methyl-1,3-cyclopentadiene rapidly rearranges to give a mixture of that compound and its 1-methyl and 3-methyl isomers. Explain how this isomerization occurs.

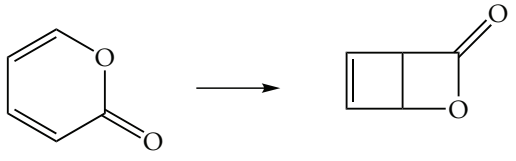


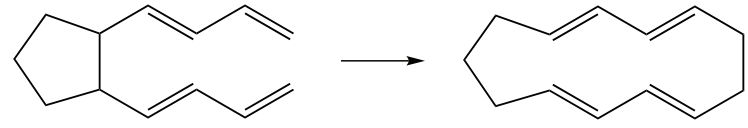
EXERCISES

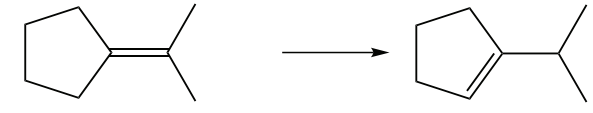
Classification of Pericyclic Reactions

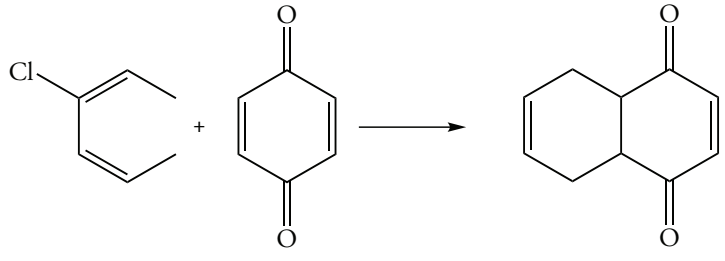
25.1 Classify each of the following reactions as electrocyclic, cycloaddition, or sigmatropic.

(a) 

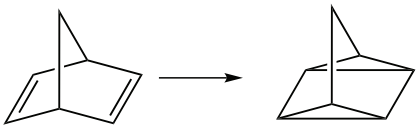
(b) 

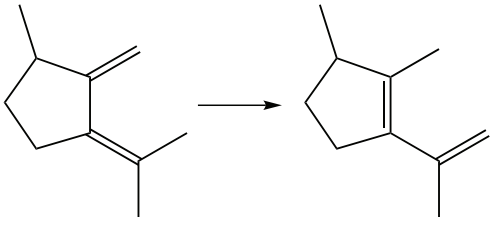
(c) 

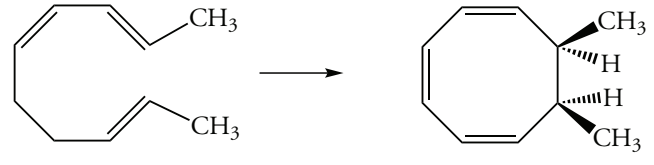
(d) 

(e) 

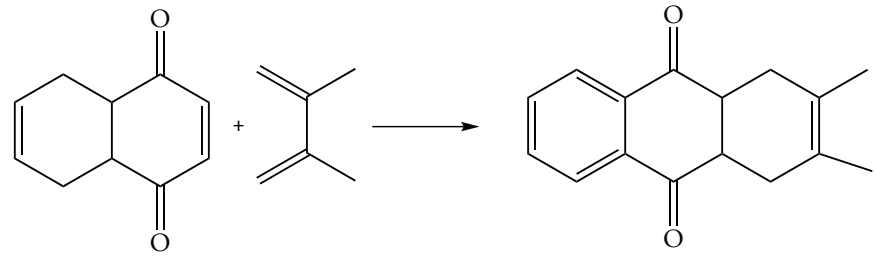
25.2 Classify each of the following reactions as electrocyclic, cycloaddition, or sigmatropic.

(a) 

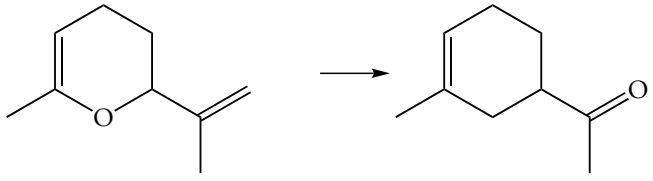
(b) 

(c) 

(d)



(e)



Molecular Orbitals

25.3 (a) What π molecular orbital would account for the thermal [1,7] sigmatropic shift in previtamin A? (b) What is the symmetry of the molecular orbital?

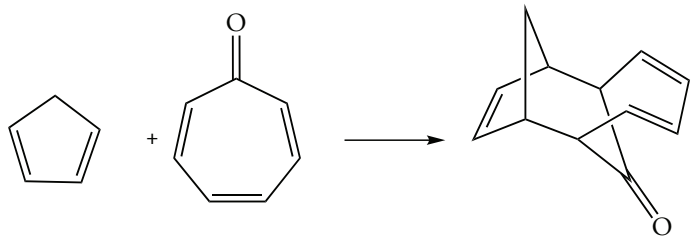
25.4 (a) What π molecular orbital would account for the thermal [1,7] sigmatropic shift in previtamin A? (b) What is the symmetry of the molecular orbital?

Symmetry-Allowed Reactions

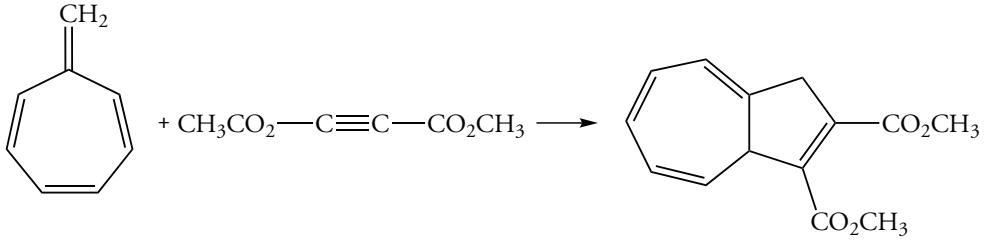
25.5 Describe the stereochemistry associated with each of the following symmetry-allowed reactions.
(a) a thermal [4 + 6] cycloaddition
(b) a photochemical [2 + 6] cycloaddition
(c) a thermal [1,7] sigmatropic rearrangement
(d) a photochemical [1,3] sigmatropic rearrangement

25.6 Describe the motion that occurs in each of the following symmetry-allowed reactions.
(a) thermal ring closure of a triene to a cyclohexadiene
(b) photochemical ring closure of a diene to a cyclobutene
(c) thermal ring opening of a cyclic triene to a tetraene
(d) photochemical ring opening of a cyclic diene to a triene

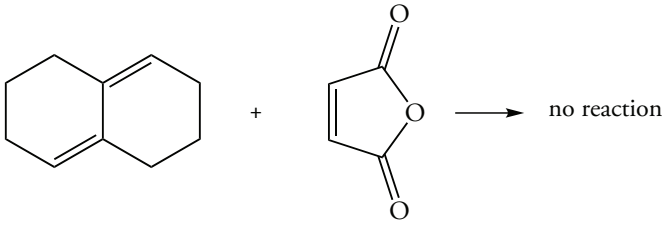
25.7 (a) Classify the following thermal cycloaddition reaction. Is the reaction symmetry allowed? (b) What π molecular orbitals are required to explain your answer? (c) What are their respective symmetries?



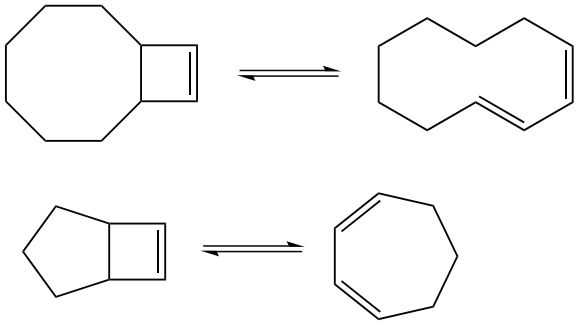
25.8 (a) Show why the following thermal reaction is regarded as a [2 + 8] cycloaddition. (b) What π molecular orbitals are required to determine if the reaction is symmetry allowed? (c) What are their respective symmetries?



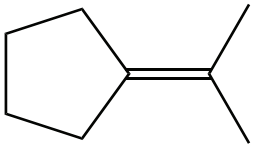
25.9 The following diene does not undergo a Diels–Alder reaction with maleic anhydride. Explain why this symmetry-allowed reaction does not occur.



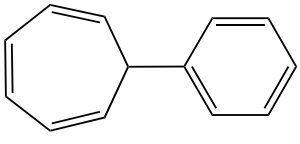
25.10 The ring-opening reaction of a cyclobutene ring fused to an eight-membered ring occurs at temperatures below 200 °C. Even though a structurally related compound with a cyclobutene ring fused to a five-membered ring is more strained, this ring-opening reaction requires temperatures near 300 °C. Explain why.



25.11 Photochemical [1,3] sigmatropic shifts occur in some allylic systems. Draw the structures of the products resulting from the following alkene. Which product should predominate?

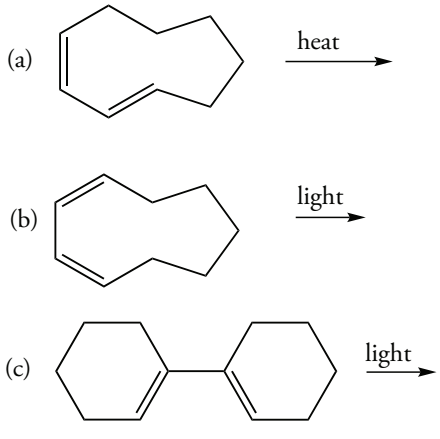


25.12 Explain why the following compound cannot undergo a [1,7] sigmatropic rearrangement, whereas previtamin D can. A photochemical [1,7] sigmatropic rearrangement occurs. Draw the structure of the first product formed.

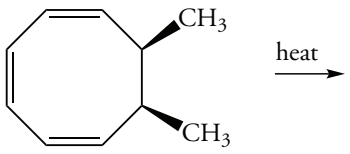


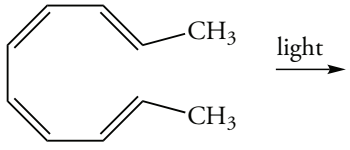
Electrocyclic Reactions

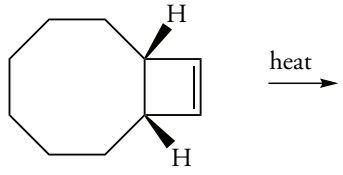
25.13 Draw the structure of the product of each of the following reactions, and indicate the stereochemistry of each product.



25.14 Draw the structure of the product of each of the following reactions and indicate the stereochemistry of each product.

(a) 

(b) 

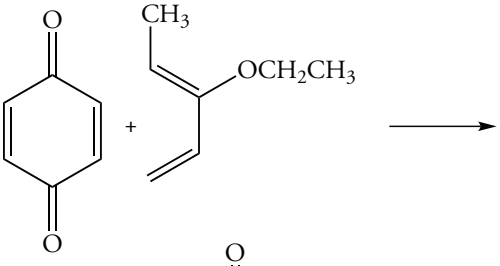
(c) 

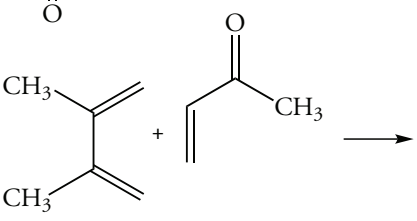
25.15 Explain why the thermal ring opening of *trans*-3,4-dimethylcyclobutene could yield two isomeric 2,4-hexadienes. Explain why only one isomer forms.

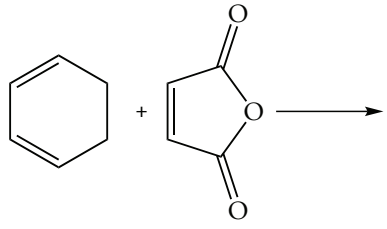
25.16 Which of the following compounds cannot undergo a thermal electrocyclic ring closure?
(a) (2*E*,4*Z*,6*E*)-2,4,6-octatriene
(b) (2*E*,4*E*,6*E*)-2,4,6-octatriene
(c) (2*E*,4*Z*,6*Z*)-2,4,6-octatriene

Cycloaddition Reactions

25.17 Draw the structure of the product of each of the following reactions.

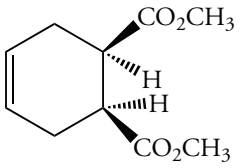
(a) 

(b) 

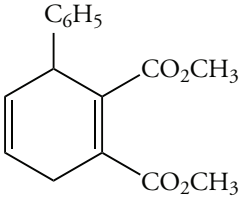
(c) 

25.18 What reactants are required to produce each of the following compounds via a Diels–Alder reaction?

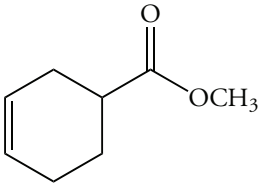
(a)



(b)



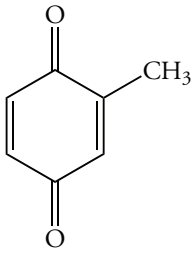
(c)



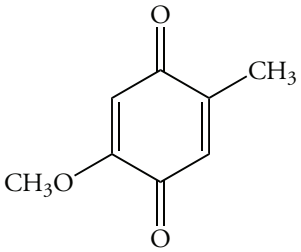
25.19 Explain why 1,3-cyclopentadiene reacts faster than 1,3-butadiene with maleic anhydride.

25.20 Explain why (2*Z*,4*Z*)-hexadiene does not react with maleic anhydride even though the diene has two methyl groups that increase the electron density of the diene.

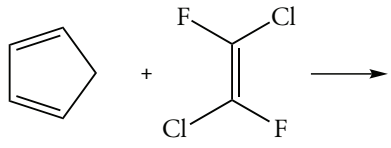
25.21 One equivalent of 1,3-butadiene reacts with the following quinone to give a single product. Draw the structure and explain why it forms.



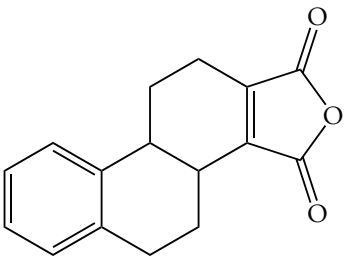
25.22 One equivalent of (*E*)-1,3-pentadiene reacts with the following quinone to give a mixture of two products. Draw their structures and explain why they form.



25.23 Draw the structure of the Diels–Alder product of the following combination of reactants,



25.24 What reactants are required to produce each of the following compounds via a Diels–Alder reaction?



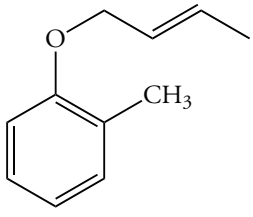
Sigmatropic Rearrangements

25.25 Explain why *cis*-1,2-divinylcyclobutane undergoes a [3,3] sigmatropic rearrangement faster than 1,5-hexadiene.

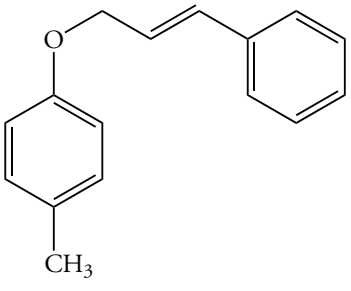
25.26 (a) What type of reaction occurs in the conversion of allyl vinyl ether into 4-pentenal? (b) Why does the reaction have a large equilibrium constant?

25.27 Draw the structure of the product of the Claisen rearrangement of each of the following compounds.

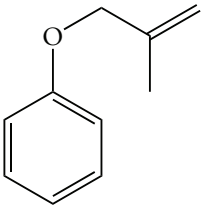
(a)



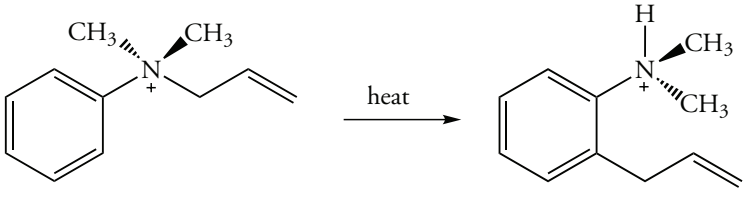
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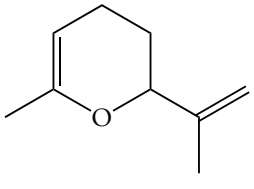
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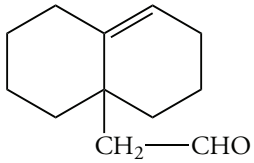
25.28 Write a mechanism to account for the following rearrangement reaction.



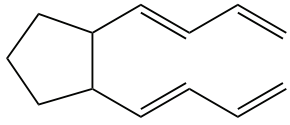
25.29 The following compound undergoes a Claisen-type rearrangement to yield a ketone. Draw the structure of the product.



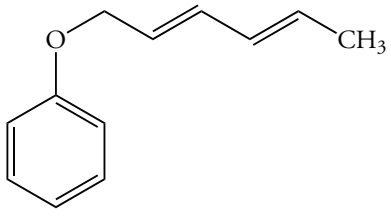
25.30 What reactant is required to yield the following aldehyde by a Claisen-type rearrangement?



25.31 (a) Draw the product of a thermal [5,5] sigmatropic rearrangement of the following compound. (b) Does the reaction occur by a suprafacial or antarafacial process?

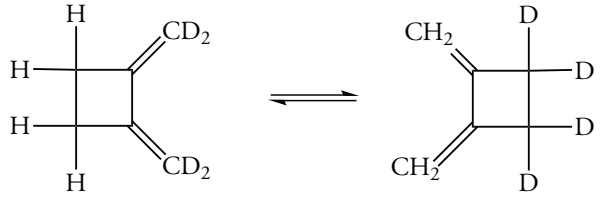


25.32 The following ether undergoes a thermal [5,5] sigmatropic rearrangement. Draw the structure of the product.

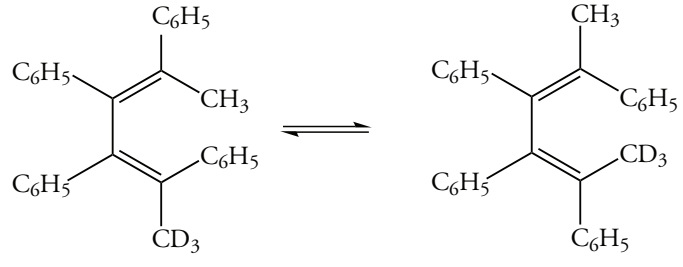


Multiple Pericyclic Reactions

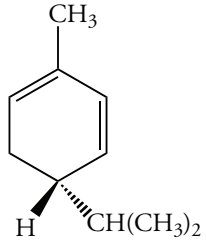
25.33 The following thermal isomerization reaction occurs by two similar sequential pericyclic reactions. Identify them and draw the structure of the intermediate compound.



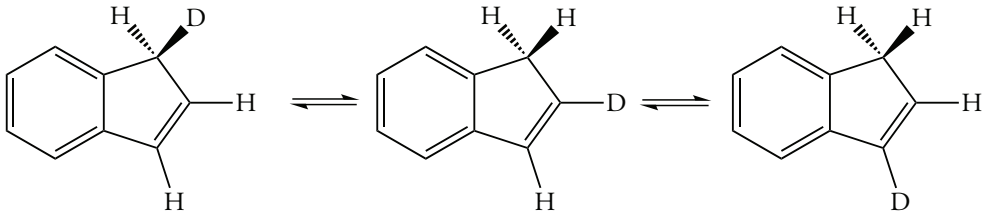
25.34 The following thermal isomerization occurs by two similar, sequential pericyclic reactions. Identify them and draw the structure of the intermediate compound.



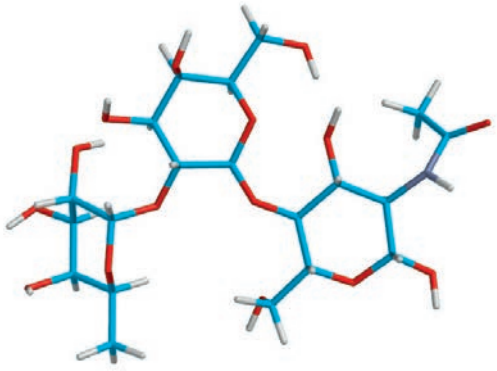
25.35 The following compound can lose its optical activity when heated. Two similar sequential pericyclic reactions are required to account for this result. Identify them and draw the structure of the intermediate compound.



25.36 The following isomerization reactions occur by related sequential pericyclic processes. Draw the structure of the intermediate compound involved in each reaction.



26 Carbohydrates



Type O Blood Group Antigen

26.1 CARBOHYDRATES IN THE BIOSPHERE

If the importance of biological molecules were measured by abundance, carbohydrates would hold first prize. They are the most abundant molecules in the biological world. The term carbohydrate, which means "hydrate of carbon," was suggested for compounds with the empirical formula $(CH_2O)_n$ in 1844. Although the name remains, many compounds classified as carbohydrates today do not have the empirical formula $(CH_2O)_n$. The name carbohydrates now includes a wide range of structures—from simple molecules with as few as three carbon atoms to very large molecules consisting of thousands of five- or six-membered rings. Carbohydrates are polyhydroxy aldehydes or ketones, or compounds that can be hydrolyzed to form polyhydroxy aldehydes or ketones. Their functions are as varied as their structures. They provide a major source of metabolic energy to most organisms and are important structural components in many cells. Carbohydrates bound to cell surfaces are also the antigenic determinants that uniquely define the identity of every person. Carbohydrates are essential components of DNA and RNA, and many proteins are attached to carbohydrates. In short, carbohydrates are ubiquitous; and they play a part in dozens of biochemical processes.

26.2 CLASSIFICATION OF CARBOHYDRATES

Carbohydrates fall into three large structural classes that are based upon the number of structural units they contain.

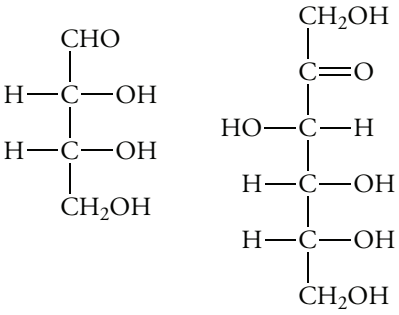
1. **Monosaccharides** are the simplest carbohydrates. They typically contain three to six carbon atoms and cannot be hydrolyzed into smaller molecules. Examples include glucose and fructose.
2. **Oligosaccharides** contain a few monosaccharides—typically 2–10 or so. Hydrolysis of oligosaccharides may yield identical monosaccharides, or two or more different monosaccharides. Oligosaccharides are called disaccharides, trisaccharides, and so forth, depending on the number of linked monosaccharide units. The disaccharide lactose, or "milk sugar," for example, contains one molecule of glucose and one of galactose. Maltose, another disaccharide, contains two glucose units.
3. **Polysaccharides** contain thousands of covalently linked monosaccharides. Those with only one type of monosaccharide subunit are called homopolysaccharides. Examples include starch and cellulose made by plants. Hydrolysis of the homopolysaccharide cellulose yields only glucose. Glycogen, sometimes called animal starch, is another homopolysaccharide of glucose. Polysaccharides with more than one type of monosaccharide are called heteropolysaccharides.

The monosaccharides in oligo- and polysaccharides are linked by acetal or ketal bonds, called **glycosidic bonds** in carbohydrate chemistry. These bonds link the aldehyde or ketone site of one monosaccharide and a hydroxyl group of another monosaccharide. Hydrolysis of the glycosidic bonds yields the component monosaccharides.

Monosaccharides can be further classified by their most highly oxidized functional group. Monosaccharides are called **aldoses** if their most highly oxidized functional group is an aldehyde and **ketoses** if their most highly oxidized functional group is a ketone. The suffix *-ose* indicates that a compound is a carbohydrate. The prefix aldo- or keto- indicates that the compound is an aldehyde or ketone. The prefixes tri-, tetr-, pent-, and hex- indicate the number of carbon atoms in an aldose or ketose. Aldoses are numbered from the carbonyl carbon atom; ketoses are numbered from the end of the carbon chain closest to the carbonyl carbon atom.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00026-7
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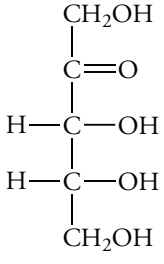
Fisher projection structures (Section 8.4) of two monosaccharides are shown below.



an aldotetrose a ketohexose

Problem 26.1

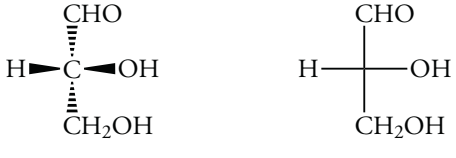
D-Ribulose, which has the following structure, is an intermediate in the pentose phosphate pathway that produces ribose, a precursor for nucleic acid biosynthesis. Classify D-ribulose by chain length and its carbonyl group.



D-ribulose

26.3 CHIRALITY OF MONOSACCHARIDES

We will often draw the structures of open-chain monosaccharides in their Fischer projection formulas. We recall that in a Fischer projection formula, a vertical line represents the carbon chain. Groups attached to the ends of the vertical line represent bonds going into the page, and horizontal lines represent bonds coming out of the page. By convention, the carbonyl carbon atom, the most oxidized carbon atom in these compounds, is placed near the "top" in the Fischer projection formula. The simplest aldose, glyceraldehyde, has three carbon atoms, one of which is a stereogenic center. This aldotriose can exist in two enantiomeric forms. The naturally occurring *R* isomer is dextrorotatory; that is, it rotates light in a clockwise (+) direction. It's specific rotation, $[\alpha]_D^{25}$, is +13.5°. However, we recall that the designation *R* defines the configuration of the chiral center, and that the optical rotation for an *R* stereoisomer is an experimental parameter that can be either (+) or (–).

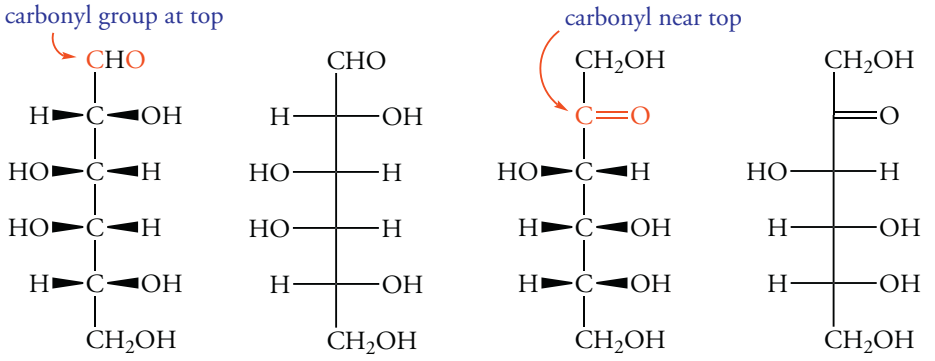


(*R*)-glyceraldehyde
$[\alpha]_D^{25} = +13.5°$

Fischer projection

In the Fischer projection formula, the carbon atoms of the chain are not shown, but are implicit: they exist where the horizontal and vertical lines cross.

Monosaccharides with two or more stereogenic centers are arranged with the carbon backbone drawn vertically in the plane of the page, with the attached hydrogen atoms and hydroxyl groups pointing out to the right and the left from the carbon chain.



Fischer projection

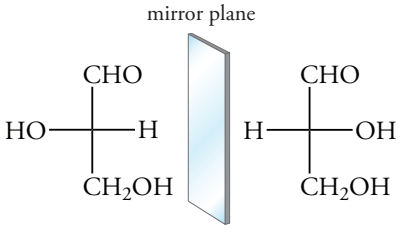
D-galactose

Fischer projection

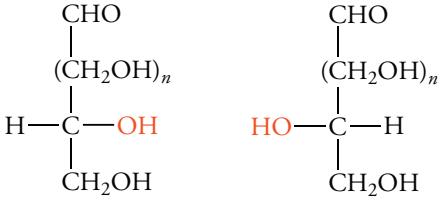
D-fructose

Aldoses

The stereochemistry of each stereogenic center of a monosaccharide can be indicated by the *R*,*S* notation. However, the Fischer projection formula, devised late in the nineteenth century by the German chemist Emil Fischer, remains in common use for carbohydrates and amino acids. In the Fischer stereochemical system, the configurations of all stereogenic centers depend on their relation to the naturally occurring stereoisomer of glyceraldehyde. This aldotriose has the hydroxyl group on its chiral C-2 atom, located on the right in the projection formula. Its configuration is symbolized D, so the naturally occurring isomer is designated D-glyceraldehyde. Its enantiomer, called L-glyceraldehyde, has the hydroxyl group on the left at the chiral carbon atom in the Fischer projection formula.



Using the *R*,*S* notation, D-glyceraldehyde is the *R* enantiomer. The *R*,*S* configuration of each of the stereogenic centers of longer chain monosaccharides can be used to name the many possible isomers. Fischer's system of carbohydrate stereochemistry describes the stereogenic centers with respect to one reference center. The configuration of the highest numbered stereogenic center is used to assign the configuration of a compound as either D or L. Because the numbering of the carbon chain assigns the highest possible number to the carbonyl carbon atom, the highest numbered stereogenic center is the farthest from the most highly oxidized carbon atom. Since the configurations of all the other sterogenic centers depend on their relation to the chiral center of D-glyceraldehyde, they are all correct too!

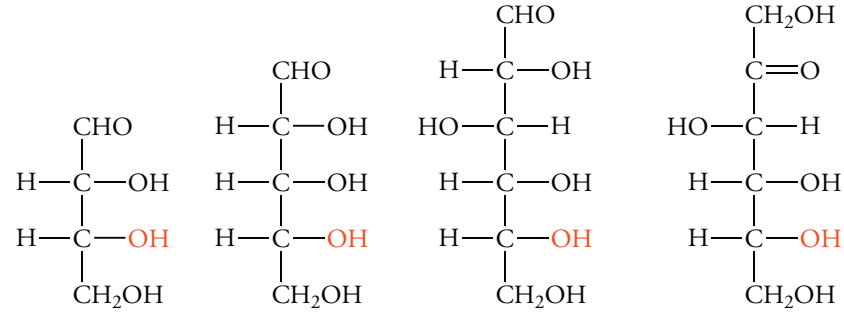


a D-aldose

an L-aldose

The configurations of the hydroxyl groups of a monosaccharide relative to one another distinguish any given monosaccharide from other diastereomers. For example, the aldopentose with all hydroxyl groups at the three chiral carbon atoms on the same side in the Fischer projection formula is called ribose. The assignment of one enantiomer of ribose to the D or L series is then made by reference to C-4, the highest numbered chiral carbon atom in the five-carbon compound. The name D-ribose defines the absolute configuration at every stereogenic center in the molecule.

This apparently arbitrary method of stereochemical assignments of carbohydrates is based on their biosynthetic origins. Cells synthesize monosaccharides from the three-carbon precursor D-glyceraldehyde, extending the chain from C-1. Nearly all naturally occurring monosaccharides have the same configuration at the highest numbered chiral center as D-glyceraldehyde. This biosynthetic relationship explains why the stereogenic carbon atom farthest from the carbonyl group determines whether the compound is D or L.



Fischer projections of the aldotetroses, aldopentoses, and aldohexoses of the D series are shown in Figure 26.1. D-Glyceraldehyde, at the top of the "tree," is the parent aldose. When we insert a new stereogenic center (H—C—OH) between the carbonyl carbon atom and the stereogenic center below, the resulting molecules are D aldotetroses. Because the new CHOH group can have its OH group on the right or left, two aldotetroses, D-erythrose and D-threose, are possible. Note that aldotetroses contain two nonequivalent stereogenic centers, so $2^2 = 4$ stereoisomers are possible. The two L aldotetroses are not shown in Figure 26.1. D-Erythrose and L-erythrose are enantiomers, as are D-threose and L-threose.

Inserting a new stereogenic center (H—C—OH), which can have either of two configurations, between the carbonyl carbon atom and the stereogenic center at C-2 in D-erythrose, leads to two D aldopentoses. D-Ribose and D-arabinose. Similarly, inserting a new stereogenic center (H—C—OH) between the carbonyl carbon atom and the stereogenic center at the C-2 atom in D-threose yields D-xylose and D-lyxose. Repeating the process one more time in each of the four D aldopentoses gives a total of eight D aldohexoses. D-Glucose and D-galactose are the most widely found in nature. D-Mannose and D-talose occur in smaller amounts. The others are extremely rare.

The isomeric monosaccharides shown in any group in Figure 26.1 are diastereomers. They are not enantiomers because they are not mirror images. To write the enantiomer of a monosaccharide of the D series, we must reverse the configuration of each stereogenic center because one molecule must be the mirror image of the other. The enantiomeric relationship of the glucose isomers is shown in Figure 26.2.

Figure 26.1 Structures of D-Aldoses

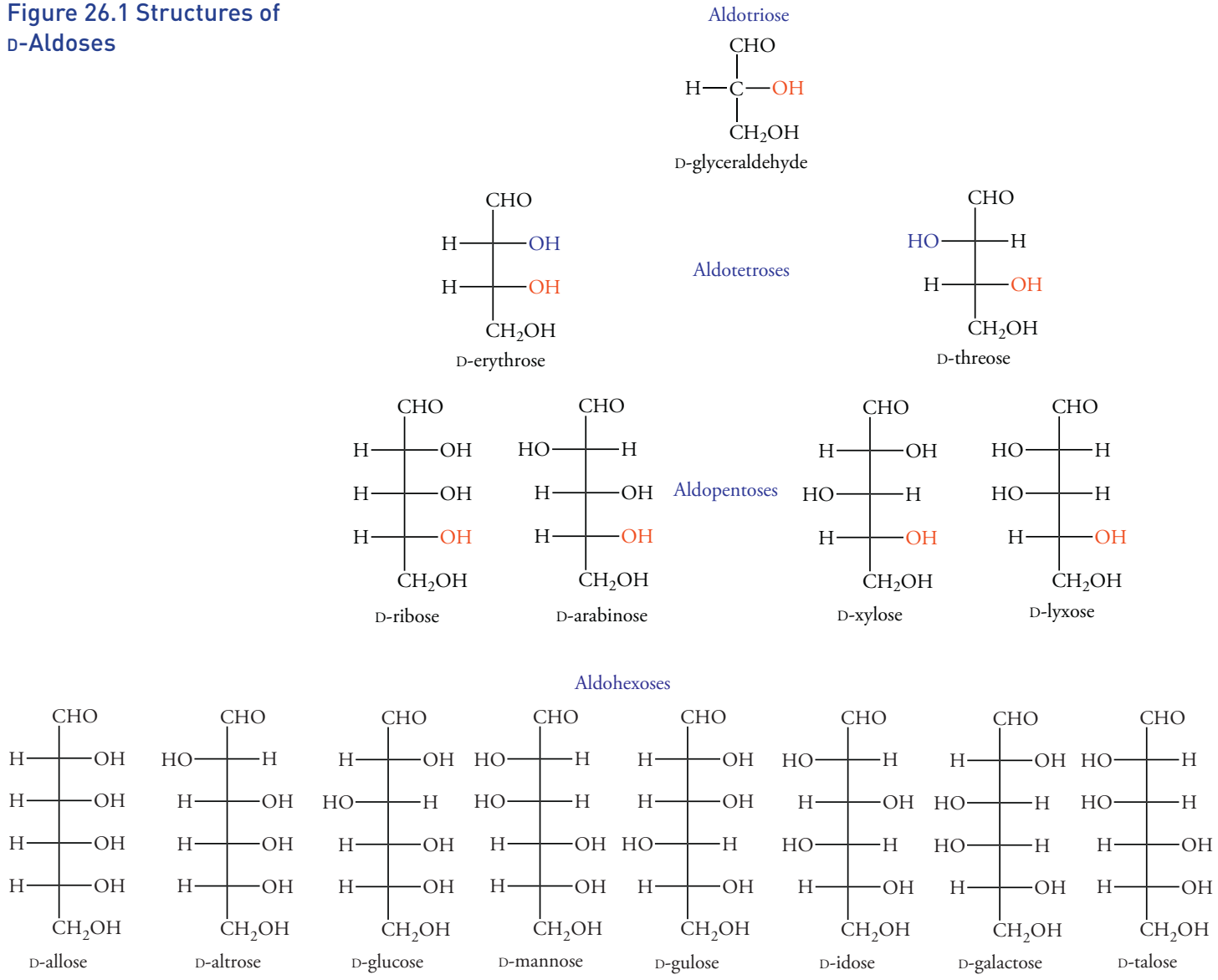
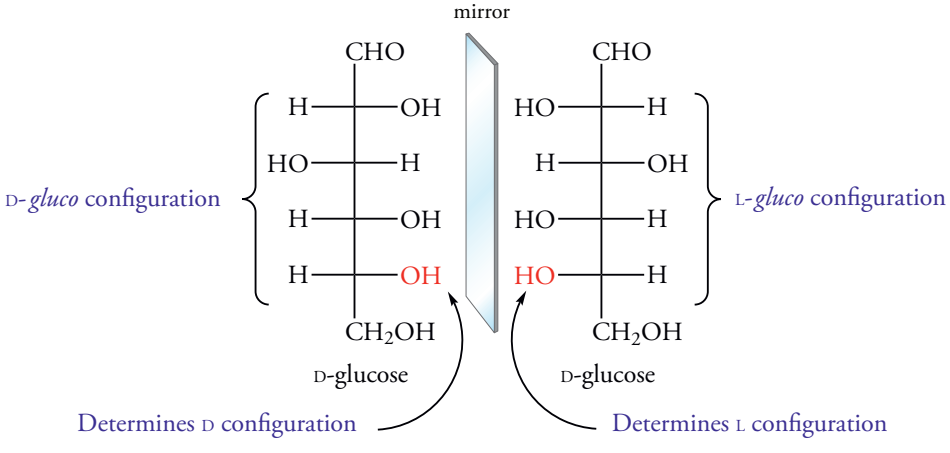


Figure 26.2 Enantiomeric Relationship of D- and L-Monosaccharides

The D- and L-monosaccharides have reversed, mirror image configurations at every chiral center.



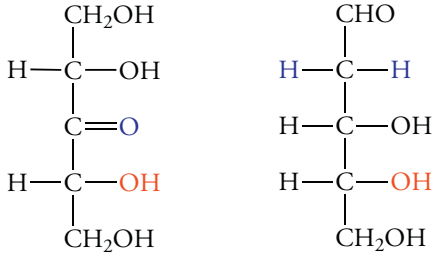
Ketoses

Ketoses also play a pivotal role in metabolism. The Fischer projections of the D-ketotetroses, D-ketopentoses, and D-ketohexoses are shown in Figure 26.3. The "parent" ketose is the ketotriose dihydroxyacetone. We can construct ketoses from dihydroxyacetone by inserting chiral centers (H—C—OH) one at a time between the ketone carbonyl carbon atom and the carbon atom directly below it.

The simplest ketose, dihydroxyacetone, is not chiral. This ketose forms in the metabolism of glucose as a phosphate ester at the C-3 hydroxyl group. Fructose, the most important ketohexose, results from isomerization of glucose during glycolysis, a metabolic pathway that all cells use to degrade glucose and produce energy. The ketopentoses ribulose and xylulose are intermediates in the pentose phosphate pathway, another important metabolic pathway that produces the ribose necessary for ribonucleic acids.

Less Common Monosaccharides

Most aldoses and ketoses are unbranched compounds with an oxygen functional group at each carbon atom. However, a few structural variations occur in some uncommon monosaccharides. Most of these compounds are named using the more common monosaccharides as the parent. Most ketoses have the carbonyl carbon atom at C-2 and can isomerize to aldoses (Section 26.4). However, a 3-keto isomer of ribose exists. A more common structural variation is substitution of one or more hydroxyl groups by hydrogen. The most important example of such a *deoxy* sugar is 2-deoxyribose, which is present (in cyclic form) in DNA.

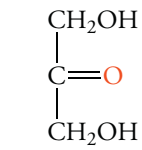


(a 3-ketopentose) 2-deoxy-D-ribose

Another structural variation replaces a hydroxyl group with an amine group and its derivatives. These **amino sugars** are components of some antibiotics. They also occur in polysaccharides contained in the exoskeleton of arthropods and are components of blood group antigens. The polysaccharide found in lobster shells contains the *N*-acetyl derivative of D-2-glucosamine; that is, it is *N*-acetylglucosamine.

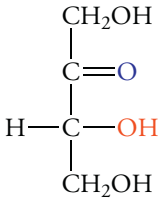
Figure 26.3 Structures of D-2-Ketoses

Ketotriose



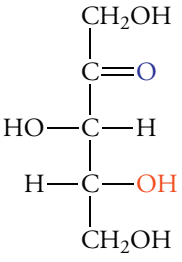
dihydroxyacetone

Ketotetrose

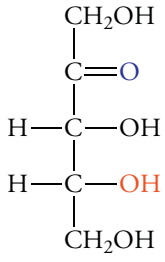


D-erythulose

Ketopentoses

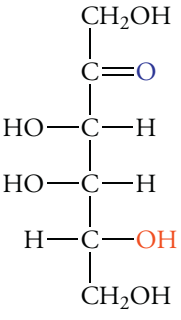


D-xylulose

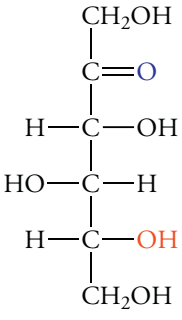


D-ribulose

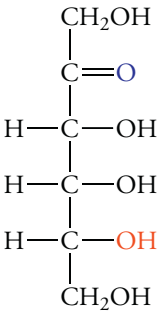
Ketohexoses



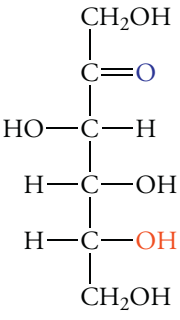
D-tagatose



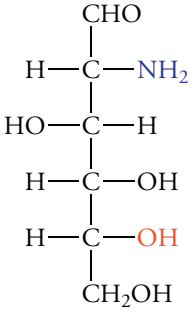
D-sorbose



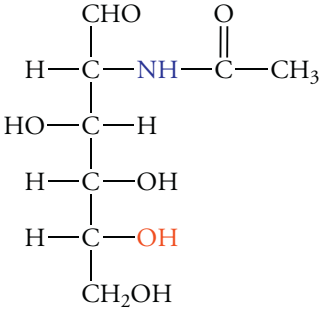
D-psicose



D-fructose

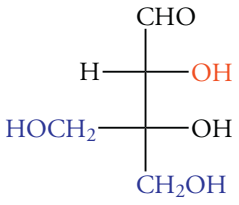


D-2-glucosamine



N-acetyl-D-2-glucosamine

Another structural variation replaces a hydroxyl group with an amine group and its derivatives. A few monosaccharides have branched structures. D-Apiose, which is present in parsley and many other plants, is an example. Note that C-3 is not a stereogenic center because it is bonded to two hydroxymethyl groups.



D-apiose

Problem 26.2

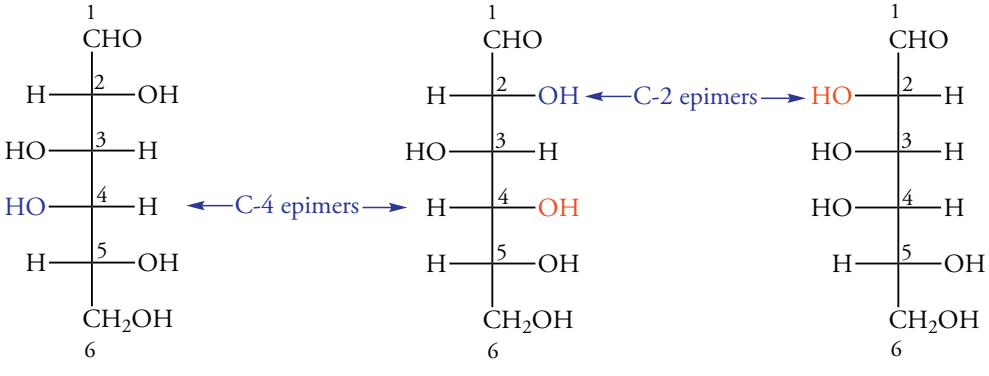
Draw the structure of each of the following monosaccharides.
(a) L-arabinose, the enantiomer of D-arabinose
(b) a 3-ketose structurally related to D-glucose
(c) 6-deoxymannose

26.4 ISOMERIZATIONS OF MONOSACCHARIDES

The conversion of one monosaccharide to another requires an inversion of configuration at least one stereogenic center. For compounds that contain two or more stereogenic centers, the inversion at a single stereogenic center changes the physical properties of the molecule because the resulting isomer is a diastereomer, not an enantiomer. Because there are two or more hydroxyl groups in monosaccharides, the selective inversion of configuration at one stereogenic center usually requires the selective protection of other hydroxyl groups in the form of cyclic acetals. In principle, chemical reactions can invert the configuration at any stereogenic center, but in practice the reaction requires many synthetic steps. Each step involves chemistry that we have already discussed, and we will not elaborate on the synthetic details with the single exception of the special case of inversion at a single center, a reaction called **epimerization**.

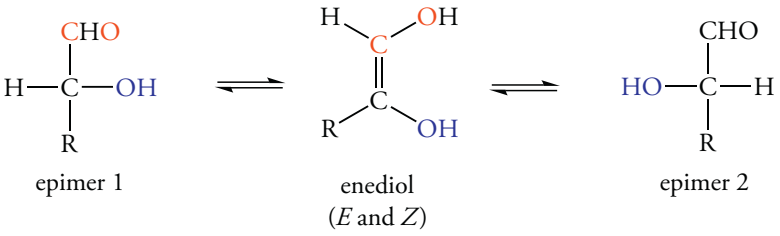
Epimers

One stereogenic center of a monosaccharide can be easily inverted. Diastereomers that contain two or more stereogenic carbon atoms, but differ in configuration at only one stereogenic center, are called **epimers**. For example, the diastereomers D-glucose and D-galactose are epimers because they differ in configuration only at C-4. D-Glucose and D-mannose are epimers that differ in configuration at C-2.



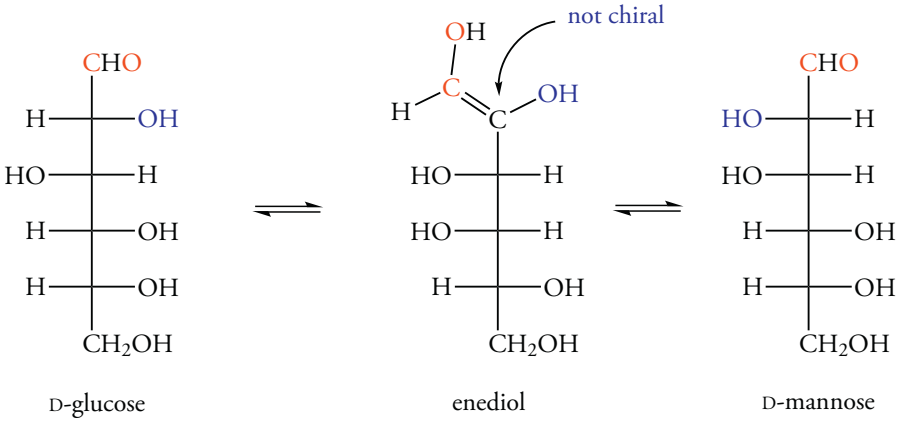
D-galactose D-glucose D-mannose

The interconversion of epimers such as D-glucose and D-mannose at C-2 illustrates a chemical reaction we discussed in Chapter 22. The α-hydrogen atom of an aldehyde is enolizable, and in the presence of a weak base, it undergoes a keto-enol tautomerization reaction to produce a small amount of an isomeric enol. In an aldose, the α carbon atom is chiral and has a hydroxyl group bonded to it. Tautomerization yields an **enediol** in which the α-carbon atom is not chiral. In the reverse reaction, to regenerate the aldose, a stereogenic center forms again at the α-carbon atom. It can have either of two configurations, and two C-2 epimers result.



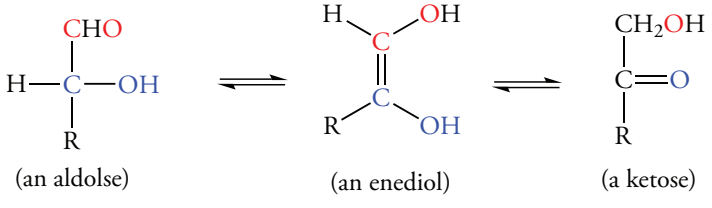
For example, D-glucose can be converted to D-mannose by way of an enediol intermediate (Figure 26.4). A specific enzyme called an **epimerase** catalyzes this reaction in cells.

Figure 26.4
Isomerization of Aldoses via an Enediol Intermediate

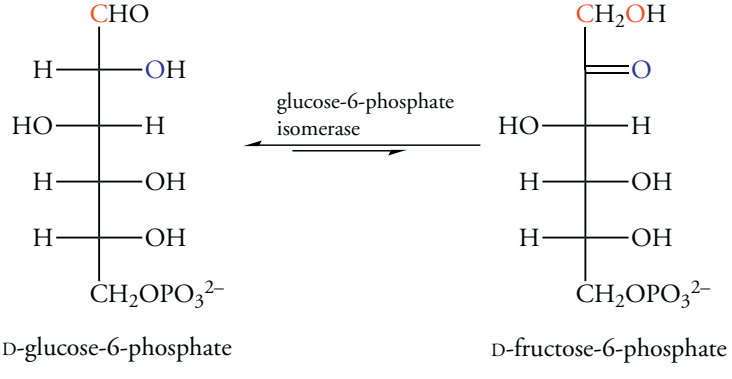


Interconversion of Aldoses and Ketoses

An enediol has a hydroxyl group on each double-bonded carbon atom. Hence, it is the enol of a ketose as well as two enantiomeric aldoses. The original C-1 of the aldose becomes a primary alcohol; the C-2 secondary alcohol becomes a ketone.



Therefore, glucose, mannose, and fructose can all be in equilibrium with the same enediol. This isomerization process occurs in biochemical reactions near pH 7 for several aldoses and ketoses in enzyme-catalyzed reactions. The isomerization of glucose and fructose occurs by way of their 6-phosphate esters and is catalyzed by glucose 6-phosphate isomerase. The equilibrium constant for the formation of fructose 6-phosphate from glucose 6-phosphate is approximately 0.3. This reaction is one of the initial steps in glycolysis.

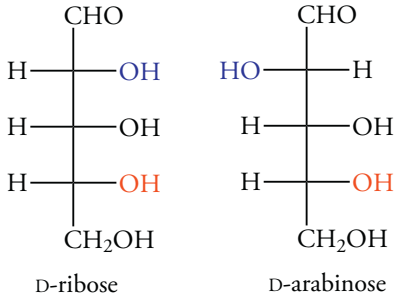


Problem 26.3

Which aldopentose is a C-2 epimer of D-ribose?

Sample Solution

Look at the structure of D-ribose and examine the configuration at C-2. The hydroxyl group is on the right side of the Fischer projection formula. Write a structure that has the same configuration at the C-3 and C-4 atoms, but place the hydroxyl group at the C-2 atom on the left side. This compound is D-arabinose.

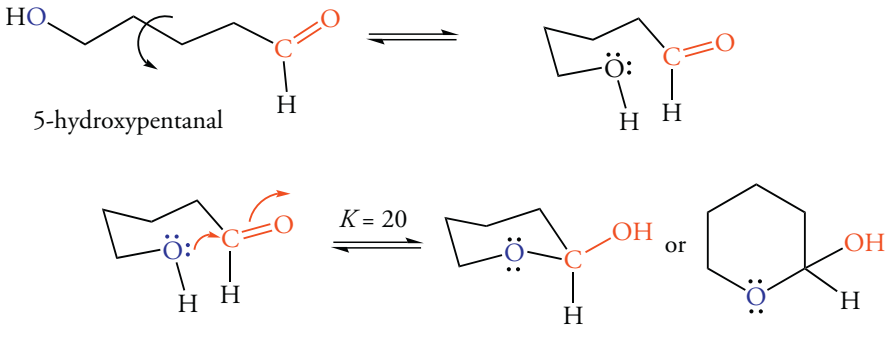


Problem 26.4

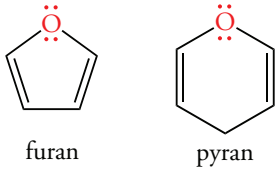
Ribulose 5-phosphate is converted to xylulose 5-phosphate in one of the steps of the pentose phosphate pathway. Suggest a mechanism for this reaction.

26.5 CYCLIC MONOSACCHARIDES: HEMIACETALS AND HEMIKETALS

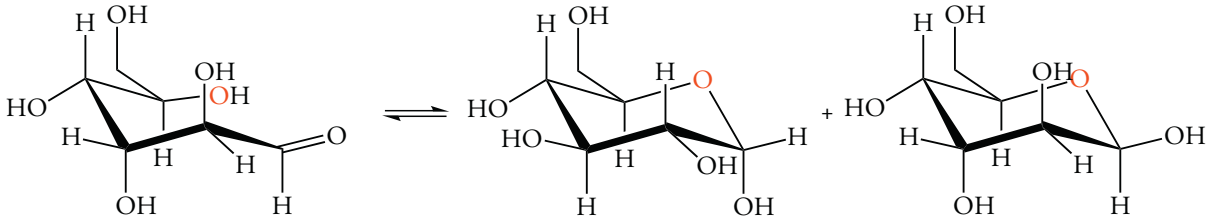
We recall that aldehydes and ketones react reversibly with alcohols to form hemiacetals and hemiketals, respectively (Section 19.6). With the hydroxyl group and the carbonyl group in the same molecule, the equilibrium constant for the formation of a cyclic hemiacetal in an intramolecular reaction is larger than for an intermolecular reaction. Cyclic hemiacetals containing five or six atoms in the ring are the most common.



The cyclic hemiacetal or hemiketal forms of aldo- and ketohexoses and pentoses are the predominant forms of these sugars, rather than the open-chain structures we have discussed to this point. Cyclic hemiacetals and hemiketals of carbohydrates that contain five-membered rings are called **furanoses**. Cyclic hemiacetals and hemiketals that contain six-membered rings are called **pyranoses**. These names are based the cyclic rings of furan and pyran.

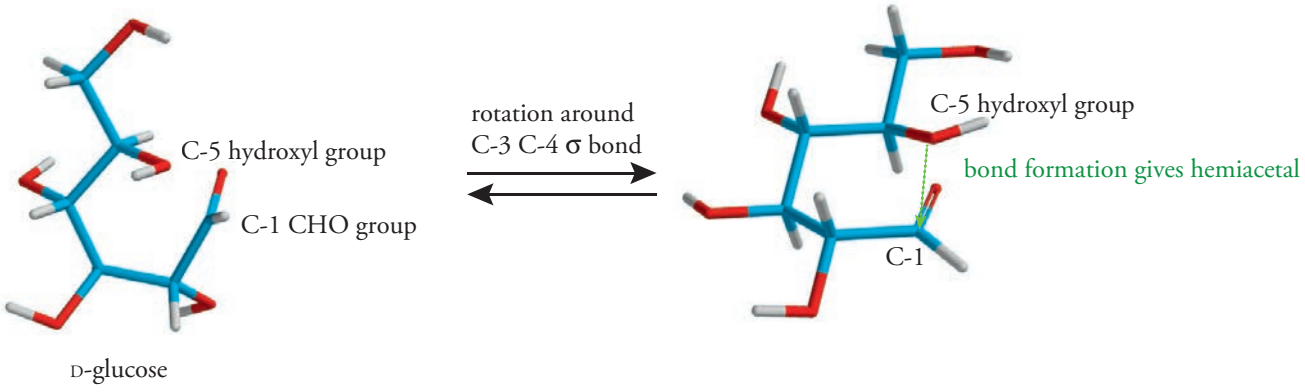


When glucose and other open-chain aldohexoses form a cyclic hemiacetal, the resulting cyclic compound has a chair conformation. The cyclic hemiacetal has four different groups that are attached to C-1, which was the original carbonyl group. Thus, a new stereogenic center and two configurations are possible. If the hydroxyl group of the hemiacetal is axial, the compound is α-D-glucopyranose. If it is equatorial, the compound is β-D-glucopyranose.



D-glucose α-D-glucopyranose β-D-glucopyranose

The conformation of the six-membered ring of glucose is a chair. In its most stable form, all of the hydroxyl groups of the hemiacetal are equatorial, and the compound is α-D-glucopyranose. If the hydroxyl group at C-1 is axial, the compound is α-D-glucopyranose. The α and β forms of D-glucopyranose are diastereomers.

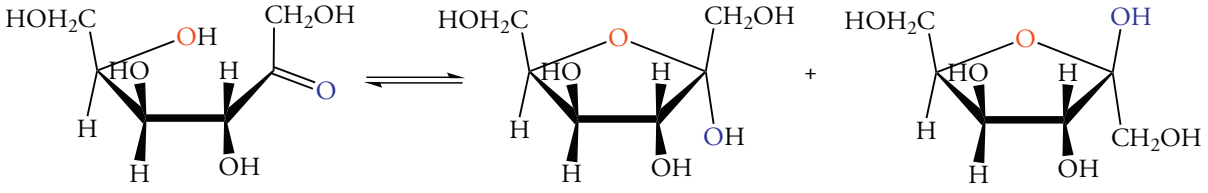


D-glucose

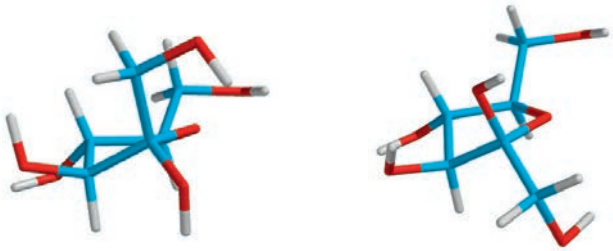


α-D-glucopyranose D-glucose β-D-glucopyranose

Monosaccharides can also cyclize to give five-membered rings called furanoses. These too can exist as α- and β-stereoisomers. For example, fructose cyclizes to give the isomers shown below.



D-fructose α-D-fructofuranose β-D-fructofuranose



α-D-fructofuranose β-D-fructofuranose

The "pyrano" part of the names α- and β-D-glucopyranose and other pyranoses is often omitted since it is understood that glucose can only exist as an α or β isomer when it is cyclic. Similarly, the "furano" part of the names of furanoses is often omitted. So the names are often shortened to α- and β-D-glucose or α- and β-D-fructose. The α and β forms of D-glucose and fructose are diastereomers that differ in configuration at one stereogenic center. Hence, they are epimers. Compounds whose configurations differ only at the hemiacetal center are a special type of epimer called **anomers**. The stereogenic carbon atom at the hemiacetal center that forms in the cyclization reaction is called the **anomeric carbon** atom.

Aldohexoses are most stable as pyranoses. The percentages of the α and β anomers of the pyranoses and furanoses at equilibrium are given in Table 26.1.

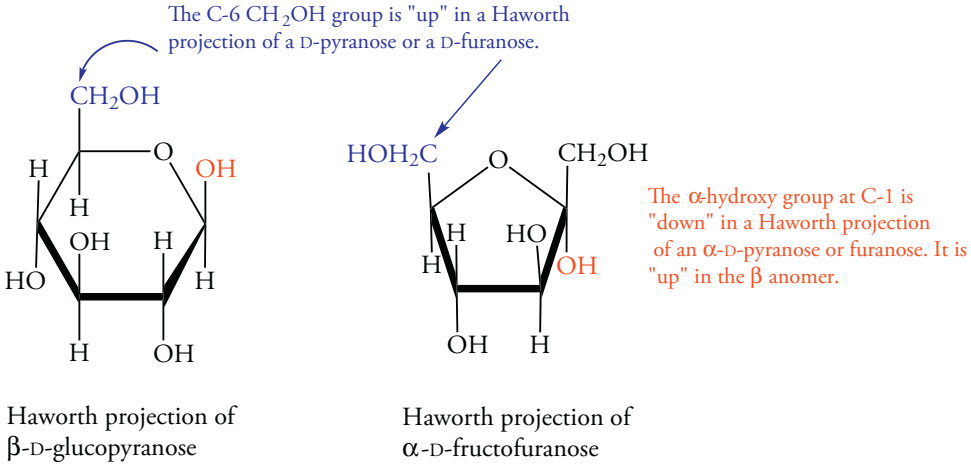
Table 26.1
Composition of Monosaccharides at Equilibrium in Solution (in percent)

Monosaccharide	*Pyranose*		*Furanose*	
	α	*β*	*α*	*β*
D-Glucose	36	64		
D-Mannose	67	32	0.8	0.2
D-Galactose	31	69		
D-Allose	18	70	5	7
D-Altrose	27	40	20	13
D-Idose	38	38	10	14
D-Talose	40	29	20	11
D-Arabinose	63	34	2	1
D-Ribose	20	56	6	18
D-Xylose	27	63		
D-Fructose	2	66	7	25

Haworth Projection Formulas

A Haworth projection formula represents the conformation of a cyclic hemiacetal or hemiketal as a planar structure viewed edge-on. The carbon atoms are arranged clockwise with C-1 of the aldohexose or aldopentose on the right. For hemiketals C-2 is placed on the right. Groups that are equatorial in the chair conformation are "up" in the Haworth projection. The C-6 CH_2OH group is *always* up in the Haworth projection of a D-monosaccharide whether it is a pyranose or a furanose (Figure 26.5).

Figure 26.5
Haworth Projections of a Pyranose and a Furanose



Haworth projection of β-D-glucopyranose

Haworth projection of α-D-fructofuranose

Mutarotation

When D-glucose crystallizes from methanol, α-D-glucose, which melts at 146 °C, forms. It has $[\alpha]_D$ = +112.2°. On the other hand, when β-D-glucose crystallizes from acetic acid, the β anomer, which melts at 150 °C, forms. It has $[\alpha]_D$ = +18.7° (Figure 26.6). The α and β isomers are diastereomers, so it is not surprising that they have different physical properties.

When α-D-glucose dissolves in water, the optical rotation of the solution slowly changes from the initial value of +112.2° to an equilibrium value of +54°. If β-D-glucose dissolves in water, the rotation of the solution slowly changes from the initial value of +18 7 to the same equilibrium value of +54°. This gradual change in rotation to an equilibrium point is known as **mutarotation**. Mutarotation results from the interconversion of the cyclic hemiacetals with the open-chain form in solution. Ring opening followed by recyclization can form either the α or β anomer. At equilibrium, the solution contains 36% of the α anomer and 64% of the β anomer of glucose, with less than 0.01% of the open-chain form. In cells, an enzyme called mutarotase catalyzes the mutarotation of glucose.

Although the mutarotation of glucose interconverts only anomeric pyranose forms, some aldohexoses form a four-component mixture of anomeric pyranoses and anomeric furanoses. Fructose also forms a four-component mixture of anomeric furanoses and pyranoses.

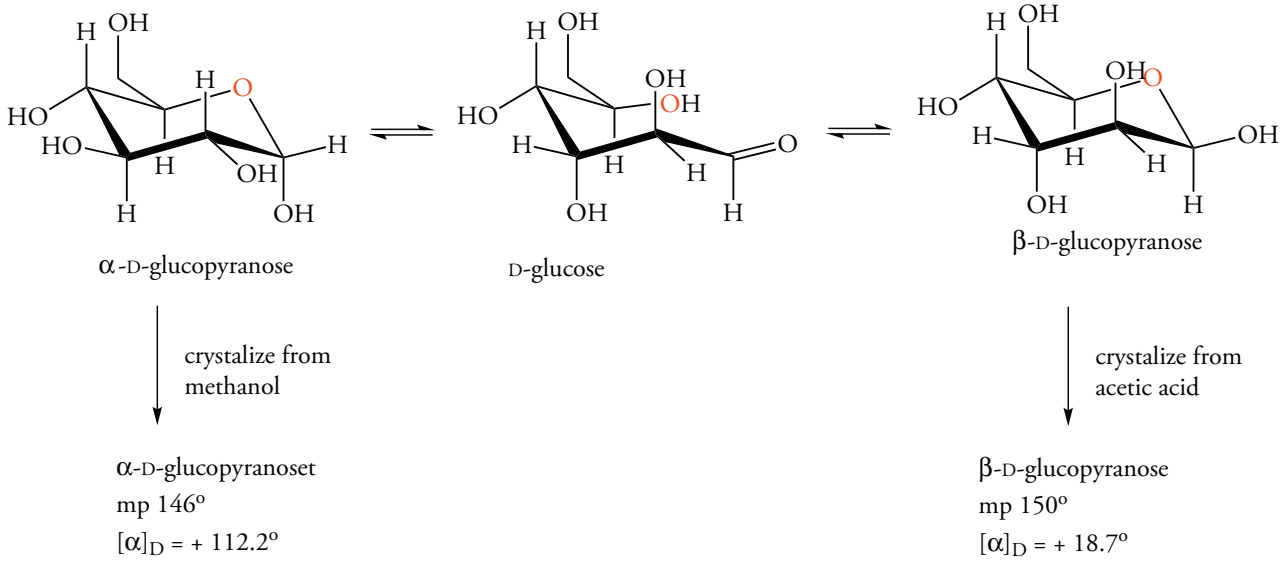


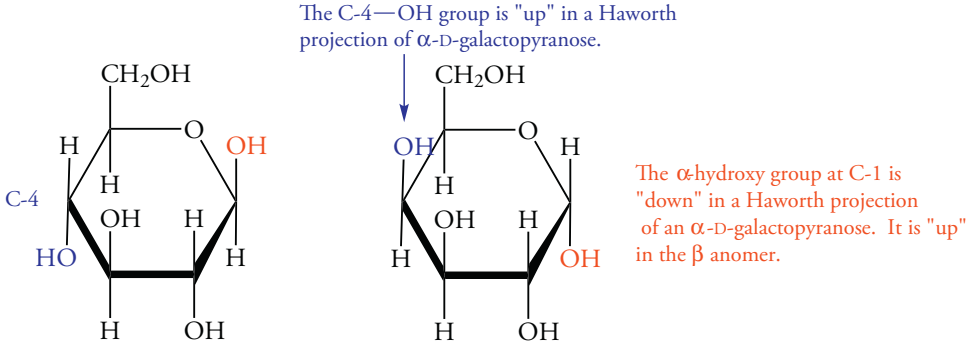
Figure 26.6 Interconversion of Anomers and Mutatrotation

Problem 26.5

Draw the Haworth projection of the α anomer of the pyranose form of D-galactose, that is, α-D-galactopyranose.

Sample Solution

Draw a pyranose ring containing five carbon atoms and one oxygen atom. For the D configuration, the —CH_2OH group is "up," above the plane of the ring. Since galactose is the C-4 epimer of glucose, and since the hydroxyl group at C-4 is down in glucose, it is "up" in galactose. The α anomer has a hydroxyl group below the plane of the ring at the anomeric carbon atom, C-1.



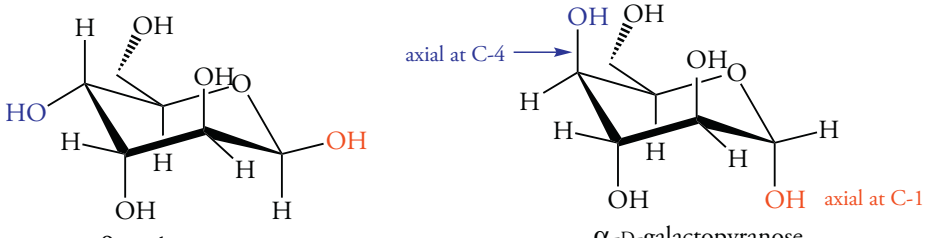
Haworth projection of
β-D-glucopyranose

Problem 26.6

Draw the chair conformation of α-D-galactopyranose using glucose as a reference.

Sample Solution

We recall that the β anomer of glucose has all of its hydroxyl groups in equatorial positions. The α anomer of galactose must have an axial hydroxyl group at C-1, the anomeric carbon atom. We also recall that galactose is the C-4 epimer of glucose. Therefore, the hydroxyl group at C-4 must be axial.



β-D-glucopyranose

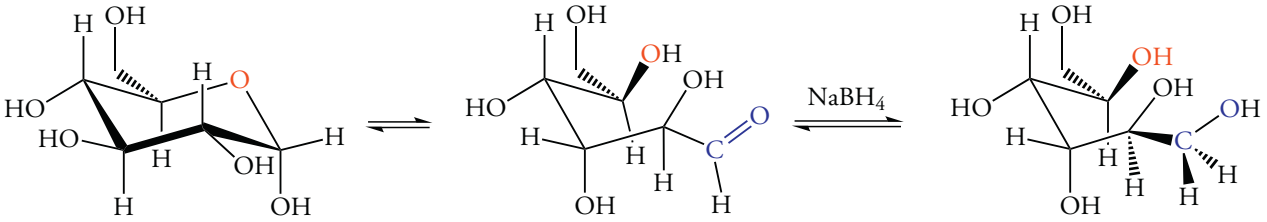
α-D-galactopyranose

26.6 REDUCTION AND OXIDATION OF MONOSACCHARIDES

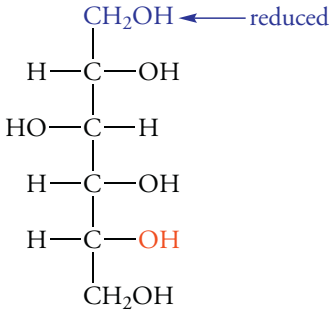
Although five- and six-carbon monosaccharides exist predominately as hemiacetals and hemiketals, they undergo the characteristic reduction and oxidation reactions of simple aldehydes and ketones. The reduction or oxidation reaction occurs by way of the carbonyl group in the small amount of the open-chain form of the monosaccharide in equilibrium with its cyclic hemiacetal or hemiketal. As the reduction or oxidation occurs, the equilibrium shifts to produce more of the carbonyl form until eventually all the monosaccharide reacts.

Reduction of Monosaccharides

Treating an aldose or ketose with sodium borohydride reduces it to a polyalcohol called an **alditol**. The alditol derived from D-glucose is called D-glucitol. D-Glucitol occurs in some fruits and berries. It is produced and sold commercially as the sugar substitute called sorbitol.



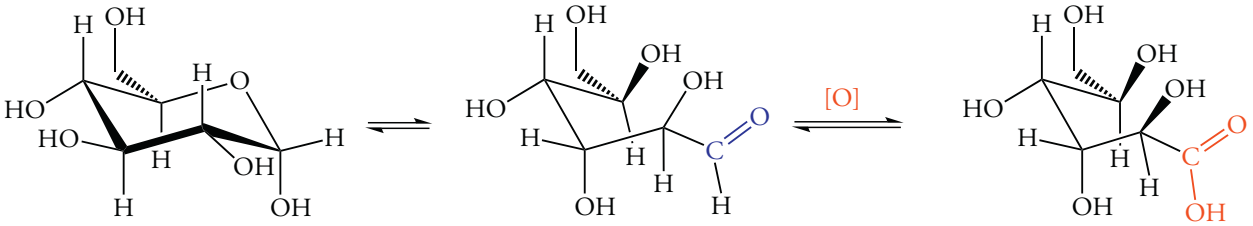
α-D-glucopyranose D-glucose D-glucitol



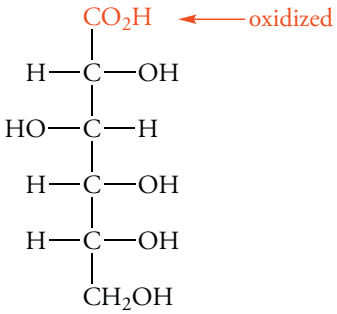
D-glucitol (D-sorbitol)
(an alditol)

Oxidation of Monosaccharides

In Chapter 18, we saw that aldehydes are oxidized by Tollens's reagent, Benedict's solution, and Fehling's solution. These reagents also oxidize open-chain aldoses that exist in equilibrium with the cyclic hemiacetal form. When some of the open-chain form reacts, the equilibrium shifts to form more compound for subsequent oxidation, and eventually all the aldose is oxidized. Oxidation yields a product with a carboxyl group at the original C-1 atom. This product is called an **aldonic acid**.



α-D-glucopyranose D-glucose D-gluconic acid

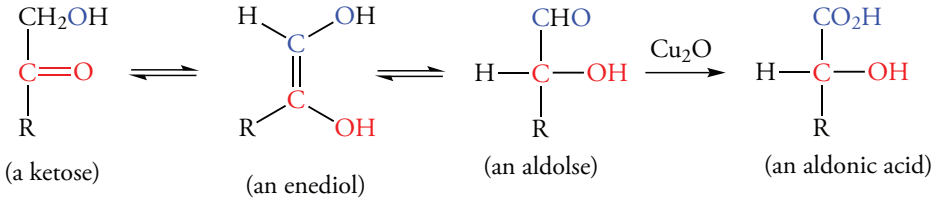


D-gluconic acid
(an aldonic acid)

If Tollens's reagent is used as the oxidizing agent, metallic silver forms a mirror on the walls of the test tube. If Benedict's solution is used, a red precipitate of Cu_2O indicates that a reaction has occurred. Aqueous bromine at approximately pH 6 can also oxidize aldoses to aldonic acids. This reagent is the preferred method for the laboratory synthesis of aldonic acids. None of these oxidizing agents oxidize any of the hydroxyl groups in an aldose.

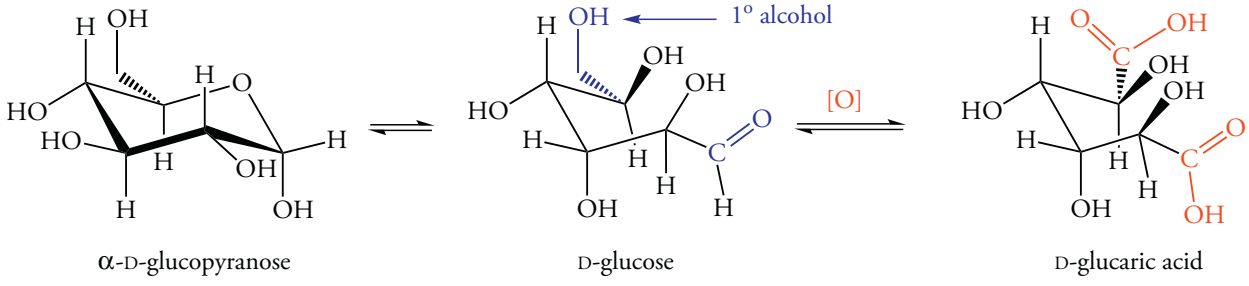
Benedict's solution also oxidizes ketoses. We certainly do not expect this because Benedict's solution does not oxidize ketones. However, α-hydroxy ketones tautomerize in basic solution,

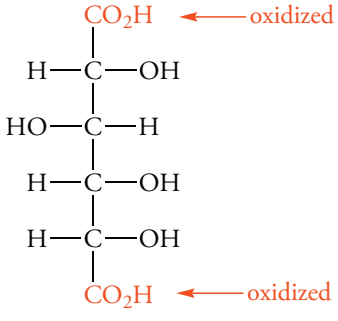
and Benedict's solution is basic. The tautomer of a ketose is an enediol that not only reverts to the α-hydroxy ketone but also forms an isomeric α-hydroxy aldehyde.



Shifting a hydrogen atom from the C-2 hydroxyl group to C-1 in regenerates the original ketose. However, tautomerization forms an aldose. In basic solution, then, a ketose, such as fructose, is in equilibrium with an aldose such as glucose. The aldose reacts with Benedict's solution, and more ketose is converted into aldose. The equilibrium shifts, as predicted by Le Chatelier's principle, and eventually all the ketose is converted to an aldose. And the aldose is oxidized to an aldonic acid.
Carbohydrates that react with Benedict's solution are called **reducing sugars**. The term reducing refers to the effect of the carbohydrate on Benedict's solution. It oxidizes the carbohydrate, but the carbohydrate reduces Benedict's solution. Both aldoses and ketoses are reducing sugars.

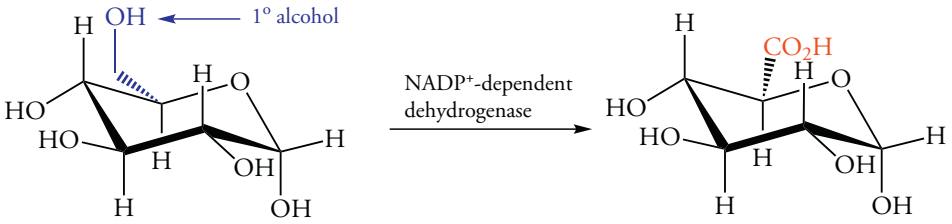
Stronger oxidizing agents can oxidize other hydroxyl groups of aldoses. For example, dilute nitric acid oxidizes both the aldehyde group and the primary alcohol of aldoses to give **aldaric acids**.





D-glucaric acid
(an aldaric acid)

Cells can enzymatically oxidize the terminal —CH_2OH group of an aldose without oxidizing the aldehyde group. The product is a **uronic acid**. The responsible for this reaction uses $NADP^+$ (nicotinamide adenine dinucleotide phosphate, a close structural relative of NAD+) as the oxidizing agent. The enzyme is an $NADP^+$-dependent dehydrogenase. An example of this reaction is the oxidation of D-glucose to give D-glucuronic acid, a complex polysaccharide hyaluronic acid, found in the vitreous humor of the eye.



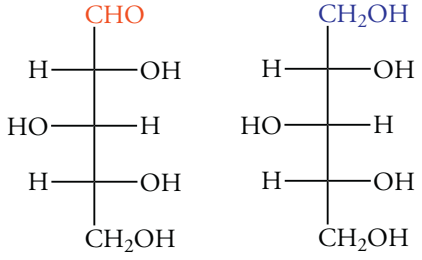
α-D-glucopyranose D-glucuronic acid

Problem 26.7

Draw the Haworth projection of the α anomer of the pyranose form of D-galactose, that is, α-D-galactopyranose.

Sample Solution

Draw a pyranose ring containing five carbon atoms and one oxygen atom. For the D configuration, the —CH_2OH group is "up," above the plane of the ring. Since galactose is the C-4 epimer of glucose, and since the hydroxyl group at C-4 is down in glucose, it is "up" in galactose. The α anomer has a hydroxyl group below the plane of the ring at the anomeric carbon atom, C-1.



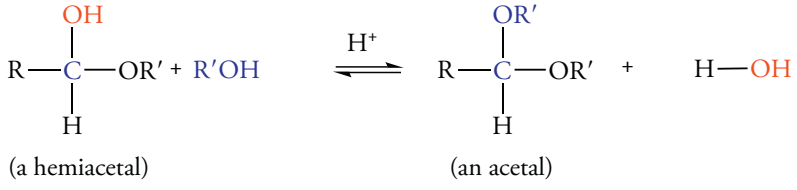
D-xylose D-xylitol

Problem 26.8

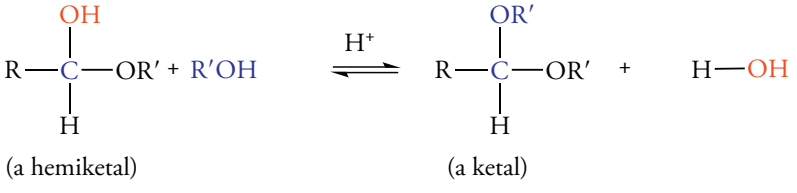
Is ribulose a reducing sugar?

26.7 GLYCOSIDES

In Chapter 19, we saw that hemiacetals and hemiketals react with alcohols to yield acetals and ketals, respectively. Acid catalyzes the reaction, shifting the equilibrium to the right if there is excess alcohol or the water that forms is removed. In this substitution reaction, an —OR group replaces the —OH group.



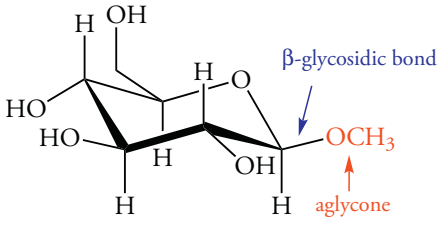
(a hemiacetal) (an acetal)



(a hemiketal) (a ketal)

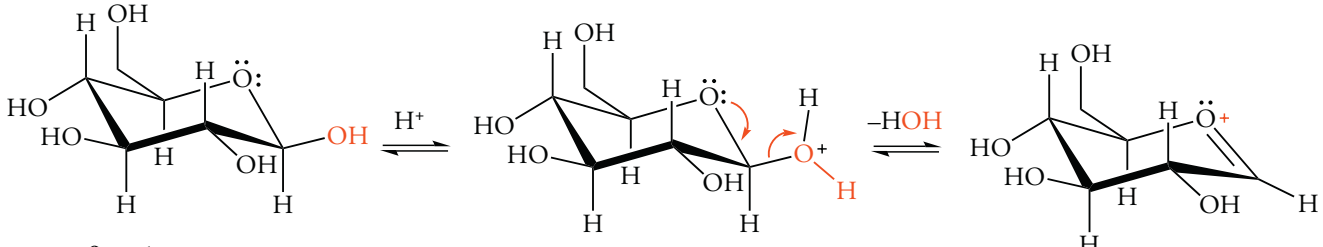
The hemiacetal and hemiketal forms of monosaccharides also react with alcohols to form acetals and ketals. These acetals and ketals are called **glycosides**, and the new carbon–oxygen bond is called a **glycosidic bond**. The group bonded to the anomeric carbon atom of a glycoside is an **aglycone**. In most aglycones, an oxygen atom from an alcohol or phenol bonds to the anomeric carbon atom. However, nucleosides, nucleotides, nucleic acids, and several coenzymes contain aglycones with a nitrogen atom.

Glycosides are named by naming the aglycone group first and then replacing the *-ose* ending of the carbohydrate with *-oside*. The configuration at the glycosidic carbon atom must be indicated as either α or β.

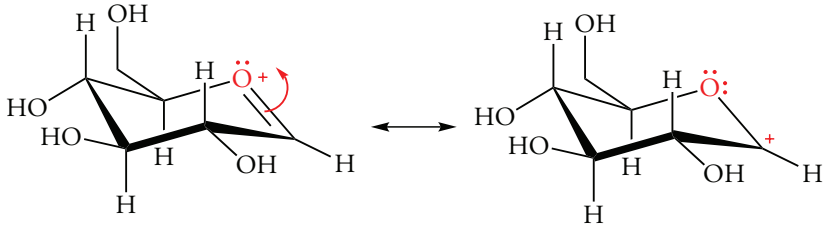


methyl β-D-glucopyranoside

Because hemiacetals and hemiketals exist in equilibrium as α or β anomers, two possible glycosides may form. Protonation of the C-1 hydroxyl group followed by loss of water yields a carbocation that is resonance stabilized by the oxygen atom in the ring. It is an acylium ion, or oxocarbocation.



β-D-glucose



resonance-stabilized oxocarbocation intermediate

This carbocation may be attacked by the nucleophilic oxygen atom of an alcohol from either the top or the bottom of the structure. Subsequent loss of a proton to the solvent yields the mixture of α and β anomers (Figure 26.7).

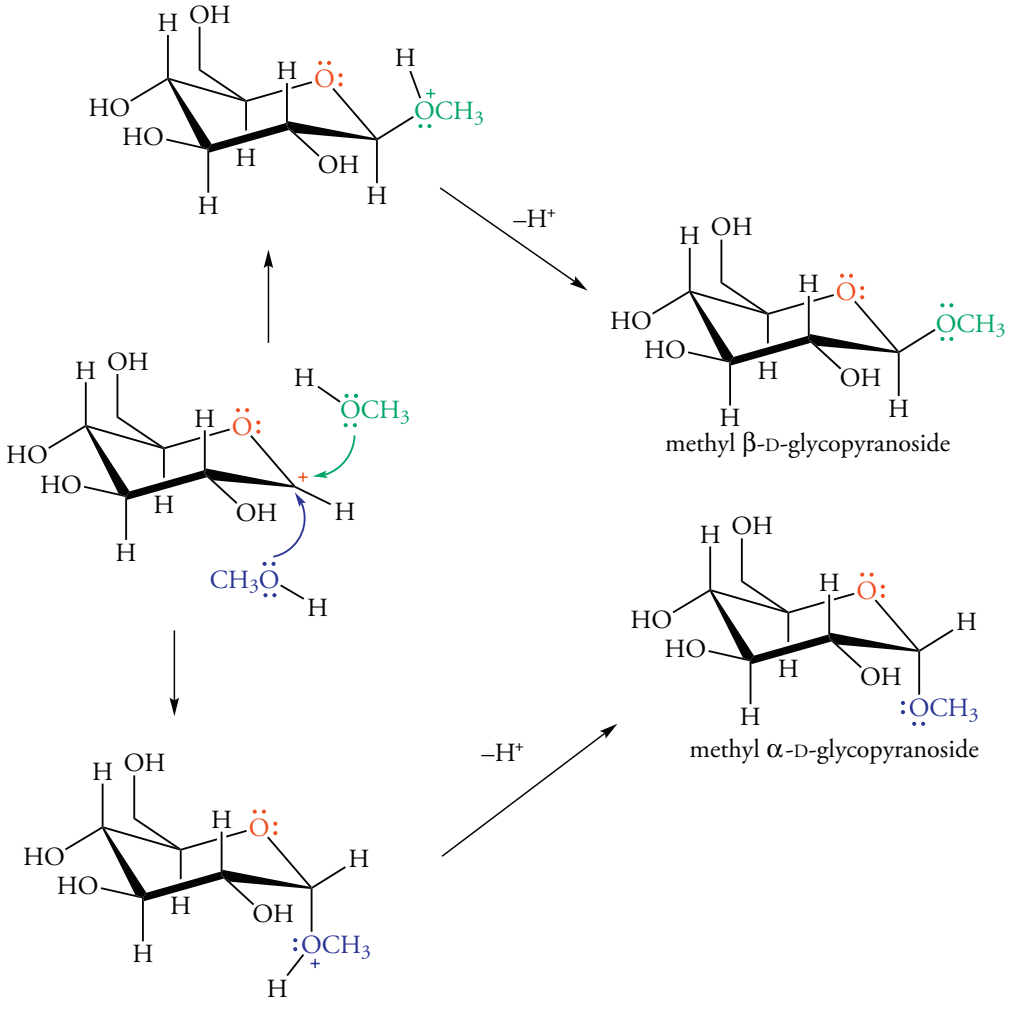


Figure 26.7 Formation of α and β Glysosides

The anomeric glycosides are diastereomers with different physical properties. Like ordinary acetals and ketals, they are stable in neutral or basic solution. Therefore, they are not reducing sugars because they do not hydrolyze to form a free aldehyde group in Benedict's solution, which is basic. However, glycosides are hydrolyzed in acid solution by the reverse of the reactions shown in Figure 26.7.

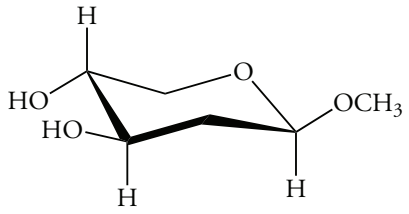
Problem 26.7

Draw the Haworth projection of the α anomer of the pyranose form of D-galactose, that is, α-D-galactopyranose.

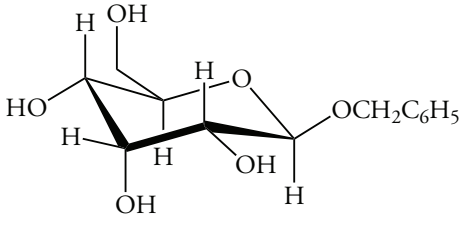
Problem 26.9

What cyclic precursors are required to form each of the following acetals?

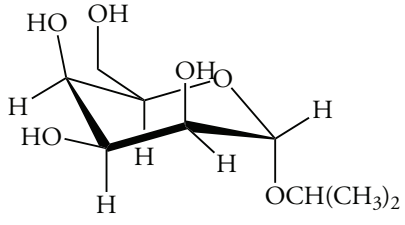
(a)



(b)



(c)



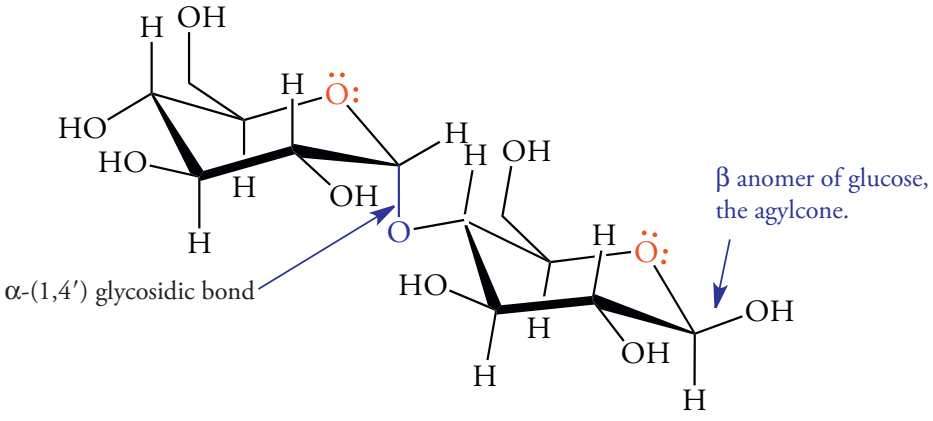
26.8 DISACCHARIDES

Disaccharides are glycoside formed from two monosaccharides. One monosaccharides unit is a hemiacetal or hemiketal. It is bonded to the second monosaccharide through its anomeric carbon, to the second monosaccharide, which is the aglycone. Disaccharides are often linked by a glycosidic bond between C-1 of the hemiacetal of an aldose to C-4 of the second monosaccharide. Such glycosidic bonds are named (1,4′). The "1" refers to the anomeric carbon of the first monosaccharide, and the "4′" refers to C-4 of the second monosaccharide. The glycosidic bond is also sometimes written as (1 → 4). Maltose, lactose, and cellobiose all have (1,4′) glycosidic bonds. The configuration at the anomeric carbon (C-1) is designated α or β, as we have seen.

In principle, any of the hydroxyl groups of the aglycone could provide the linkage between the two monosaccharides, and in fact, every possible linkage has been found in naturally occurring disaccharides. We will consider four disaccharides: maltose, cellobiose, lactose, and sucrose.

Maltose

Maltose consists of two molecules of glucose that are linked by an α-(1,4′) glycosidic bond. Maltose results from the enzymatic hydrolysis of amylose, a homopolysaccharide (Section 26.9), by the enzyme amylase. Maltose is converted to two molecules of glucose by the enzyme maltase, which hydrolyzes the glycosidic bond. Commercial maltose is produced from starch that has been treated with barley malt. Figure 26.8 shows both a bond-line structure and a molecular model of maltose.



4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranose
(maltose)

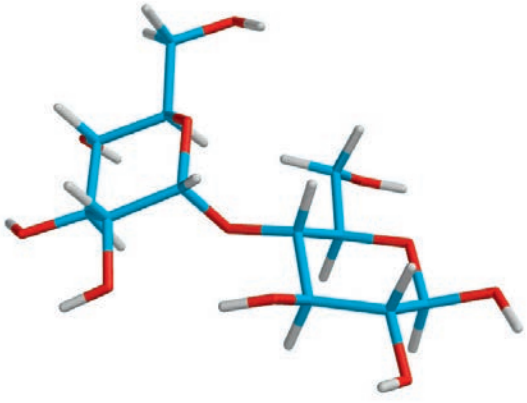


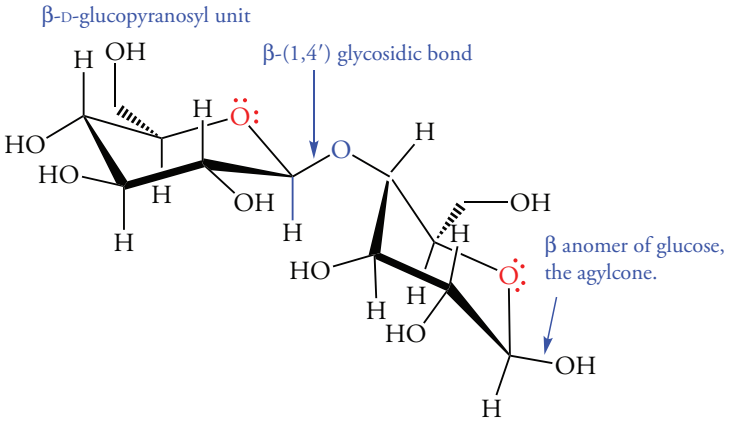
Figure 26.8 Structure of Maltose
The monosaccharide unit on the left is the hemiacetal of the α-D-glucopyranosyl unit. It is linked by an α-(1,4′) glycosidic bond to β-D-glucopyranose, the aglycone. The oxygen atom of the glycosidic bond is approximately in the center of the structure, between the two rings. It is projected down, axial, and therefore α. It is linked to C-4 of the aglycone, and so the link is axial–equatorial.

Maltose has a more formal, IUPAC of name: 4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranose. This rather forbidding name is not quite as bad as it looks. The term in parentheses refers to the glucose unit on the left, which contributes the acetal portion of the glycosidic bond. The term *-pyrano-* tells us that this part of the structure is a six-membered ring, and the suffix *-osyl* indicates that the ring is linked to a partner by a glycosidic bond. The prefix 4-*O*- refers to the position of the oxygen atom on the aglycone, the right-hand ring. The term β-D-glucopyranose describes the aglycone.

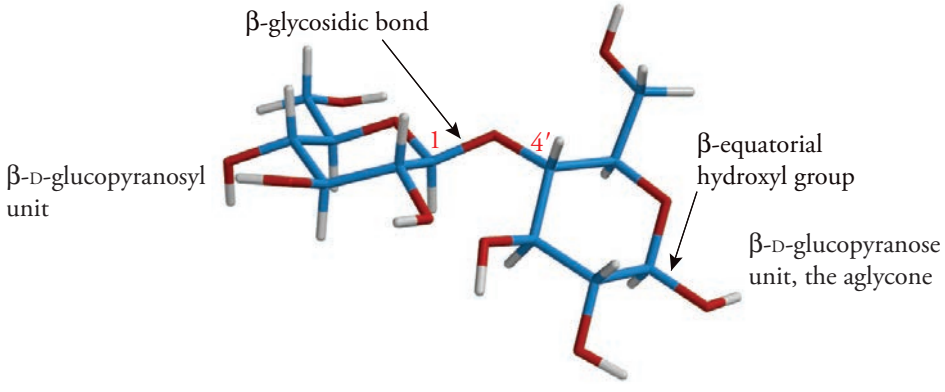
Because the aglycone is a hemiacetal, maltose undergoes mutarotation. For the same reason maltose is a reducing sugar. The free aldehyde formed by ring opening can react with Benedict's solution. The acetal part of the structure is called the "nonreducing end" of the disaccharide. If we do not want to specify the configuration of the aglycone, we use the name 4-*O*-(α-D-glucopyranosyl)-D-glucopyranose.

Cellobiose

Cellobiose consists of two molecules of glucose that are linked by an β–(1,4′) glycosidic bond. Cellobiose thus differs from maltose by its configuration at the glycosidic bond. As in maltose, the aglycone of cellobiose is a hemiacetal, and it can be either α or β. Because the aglycone is a hemiacetal, cellobiose undergoes mutarotation. For the same reason cellobiose is a reducing sugar. The free aldehyde formed by ring opening can react with Benedict's solution. Although the aglycone can be either α or β, the glycosidic bond is always β in cellobiose. Figure 26.9 shows a molecular model of cellobiose.



4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose
(cellobiose)



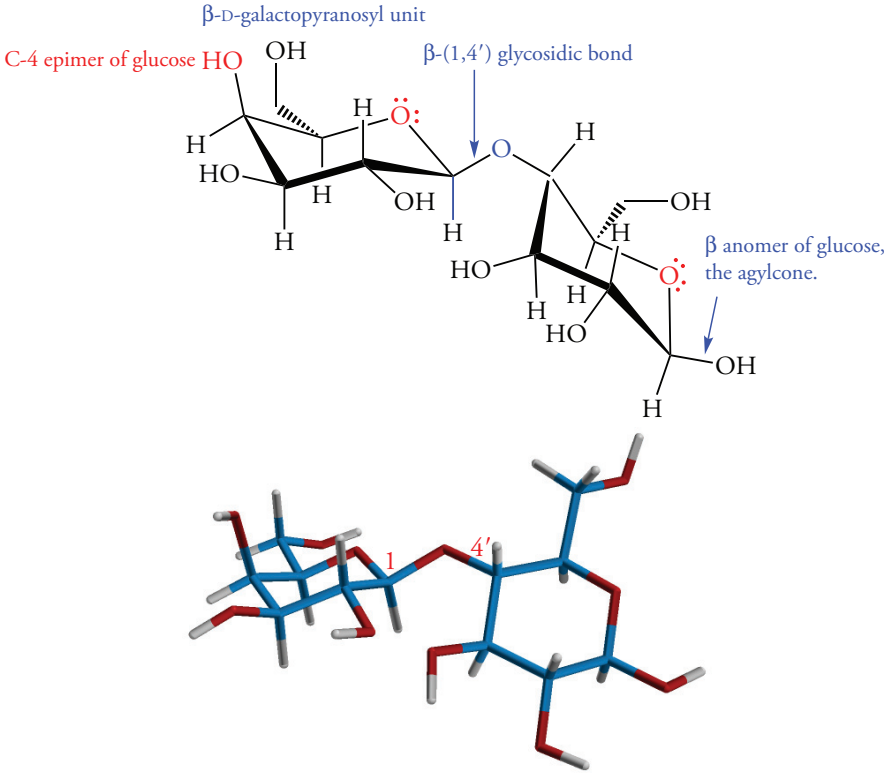
4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose
(cellobiose)

Figure 26.9 Structure of cellobiose

The monosaccharide unit on the left is the β-D-glucopyranosyl portion of cellobiose. It is linked by a β-(1,4′) glycosidic bond to β-D-glucopyranose, the aglycone. The oxygen atom of the glycosidic bond is approximately in the center of the structure, between the two rings. It is projected up, equatorial, and therefore it is β. It is linked to C-4 of the aglycone, and so the link is equatorial–equatorial.

Lactose

Lactose, often called milk sugar (Latin, *lac*, milk), is a disaccharide found in the milk of many mammals, including humans and cows. The IUPAC name of lactose is 4-*O*-(β-D-galactopyranosyl)-D-glucopyranose. We recall that galactose is the C-4 epimer of glucose, so when we reverse the configuration at C-4, the hydroxyl group switches from equatorial to axial. The pyranosyl group in both lactose and cellobiose is linked by a β-(1,4′) glycosidic bond to D-glucose. Humans have an enzyme called β-galactosidase (also known as lactase) that hydrolyzes the β-(1,4′) glycosidic bond. However, β-galactosidase does not hydrolyze the β-(1,4′) glycosidic bond in cellobiose. Figure 26.10 shows a molecular model of lactose.



4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranose
(lactose)

Figure 26.10 Structure of Lactose
The monosaccharide unit on the left is the β-D-galactopyranosyl portion of cellobiose. It is linked by a β-(1,4′) glycosidic bond to β-D-glucopyranose, the aglycone. Galactose is the C-4 epimer of glucose. Thus, the hydroxyl group at C-4, which is equatorial in glucose, is axial in galactose.

As in maltose and cellobiose, the aglycone of lactose is a hemiacetal, and it can be either α or β. Because the aglycone is a hemiacetal, lactose undergoes mutarotation. For the same reason lactose is a reducing sugar. The free aldehyde formed by ring opening can react with Benedict's solution. Thus, a solution of lactose contains both the α and β anomer at the "reducing end" of the disaccharide. Although the aglycone can be either α or β, the glycosidic bond is always β in lactose.

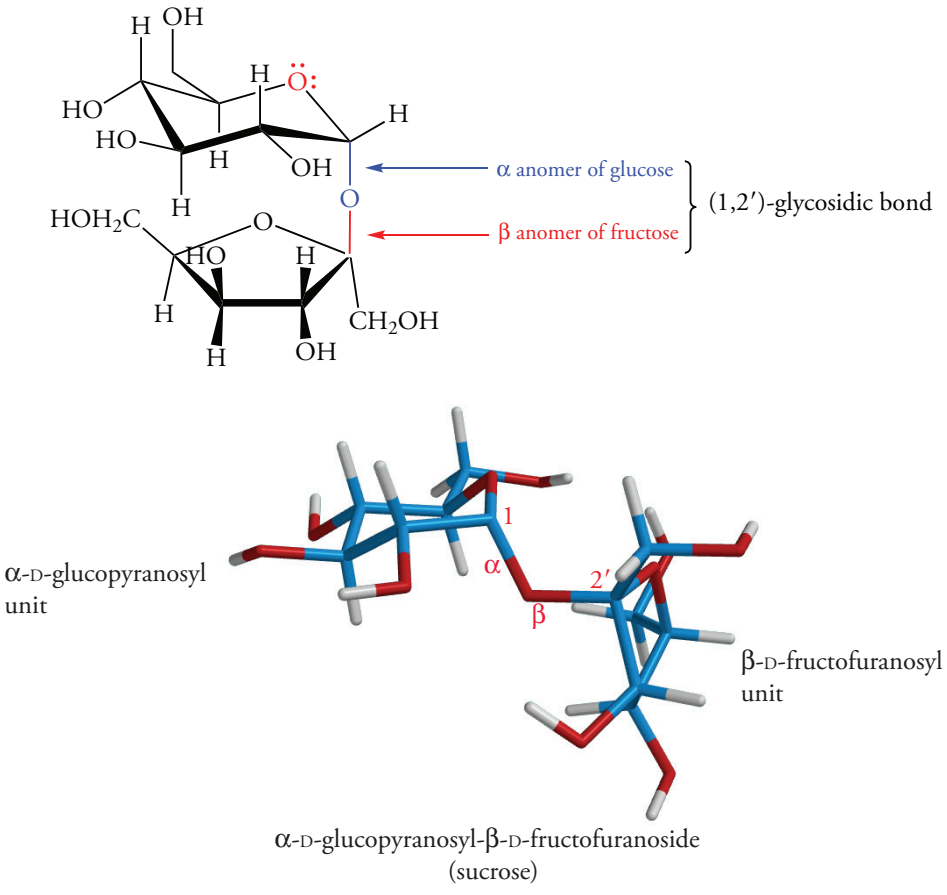
The hydrolysis of lactose gives galactose and glucose. The galactose is converted to glucose by the action of an NAD-dependent enzyme called UDP-galactose-4-epimerase. This enzyme oxidizes the C-4 hydroxyl group to a keto group and then adds a hydride anion back from the other side.

Sucrose

We noted at the start of this section that some disaccharides have a glycosidic linkage between both anomeric centers. Sucrose, common table sugar, is a disaccharide of α-D-glucpyranose and β-D-fructofuranose in which the anomeric centers are linked (1,2′). Figure 26.11 shows a molecular model of sucrose. Sucrose has both an acetal and a ketal functional group. Neither ring can exist in equilibrium with either an aldehyde or a ketone. As a result, sucrose cannot undergo mutarotation and is not a reducing sugar. The systematic name, α-D-glucopyranosyl-β-D-fructofuranoside, ends in the suffix *-oside*, indicating that sucrose is not a reducing sugar.

Figure 26.11 Structure of sucrose

The monosaccharide unit on the left is the α-D-galactopyranosyl portion of sucrose. It is linked by a (1,2′) glycosidic bond to β-D-fructofuranose. Thus, the anomeric carbons of the monomers are linked by a glycosidic bond. Sucrose is an acetal. Therefore, it is a nonreducing sugar.



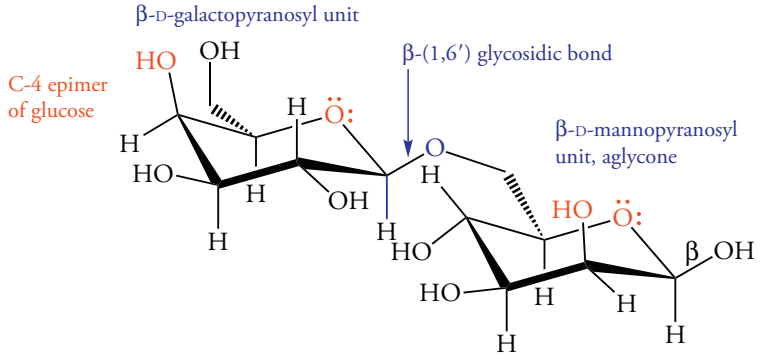
Problem 26.10

Describe the structure of the following disaccharide. Which monosaccharides does it contain, and how are they linked?

Sample Solution

The hemiacetal center located on the aglycone ring (at the right) has a hydroxyl group in the β configuration. The glycosidic bond is from C-1 of the acetal ring (on the left) to C-6 of the aglycone ring. Furthermore, the oxygen bridge is formed through the β-glycosidic bond. Thus, the bridge is β-(1,6′).

Next examine both rings to determine the identity of the monosaccharides. The ring on the left is galactose, the C-4 epimer of glucose. The ring on the right is mannose, the C-2 epimer of glucose. Mannose has an axial hydroxyl group at C-2. The compound is 6-*O*-(β-D-galactopyranosyl)-β-D-mannopyranose.



6-*O*-(β-D-galactopyranosyl)-β-D-mannopyranose

26.9 POLYSACCHARIDES

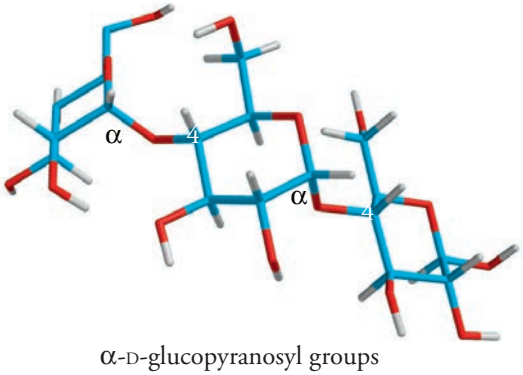
As their name indicates, polysaccharides contain many monosaccharide units. If they are all the same, the molecule is a homopolysaccharide. The polymers **amylose** and **amylopectin** are examples of homopolysaccharides in which all the monomers are glucose. If the polymer contains two or more different kinds of monosaccharides, it is a heteropolysaccharide. Examples of heteropoylsaccharides include hyaluronic acid; heparin, an anticoagulant in blood; and chondroitin, a component of cartilage and tendons. The structures of heteropolysaccharides are more complex than those of homopolysaccharides, and we will discuss only homopolysaccharides.

The homopolysaccharide starch contains only glucose. Potatoes, rice, wheat, and other cereal grains contain starch. About 20% of starch is amylose and 80% amylopectin. Because starch is a mixture of amylose and amylopectin, it has a variable "molecular weight" that depends on its source.

Amylose is a linear polymer with 200–2000 α-D-glucopyranosyl units linked by α-(1,4′) glycosidic bonds. The molecular weight of amylose from various sources ranges from 40,000 to 400,000. When we say that a polymer is "linear," we do not mean that the polymer chain travels in a straight line, but that is has no branches. In fact, amylose coils into a helix. Figure 26.12 shows a three-residue fragment of amylose.

Amylopectin is a branched polymer of α-D-glucopyranosyl units. As in amylose, the backbone of amylopectin is linked by α-(1,4′) glycosidic bonds. The branches in amylopectin link short chains of amylose by α-(1,6′) glycosidic bonds. Each chain in amylopectin contains about 25 α-D-glucopyranosyl units (Figure 26.13). The molecular weight of amylopectin can be as high as 1 million. An amylopectin molecule can have as many as 300 interconnected chains.

Starch is synthesized by plants. Animals contain a glucose storage polymer that is closely related to starch called **glycogen**. Glycogen resembles amylopectin, but glycogen has more, and shorter, branches than amylopectin. The average chain length in glycogen is 12 glucose units. Glycogen has a molecular weight greater than 3 million. Glycogen is a source of metabolic energy during periods of diminished food intake. Although cells throughout the body store glycogen, the liver stores the largest amount. An average adult carries enough glycogen for about 15 hours of normal activity.



α-D-glucopyranosyl groups
(trisaccharide fragment of amylose)

Figure 26.12 Three α-D-Glucopyranosyl Groups in Amylose When we say that a polymer is "linear," we do not mean that its conformation maps onto a straight line, but that the polymer contains no branches. In fact, amylose coils into a helix.

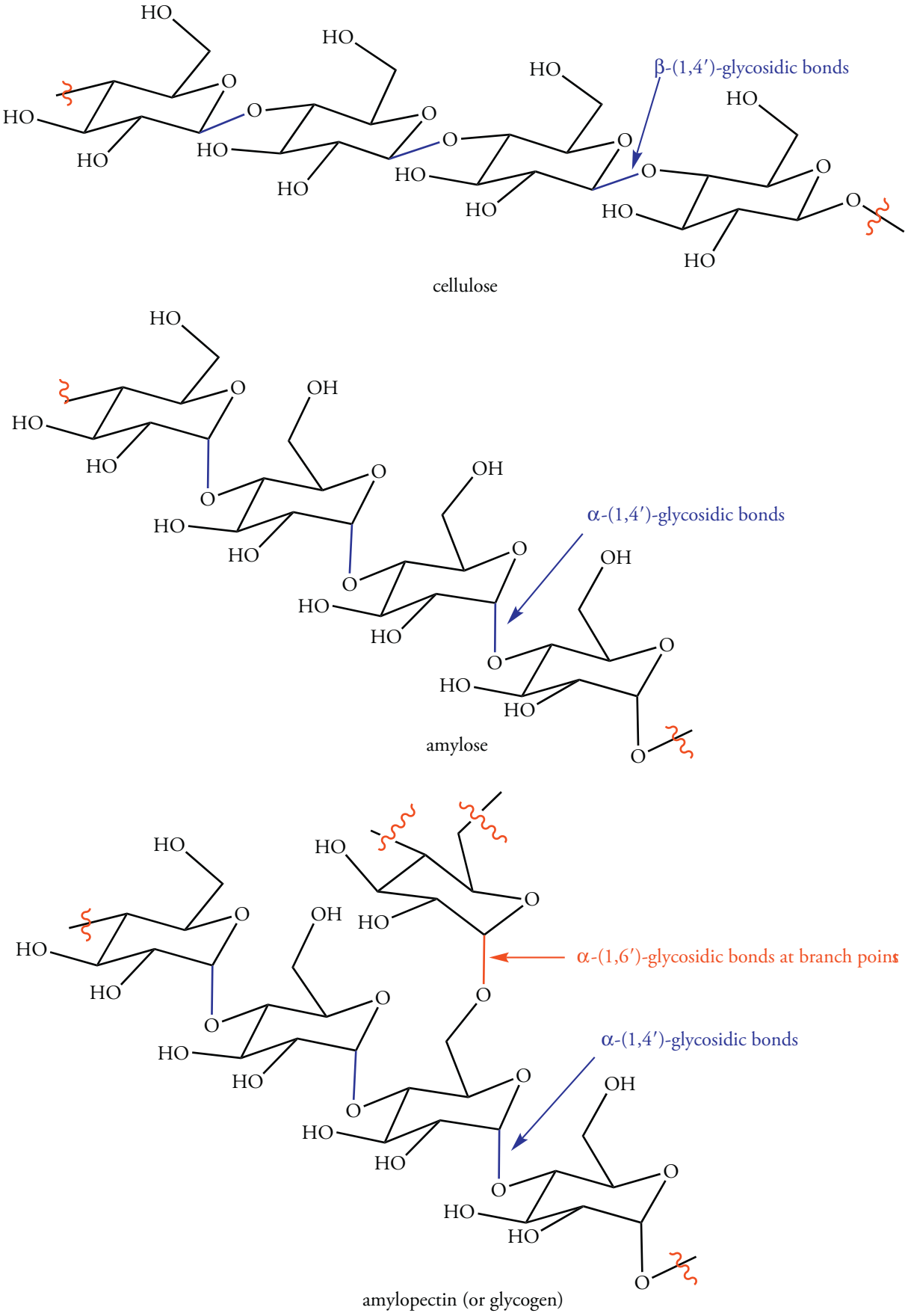


Figure 26.13 Structures of Polysaccharides

Cellulose is a polymer of β-glucopyranosyl residues that are linked β-(1,4′). The size of cellulose molecules depends upon their source. They typically contain 5000–10,000 glucose units (Figure 26.13). Certain algae produce cellulose molecules with more than 20,000 glucose units.

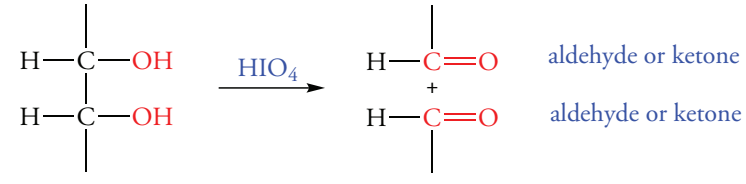
Starch and cellulose differ by one structural feature, but this difference has great biological importance. Starch, whose glucosyl units are linked α-1,4′, can be digested by most animals. Cellulose, whose glucosyl units, can be digested only by certain microorganisms and animals that harbor these microorganisms in their digestive tracts. These microorganisms produce enzymes that hydrolyze β-(1,4′) glycosidic bonds.

26.10 CHEMICAL DETERMINATION OF MONOSACCHARIDE STRUCTURES

In many areas of chemistry, chemical methods of structure proof have given way to spectroscopic methods (Chapter 14) and analysis by mass spectrometry. In the field of carbohydrate chemistry, however, chemical reactions play an important part in the elucidation of the structures of unknown carbohydrates. The reason for this is that many proteins and lipids contain carbohydrates that have very complex structures, and these do not yield easily to spectroscopic methods. Also, since it is notoriously difficult to crystallize many carbohydrates, proof of structure by X-ray crystallography is often not possible. In this section we will discuss methods for determining determine the structure of a monosaccharide by chemical methods. Several synthetic reactions can be used to convert one monosaccharide into another. If the structure of a related monosaccharide is known, and the mechanism of the reaction that interconverts them is well understood, then the structure of the unknown monosaccharide can be established.

Periodate Oxidation

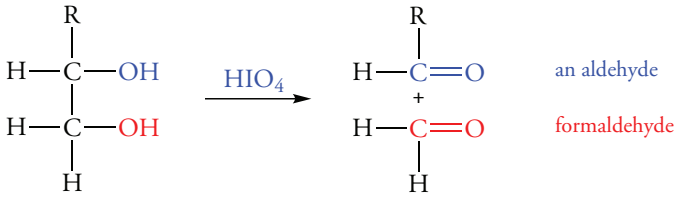
We recall that periodate cleaves vicinal diols to give carbonyl groups at each carbon atom originally bearing a hydroxyl group. One mole of periodate is required for each carbon–carbon bond cleaved.



vicinal diol in monosaccharide

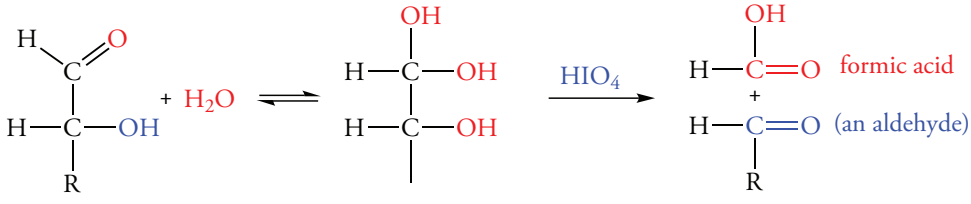
The reaction of monosaccharides with periodate gives a mixture of oxidation products that result from the degradation of the entire molecule. The products include formaldehyde, formic acid, and carbon dioxide. The number of equivalents of each oxidation product indicates whether the monosaccharide is an aldose or a ketose and how many adjacent centers have oxygen-containing functional groups. Glucose reacts with five moles of periodate to give one mole of formaldehyde and five moles of formic acid. Fructose also reacts with five moles of periodate, but gives two moles of formaldehyde, three moles of formic acid, and one mole of carbon dioxide.

We will examine the products that would result from cleaving of all the possible combinations of bonds in a monosaccharide. We will do so by considering various subunits of the structure. However, all the subunits react, so we must analyze all carbon–carbon bonds and the attached functional groups to determine the products that can form. First, consider the subunit that contains a primary hydroxyl group. This structural feature exists at the highest numbered carbon atom of an aldose. The unit also occurs at C-1 and the highest numbered carbon atom of a ketose.



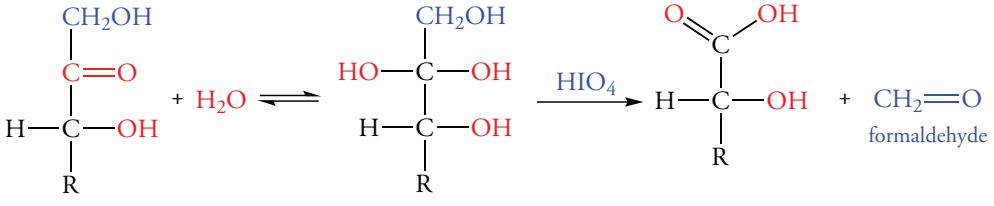
vicinal diol at
1° alcohol

We recall that carbonyl groups react with water to give hydrates, and that the equilibrium constant for forming hydrates is greater for aldehydes than for ketones. The carbonyl groups of carbohydrates also form hydrates, and they react with periodate. Oxidation of the hydrated aldehyde yields formic acid. This reaction does not stop after one oxidation step. The aldehyde group is oxidized to formic acid in the first step, and each secondary alcohol that is oxidized to an aldehyde by periodate in the first step gives a mole of formic acid in subsequent oxidation steps. That's why oxidation of glucose yields five moles of formic acid.



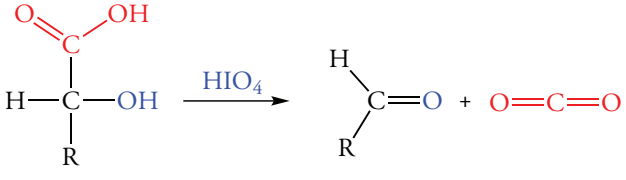
(an aldose)

Ketones also form hydrates, although in smaller amounts than aldehydes. Nevertheless, when a hydrate forms, it is cleaved to give a carboxylic acid. Even though there is only a small concentration of hydrated ketone, its subsequent removal by oxidation pulls the reaction to completion.



(a ketose) (a carboxylic acid)

In a subsequent step, the hydroxyl group of the carboxylic acid and a hydroxyl group at the α-carbon atom form an iodate ester and the carbon–carbon bond is cleaved. Oxidation of the carboxylic acid group yields carbon dioxide.

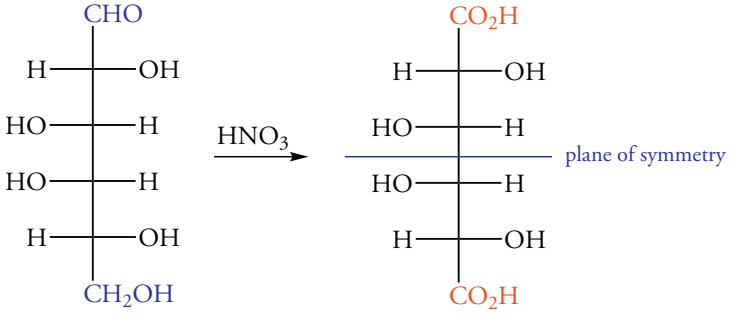


Thus, the carbon dioxide from the periodate oxidation of fructose is derived from C-2. The primary alcohols of C-1 and C-6 yield formaldehyde. All the secondary alcohols yield formic acid. The number of equivalents of periodate consumed indicates the number of carbon atoms in the monosaccharide that can be oxidized. The following functional groups are identified by the oxidation products:

1. Primary alcohols give formaldehyde.
2. Secondary alcohols give formic acid.
3. Aldehydes give formic acid.
4. Ketones give carbon dioxide.

Oxidation and Optical Activity

We recall dilute nitric acid oxidizes aldoses to aldaric acids. The symmetry properties of the aldaric acid provide information about the possible configurations of the secondary hydroxyl groups. If the aldonic acid formed by oxidation is optically inactive, the hydroxyl groups occur in a symmetrical arrangement. For example, D-galactose gives an optically inactive aldaric acid



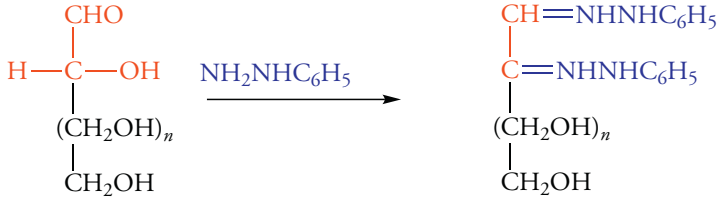
D-galactose optically inactive aldaric acid

This experiment by itself does not establish the identity of D-galactose because D-allose also gives an optically inactive aldaric acid. However, this experiment separates the aldohexoses into two groups of compounds: the six that give optically active aldaric acids and the two that give optically inactive aldaric acids. Additional methods are required in conjunction with this method to determine the structure.

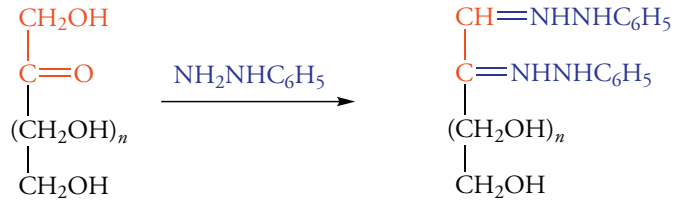
Formation of Osazones

Because they have many hydroxyl groups, monosaccharides are very soluble in water, and they are difficult to crystallize. Long ago, Emil Fischer found that phenylhydrazine reacts with monosaccharides to give yellow crystalline derivatives called osazones. The identity of an "unknown" monosaccharide can be established by comparing the melting point of its osazone with those of known osazones.

We recall that hydrazine and 2,4-dinitrophenylhydrazine react with carbonyl compounds to give hydrazones. However, monosaccharides do not give simple phenylhydrazone derivatives. After the initial formation of a phenylhydrazone, further reaction occurs to give the osazone, which has two molecules of phenylhydrazine incorporated into it.



(an aldose) (an osazone)



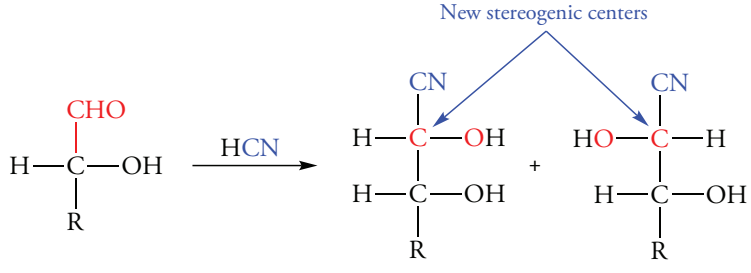
(a ketose) (an osazone)

The formation of an osazone from the initial hydrazone results from oxidation of the adjacent alcohol to a carbonyl by one mole of phenylhydrazine. We will not consider the mechanism of this reaction, but the by-products are aniline, ammonia, and water. The carbonyl group generated then reacts with another molecule of phenylhydrazine to give the second phenylhydrazone unit. The product precipitates at this point, and no further reaction occurs.

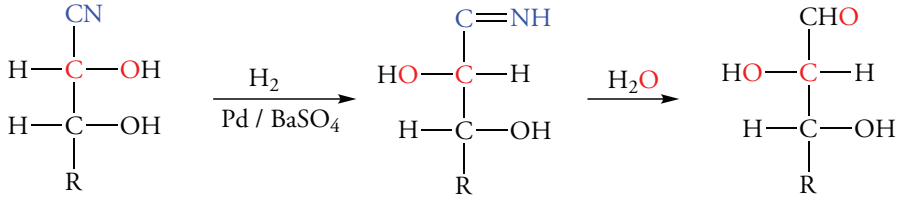
Two aldoses that are C-2 epimers give the same osazone because the C-2 stereogenic center is converted to a trigonal center in the osazone. Therefore, both mannose and glucose give the same osazone. The method can be used to establish the configuration of all stereogenic centers in a compound if its osazone is identical to the osazone of another compound whose total configuration is known. Only the configuration of one center is reversed in the "unknown" compound compared to the known compound. However, there is a structurally related ketose that also gives the same osazone. Fructose, glucose, and mannose all give the same osazone because the configurations of C-3, C-4, and C-5 are the same in all three compounds.

Chain Extension of Aldoses

The Kiliani–Fischer synthesis extends chains of monosaccharides using the formation of a cyanohydrin to generate the additional stereogenic center. In the first step, one enantiomeric form of an aldose reacts with HCN to give a mixture of diastereomeric cyanohydrins. We recall that the formation of an additional stereogenic center in a chiral compound results in some stereoselectivity. A mixture results, but because diastereomers have different physical properties, the reaction mixture can be separated to give two cyanohydrins.

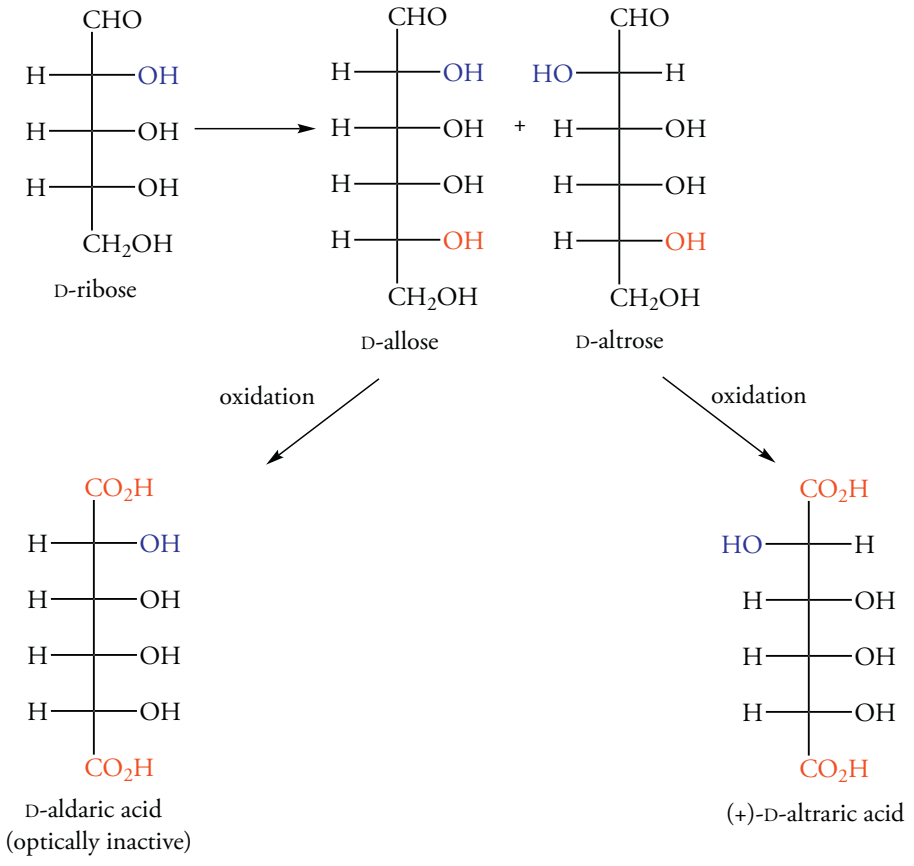


In the second step of the Kiliani–Fischer synthesis, the nitrile is partially reduced to an imine using a deactivated palladium catalyst similar to the Lindlar catalyst used to partially reduce alkynes to alkenes. The imine hydrolyzes to form an aldehyde under the reaction conditions.



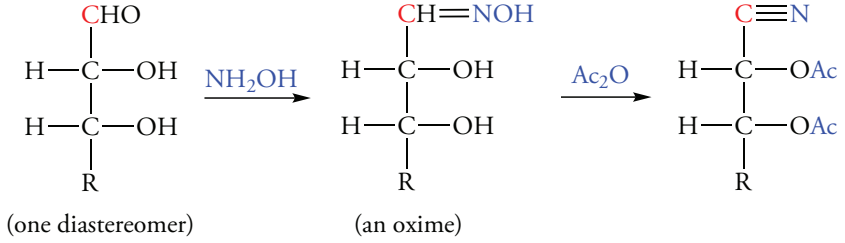
(one diastereomer) (one imine intermediate) (an extended aldose)

Because two products form, we still need information from other reactions to establish the structure of each. For example, ribose gives two structures whose configuration at all centers except C-2 is known. One product is oxidized to give an optically inactive glycaric acid. It must be allose. The other product must therefore then be altrose. If altrose is oxidized, the product is an optically active aldaric acid.

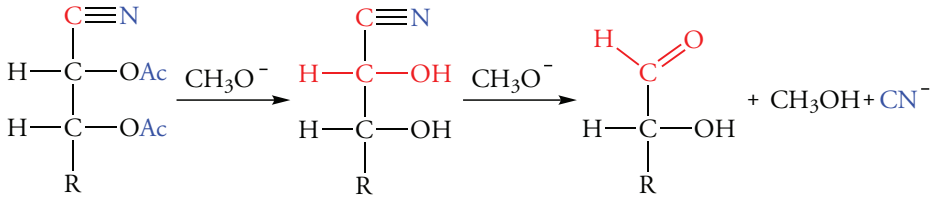


Chain Shortening of Aldoses

The **Wohl degradation** shortens an aldose chain by one carbon atom in a series of steps, one of which is loss of HCN from a cyanohydrin. In the first step, an oxime forms. Then, acetic anhydride is used to dehydrate the oxime and form a nitrile. All hydroxyl groups are converted into acetate esters under the reaction conditions.



In the third step, sodium methoxide is used to remove the acetate groups. The methoxide ion attacks the carbonyl carbon atom to form a tetrahedral intermediate, from which the aldose subsequently leaves. The removal of all acetate groups yields a cyanohydrin. Under basic conditions, it loses HCN to yield a chain-shortened aldose.



The total transformation converts the original C-2 stereogenic center into an aldehyde carbon atom. The stereochemistry of the remaining stereogenic centers is undisturbed, so a single product results. In the case of glucose, the product is arabinose. Because mannose is the C-2 epimer of glucose, the Wohl degradation of mannose also yields arabinose. The method therefore establishes that the configurations of all other carbon atoms except C-2 are identical in glucose and mannose.

Problem 26.11

(a) What are the products of the periodate oxidation of 2-deoxyribose? (b)How many moles of periodate are required for complete oxidation?

Problem 26.12

Draw the structures of an aldose and a ketose that give the same osazone as xylose.

Problem 26.13

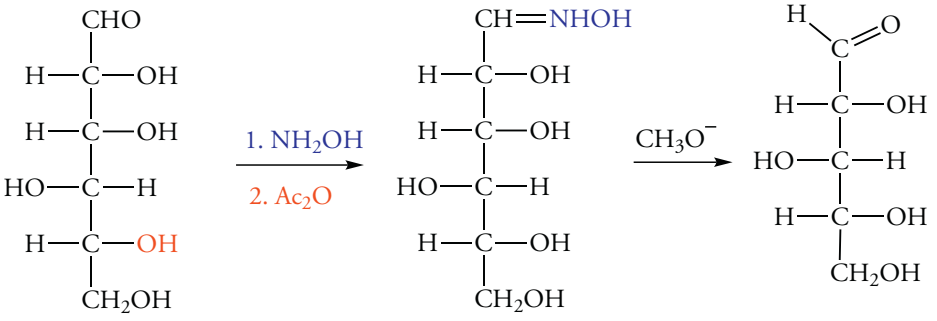
(a) What are the products of the Kiliani–Fischer chain extension of D-ribose? (b) Which products, if any, would give an optically inactive aldaric acid when oxidized by nitric acid?

Problem 26.14

(a) What is the product of the Wohl degradation of gulose? (b) Will the aldaric acid resulting from oxidation by nitric acid be optically active or inactive?

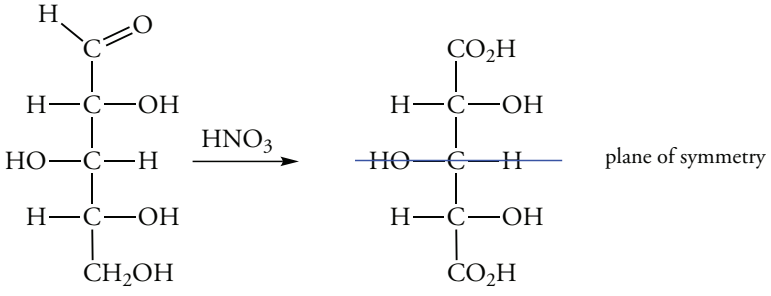
Sample Solution

Formation of an oxime followed by acetylation and subsequent hydrolysis gives a chain-shortened aldose. The configuration of the C-2, C-3, and C-4 chiral centers of the product is the same as the C-3, C-4, and C-5 of gulose.



D-gulose D-xylose

Oxidation of the aldopentose (which is xylose) gives an aldaric acid called xylaric acid that has a plane of symmetry and is optically inactive.

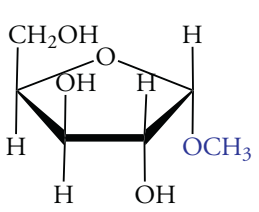


xylaric cid

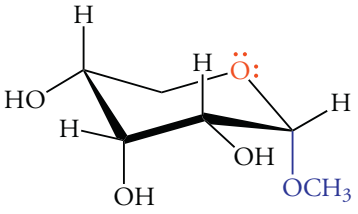
26.11 DETERMINATION OF RING SIZE

To determine the ring size of a monosaccharide, it is necessary to maintain the ring and prevent it from equilibrating with other isomeric structures. Because glycosides have "protected" anomeric centers, they do not undergo mutarotation, and they do not react with most reagents under neutral or basic conditions. Hence, chemical reactions can be carried out at other sites in the glycoside to determine the ring size and configuration of the monosaccharide.

First, the monosaccharide is treated with methanol and HCl to obtain the methyl glycoside. The methyl glycosides of the furanose and pyranose forms of D-ribose provide an example.

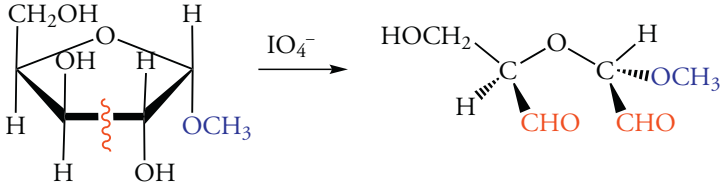


methyl α-D-ribofuranoside



methyl α-D-ribopyranoside

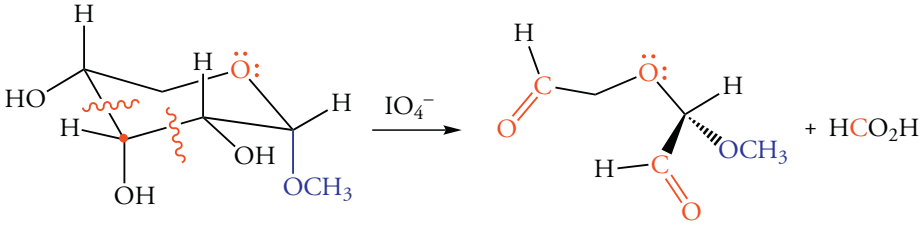
There is only one vicinal arrangement of hydroxyl groups in the furanoside. Therefore, only one equivalent of periodate reacts, and a dialdehyde product forms. (In practice, this product is somewhat unstable, and it is oxidized using bromine water to give the more stable diacid.)



methyl α-D-ribofuranoside dialdehyde product

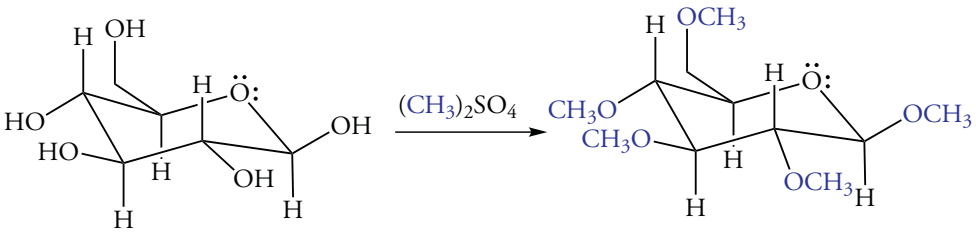
The configuration at the stereogenic center that corresponds to the original C-4 atom in the glycoside indicates whether the monosaccharide is D or L. The product of a D-monosaccharide has the *R* configuration at that center. The configuration at C-1 of the glycoside remains in the dialdehyde (or diacid) product. If it is *S*, the glycoside is the α anomer.

The pyranoside therefore gives different results than the furanoside. Two bonds are cleaved in the pyranoside, and one mole of formic acid is produced from C-3.



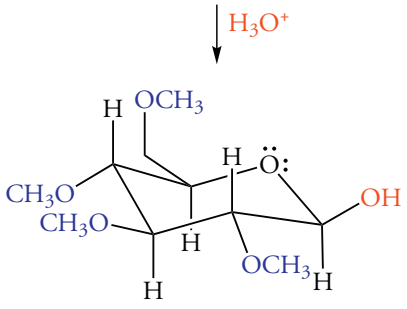
methyl α-D-ribopyranoside dialdehyde product

The size of the ring of a monosaccharide can also be determined by treating it with dimethyl sulfate, which methylates all hydroxyl groups. For example, β-D-glucopyranoside reacts with dimethyl sulfate to give methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside. Treating the glycoside with dilute acid hydrolyzes the acetal. Because all other oxygen atoms are protected as ethers, they do not hydrolyze under the mild acid conditions that hydrolyze acetals.



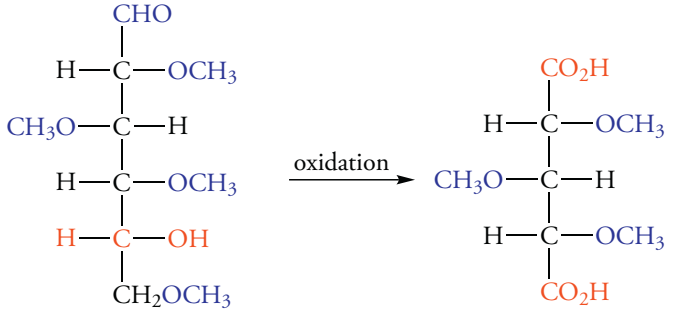
β-D-glucopyranose

methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside



2,3,4,6-tetra-*O*-methyl-β-D-glucopyranose

Because the original monosaccharide was a pyranose, the only "free" hydroxyl group in the open-chain form is at C-5. Vigorous oxidation breaks the C-5 to C-6 bond, and gives a diacid with one less carbon atom than the original monosaccharide. The ether functional groups are unaffected, and the configurations at stereogenic centers C-2, C-3, and C-4 remain the same as they were in D-glucose.



2,3,4,6-tetra-*O*-methyl-D-glucose

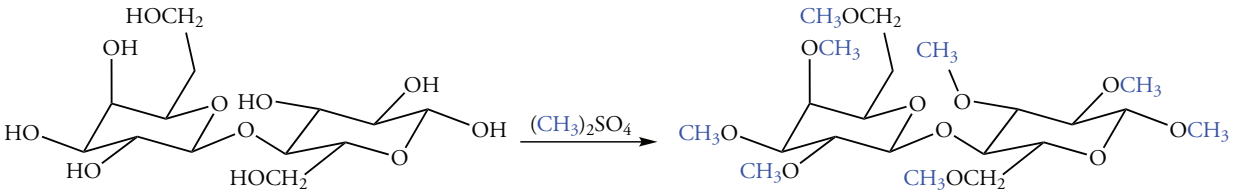
dicarboxylic acid product

26.12 STRUCTURE OF DISACCHARIDES

In determining the structure of a disaccharide, hydrolysis data establish the identity of the component monosaccharides. However, three questions remain.

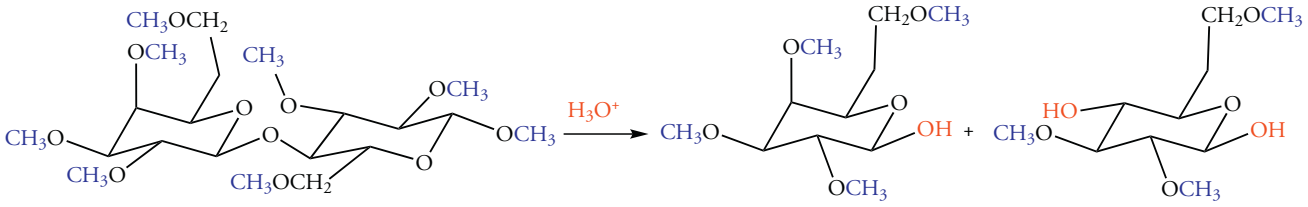
1. What is the configuration at the acetal or ketal center?
2. What are the sites of the glycosidic linkage?
3. Are the component monosaccharides furanoses or pyranoses?

The configuration at the acetal center is often established using enzymes that stereospecifically hydrolyze both the types of monosaccharide, and the configuration of the glycosidic center. For example, the enzyme β-galactosidase cleaves only the β-glycosidic linkage of galactose. The site of a glycosidic linkage is established by complete methylation of the disaccharide followed by hydrolysis. For example, methylation of lactose yields octamethyllactose. Seven of the methyl groups are present as ethers and one as a methyl glycoside.



lactose octamethyllactose

Hydrolysis of the octamethyllactose with dilute acid cleaves the glycosidic linkage joining the two monosaccharides and the methyl glycoside. The products are 2,3,4,6-*O*-tetramethyl-D-galactose and 2,3,6-*O*-trimethyl-D-glucose.



octamethyllactose 2,3,4,6-tetra-*O*-methyl-D-galactoset 2,3,6-tri-*O*-methyl-D-glucose

Hydrolysis of the octamethyllactose with dilute acid cleaves the glycosidic linkage joining the two monosaccharides and the methyl glycoside. The products are 2,3,4,6-*O*-tetramethyl-D-galactose and 2,3,6-*O*-trimethyl-D-glucose.

The structure of 2,3,4,6-*O*-tetramethyl-D-galactose is established by vigorous oxidation to a five-carbon carboxylic acid. Since the hydroxyl group at C-5 was the only one not methylated, galactose must exist as a pyranose.

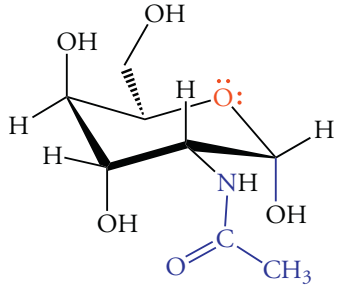
Hydroxyl groups at both C-4 and C-5 are not methylated in the oxidation product derived from glucose. If the glycosidic linkage with galactose was with C-4 of glucose, then glucose would have to exist as a pyranose using the C-5 hydroxyl group. However, if the glycosidic linkage with galactose was with C-5 of glucose, then glucose would have to exist as a furanose formed from the C-4 hydroxyl group.

26.13 HUMAN BLOOD GROUP ANTIGENS

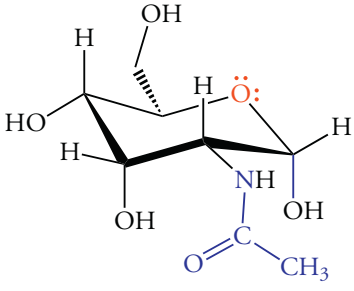
Complex carbohydrates coat the surfaces of nearly all human cells, acting as markers called **antigenic determinants** that identify the cell. Some of these markers identify the cell as "self." These molecules enable the immune system to avoid attacking the body's own cells, instead recognizing and destroying foreign cells.

Human blood cells contain antigenic determinants that divide blood into three major types, designated A, B, and O. The classification of blood groups relies upon differences in the structures of oligosaccharides bound to a protein called glycophorin that is embedded in the membrane of red blood cells (erythrocytes).

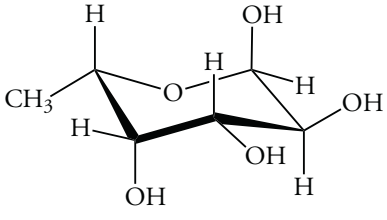
The blood group oligosaccharides contain several monosaccharides: galactose (Gal), *N*-acetylgalactosamine (GalNAc), and *N*-acetylglucosamine (GlcNAc). They also contain the rather unusual sugar 6-deoxyl-α-L-galactose, which has the common name α-L-fucose.



N-acetylgalactosamine (GalNAc)



N-acetylglucosamine (GlcNAc)



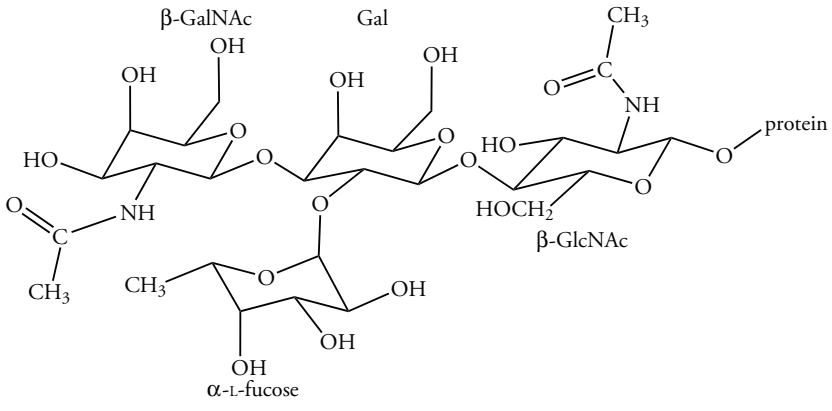
6-deoxy-α-L-galactose (α-L-fucose)

The α-L-fucose moiety of each blood group is attached to a trisaccharide in blood groups A and B and to a disaccharide in blood group O. In each oligosaccharide, the β-galactose residue is attached to α-L-fucose by an α-1,2′-glycosidic bond. The sugar at the reducing end of these oligosaccharides is linked to glycophorin by an α-glycosidic bond to the hydroxyl group of a serine residue in the protein.

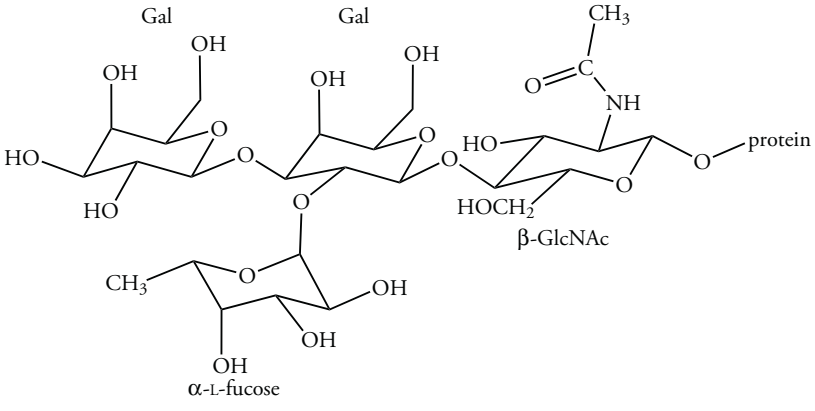
Each blood group is further subdivided into two types of chains called type 1 and type 2 that differ in their glycosidic linkages. In a type 1 chain, the β-Gal moiety is linked to β-GlcNAc by a 1,4′-glycosidic bond. In a type 2 chain, the β-Gal moiety is linked to β-GlcNAc by a 1,3′glycosidic bond.

A person with type A blood makes antibodies that attack type B blood, forming clumps of type B cells. Similarly, a person with type B blood makes antibodies that attack type A blood, forming clumps of type A cells. However, a person with type A or type B blood does not make antibodies to type O blood. Thus, type O persons are called "universal donors." They are not, however, universal acceptors because they produce antibodies to both type A and type B blood.

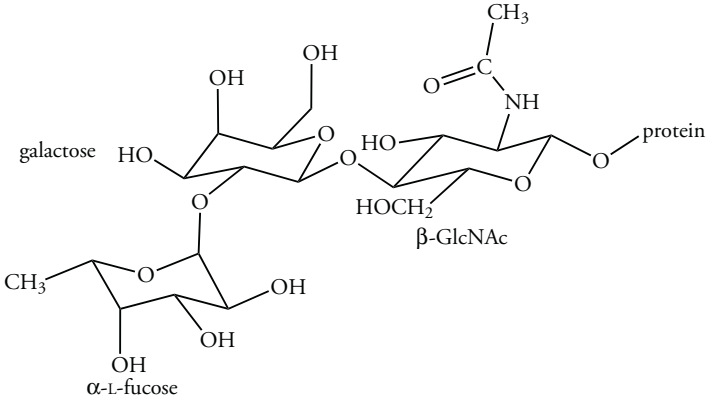
Type A



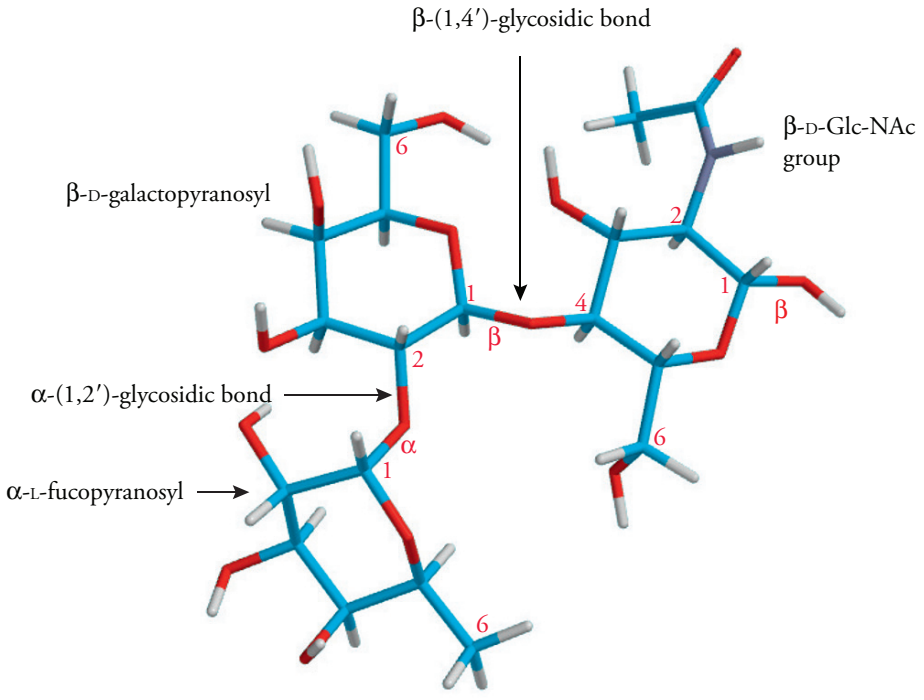
Type B



Type O



The three-dimensional conformations of these blood groups are highly complex, as the molecular model for the type O blood group shows.

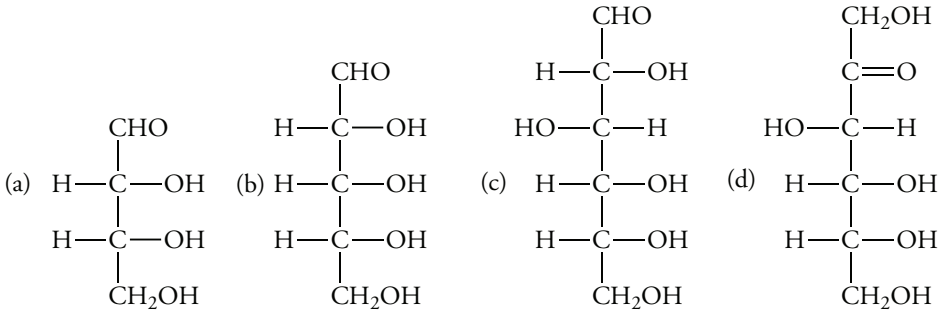


Type O Blood Group Antigen

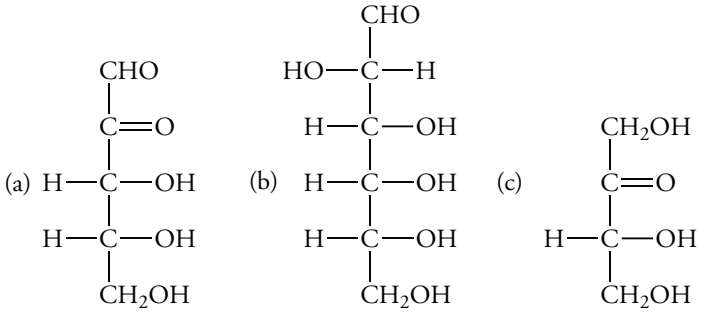
EXERCISES

Classification of Monosaccharides

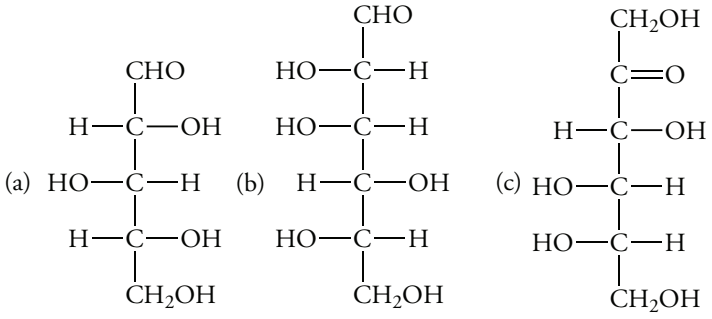
26.1 Classify each of the following monosaccharides.



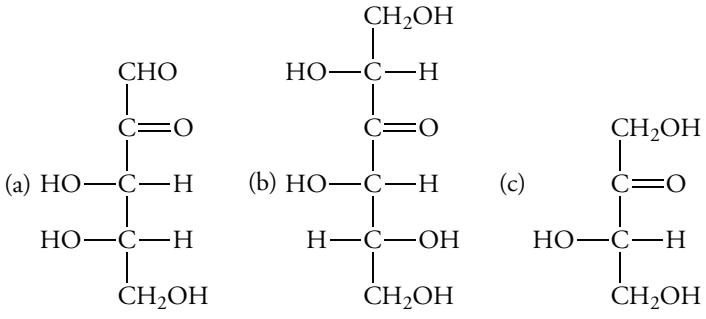
26.2 Classify each of the following monosaccharides.



26.3 Classify each of the following monosaccharides.



26.4 Classify each of the following monosaccharides.



Fischer Projection Formulas

26.5 Draw the Fischer projection formulas of the isomeric D-3-ketopentoses.

26.6 Draw the Fischer projection formulas of the isomeric D-3-ketohexoses.

26.7 Draw the Fischer projection formula of each of the following monosaccharides.
(a) L-xylose (b) L-erythrose (c) L-galactose (d) L-ribose (e) L-fructose

26.8 Draw the Fischer projection formula of each of the following monosaccharides.
(a) 6-deoxy-L-galactose (b) 3-deoxy-D-ribose (c) 2,6-dideoxy-D-allose (d) 6-deoxy-L-mannose

Haworth Projection Formulas

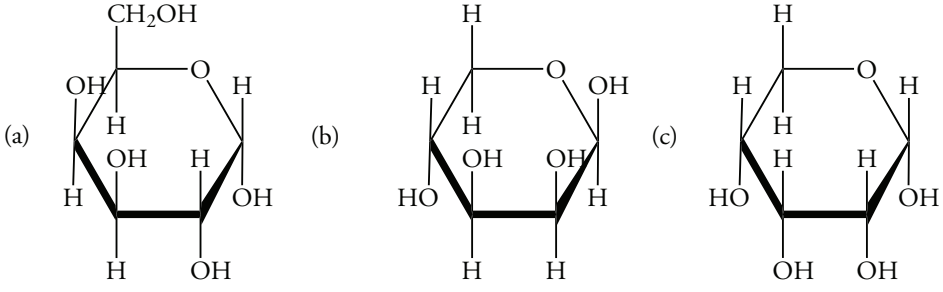
26.9 Draw the Haworth projection formula of the hemiacetal of 5-hydroxyhexanal.

26.10 Draw the Haworth projection formula of the hemiketal of 5-hydroxy-2-hexanone.

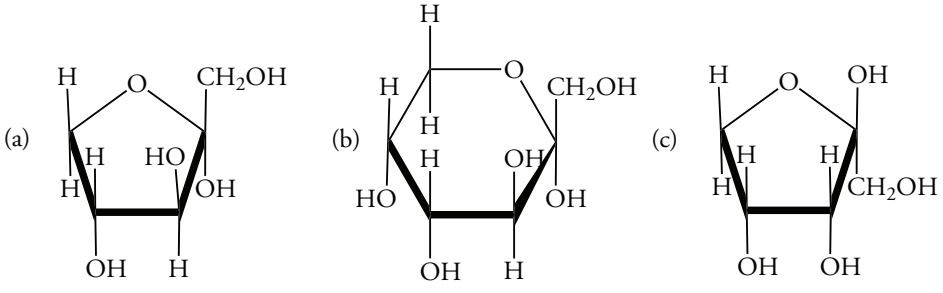
26.11 Draw the Haworth projection formula of the pyranose form of each of the following compounds.
(a) α-D-mannose (b) β-D-galactose (c) α-D-glucose (d) α-D-galactose

26.12 Draw the Haworth projection formula of the pyranose form of each of the following compounds.
(a) α-D-fructose (b) β-D-fructose (c) α-D-ribulose (d) β-D-xylulose

26.13 Identify the monosaccharide represented by each of the following structures. Name each compound.



26.14 Identify the monosaccharide represented by each of the following structures. Name each compound.

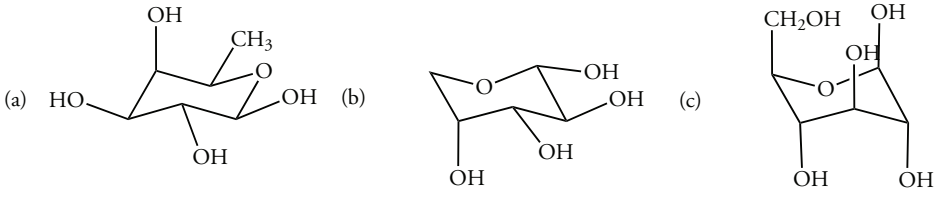


Conformations of Monosaccharides

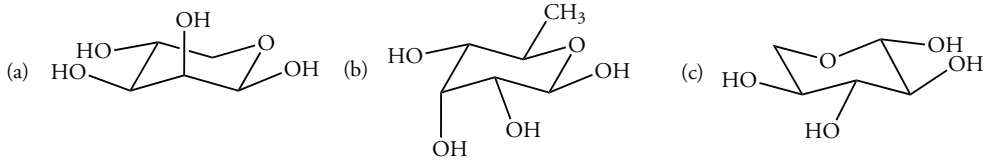
26.15 Draw the chair conformation of β-galactopyranose and β-mannopyranose, and compare the number of axial hydroxyl groups in each compound.

26.16 Draw the standard chair conformation of β-talopyranose and β-allopyranose, and compare the number of axial hydroxyl groups in each compound.

26.17 Identify each of the following monosaccharides.

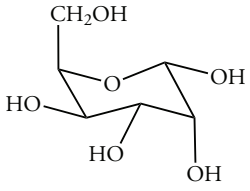


26.18 Identify each of the following monosaccharides.



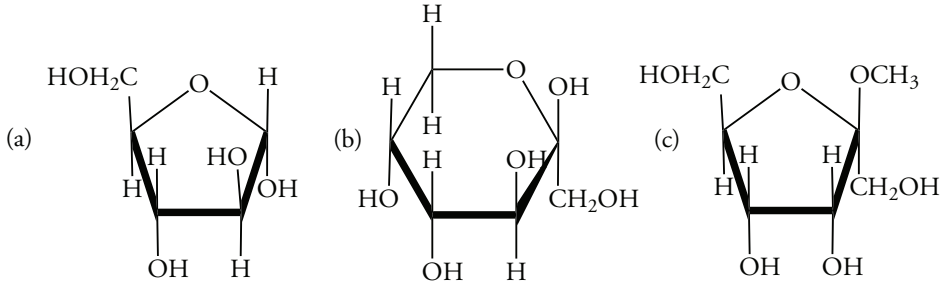
26.19 Write the conventional chair conformation of α-D-idose. Convert it to an alternate conformation by a chair–chair interconversion. Determine which conformation is more stable.

26.20 Identify and name the following aldohexose.

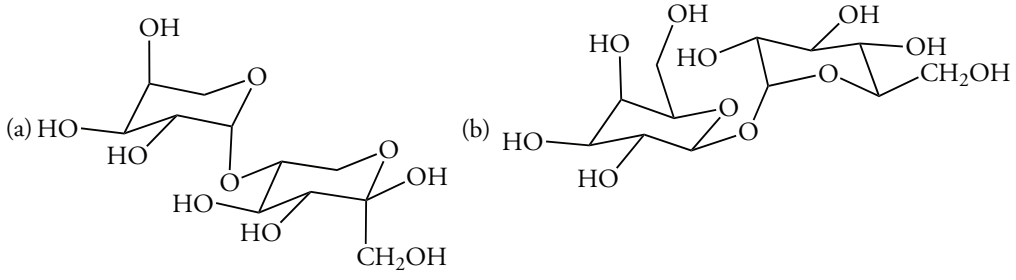


Mutarotation

26.21 Which of the following compounds can mutarotate?



26.22 Which of the following compounds can mutarotate?



26.23 The $[\alpha]_D$ values of the α and β anomers of D-galactose are +150.7° and +52.8°, respectively. In water, mutarotation of D-galactose results in a specific rotation of +80.2°. Which anomer predominates?

26.24 The $[\alpha]_D$ of the α and β anomers of D-mannose are +20.3° and −17.0°, respectively. In water, mutarotation of D-mannose results in a specific rotation of +14.2. Disregarding the furanose forms present (<1%), calculate the percent of the α anomer.

26.25 In solution D-ribose forms an equilibrium mixture containing 6% α-furanose, 18% β-furanose, 20% α-pyranose, and 56% β-pyranose. Explain why β-pyranose forms predominates at equilibrium.

26.26 Suggest a season why D-glucose, D-mannose, D-galactose, and D-aldose all have larger percentages of the pyranose form than the other four diastereomeric aldohexoses.

Reduction of Monosaccharides

26.27 Draw the Fischer projections of the alditols of D-erythrose and D-threose. One compound is optically active, and the other is a *meso* compound. Explain why.

26.28 Which of the alditols of the D-pentoses are optically inactive? Explain why.

26.29 Reduction of D-fructose with sodium borohydride yields a mixture of two alditols. Explain why. Name the two alditols.

26.30 Reduction of D-tagatose with sodium borohydride yields a mixture of galactitol and talitol. What is the structure of D-tagatose?

26.31 What relationship exists between the reduction products of D-galactose and L-galactose?

26.32 Explain why the alditol of D-glucose is identical to the alditol of L-gulose.

Oxidation of Monosaccharides

26.33 Draw the structures of each of the following compounds.
(a) D-mannonic acid (b) D-galactonic acid (c) D-ribonic acid (d) D-arabonic acid

26.34 Draw the structures of each of the following compounds.
(a) D-allonic acid (b) D-talonic acid (c) D-xylonic acid (d) D-lyxonic acid

26.35 Oxidation of D-erythrose and D-threose with nitric acid yields aldaric acids, one of which is optically inactive. Which one? Explain why.

26.36 Which of the D-aldopentoses will yield optically inactive aldaric acids when oxidized with nitric acid?

Isomerization of Monosaccharides

26.37 Draw the structures of the aldose and ketose that can exist in equilibrium with D-allose in basic solution.

26.38 Draw the structures of the aldose and ketose that can exist in equilibrium with D-galactose in basic solution.

26.39 Draw the structures of one aldose and one ketose that can exist in equilibrium with D-ribose in basic solution.

26.40 Draw the structures of two aldoses that can exist in equilibrium with D-xylulose in basic solution.

26.41 Explain why an equilibrium mixture of dihydroxyacetone phosphate and D-glyceraldehyde 3-phosphate contains the two compounds in a 96:4 ratio.

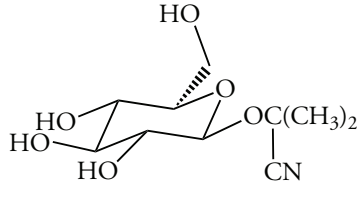
26.42 Although ketones are more stable than isomeric aldehydes by approximately 12 kJ $mole^{-1}$, fructose 6-phosphate is less stable than glucose 6-phosphate by approximately 1.7 kJ $mole^{-1}$. Explain why.

Glycosides

26.43 Draw the Haworth projection formulas of the two glycosides derived from each of the following pairs of components.
(a) the pyranose form of D-glucose and ethanol (b) the furanose form of D-fructose and phenol
(c) the pyranose form of D-ribose and methanol (d) the furanose form of D-arabinose and benzyl alcohol

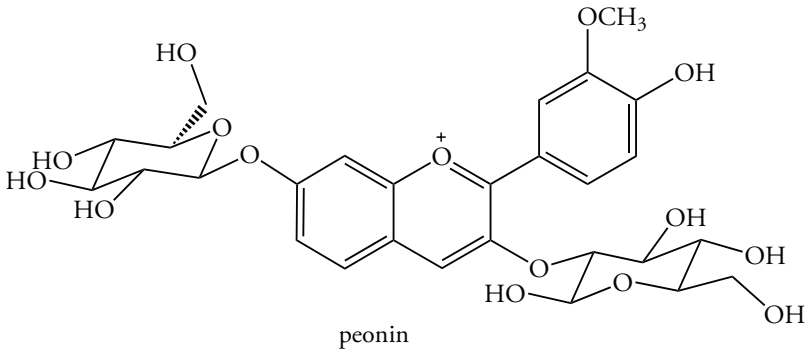
26.44 The individual, isomeric methyl acetals of D-glucose can be prepared only by a series of special reactions. Explain why each compound cannot be prepared by direct reaction of D-glucose with methanol.

26.45 Linamarin is found in manioc, a yam found in Brazil. Explain why this compound is toxic.



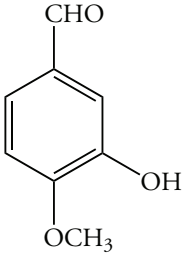
linamarin

26.46 Peonin, a red pigment found in the red peony, has the following structure. What are the monosaccharide products of the hydrolysis of peonin. Draw the structure of the aglycone. Explain why knowing the structure of the aglycone is not sufficient to determine the structure of peonin.



peonin

26.47 Vanillin is found as the β-glycoside of D-glucose. Draw the structure of the glycoside.

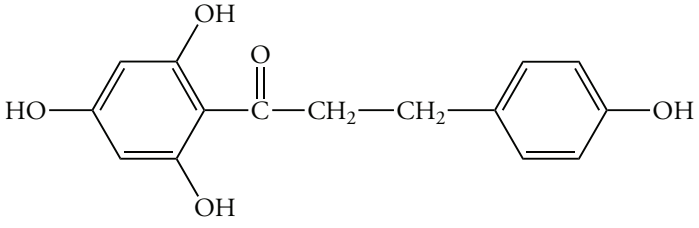


vanillin

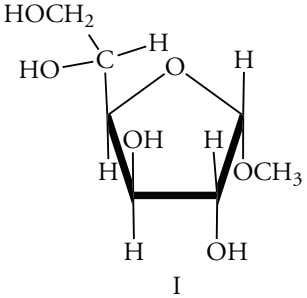
26.48 Arbutin, an antibiotic used for urinary tract infections, is methylated to give a pentamethyl derivative. The derivative is hydrolyzed to give a tetramethylglucose and *p*-methoxyphenol. What is the aglycone of arbutin?

26.49 Salicin is found in the bark of several species of fruit trees. Upon hydrolysis, it yields glucose and 2-(hydroxymethyl)phenol. The mild oxidation of salicin followed by hydrolysis of the oxidation product yields glucuronic acid and salicylic acid (2-hydroxymethyl benzoic acid). What are the possible structures of salicin?

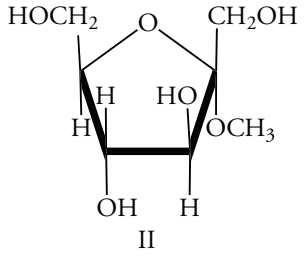
26.50 Phlorizin is a glycoside found in the root bark of certain fruit trees. Hydrolysis of phlorizin yields the following phenolic material. How many possible structures are possible for the glycoside? Explain how methylation of the glycoside using dimethyl sulfate followed by hydrolysis of the product with dilute acid can establish the structure of the glycoside.



26.51 Suggest a reason why methyl α-D-glucofuranoside (I) is more slowly hydrolyzed than methyl α-D-fructofuranoside (II) at the same pH.

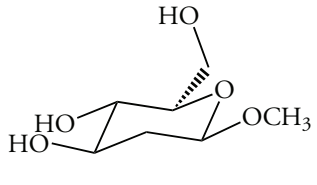


I

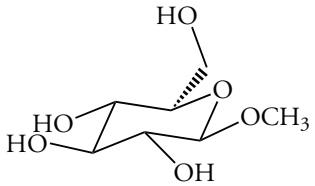


II

26.52 Suggest a reason why methyl β-D-2-deoxyglucopyranoside (I) is hydrolyzed faster than methyl β-D-glucopyranoside (II) at the same pH.

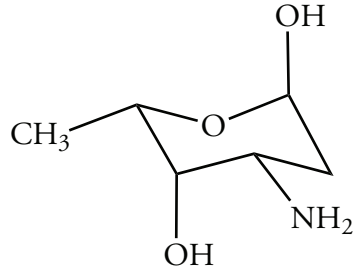


I



II

26.53 The carbohydrate daunosamine is contained in the antibiotic Adriamycin. Is daunosamine a D or L carbohydrate?



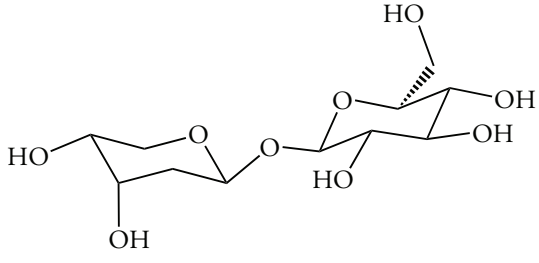
daunosamine

26.54 The melting point of methyl α-D-glucopyranoside is 166 °C. Explain why the melting point of methyl β-D-glucopyranoside, 105 °C, is different. Predict the melting point of methyl β-L-glucopyranoside.

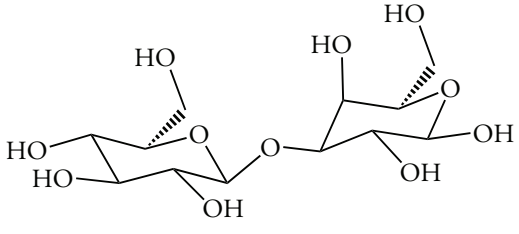
Disaccharides

26.55 Identify the component monosaccharides of each of the following compounds and describe the type of glycosidic linkage in each.

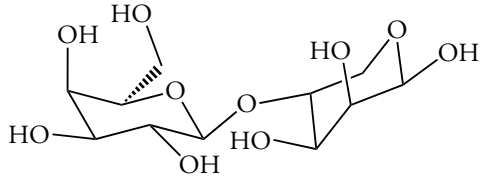
(a)



(b)

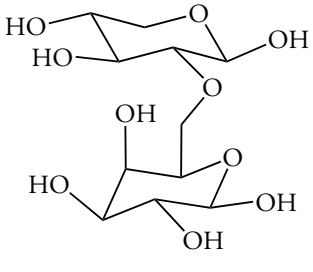


(c)

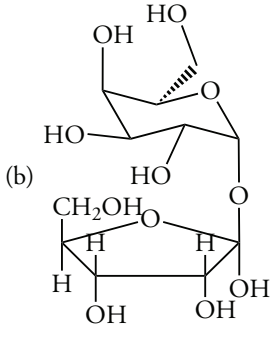


26.56 Identify the component monosaccharides of each of the following compounds and describe the type of glycosidic linkage in each.

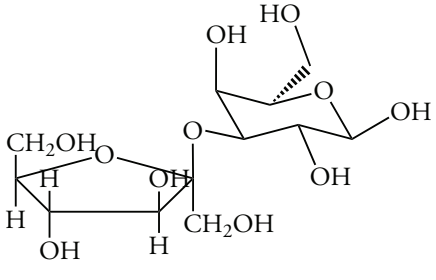
(a)



(b)



(c)

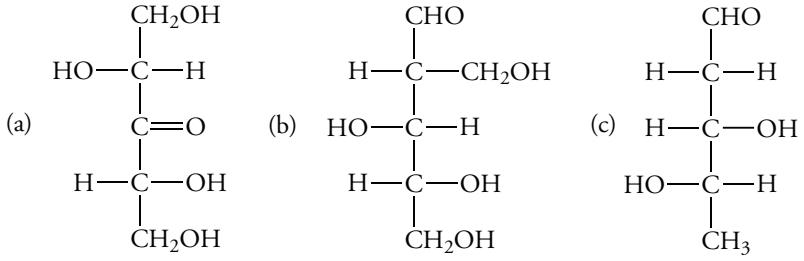


Structure Determination of Monosaccharides

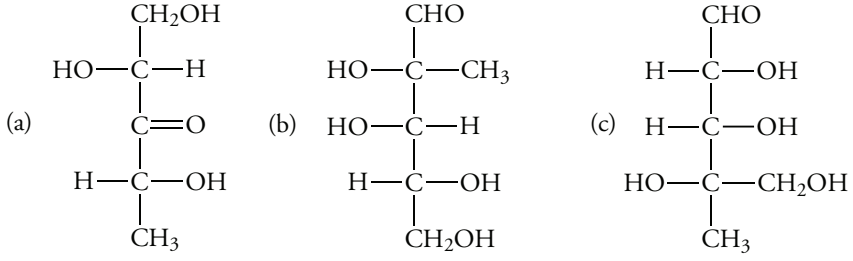
26.57 What are the products of the periodate oxidation of each of the following monosaccharides?
(a) ribose (b) ribulose (c) galactose (d) erythrulose

26.58 What are the products of the periodate oxidation of each of the following monosaccharides?
(a) xylose (b) sorbose (c) erythrose (d) idose

26.59 What are the products of the periodate oxidation of each of the following monosaccharides?



26.60 What are the products of the periodate oxidation of each of the following monosaccharides?



26.61 There are eight diastereomeric D-aldoses, but they yield only four diastereomeric osazones? Explain why.

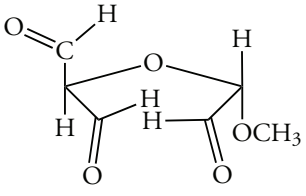
26.62 Draw the structure of the product of the reaction of 2-deoxy-D-ribose with phenylhydrazine.

26.63 A Wohl degradation is done on a monomethyl ether of D-idose. The product, when oxidized with nitric acid, gives an optically inactive compound. At what position of idose is the methyl ether located?

26.64 A Kiliani–Fischer chain extension is done on a monomethyl ether of D-glucose. One of the products, when oxidized with nitric acid, gives an optically inactive compound. At what position of idose is the methyl ether located?

26.65 An aldohexose is methylated using dimethyl sulfate, and then treated with a mild acid. The resulting product, when subjected to a strong oxidizing agent, gives an optically inactive dicarboxylic acid containing five carbon atoms. What are the possible structures of the aldohexose?

26.66 An aldohexose is converted to a methyl glycoside and then is oxidized by periodate to yield the following product. Is the aldohexose a pyranose or a furanose? What is the configuration of the anomeric center of the glycoside? What are the possible structures of the aldohexose?



Structure Determination of Disaccharides

26.67 Hydrolysis of the disaccharide primeverose yields D-xylose and D-glucose. Methylation of primeverose using dimethyl sulfate followed by mild acid hydrolysis yields 2,3,4-tri-*O*-methyl-D-xylose and 2,3,4-tri-*O*-methyl-D-glucose. What features of the structure are determined by these data?

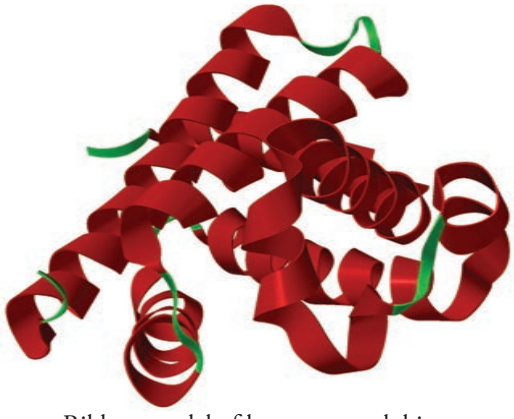
26.68 Hydrolysis of the disaccharide trehalose yields only D-glucose. Methylation of trehalose using dimethyl sulfate followed by mild acid hydrolysis yields 2,3,6-tri-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-glucose. What features of the structure are determined by these data?

26.69 Hydrolysis of the disaccharide turanose yields D-fructose and D-glucose. Methylation of turanose using dimethyl sulfate followed by mild acid hydrolysis yields 1,4,5-tri-*O*-methyl-D-fructose and 2,3,4,6-tetra-*O*-methyl-D-glucose. What features of the structure are determined by these data?

26.70 Hydrolysis of a trisaccharide yields two equivalents of glucose and one equivalent of galactose. Methylation, using dimethyl sulfate followed by mild acid hydrolysis, yields 3,6-di-*O*-methyl-D-glucose as one of the products. What features of the structure are determined by these data?

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27 Amino Acids, Peptides, and Proteins



Ribbon model of human myoglobin

The study of proteins goes back a long way. In the first half of the nineteenth century, the Dutch chemist Gerardus Johannes Mulder was studying proteins isolated from milk and eggs called albumins. He determined what he thought was the empirical formula for all albumins: $C_{40}H_{62}O_{12}N_{10}$. The Swedish chemist Jons Jacob Berzelius, one of the founders of modern chemistry, suggested that the albumins should be called *proteins*, (Greek, *proteios*, primary) because he thought they might be the most important biological substances. Although Mulder's formula was very wide of the mark—proteins contain thousands of atoms—Berzelius' guess was prophetic. Proteins participate in virtually every cellular process. We will focus narrowly in this chapter upon the structure and properties of the molecules from which proteins are made, the α-amino acids, and upon protein structure.

27.1 THE STRUCTURES OF α-AMINO ACIDS

Proteins are linear polymers of amino acids linked by secondary amide bonds. Careful hydrolysis of a protein releases up to 20 α-amino acids. All proteins from all sources, from Archaebacteria to mammals, are made from the same set of amino acids. Their sequence depends upon an underlying genetic code, which is the same for all organisms with very minor variations. Figure 27.1 shows the general structure of 19 of the 20 amino acids. In this structure, the α-carbon atom is bonded to four different groups every amino acid but one. Thus, the α-carbon is a sterogenic center. The other three groups are a hydrogen atom, a carboxyl group, an amino group, and a fourth R-group commonly called the "side chain." Based upon the configuration of D-glyceraldehyde, all of the chiral amino acids isolated from proteins have an L-configuration.

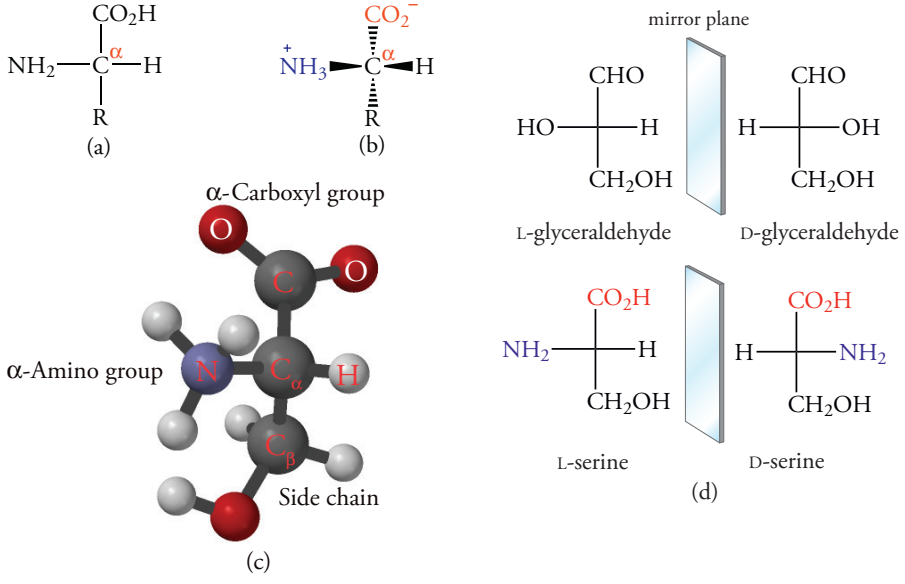


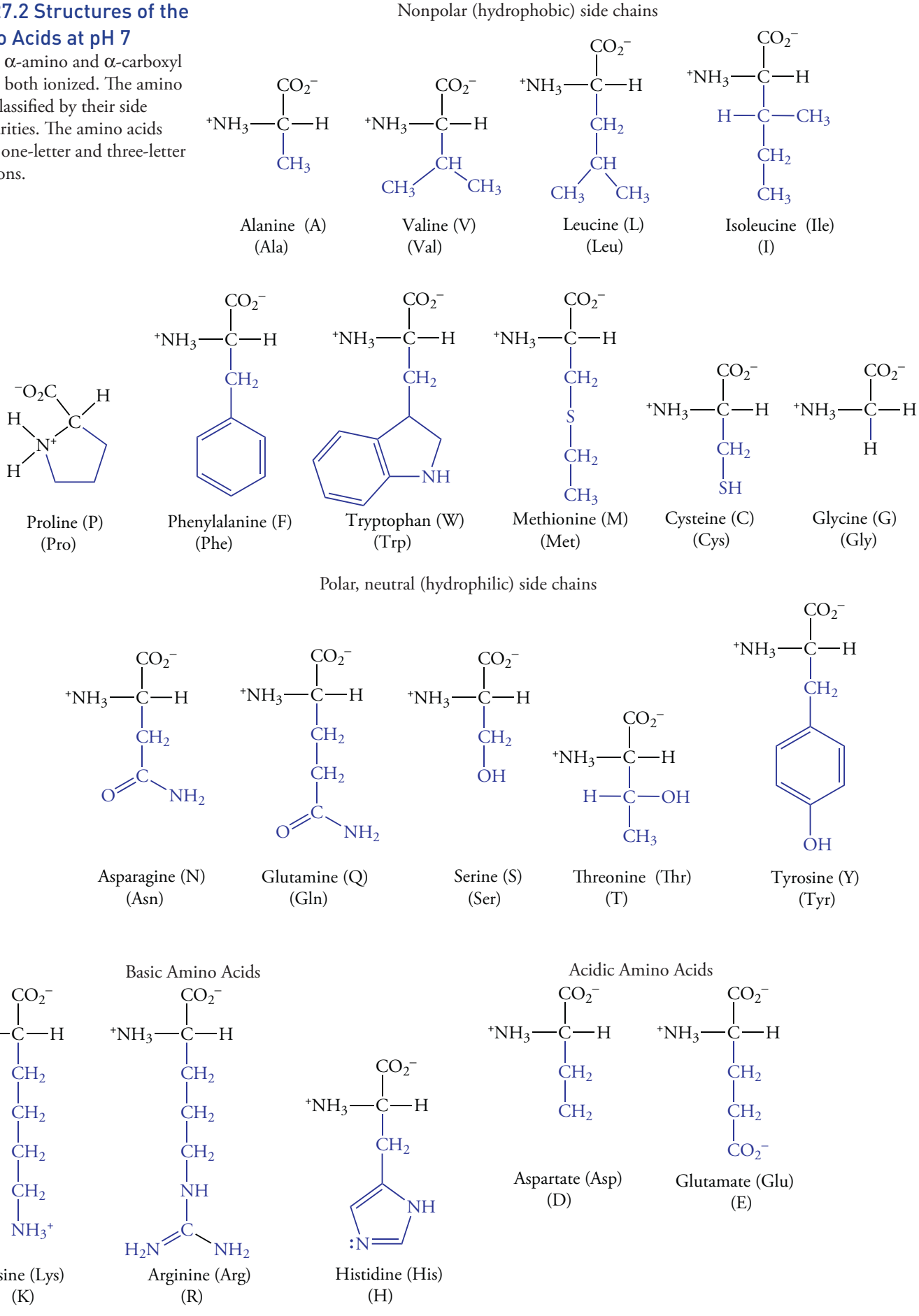
Figure 27.1 Chirality of the α-Amino Acids
(a) Planar projection of an L-amino acid in unionized form. (b) The α-carboxyl group and the α-amino group are ionized in aqueous solution at pH 7. (c) The configuration of the α-amino acids isolated from proteins is opposite to the configuration of the reference compound D-glyceraldehyde. (d) Molecular model of L-serine, whose side chain is a CH_2OH group.

One amino acid has a structure that differs from the one shown in Figure 27.1, namely, proline. Its structure is shown in Figure 27.2.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00027-9
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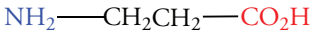
Figure 27.2 Structures of the α-Amino Acids at pH 7

At pH the α-amino and α-carboxyl groups are both ionized. The amino acids are classified by their side chain polarities. The amino acids have both one-letter and three-letter abbreviations.



Problem 27.1

What is the IUPAC name of the naturally occurring amino acid shown below?



Sample Solution

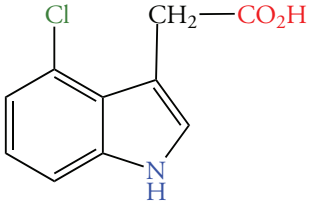
In IUPAC names, the carboxylic acid group takes precedence over amino groups. Therefore, C-1 is the carboxyl group, the parent compound is propanoic acid, and the name is therefore 3-aminopropanoic acid. Its common name is β-alanine, which is a component of pantothenic acid (vitamin B5) and some naturally occurring peptides.

Problem 27.2

Draw the structure of 1-aminocyclopropanecarboxylic acid. This compound undergoes an enzymatic decarboxylation to produce the plant hormone ethene, which is responsible for the initiation of fruit ripening.

Problem 27.3

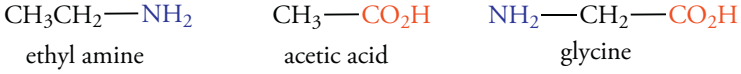
The following carboxylic acid and its methyl ester are found in green peas and many other plants. It is a plant hormone in the auxin family. Which amino acid is a likely (and in fact actual) precursor?



4-chloroindole-3-acetic acid

27.2 ACID–BASE EQUILIBRIA OF α-AMINO ACIDS

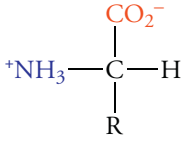
The α-amino acids have no *net* charge. However, their properties resemble those of salts rather than uncharged molecules. Amino acids have low solubilities in organic solvents but are moderately soluble in water, unlike most organic compounds of comparable molecular weight. The physical states of amino acids also differ from those of comparable carboxylic acids and amines. For example, ethyl amine is a gas, and acetic acid is a liquid at room temperature. In contrast, glycine is a solid.



ethyl amine	acetic acid	glycine
mp –84 °C	mp 16 °C	mp 232 °C

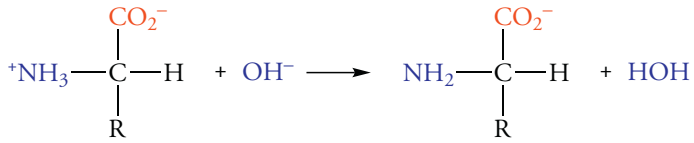
Ionic Form of Amino Acids

When an amino acid dissolves in an aqueous buffer at pH 7, its α-carboxyl group ionizes to give a carboxylate ion, and its α-amino group ionizes to give an ammonium ion. Thus, it exists as a dipolar ion, sometimes called a **zwitterion** (German, *zwitter*, hybrid). In fact, glycine is a dipolar ion in the solid state and that accounts for its high melting point. The dipolar ion acts both as an acid and a base. Thus, it is **amphoteric**.



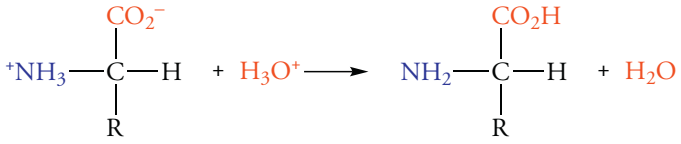
structure of a dipolar ion (zwitterion)

When an amino acid dissolves in basic solution, the carboxylate group exists as an anion and the ammonium ion exists as an unprotonated amino group. This species is the *conjugate base* of the original amino acid. It has a net charge of –1.



zwitterion conjugate base

When an amino acid dissolves in acid solution, the carboxylate group exists as carboxylic acid group and the amino group exists as an ammonium ion. This species is the *conjugate acid* of the original amino acid. It has a net charge of +1.



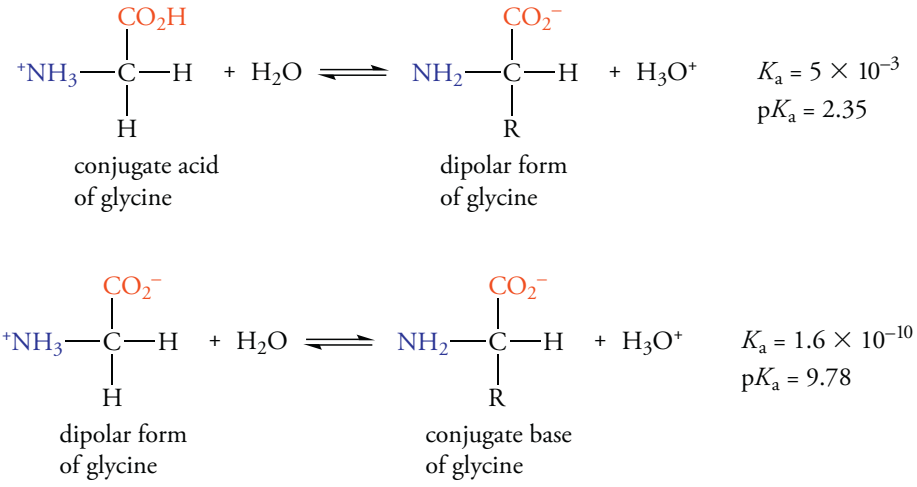
zwitterion conjugate acid

pK_a Values of α-Amino Acids

The pK_a values of the amino acids depend upon the structure of the amino acid. The pK_a values of the α-carboxyl groups range from 1.81 for histidine to 2.58 for phenylalanine. The pK_a values of the α-amino groups range from 8.8 for histidine to 10.78 for tyrosine (Table 27.1).

Table 27.1
pK_a Values of Acidic and Basic Groups in α-Amino Acids

Amino Acid	*α-CO_2H Group*	*α-NH_3^+ Group*	*Side Chain*
Glycine	2.35	9.78	
Alanine	2.35	9.87	
Valine	2.29	9.72	
Leucine	2.33	9.74	
Isoleucine	2.32	9.76	
Methionine	2.17	9.27	
Proline	1.95	10.64	
Phenylalanine	2.58	9.24	
Tryptophan	2.43	9.44	
Serine	2.19	9.44	
Threonine	2.09	9.10	
Cysteine	1.89	10.78	8.53
Tyrosine	2.20	9.11	10.11
Asparagine	2.02	8.80	
Glutamine	2.17	9.13	
Aspartate	1.99	10.00	3.96
Glutamate	2.13	9.95	4.32
Lysine	2.16	9.20	10.80
Arginine	1.82	8.99	12.48
Histidine	1.81	9.15	6.00



When an amino acid dissolves in solution, several species usually exist. When the pH of the solution equals the pK_a of the ionizing group, the concentrations of the conjugate acid and the dipolar form are equal. For example, the pK_a of the carboxyl group of glycine is 2.35, and at pH 2.35, the concentrations of the conjugate acid and the dipolar ion are equal. The pK_a of the ammonium ion of glycine is 9.78, and at pH 9.78, the concentrations of the conjugate base and the dipolar ion are equal. At pH values between 2.35 and 9.78, the dipolar ion is the major ionic form of glycine in solution.

Problem 27.4
What are the structures of the dipolar ion and conjugate base of alanine?

Problem 27.5
In what form does serine exist in 0.1 M HCl?

27.3 ISOIONIC POINT AND TITRATION OF α-AMINO ACIDS

Isoionic Points of Amino Acids

The isoionic point, pH_I, is the pH of the solution at which the concentration of the dipolar ion is a maximum. The relation of pH_I to the concentrations of the various ionic forms of an amino acid are as follows.

1. When pH_I equals pH, the amino acid has no *net* charge, and the dipolar ion is the predominant form of the amino acid.
2. When the pH is greater than pH_I, the conjugate base is the predominant form in solution and the amino acid has a net charge of –1.
3. When the pH is less than pH_I, the conjugate base is the predominant form in solution and the amino acid has a net charge of +1.

The isoionic point of an amino acid equals one-half the sum of the pK_a values of the carboxylate group and the amino group if it does not have an ionizing side chain. For example, the pK_a of the carboxyl group of alanine is 2.4, and the pK_a value of its amino group is 9.9. The isoionic point of alanine is 6.1. Table 27.2 lists the isoionic points of some amino acids.

The isoionic point of the acidic amino acids — aspartic acid and glutamic acid — equals one-half the sum of the pK_a values of the α-CO_2H group and the side chain carboxyl group. Similarly, the isoionic points of the basic amino acids— histidine, lysine, and arginine— equals one-half the sum of the pK_a values of the α-NH_3^+ group and the side chain group. Table 27.2 lists the isoionic points of some amino acids.

The pK_a values of ionizable side chains in proteins often differ from those of the free amino acids. Two factors alter pK_a values. First, α-NH_3^+ and α-CO_2H groups lose their charges when they are linked by peptide bonds in proteins, so they no longer exert strong inductive effects on their neighboring side chains. Second, the position of an ionizable side chain within the three-dimensional structure of a protein can affect its pK_a. For example, the enzyme ribonuclease A has four histidine residues. Each side chain has a slightly different pK_a value because each is in a slightly different environment.

Table 27.2
Isoionic Points

Amino Acid	pH_I
Glycine	5.97
Alanine	6.10
Valine	5.96
Leucine	5.98
Isoleucine	6.02
Methionine	5.74
Proline	6.30
Phenylalanine	5/48
Tryptophan	5.89
Serine	5.68
Threonine	5.60
Cysteine	5.07
Tyrosine	5.66
Asparagine	5.41
Glutamine	5.65
Aspartic acid	2.77
Glutamic acid	3.22
Lysine	9.74
Arginine	10.76
Histidine	7.59

Titration of Amino Acids

The pK_a values of the α-carboxyl and α-amino groups and the pK_I can be determined by titrating the conjugate acid with base. Figure 27.3 shows the titration curve for glycine, which is typical for amino acids without an ionizing side chain. As base is added, the pH increases, and some of the conjugate acid is converted to the dipolar ion. When 0.5 equivalent of base has been added, the concentrations of the α-CO_2H and α-CO_2^- groups are equal, and the pH equals pK_1. After one equivalent of base has been added, the dipolar ion is the major ionic form in solution. When 1.5 equivalents of base have been added, the concentrations of the α-NH_3^+ and α-NH_2 groups are equal, and the pH equals pK_2.

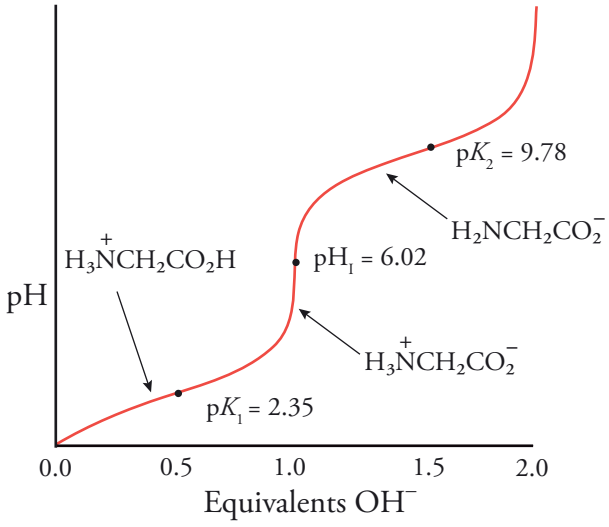


Figure 27.3 Titration Curve of Glycine

Isoionic Points of Proteins

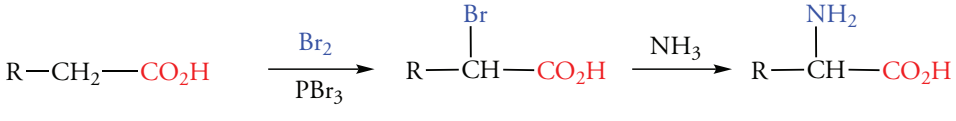
The isoionic point of a protein depends upon its amino acid composition. At its isoionic point, a protein has no net charge, and its solubility is at a minimum. As a consequence, a protein tends to precipitate form solution at its isoionic point. For example, casein, a protein in milk, has a negative charge at pH 6.3. Casein has many glutamic acid and aspartic acid residues. If acid is added to milk, these side chains are protonated, and casein precipitates. Casein is used in making cheese, and it is obtained by adding acid to milk or by adding bacteria that make lactic acid, which has the same effect.

27.4 SYNTHESIS OF α-AMINO ACIDS

Classical methods for the synthesis of amino acids illustrate many of the principles of organic synthesis that we considered in earlier chapters. Modern methods use organometallic catalysts to synthesize chiral amino acids to give high enantiomeric purity.

Amination of α-Halocarboxylic Acids

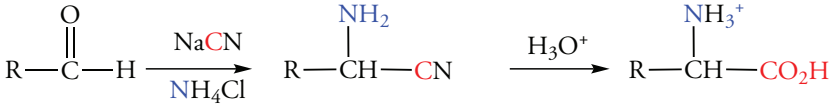
The oldest method of synthesizing α-amino acids is nucleophilic substitution of the halogen of an α-halocarboxylic acid by ammonia. The α-halocarboxylic acid is prepared by treating a carboxylic acid with Br_2 and PBr_3. This reaction, which we considered earlier, is named after its inventors, the Hell-Volhard-Zelinsky reaction. It produces a carboxylic acid with a bromine atom at the α position. The α-bromo compound reacts with ammonia by an S_N2 mechanism to give an α-amino acid.



We recall that direct substitution of alkyl halides by ammonia is often complicated by multiple alkylation of the nitrogen atom (Section 3.7). However, multiple alkylation does not occur in the synthesis of amino acids. The nitrogen atom in the amino acid is less nucleophilic than the nitrogen than in ammonia because the carboxyl group withdraws electrons from it by an inductive effect.

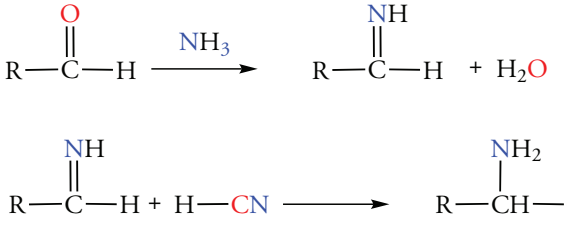
The Strecker Synthesis

A second early method of synthesizing α-amino acids starts with an aldehyde which have one less carbon atom than the desired amino acid. In the first step, an α-amino nitrile is prepared by treating a carboxylic acid with cyanide and ammonia or an ammonium salt. The nitrile is hydrolyzed to a carboxylic acid.



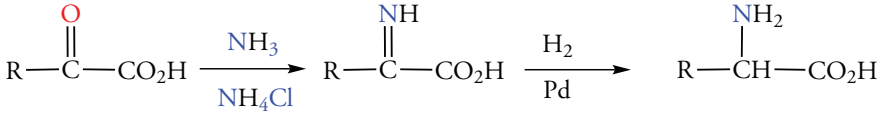
(an α-amino nitrile)

In the first step of this reaction sequence, an imine forms that is in equilibrium with an aldehyde (Section 19.10). The imine then reacts with HCN (the proton in HCN is provided by the ammonium salt). This reaction is similar to the reaction of HCN with a carbonyl group that we discussed in Section 19.2



Reductive Amination

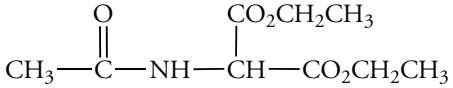
Reductive amination of aldehydes or ketones is an excellent method of producing amines, especially on an industrial scale. To form amino acids on a laboratory scale, the starting material is an α-keto acid. Ammonia reacts with the α-keto acid to give an imine. Reduction of the imine with H_2 in the presence of a palladium catalyst gives the amino acid.



The entire reaction is carried out in a single step with all reagents present. Although a carbonyl group can be reduced by hydrogen gas at high pressure, the imine is more easily reduced, and conditions are chosen to prevent reduction of the carbonyl group in the α-keto acid.

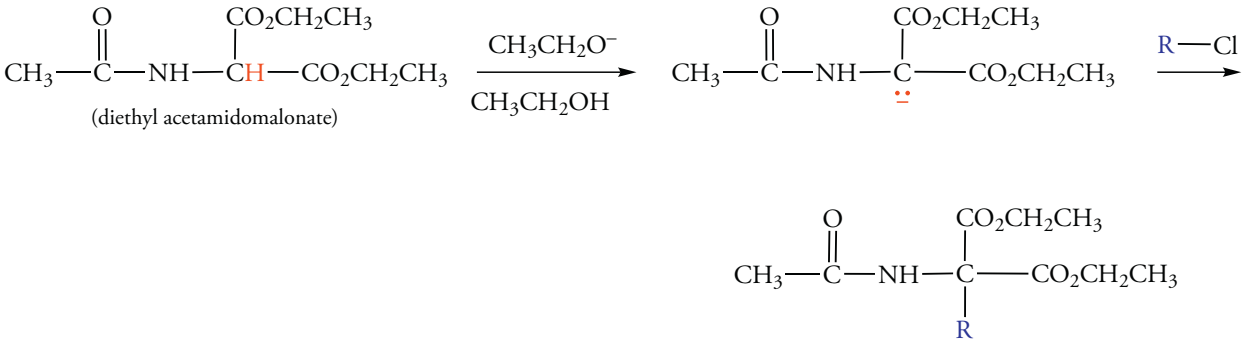
Acetamidomalonate Synthesis

One of the best methods for synthesizing amino acids is based on the chemistry of malonate esters (Section 22.17) and a modification of the Gabriel synthesis of amines (Section 23.7). Diethyl acetamidomalonate has a nitrogen atom bonded to the α-carbon of the malonate ester. This nitrogen eventually becomes the nitrogen of the final amino acid product.

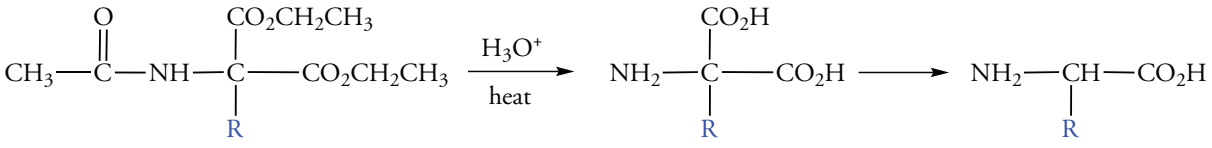


(diethyl acetamidomalonate)

We recall that the α-hydrogen of the malonate ester can be removed by an alkoxide base. In this case, the alkoxide base of choice is ethoxide since the malonate is a diethyl ester. The resulting product is an ester enolate that can be alkylated by an alkyl halide. The alkyl group of the halide is the same as the side chain of the desired amino acid.



Acid-catalyzed hydrolysis of the ester give a dicarboxylic acid. Under the reaction conditions, the amide also hydrolyzes. The resulting malonic acid spontaneously decarboxylates to give the amino acid.



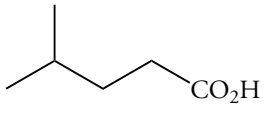
All of the methods for synthesizing amino acids we have described produce racemic mixtures. We recall, however, that racemic mixtures can be resolved by chiral chromatography (Section 8.8). We can also use organometallic reagents as chiral catalysts (Section 17.8) to produce chiral amino acids, as we will see in the next section.

Problem 27.6

What carboxylic acid is required to synthesize leucine using the amination of an α-halo carboxylic acid?

Sample Solution

In this synthesis, a bromine atom is substituted at the α position on the HVZ reaction. The halogen is then replaced by ammonia. Thus, the required acid is a carboxylic acid having the same carbon skeleton as leucine: 4-methylpentanoic acid.



4-methylpentanoic acid

Problem 27.7

What reagents are required for the Strecker synthesis of phenylalanine?

Problem 27.8

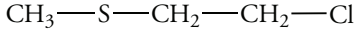
What keto acid is required to produce glutamic acid by reductive amination?

Problem 27.9

What reagents are required to synthesize methionine by the acetamidomalonate method?

Sample Solution

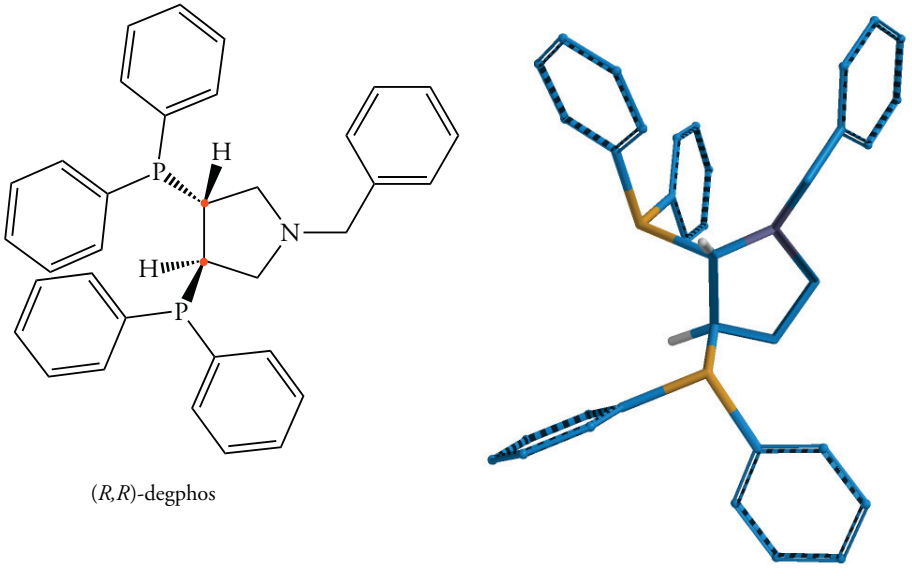
The α carbon atom, the α amino group, and the carboxyl group are derived from diethyl acetamidomalonate. The side chain of the amino acid, the R group, is derived from an alkyl halide. In this case, the side chain contains a thiomethyl group.



27.5 CHIRAL SYNTHESIS OF α-AMINO ACIDS

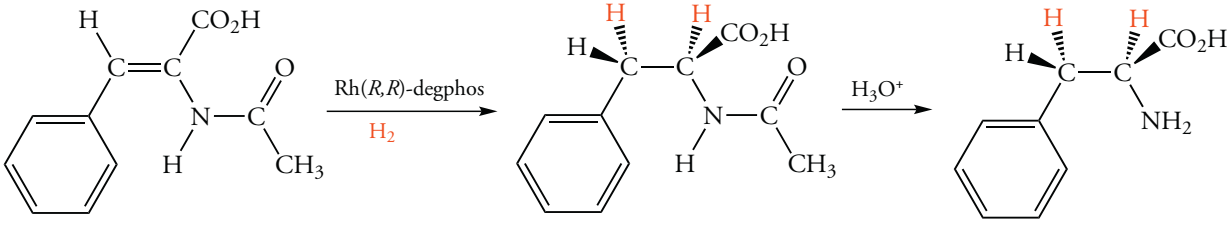
We recall that a chiral ruthenium catalyst with binaphthyl ligands can be employed to carry out chiral hydrogenation reactions (Section 17.8). Many chiral ligands have been developed, and one that is widely used for the chiral synthesis of amino acids is called **degphos**. It can be prepared with either an (*R*,*R*) or an (*S*,*S*) configuration. Since the ligand is chiral, the transition states leading to either an *R* or *S* amino acid are diastereomers. Therefore, there energies differ, and the rate of formation of one enantiomer is favored over the other.

Figure 27.4 Structure of (*R*,*R*)-degphos



(*R*,*R*)-degphos

Let's consider the catalytic reduction of the double bond of the enamide (*Z*)-2-acetamidophenylpropenoic acid by the ruthenium complex of (*R*,*R*)-degphos (Figure 27.4). This reaction leads exclusively to the *S* isomer when hydrogen adds to the *re,re* face of the alkenyl group. That is, in the reaction shown below, hydrogen adds from the bottom face to give (*S*)-*N*-acetylphenylalanine. Hydrolysis of the acetyl group gives *S*-phenylalanine. The net reaction has more than a 99% enantiomeric excess of the *S* isomer.



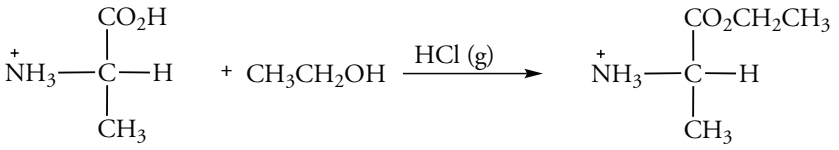
(*Z*)-2-acetamido-3-phenylpropenoic acid (*S*)-*N*-acetylphenylalanine (*S*)-phenylalanine

27.6 REACTIONS OF α-AMINO ACIDS

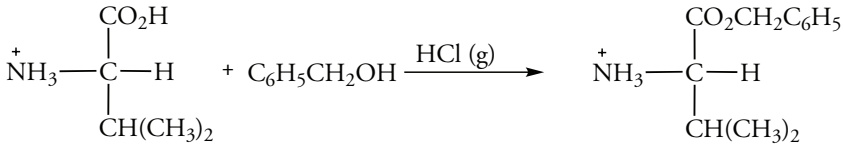
Each functional group of an amino acid undergoes characteristic reactions that we have discussed in previous chapters provided that conditions are chosen to prevent the simultaneous reaction of other functional groups. In this section, we will consider reactions of the α-carboxyl and α-amino groups that are used to synthesize peptides. These reactions are esterification of the carboxyl group and acylation of the amino group.

Esterification of the α-Carboxyl Group

The α-carboxyl group can be converted to an ester by reaction of an alcohol with gaseous HCl. Under these conditions, the α-amino group is protonated, so it is unreactive. Ethyl or benzyl esters are commonly prepared. They protect the carboxyl group from other reactions that can be carried out at the amino group.

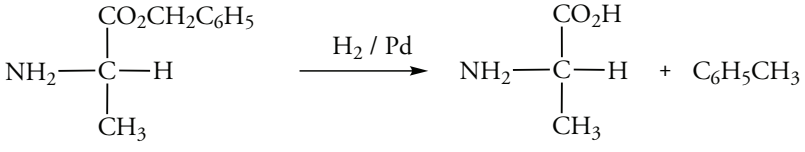


alanine alanine ethyl ester



valine valine benzyl ester

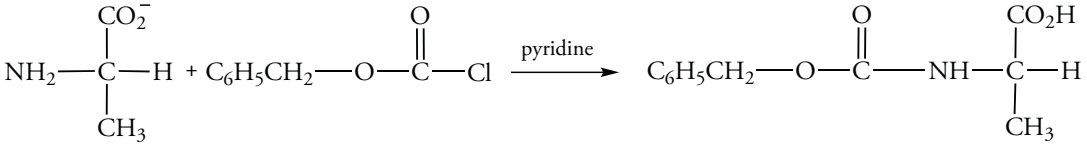
After the carboxyl group has been protected, the amino group can be covalently modified. Then the ethyl or benzyl group can be removed by acid hydrolysis. These groups can also be cleaved by catalytic hydrogenation, a process called **hydrogenolysis**. For example, hydrogenolysis of the benzyl ester of an amino acid released toluene. This reaction occurs under neutral conditions with no competing reactions.



alanine benzyl ester alanine

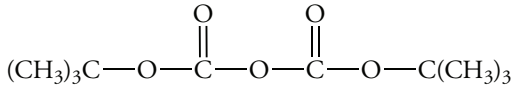
Acetylation of the α-Amino Group

The α-amino group can be converted to an amide by acylation with an anhydride such as acetic anhydride or an acyl chloride. When the amino group is thus protected, it is possible to carry out reactions at the carboxyl group. However, we recall that it is difficult to hydrolyze amides, and the deprotection of an amino group as an *N*-acetyl derivative may well also affect other functional groups. And, since we are particularly interested in reactions that are important in peptide synthesis, these reactions are highly undesirable. We'll consider two reagents that yield easily removed protecting groups. One of these is **benzyl chloroformate**, which acylates an amino group to give a benzyloxycarbonyl (Cbz) derivative. Pyridine is required to convert the amino group to a neutral form that can act as a nucleophilic.



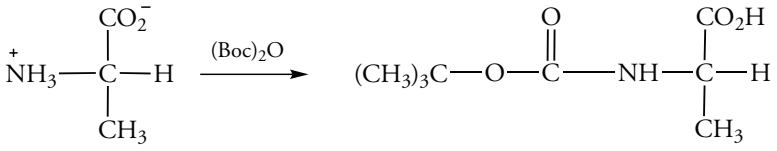
alanine benzyl chloroformate *N*-benzyloxycarbonyl alanine (Cbz alanine)

A second easily removed protecting group is ***tert*-butoxycarbonyl**, commonly abbreviated (Boc). The acid chloride of Boc, *tert*-butoxycarbonyl chloride, is highly unstable, so the Boc group is derived from its anhydride, di-*tert*-butyldicarbonate.



di-*tert*-butyldicarbonate
$(Boc)_2O$

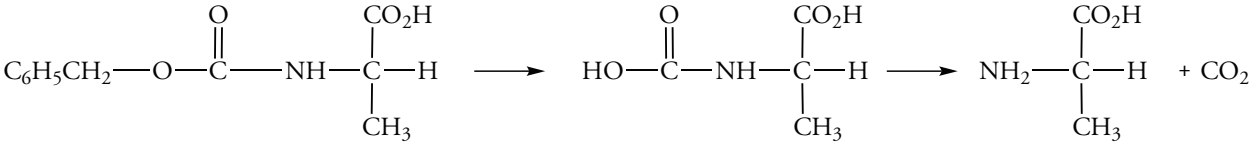
The Boc group is structurally similar to the Cbz group, but it contains a *tert*-butyl group instead of a benzyl group.



alanine

N-*tert*-butoxycarbonyl alanine
(Boc alanine)

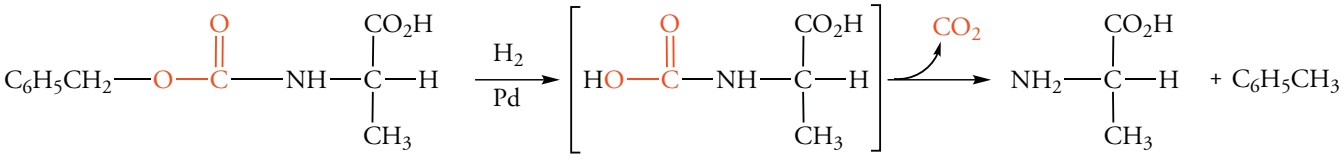
The Boc and the Cbz groups are carbamate esters. A carbamic acid is a highly unstable compound that easily decarboxylates to give an amine. Therefore, when a carbamate ester is converted to a carbamic acid, it decomposes.



N-benzyloxycarbonyl alanine
(Cbz alanine)

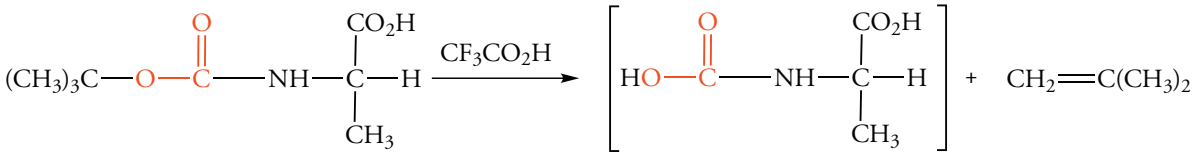
a carbamic acid

Hydrogenolysis of the Cbz derivative of an amino acid releases the amino acid, CO_2 and toluene. The carbamic acid forms as an intermediate in this process.



N-benzyloxycarbonyl alanine
(Cbz alanine)

The Boc group is very sensitive to acid. Treating the Boc derivative of an amino acid with trifluoroacetic acid leads to a carbamic acid intermediate that decarboxylates. The *tert*-butyl group is converted to 2-methylpropene (isobutylene) in the decarboxylation reaction.



N-*tert*-butoxycarbonyl alanine
(Boc alanine)

27.7 PEPTIDES

Peptide Nomenclature

A peptide is a chain of amino acids in which the α-amino group of one amino acid is bonded to the α-carboxyl group of the next. Thus, each bond linking the amino acids is a secondary amide, called a **peptide bond**. If a peptide made from two amino acids is a **dipeptide**, one made from three is a **tripeptide**, and so forth. As we have seen many times, the prefixes, *di-*, *tri-*, *tetra-*, etc., indicate the number of amino acid units from which the chain is made. Peptides that contain only few amino acids are called **oligopeptides**; peptides with many amino acids are **polypeptides**, a term synonymous with protein.

A peptide has two ends: the end with a free amino group is called the **N-terminal amino acid residue**. The end with a free carboxyl group is called the **C-terminal amino acid residue**. Peptides are named from the N-terminal acid residue to the C-terminal amino acid. Two examples of isomeric dipeptides that contain glycine and alanine are shown below and in Figure 27.5.

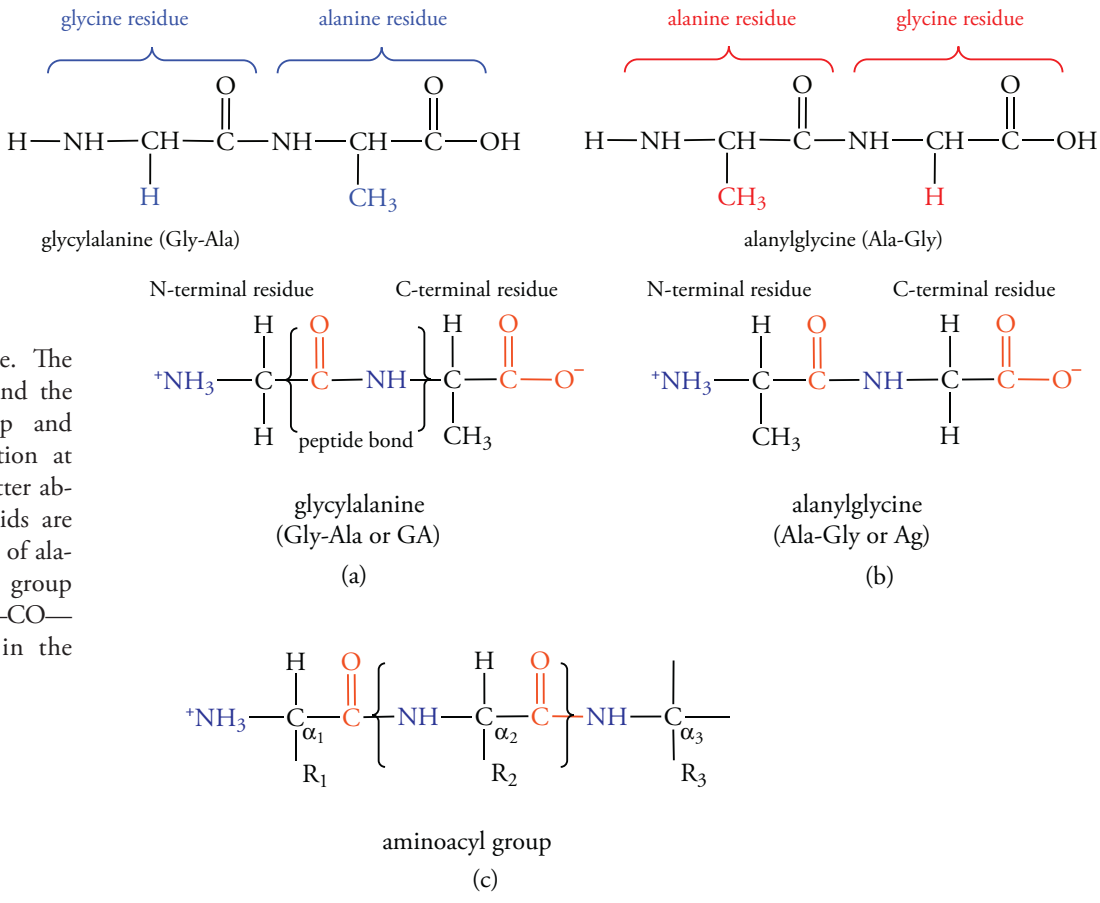


Figure 27.5 Peptide Nomenclature
(a) Structure of glycylalanine. The N-terminal α-amino group and the C-terminal α-carboxyl group and are ionized in aqueous solution at pH 7. Three-letter and one-letter abbreviations for the amino acids are commonly used. (b) Structure of alanylglycine. (c) An aminoacyl group consists of the —NH—CHR—CO— group of each amino acid in the peptide.

The number of isomers of peptides containing one each of n different amino acids is equal to $n!$, where

$$n! = 1 \times 2 \times 4 \ldots . (n-1) \times n$$

There are thus six possible isomers in a tripeptide that contains three different amino acids. The isomeric tripeptides containing glycine, alanine, and valine are Gly-Ala-Val, Gly-Val-Ala, Val-Ala-Gly, Ala-Gly-Val, and Ala-Val-Gly. For a peptide that contains one each of 20 different amino acids, there are 2,432,902,008,176,640,000 isomers! (That is, on the order of 2×10^{18} isomers.) Proteins often contain hundreds of amino acid residues, and they contain two or more amino acids of the same kind, but the number of possibilities is still astronomically large. Viewed from an evolutionary standpoint, we can say that nature has just begun to experiment.

Biological Functions of Peptides

Cells contain many peptides and polypeptides whose size range from 4 or 5 amino acids to 50 amino acids. (Chains longer than that are designated either as polypeptides or proteins.) They have a huge range of functions. Table 27.3 lists a few examples. These oligopeptides are released in small amounts. Many have very short half-lives. For example, the 14 residue peptide somatostatin, regulates the release of other hormones that play an important role in glucose metabolism, including insulin, glucagon, and secretin. Somatostatin has a half-life of only 4 min.

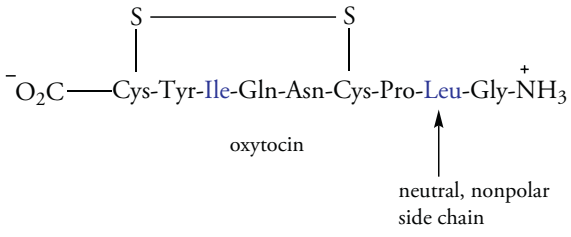
Hormones exert their effects by binding **receptor proteins**, most of which are located in cell membranes. The complex of the ligand, called an **agonist**, and the receptor protein then affect cell signaling pathways. A very large class of receptor proteins contain seven helical regions of the protein that are located in the membrane. These proteins, which act by similar mechanisms, are called **guanine protein coupled receptor** (GPCR). Subtle changes in the amino acid sequences of the membrane region of the receptors alter the specificity of the response (see Section 27.12).

This is an important area of research in many branches of biological chemistry. However, the details of hormone receptor interactions and cell signalling pathways are beyond the scope of an organic chemistry text.

Enkephalins are peptides that bind specific receptor proteins the brain cells to reduce pain. Enkephalin receptor proteins have a high affinity for opiates, including heroin, morphine, and structurally similar substances. These pain relievers are highly addictive, and the misuse of opiates causes thousands of deaths every year.

Peptides are produced by many tissues. For example, kidney cells secrete angiotensin II, which increases blood pressure by constricting blood vessels. Angotensin II is a potent vasoconstrictor, and the production of excess angiotensin II is responsible for some forms of hypertension.

Oxytocin, which is produced in the pituitary gland, causes the contraction of smooth muscle, including the uterus. It is used clinically to induce labor or to increase the strength of uterine contractions. Vasopressin, another pituitary hormone, regulates the secretion of water by the kidneys and affects blood pressure. The structures of vasopressin and oxytocin differ by only two amino acids. They are cyclic peptides that are linked by a disulfide bond between two cysteine residues.



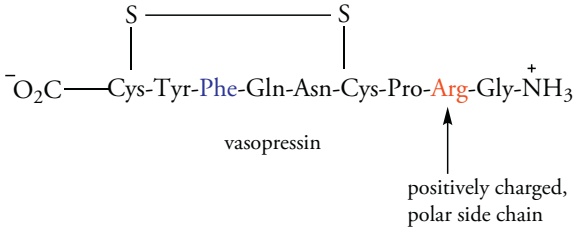


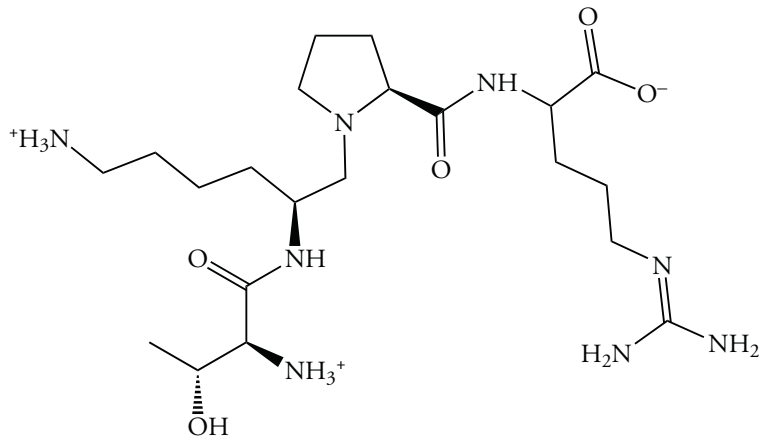
Table 27.3
Peptide Hormones

Hormone	*Amino Acid Residues*	*Receptor*	*Function*
Tuftsin	4	Immune system, cleaved from IgG	Stimulates phagocytosis
Met-enkephalin	5	δ-opioid receptor, (GCRP)	Analgesic activity
Angiotensin II	8	Angiotensin receptor AT_1, GCPR, G_q	Vasoconstriction, increased vasopressin secretion
Oxytocin	8	OXTR, GCRP, G_q	Affects uterine contractions
Vasopressin	8	V_1 receptor, GCRP	An antidiuretic
Bradykinin	9	Bradykinin receptor B_1, GCRP	Produced in response to tissue injury
Somatostatin	14	Somastostatin receptor 1 (human), GCRP	Inhibits release of other hormones
Gastrin	17	Gastrin releasing peptide receptor, GCPR	Leads to pepsin secretion
Secretin	27	Human secretin receptor (GCRP)	Stimulates pancreatic secretions
Glucagon	29	Glucagon receptor, GCRP G_s	Stimulates glucose production from glycogen
Calcitonin	32	Calcitonin receptor (CT), GCRP, G_s, G_q	Decreases calcium level in blood
Relaxin	48	RXPF1, GCRP	Relaxation of pubic joints
Insulin	51	Insulin receptor (IR), transmembrane helix (not GCRP)	Affects blood sugar level

The structures of the two peptides are similar, so it might seem surprising that their functions are so different. However, closer inspection shows that there is one small difference and one major difference in their amino acid composition. Both have a neutral, nonpolar side chain at residue 3, but residue 8 in oxytocin is the nonpolar amino acid leucine, whose side chain is a *sec*-butyl group, but residue 8 in vasopressin is arginine, whose side chain has a positive charge. As a result, the for oxytocin has a very low affinity for vasopressin and the receptor for vasopressin has a very low affinity for oxytocin. Since they bind different receptors, they have different functions.

Problem 27.10

(a) Identify each of the amino acids of tuftsin. (b) Write the name of tuftsin as three-letter abbreviations. (c) Write the name of tuftsin without abbreviations.



tuftsin

Problem 27.11

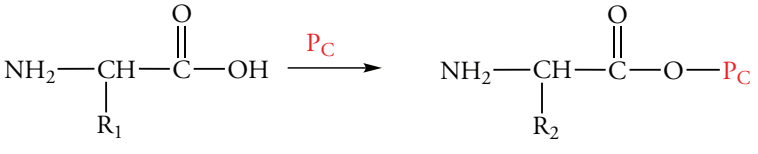
(a) How many isomeric peptides exist that contain one alanine and two glycine residues? (c) Write their names as three-letter abbreviations.

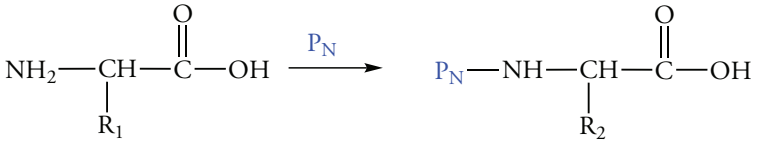
27.8 OVERVIEW OF PEPTIDE SYNTHESIS

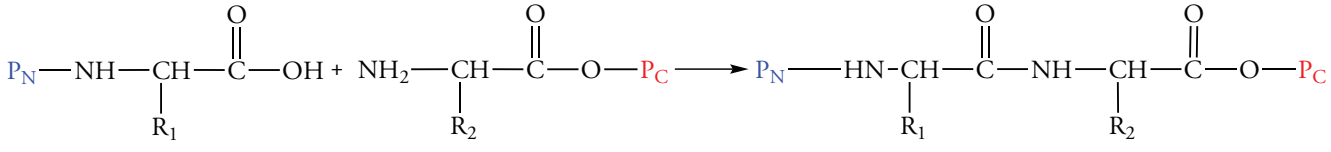
Peptides have such a wide range of physiological functions that their study is an important part of biological chemistry. Many companies provide peptides for researchers who lack the facilities of an organic chemistry laboratory and the training of synthetic organic chemists. Thus, peptide synthesis is a lucrative part of the biotechnology industry. In this section, we will consider the basic reactions required to synthesize a peptide.

We cannot simply react two amino acids under conditions that allow formation of a peptide bond if we wish to synthesize a specific dipeptide because an amino acid has two reactive positions, the α-amino group and the α-carboxyl group. For instance, reacting glycine with alanine would yield Gly-Gly, Gly-Ala, and Ala-Gly. Also, the amino acids and peptides in the reaction mixture can continue to react to give a host of other products.

The synthesis of a dipeptide having a specific sequence requires modifying both amino acids. One amino acid is protected at its carboxyl group— by a reagent we will call P_C — leaving the amino group free. The second amino acid is protected at its amino group— by a reagent we will call P_N — leaving the carboxyl group available for peptide bond formation. Only one condensation reaction is then possible.





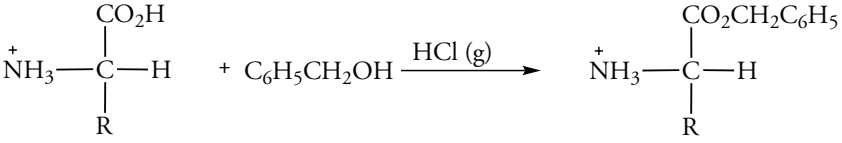


This method of peptide synthesis has several requirements.

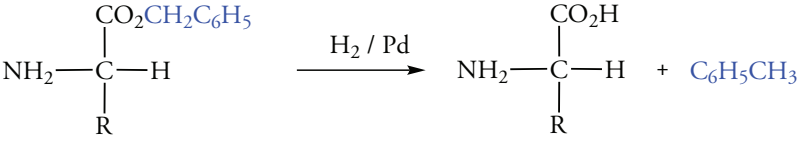
1. The carboxyl group of one amino acid must be protected.
2. The amino group of one amino acid must be protected.
3. A reagent must be chosen to form the peptide bond.
4. Conditions must be chosen to free one protecting group selectively so that the sequence can be repeated.

Protecting the Carboxyl Group

The carboxyl group can be protected by converting it to a benzyl ester. We also saw that the benzyl ester can be removed by hydrogenolysis without affecting other functional groups. Hence, the carboxyl group can be easily deprotected at the end of the synthesis.



benzyl ester

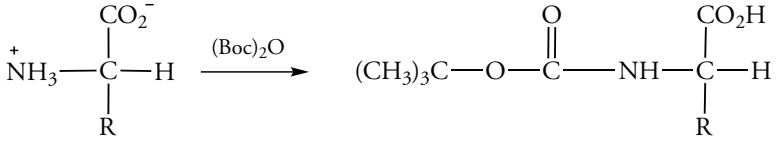


amino acid (or peptide) benzyl ester

deprotected amino acid (or peptide)

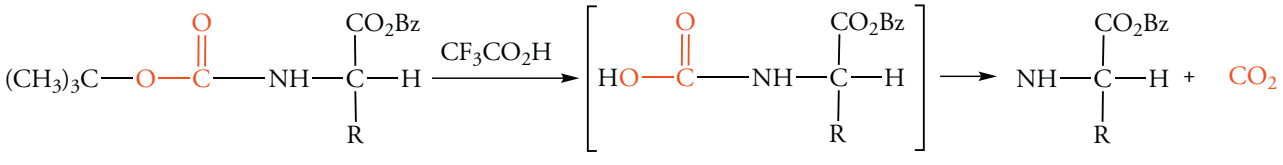
Protecting the Amino Group

We also recall that several protecting groups have been developed to protect the amino terminus of an amino acid; the *tert*-butoxycarbonyl (Boc) derivative is one example. Reaction of an amino acid with di-*tert*-butyl dicarbonate gives a Boc-amino acid.



N-*tert*-butoxycarbonyl amino acid
(a Boc-amino acid)

Note that the carbonyl group of the Boc group is bonded to both an oxygen atom and a nitrogen atom. This functional group is a carbamate, which is more easily hydrolyzed than amides or esters. The Boc group can be removed with trifluoroacetic acid. Both the amide bonds of a peptide and the protected carboxyl group are unaffected by this reaction. The by-products of the reaction are CO_2 and 2-methylpropene (isobutylene). Both are gases that escape from the reaction, pulling it to completion.



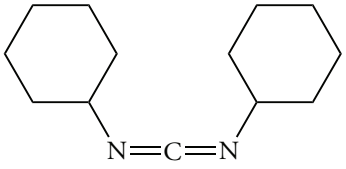
N-*tert*-butoxycarbonyl amino acid
(Boc-amino acid)

unstable carbamate derivative of
an amino acid

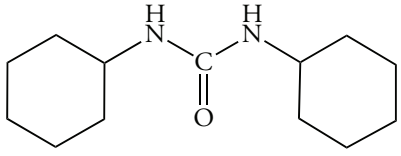
+ $CH_2{=}C(CH_3)_2$

Peptide Bond Synthesis

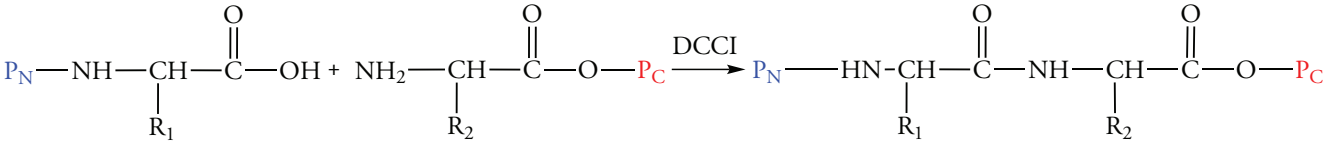
The protecting groups of both the amino and the carboxyl group are sensitive to acids and bases, so the condensation of two protected amino acids to form a peptide bond must be carried out under neutral conditions. It turns out that a reagent called dicyclohexylcarbodiimide (DCCI) causes condensation of two amino acids by removing the elements of water. The reaction has a very high yield, and no other functional groups are modified. The by-product of the reaction is dicyclohexylurea.



dicyclohexylcarbodiimide
(DCCI)

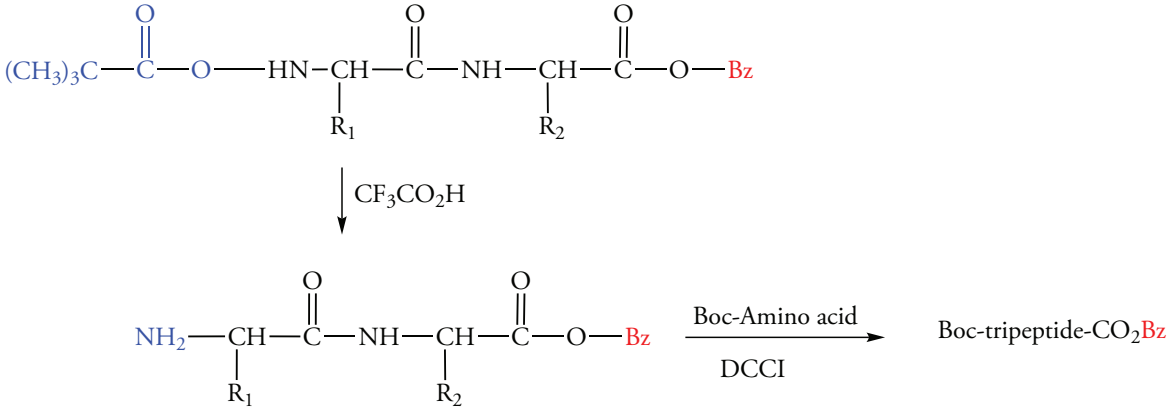


dicyclohexylurea



Polypeptide Synthesis

The dipeptide that is protected at both the carboxyl and amino terminus is deprotected by hydrolysis of the Boc group at the N-terminal amino acid. The dipeptide can only react at the free amino group. Reaction with another Boc-amino acid and DCCI yields a tripeptide. At the end of the synthesis, the final peptide is released by hydrolysis with base.



Experimental Limitations

One limitation of every synthetic method is mechanical losses that result from the isolation and purification of products. The product, in this case a peptide, must be separated from remnants of protecting groups, coupling agents, and by-products. Thus even reactions that yield a single regiospecific product may not produce a high isolated yield. The problem is compounded when many consecutive reactions are required in peptide synthesis. For example, a synthetic sequence required to prepare a peptide that contains 25 amino acid residues required a total of 100 steps. If the product of each step is isolated in 90% yield, the final yield would be extremely small because the amount of each product formed is controlled by the product that formed in the previous reaction. We obtain the fraction of product by multiplying the yields for each step. Thus, after 25 steps, the yield would be an infinitessimal 0.0026%.

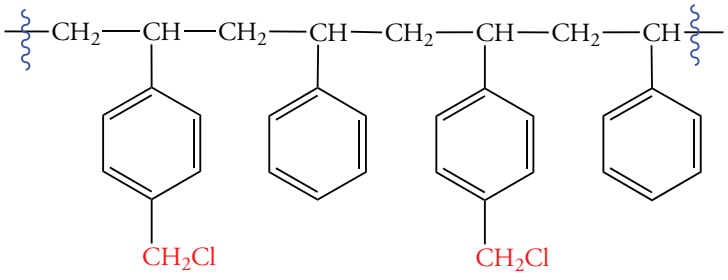
$$(0.90)^{100} = 0.000026$$

The problem becomes even worse as the number of amino acid residues in a polypeptide increases. For relatively large peptides that contain in excess of chemical synthesis by conventional means is clearly out off the question.

27.9 SOLID-PHASE PEPTIDE SYNTHESIS

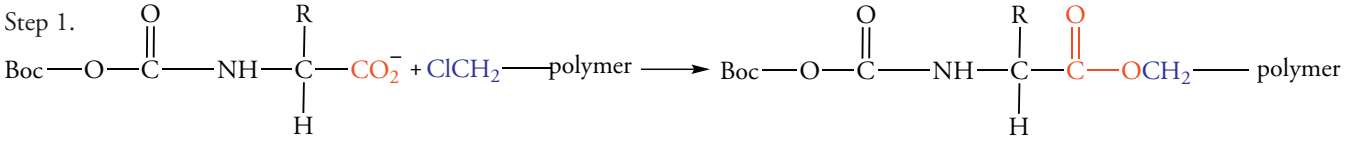
The solid-phase synthesis of polypeptides was developed by R. B. Merrifield at Rockefeller University beginning in the 1960s. This method has undergone continuous development and refinement in the ensuing decades, but the overall method has remained the same. The solid-state method uses a polymer with reactive sites that chemically bind to the developing peptide chain. This technique circumvents the problems associated with low yields due to separation and purification. Because the polymer is very insoluble, it can be filtered and washed without mechanical losses. The developing protein chain attached to the polymer is "dangling" off the polymer and is in contact with any reagents added in solution. As a result, a large number of steps can be carried out on the peptide, and the product remains linked to a solid that can be separated from impurities in solution.

One polymer used in solid-phase synthesis is an addition polymer of styrene in which some of the benzene rings have a —CH_2Cl group. As few as 1 out of 10 rings bear chloromethyl groups. The general structure of the chloromethylated polystyrene is shown below.



chloromethylated polystyrene

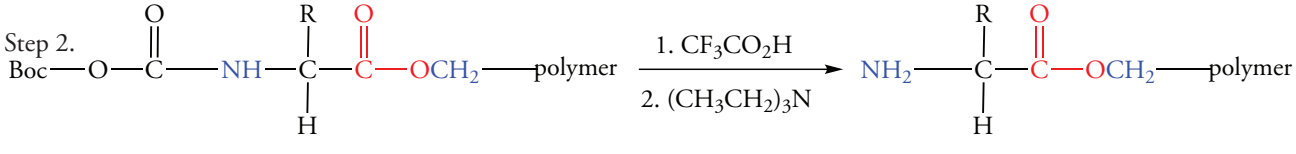
We recall that benzyl halides are reactive in substitution reactions. Even relatively weak nucleophiles such as carboxylate salts react with benzyl halides to yield benzyl esters. Thus, a solution of a carboxylate salt of an N-protected amino acid in an aprotic solvent such as DMF readily gives an ester. This first step, using a shorthand representation of the polymer, is shown below.



(*N*-protected Boc-amino acid)

(polymer bound *N*-protected Boc-amino acid)

The polymer-bound N-protected amino acid is filtered and then washed with solvent. The product is then treated with CF_3CO_2H to deprotect the amino group by removing the Boc group in step 2. Subsequent treatment with an amine base neutralizes the ammonium group of the amino acid and yields a polymer-bound amino acid. No impurities remain in the solution.

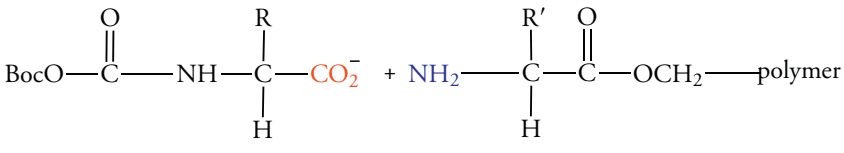


(polymer bound N-protected Boc-amino acid)

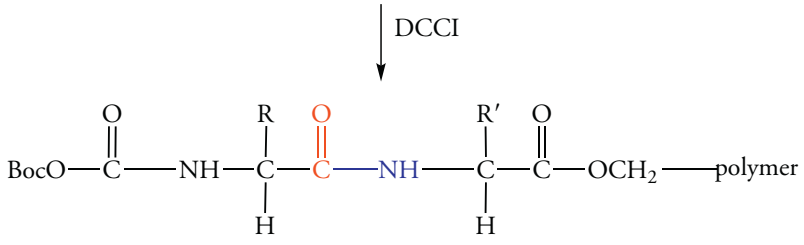
(polymer bound amino acid)

The polymer-bound amino acid is then reacted with a solution of an N-protected amino acid and DCCI in step 3, yielding a polymer-bound N-protected dipeptide.

Step 3.



a Boc-amino acid polymer bound amino acid



N-protected polymer bound dipeptide

The polymer-bound amino acid is then reacted with a solution of an N-protected amino acid and DCCI in step 3, yielding a polymer-bound N-protected dipeptide. This cycle can be repeated many times. Peptide containing up to 80 amino acid residues can be synthesized in reasonable yield. R. B. Merrifield was awarded the Nobel Prize in Chemistry in 1984 for inventing solid state peptide synthesis.

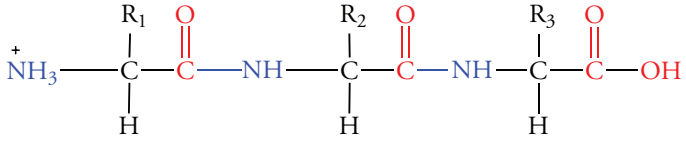
27.10 DETERMINATION OF THE AMINO ACID COMPOSITION OF PROTEINS

Determination of the Amino Acid Composition of Proteins by Chemical Methods

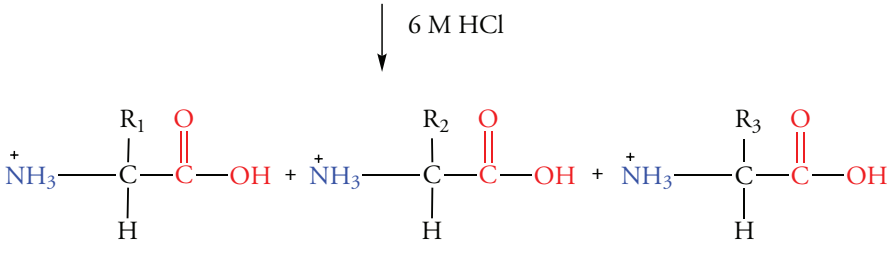
At one time, determining the amino acid composition was a difficult and time-consuming process. This analysis is not performed automatically in an instrument called an amino acid analyzer. This process has four steps. About 10 μg of protein are required. Modern instruments can detect about 5 nmol of a given amino acid.

1. Hydrolysis of the protein in HCl.
2. Synthesis of derivatives of the amino acids released in step 1.
3. Separation of the covalently modified amino acids by high-performance liquid chromatography (HPLC).
4. Analysis of the chromatographic data.

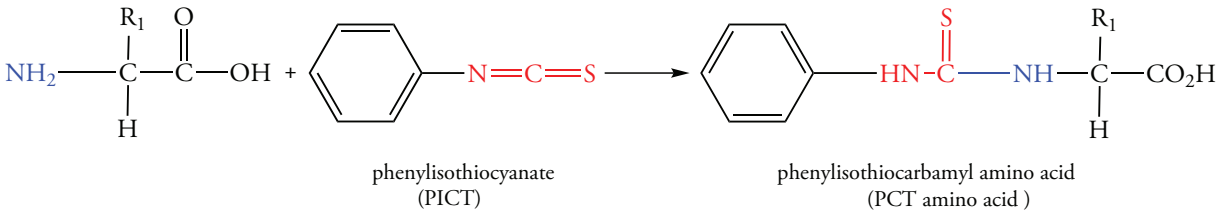
Step 1. Acid-catalyzed hydrolysis. We recall that amides, and therefore peptide bonds, are quite stable and the fairly stringent conditions are required for this reaction. The protein is hydrolyzed in 6 M HCl for about an hour at a temperature of 150 °C. This process is not as straightforward as it might seem since amino acid residues are not affected in the same way by acid hydrolysis. Thus, the Asn and Gln, which contain amide bonds in their side chains, are concerted to Asp and Glu, respectively. Tryptophan and cysteine are completely destroyed by acid hydrolysis. Therefore, a sample of the protein has to be hydrolyzed under a variety of conditions for an accurate analysis. Since we are primarily interested in basic principles, we will not consider the hydrolysis reactions in greater detail.



tripeptide



Step 2. Synthesis of amino acid derivatives. The amino acids released by hydrolysis of the protein are converted to phenylthiocarbamyl (PTC) amino acids by reaction with phenylisothiocyanate (PICT).



phenylisothiocyanate (PICT)

phenylisothiocarbamyl amino acid (PCT amino acid)

Step 3. Separation of the covalently modified amino acids by high performance liquid chromatography (HPLC). The PCT derivatives are separated by HPLC. The PCT derivatives are detected by UV spectroscopy; λ_{max} for the PCT derivatives is 254 nm. Figure 27.6 shows a sample result of the chromatographic separation.

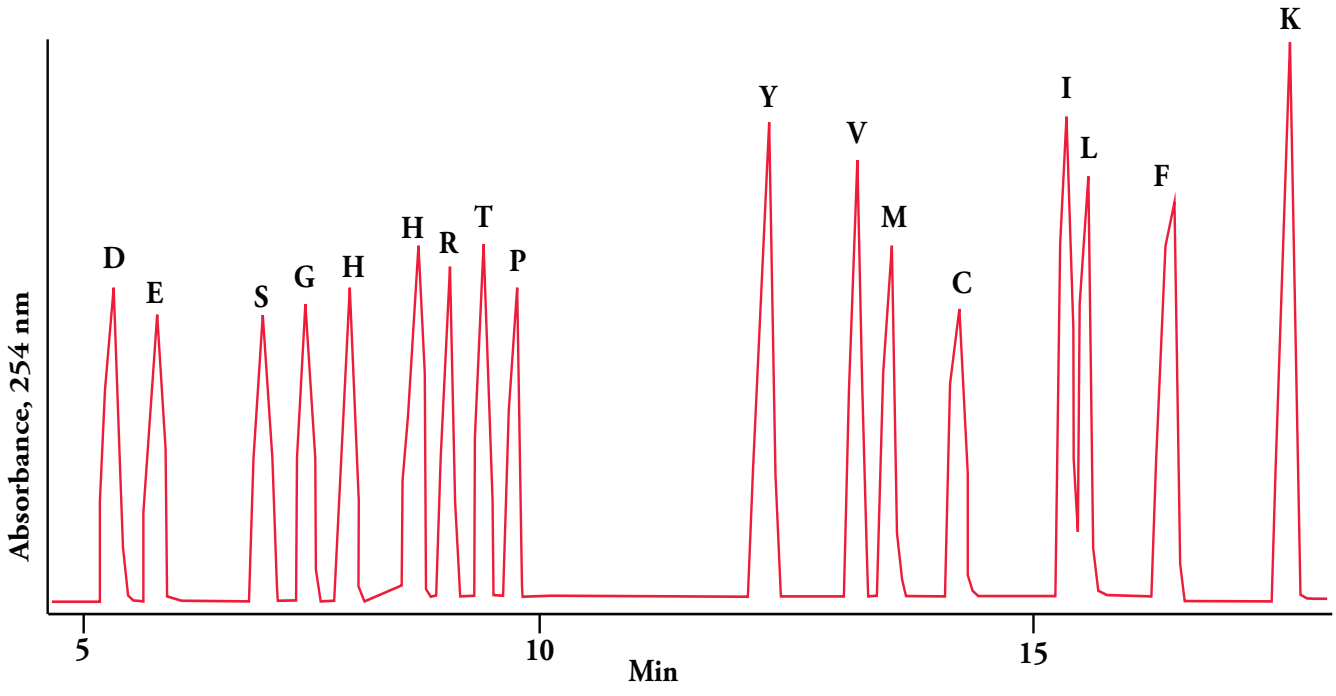


Figure 27.6 HPLC Separation of PCT Amino Acids

Step 4. Analysis of the chromatographic data. Each chromatographic peak is identified by comparison to the retention times (in minutes) of known PCT derivatives. In commercial instruments, a system for data analysis is linked to the amino acid analyzer. The amount of each amino acid in the sample is calculated by dividing the peak area of each peak. Since the extinction coefficients for the amino acids differ, their absorbances also differ (Section 11.10), and the concentrations of are corrected to account for this difference.

Table 27.4 gives the amino acid composition of human lysozyme, also called α-lactalbumin. Lysozyme hydrolyzes the cell walls of gram-positive bacteria and provides a natural defense against bacterial infection. It is present, for instance, in the eye and helps to prevent eye infections. Lysozyme contains 120 amino acids.

Table 27.4
Amino Acid Composition of Human Lysozyme

Amino Acid	*Number of Amino Acids*	*Per Cent Composition*
Ala	5	4.1
Arg	1	0.8
Asn	4	3.3
Asp	12	9.8
Cys	8	6.5
Gln	7	4.9
Glu	8	6.5
Gly	6	9.8
His	2	11.4
Ile	12	9.8
Leu	14	11.4
Lys	12	9.8
Met	2	1.6
Phe	4	3.3
Pro	2	1.6
Ser	8	6.5
Thr	7	5.7
Trp	3	2.4
Tyr	4	3.3
Val	2	1.6

27.11 DETERMINATION OF THE AMINO ACID SEQUENCE OF PROTEINS

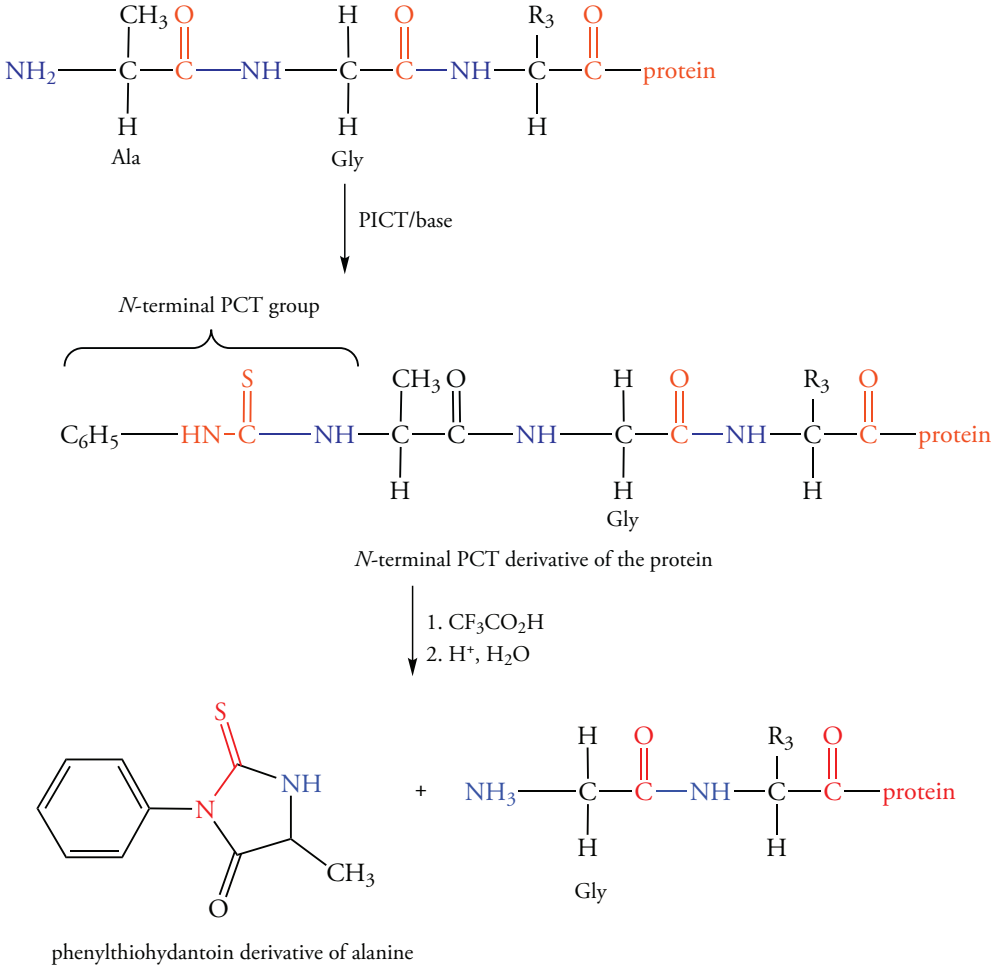
Chemical methods for determining the sequence of amino acids in a protein couples identification of the end N-terminal amino acid by an automated amino acid sequencer to an automated amino acid analyzer. Modern instruments can determine sequences for protein or peptide samples that contain 10–100 picomoles, pm (1 pm = 10^{-12} moles). The overall process requires several automated steps.

The Edman Degradation

The identity of the N-terminal amino acid of a polypeptide is determined by a method invented by Pehr Edman called the **Edman degradation**. In the Edman degradation, the polypeptide is treated with phenyl isothiocyanate—the Edman reagent— which reacts with the N-terminal amino acid to give an N-terminal PTC derivative or the protein. This derivative forms by addition of the terminal N—H bond across the C=N of the phenyl isothiocyanate. After the adduct has formed, anhydrous trifluoroacetic acid is added to the reaction mixture. This reagent cleaves the polypeptide at the N-terminal residue. Under these conditions, the peptide bonds in the protein do not break (Figure 27.7). Reaction of the N-terminal amino acid with phenylisothiocyanate (PITC) gives the N-terminal PCT derivative of the protein, which is exactly analogous to the reaction of amino acids with PICT. This derivative is treated with trifluoroacetic acid, and then water is added. These steps release the first amino acid as its phenylthiohydantoin (PTH) derivative. The other peptide bonds of the protein, which now contains one less amino acid, are not affected.

Figure 27.7 Edman Degradation

First, the peptide is converted to its N-terminal PCT derivative by treatment with phenylisothiocyanate. Next, the PCT protein is treated with trifluoroacetic acid, then with water to give the phenylthiohydantoin derivative. The N-terminal amino acid is released in this step. The other peptide bonds are not affected.

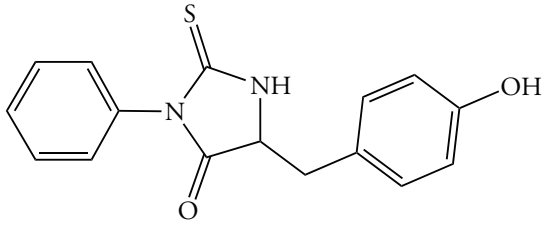


A complex cyclization reaction occurs to give a substituted phenylthiohydantoin. This ring contains the carbonyl carbon atom, the α-carbon atom, and the amino nitrogen atom. The R group of the amino acid is attached to the ring. The PTH derivative of the N-terminal amino acid is then automatically transferred to an amino acid analyzer. Comparison with the phenylthiohydantoin of known amino acids establishes the identity of the amino acid.

Because the Edman degradation does not cleave the peptide bonds in the protein, it can be repeated to sequentially identify the amino acids from the N-terminal amino acid of the molecule. The yield of the Edman degradation approaches 100%, and sequences of 30 residues of a polypeptide can be determined from 5-picomole (5×10^{-12} mole) samples. This means that the sequence of a peptide with 30 amino acid residues, with a molecular weight of about 3000, can be determined from a 15 nanogram sample!

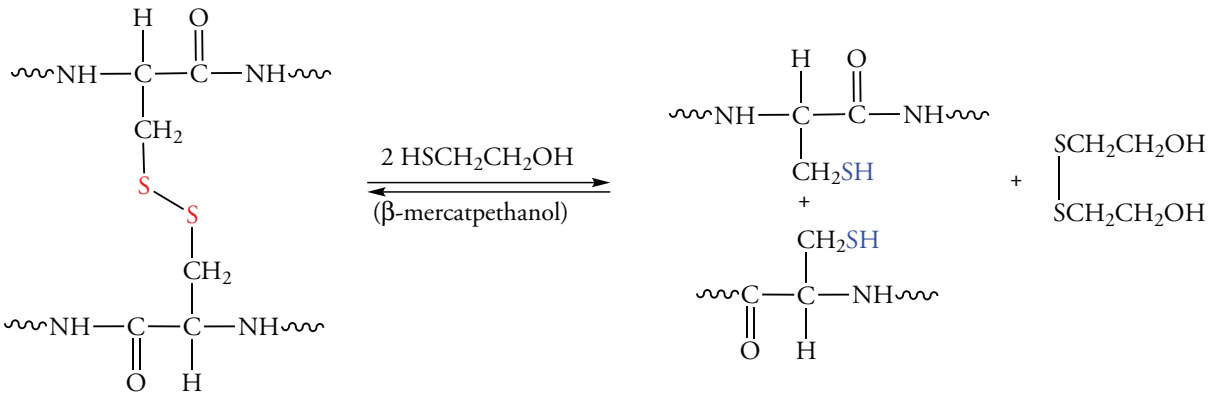
Problem 27.12

β-Endorphin, a peptide that contains 31 amino acid residues, has analgesic effects and promotes the release of growth hormone and prolactin. Treating β-endorphin with phenyl isothiocyanate followed by hydrolysis with anhydrous trifluoroacetic acid, and then with water, releases the following phenylthiohydantoin. What is the N-terminal amino acid of the peptide?



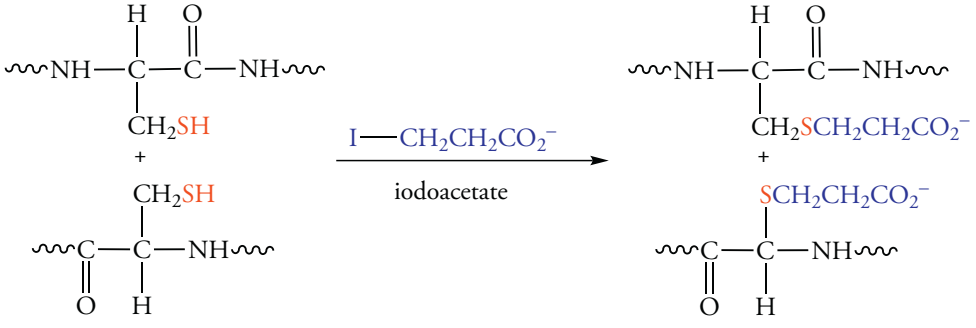
Blocking Cystine Residues

If a protein contains a chain internally linked by one or more cystine residues, the disulfide bonds of these residues must be cleaved. Treating the protein with excess β-mercaptoethanol converts cystine to two cysteine residues. This is a reversible disulfide bond exchange in which the protein is oxidized, and the β-mercaptoethanol is reduced.



cystine residue — 2 cysteine residues

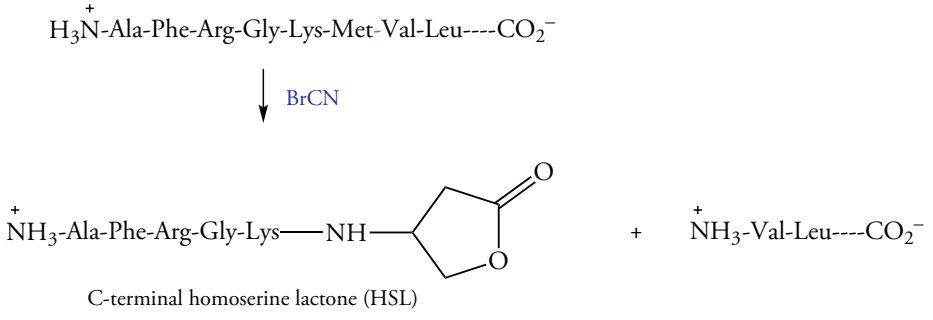
To prevent disulfide bonds from forming again, the protein is treated with iodoacetate, which converts the cysteine residues to *S*-carboxymethylcysteine residues. This reaction occurs by an S_N2 mechanism in which the nucleophilic sulfur atom displaces iodide.



cysteine residues — *S*-Carboxymethylcysteine residues

Peptide Cleavage at Methionine Residues

If a protein contains methionine residues, the polypeptide chain can be cleaved by cyanogen bromide (BrCN), which produces a C-terminal peptidyl homoserine lactone (HSL) residue. Most proteins contain only a few methionine residues, so only a few fragments result from this reaction.

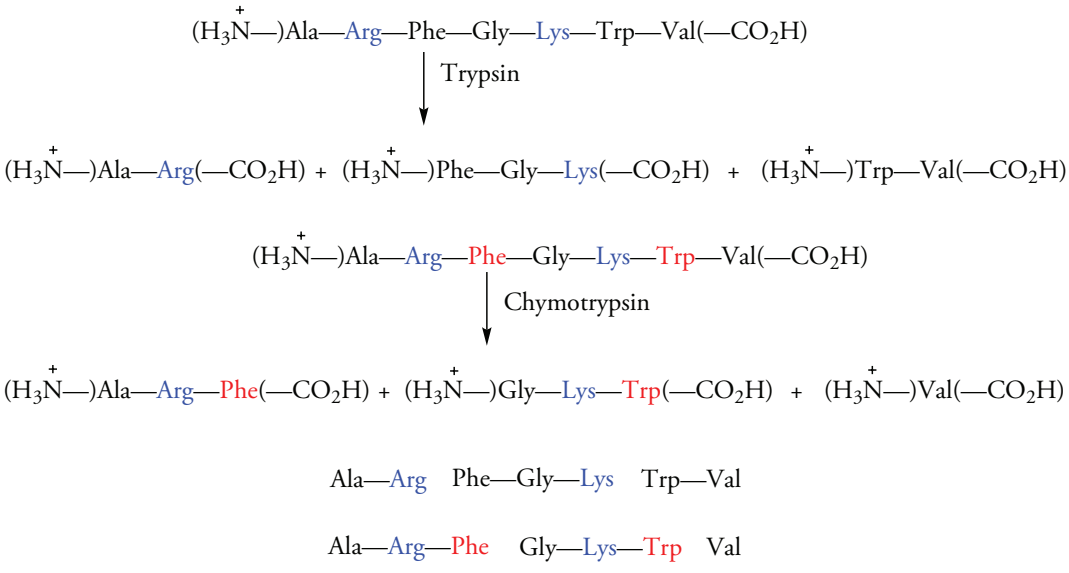


C-terminal homoserine lactone (HSL)

Enzymatic Cleavage of Polypeptide Chains

Many proteins contain hundreds of amino acids. To determine their sequences other reactions are required to provide sequences short enough to be determined by Edman degradation. Enzymatic cleavage by two enzymes, trypsin and chymotrypsin, is used to produce smaller peptides. Trypsin cleaves polypeptide chains on the C-terminal side of basic residues such as arginine and lysine. Chymotrypsin cleaves the polypeptide on the C-terminal side of aromatic residues.

The sequences each oligopeptide fragment produced in these enzymatic reactions are determined by Edman degradation. Then, in the final step, the fragments are aligned to provide the entire sequence.



Ala—Arg Phe—Gly—Lys Trp—Val

Ala—Arg—Phe Gly—Lys—Trp Val

Primary Structures and Evolutionary Relationships

The primary structures of thousands of protein are known. Comparing the primary structures of proteins that are common to many species reveals evolutionary relationships. As organisms evolve, their genes change through mutation. Since the primary structure of a protein reflects the gene coding for it, differences among primary structures are a record of evolutionary change. Comparing the amino acid sequences of proteins found in different species thus opens a window to the past. In a sense, then, proteins can be regarded as living fossils.

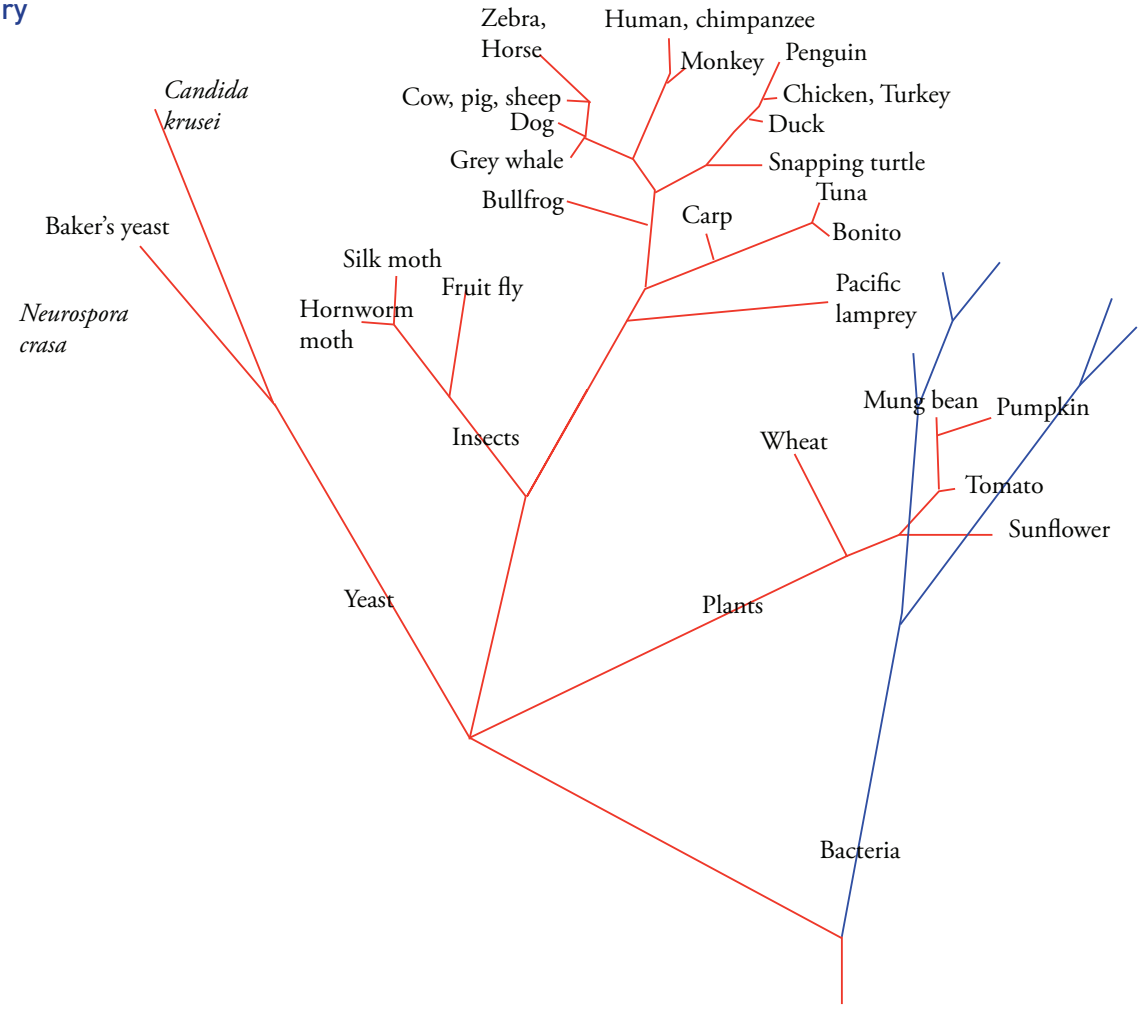
In closely related species, the primary structures of common proteins are similar. Counting the number of differences in amino acid sequences among these proteins gives some idea of how far various species have diverged in the course of evolution. For example, the protein cytochrome *c* is an excellent protein for evolutionary comparisons because it is found in the respiratory electron transport system, which is present in all aerobic organisms (Figure 27.8).

Figure 27.8 shows that as evolutionary lines diverge, the number of sequence variations increases so that closely related species have few differences and distantly related species have many difference in primary structure. Thus, human and chimpanzees have identical cyctochrome *c* sequences. The primary structures of cytochrome *c* molecules from California gray whales differ from that of pigs, cows, and sheeps by only two residues. We conclude that the whale has evolved from land animals related to modern hoofed animals. Gray whale cytochrome *c* differs from human cytochrome *c* 10 residues.

Peking duck and penguins also have cytochrome *c* sequences that differ by only three residues, but they differ by 11 residues from bullfrogs. Thus, these species are closely related to each other but distantly to bullfrogs.

The difference between human cytochrome *c* and baker's yeast cytochrome *c* is 45 residues, which we do not find particularly surprising since these are distantly related species. However, 59 of the 104 residues in cycotchrome *c* are identical. Identical residues are essential for the structure and function of the protein.

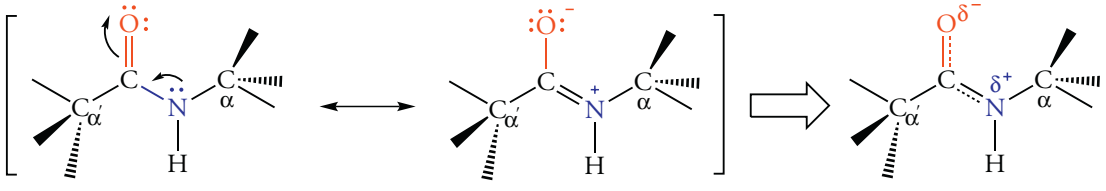
Figure 27.8 Evolutionary Family Tree for Cytochrome *c*



27.12 BONDING IN PROTEINS

Structure of the Peptide Bond

The carbonyl group of one amino acid and the amino group of the next by secondary amides called peptide bonds. The lone pair on the nitrogen of the peptide bond is delocalized onto the carbonyl carbon, and the peptide bond is resonance stabilized.



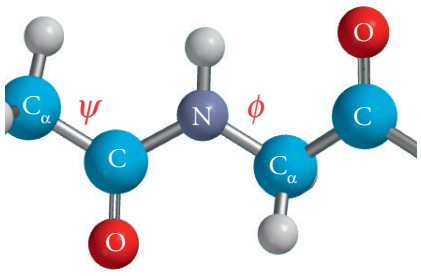
contributing structure 1 | contributing structure 2 | resonance hybrid

The C—N bond length in a peptide bond has about 50% double bond character, and the formal charges on the nitrogen and oxygen atoms are about +½ and –½, respectively. We recall that rotation around double bonds does not occur. Similarly, rotation around the partial C—N double bond is restricted and does not occur at room temperature. As a result, the overwhelming majority of peptide bonds in proteins have *trans* configurations. However, free rotation does occur around the C—C_a and C—$C_{a'}$ single bonds. In peptide and protein nomenclature, the N—C_a bond is called phi (ϕ) and the C—C_a bond is called psi (ψ). Rotations around these bonds give rise to a vast number of conformations of the polypeptide chain (Figure 27.9).

Figure 27.9 Structure of the Peptide Bond

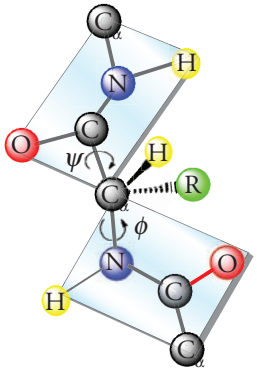
(a) Rotation around the C—N bond, which has 50% double bond character, does not occur at room temperature. However, rotation around the N—C_a bond (ϕ) and the C—C_a bond (ψ) is possible, and many conformations are possible in peptides and proteins.
(b) we can think of the α-carbon as a "hinge" between two planar peptide bonds. If one takes two note cards and links them with a swivel, it is easy to see that many arrangements are possible. However, some ϕ and ψ are not possible because of steric interference of the side chain R group. Glycine, for example, can assume many more conformations than amino acids like proline and tryptophan.

(a)



trans configuration of peptide bond

(b)



The α-Helix

One of the most common structural features in proteins is a repeating conformation called the **alpha helix**. In this conformation, the values of ϕ and ψ are –57° and 47°, respectively. Figure 27.10 shows the structure of an α-helix. The hydrogen bonds are approximately parallel to the long axis of the helix. In Figure 27.9a, amino acid side chains are shown. Figure 27.9b the polypeptide backbone and hydrogen bonding pattern in the helix. Some amino acids are more likely than others to be present in an α-helix. Proline, which lacks an N—H bond, and therefore cannot form a hydrogen bond, is never found in an α-helix. Furthermore, its five-membered pyrrolidine ring cannot assume the ϕ/ψ angles required for a helix. Nonpolar, hydrophobic amino acids such a leucine, valine, and phenylalanine are often found in α-helices; polar, charged side chains are less common. The carbonyl oxygen atom of the peptide bond is a hydrogen bond acceptor, and the peptide bond nitrogen atom is a hydrogen bond donor.

The α-helix is right-handed. Left-handed α-helices are not observed. Why not? We recall that a helix is a chiral structure so that right- and left-handed helices are mirror images, and we know that enantiomers have the same energy. However, the α-amino acids are chiral (except glycine), and a right-handed α-helix of L-amino acid residues and a left-handed α-helix of L-amino acid residues are *not* enantiomers, they are diastereomers. We know that diastereomers have different energies. A right-handed α-helix of L-amino acid residues is more stable than its diastereomer because in the left-handed configuration there is considerable steric hindrance among side chains, so it does not form.

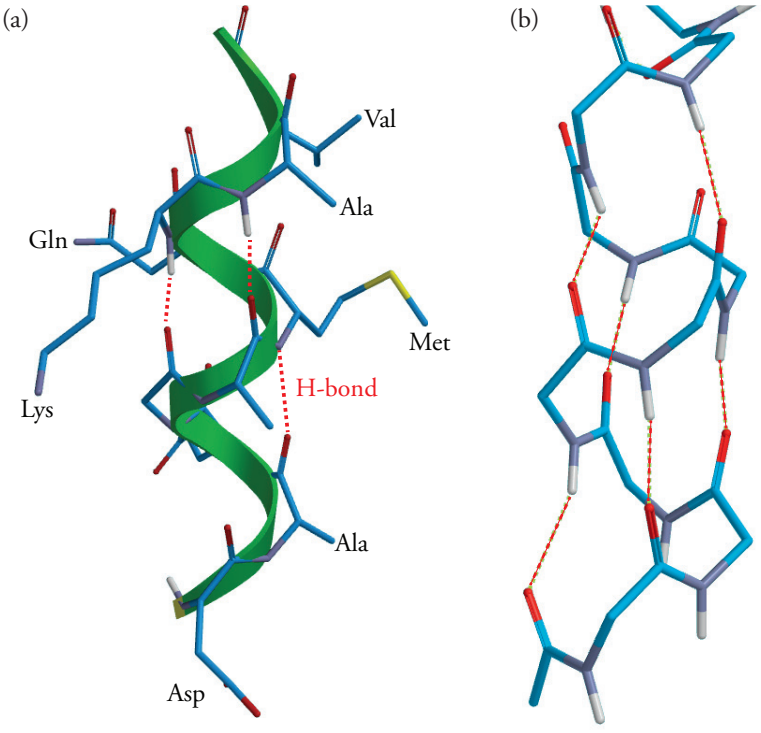


Figure 27.10 Dimensions of an α-Helix
The distance between amino acid residues in an α-helix is 0.15 nm. The distance required for one turn of the helix, its pitch, is 5.4 nm.

β-Pleated Sheets

Many proteins contain a type of secondary structure in which the polypeptide chain has a completely extended conformation. Two adjacent regions of fully extended polypeptide chains form hydrogen bonds at that link the chains at approximately right angles to the long axis of the chain. This type of secondary structure is called a β-**pleated sheet**. There are two kinds of β-pleated sheets, called **parallel** and **antiparallel**. In a parallel β-pleated sheet, the C- and N-termini of the sheet are together (Figure 27.11); in the antiparallel β-pleated sheet, they are opposed (Figure 27.12).

Figure 27.11 Hydrogen Bonding In Parallel β-Pleated Sheet

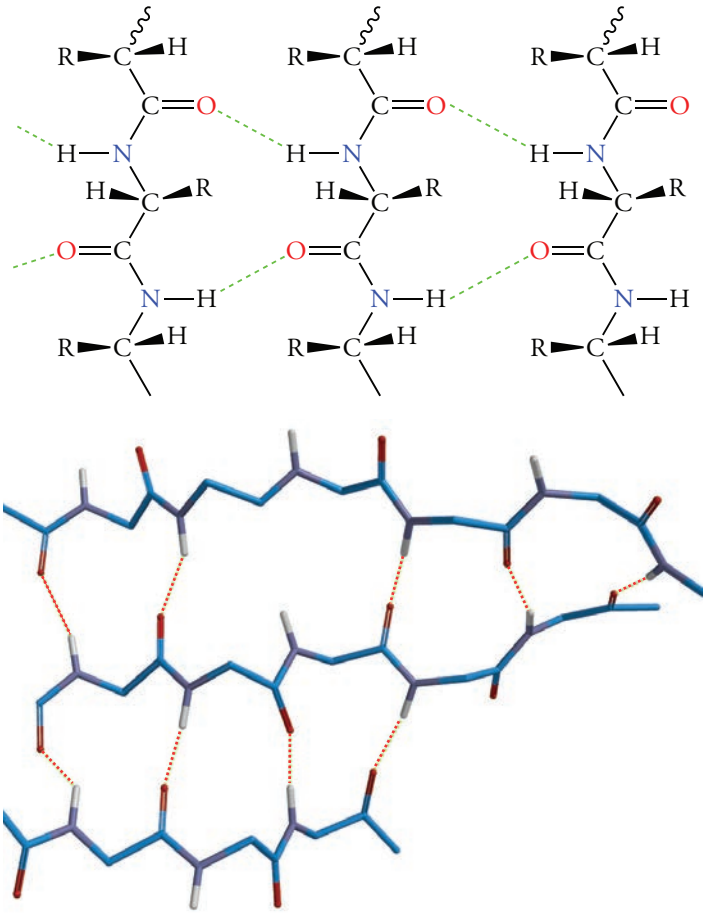
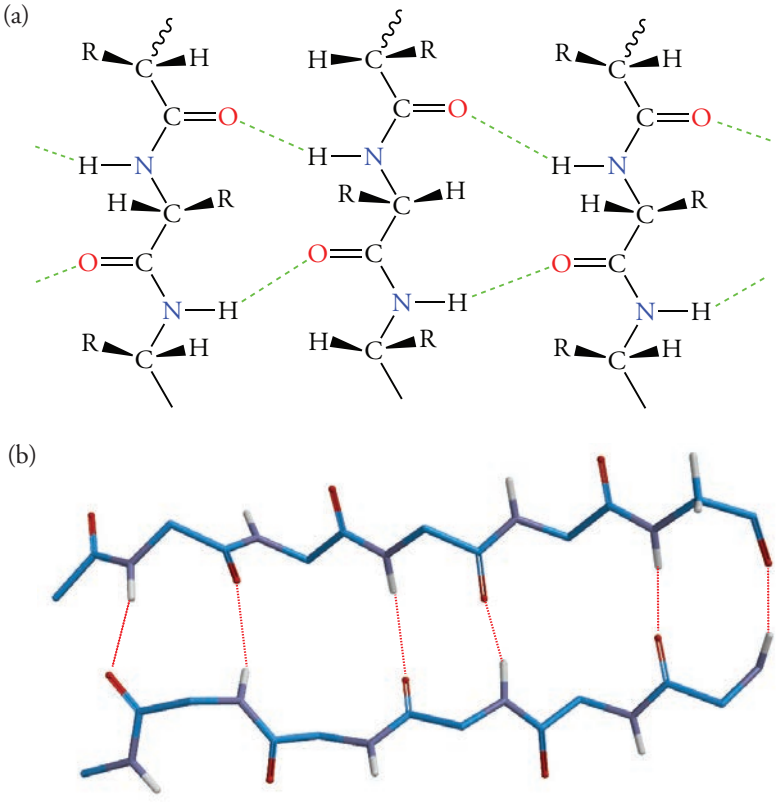


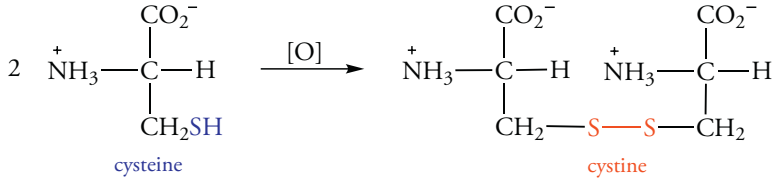
Figure 27.12 Hydrogen Bonding in an Antiparallel β-Pleated Sheet

(a) Bond-line structure of an antiparallel β pleated sheet.
(b) Molecular model of an antiparallel β pleated sheet showing only the polypeptide backbone and the hydrogen bonds.



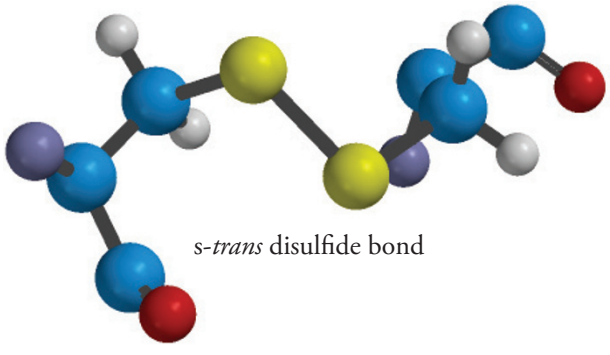
Disulfide Bonds

Many proteins—especially relatively small ones containing fewer than 100 amino acid residues—have a high cysteine content. Each of these cysteine residues has a sulfhydryl group (—SH) that can be oxidized to form a disulfide bond. The dimer of cysteine itself is called, somewhat confusingly, **cystine** (note the "missing e" in the name).



Disulfide bonds form after a protein has folded into its biologically active conformation. Once disulfide bonds have formed, the protein conformation is much less flexible. We recall that conformations around sigma bonds can be either s-*cis* or s-*trans* and that the s-*trans* conformation is usually more stable because it minimizes steric repulsion. When disulfide bonds exist in proteins, they nearly all have an s-*trans* conformation (Figure 27.13).

Figure 27.13 Conformation of an s-*trans* Disulfide Bond



Intrachain disulfide bonds occur in small peptides such as oxytocin and vasopressin, as we saw in Section 27.6. Disulfide bonds can also link a cysteine residue in one polypeptide chain with a cysteine residue in another polypeptide chain as in the polypeptide insulin.

Hydrophobic Interactions

Proteins contain many nonpolar side chains. These side chains are repelled by water and tend to associate with one another on the "inside" of a folded protein molecule, out of contact with water. The tendency of nonpolar side chains to collect out of contact with the solvent is called the **hydrophobic effect**. The hydrophobic interactions in proteins are similar to those in the micelle of a soap (Section 21.5) or the bilayer of lipids in membranes. Hydrophobic interactions among nonpolar side chains in proteins are weak, but abundant, and are primarily responsible for maintaining the folded conformation of a protein.

27.13 PROTEIN STRUCTURE

The highest operation in nature and in art is the attainment of significant form. Goethe

Globular proteins are compact, more or less spherical molecules. The term globular sounds rather uninspiring, but globular proteins have a wonderful diversity of forms. The term globular does not in the least imply structural monotony or simplicity. Most globular proteins are soluble in the cytosol or in the lipid phase of biological membranes. Globular proteins are the primary agents of biological action in the cell. Most globular proteins are protein catalysts called enzymes. Some globular proteins transport oxygen and lipids in the blood. Some are hormones or membrane-bound receptors that mediate the action of hormones. The globular proteins called immunoglobulins, or antibodies, are the first lines of defense against pathogenic bacteria and viruses.

We can describe the structure of globular proteins in terms of four levels of structure. Each structural level has properties that cannot be deduced from a knowledge of the lower levels of structure.

1. The **primary structure** of a protein consists of its linear sequence of amino acid residues. Although it is the simplest level of structural organization, in many ways, it is the most important, since the primary structure determines the conformation and function of a protein.
2. The **secondary structure** of a protein consists of regularly repeating conformations of the polypeptide backbone such as α-helices and β-pleated sheets.
3. The **tertiary structure** of a protein consists of its three-dimensional conformation. Many proteins contain regions called **domains** that are relatively independent structural units.
4. Many proteins exist in cells in complexes that contain two or polypeptide chains. These complex assemblies are called the **quaternary structure** of the protein. Table 27.5 gives a few examples.

Table 27.5
Examples of Proteins Having Quatenary Structure

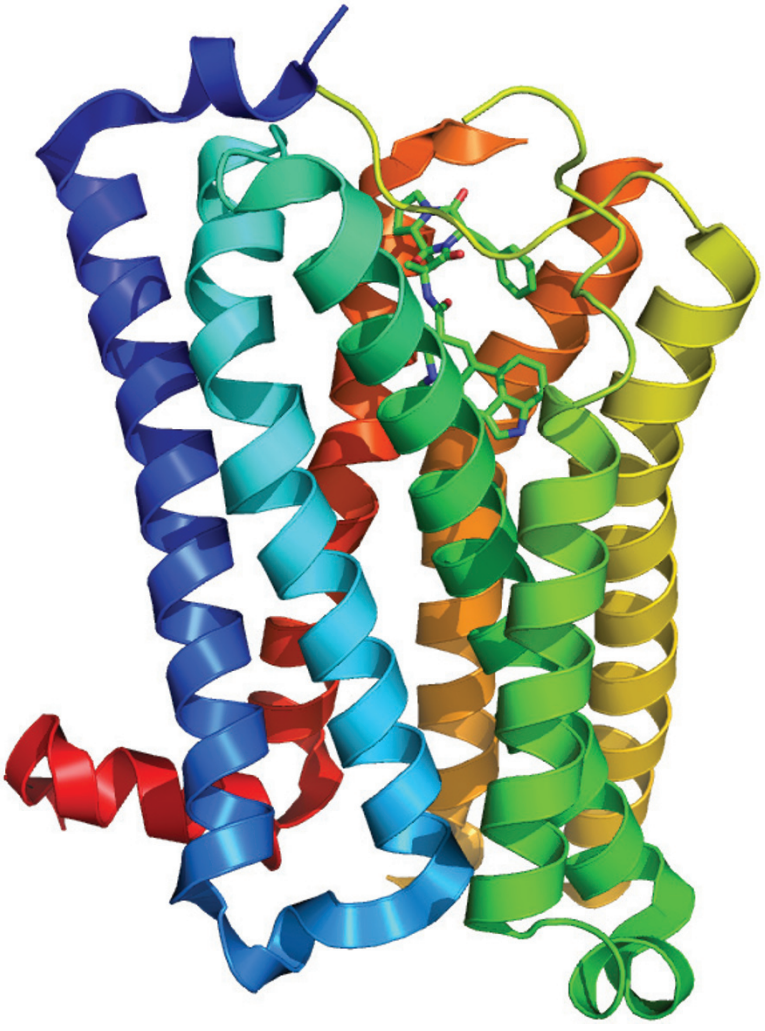
Protein	*Molecular Weight*	*Number of Subunits*	*Function*
Alcohol Dehydrogenase	80,000	4	Enzymatic reaction in fermentation
Aldolase	150,000	4	Enzymatic reaction in glycolysis
Fumarase	194,000	4	Enzymatic reaction in citric acid cycle
Hemoglobin	65,000	4	Oxygen transport in blood
Insulin	11,500	2	Hormone that regulates metabolism of glucose

In our discussion of peptide functions, we discussed a family of closely related proteins called guanine nucleotide, coupled receptor proteins. We noted that the hormone binding regions of these receptors were located in a region of seven helices within the membrane. Figure 27.14 shows the seven-helix bundle in the membrane region of the serotonin receptor.

We recall that the primary sequences of the guanine nucleotide protein receptors (GCPR) have similar sequences and that closely similar sequences correspond to close evolutionary ancestry. When we look at the sequences of the serotonin receptor, we find that membrane helix 5 plays an important part in ligand specificity. When we align the sequences of many GCPRs, we find that the secondary structures are also aligned, so sequence alignment can be extended to structure alignment (Figure 27.15).

Figure 27.14 Ribbon Diagram of the Membrane Region of the Serotonin Receptor

The seven helix region of the serotonin receptor is the site of serotonin binding. The serotonin receptor is a member of the G-coupled receptor protein family. These proteins have similar structures. Their different specificities depend upon differences in primary structure at the ligand bindings site.



A small protein called 1GB1, which contains the ligand (antigen) binding site at the N-terminus of an immunoglobulin, is shown in Figure 27.15. This region, which has 56 amino acid residues, contains antiparallel β-pleated with four strands. An α-helix sits on top of the β-pleated sheet.

Helices and sheets can combine in many other ways. For example, an enzyme that catalyzes a reaction in the degradation of glucose (glycolysis) called triose phosphate isomerase, which has 248 amino acid residues, contains many "strand-helix-strand" motifs β-α-β (Figure 27.16). The β strands form a parallel β-pleated sheet. Figure 27.17 shows the tertiary structure of triose phosphate isomerase.

Figure 27.15 Structure of 1GB1

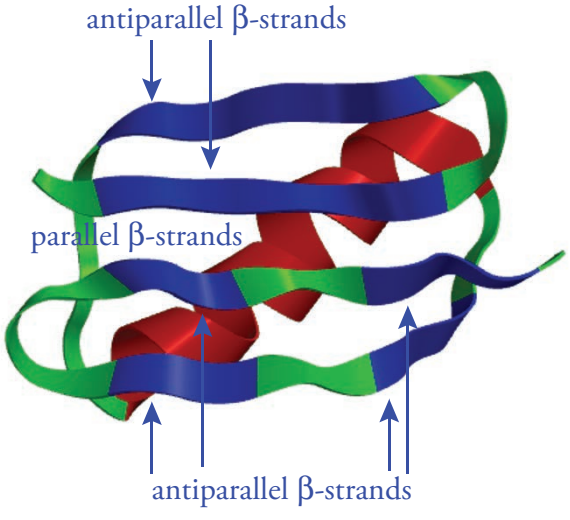


Figure 27.16 Parallel β Strands and an α-Helix in a β-α-β Arrangement

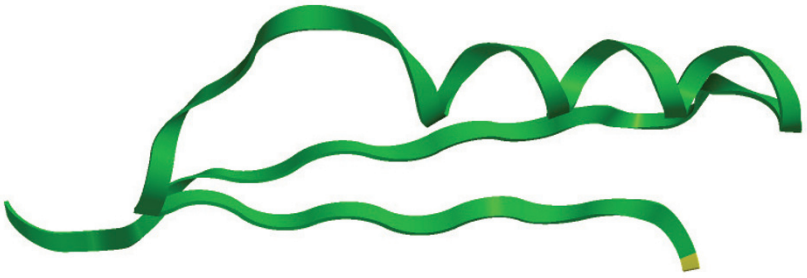
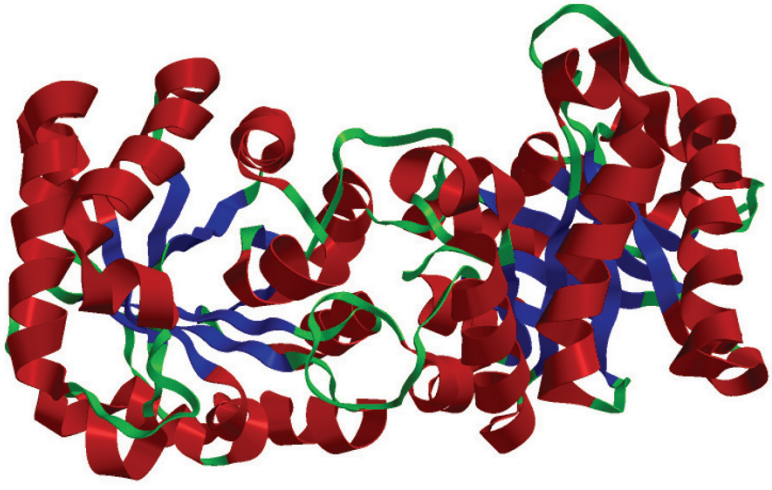


Figure 27.17 Tertiary Structure of Triose Phosphate Isomerase

The α-helices are shown in red, β-pleated sheets are blue, and less structured "loops" are shown in green.



27.14 OXYGEN STORAGE AND TRANSPORT: MYOGLOBIN AND HEMOGLOBIN

Humans and other vertebrates transport oxygen in red blood cells called **erythrocytes** (Greek, *erythro*, red; *kytos*, cell). A mature human erythrocyte is essentially a sack that carries hemoglobin. Hemoglobin transports oxygen throughout the body; myoglobin stores oxygen in cardiac and skeletal muscle until it is consumed during metabolism.

Myoglobin

We will begin our discussion with myoglobin. Myoglobin accounts for about 8% of total muscle protein in diving mammals such as seals and whales that store large amounts of oxygen for use during dives. These animals do not contain hemoglobin.

The structure of myoglobin was determined in 1960. Most of the amino acid residues in myoglobin are in α-helices (Figure 27.18). The oxygen binding site in myoglobin is not the protein itself, but a **heme** group. Heme contains Fe^{2+}, and O_2 is the ligand that binds it (Figure 27.19). Both carbon monoxide and cyanide have a higher affinity for heme than oxygen. In high concentrations, they inhibit oxygen binding; hence, they are fatal.

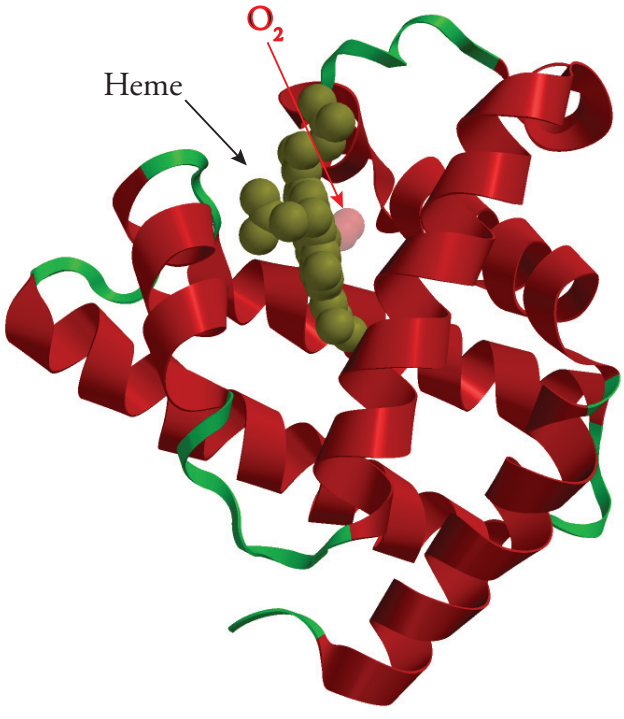


Figure 27.18 Structure of Oxymyoglobin.
The α-helices are shown in red, and less structured "loops" are shown in green.

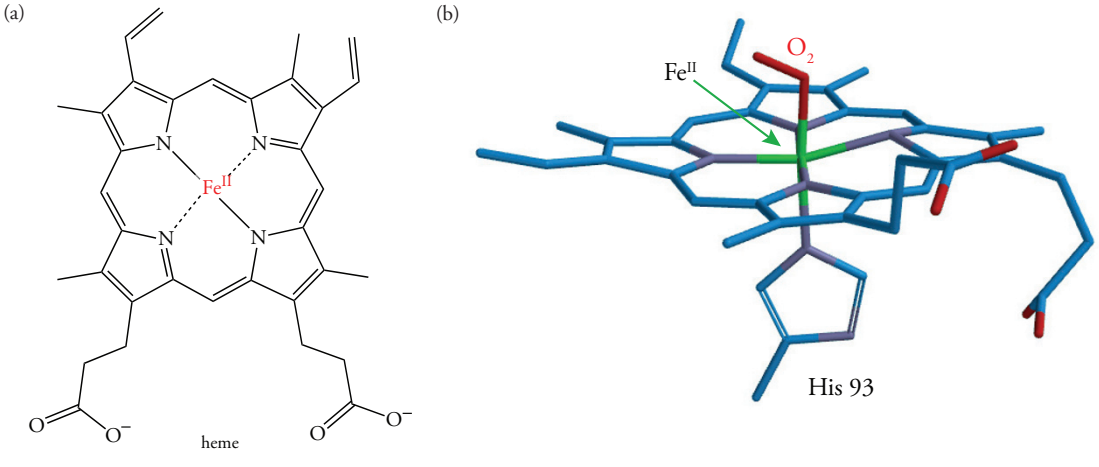


Figure 27.19 Heme
(a) Bond-line structure of heme. (b) Structure of the heme group bound to myoglobin via a bond from a nitrogen on histidine 93 and the Fe^{II} ion. Oxygen binds on the opposite side of the histidine.

Hemoglobin

Hemoglobin has a quaternary structure. It consists of two pairs of different proteins, designated the α and the β chains. There are 141 and 146 amino acids in the α and β chains of hemoglobin, respectively. As in myoglobin, each subunit is linked covalently to a molecule of heme. Thus, hemoglobin binds four O_2 molecules. The two identical α chains and the two identical β chains are arranged tetrahedrally (Figure 27.20). These units are held together by hydrophobic interactions, hydrogen bonding, and ion pairs (salt bridges) between oppositely charged amino acid side chains.

The subunits of hemoglobin do not act independently. When one subunit binds O_2, its conformation changes. When a change in conformation at one site of an oligomeric protein is caused by a change in a spatially separated site of the oligomer, the change is called an **allosteric** effect, and the protein is called an **allosteric protein**. Hemoglobin is an allosteric protein. When one heme group in hemoglobin binds oxygen, it is easier for successive oxygen molecules to bind at the remaining three sites. Thus, once oxygenation occurs at one heme, there is cooperation at all other sites in hemoglobin.

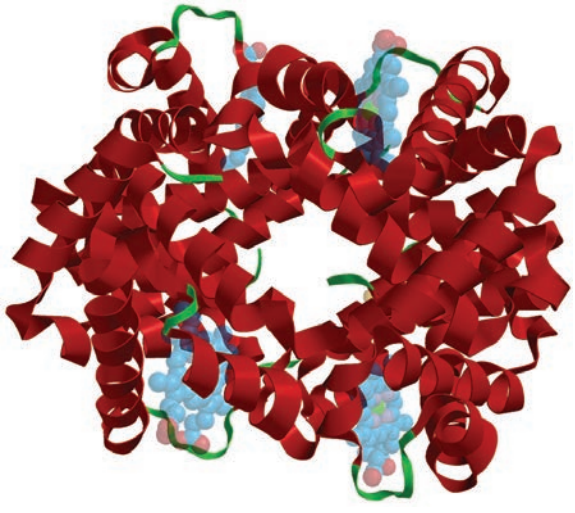


Figure 27.20 Structure of Deoxyhemoglobin.
The α and β subunits of hemoglobin interact cooperatively, and when one heme binds O_2, the each of the others rapidly binds O_2.

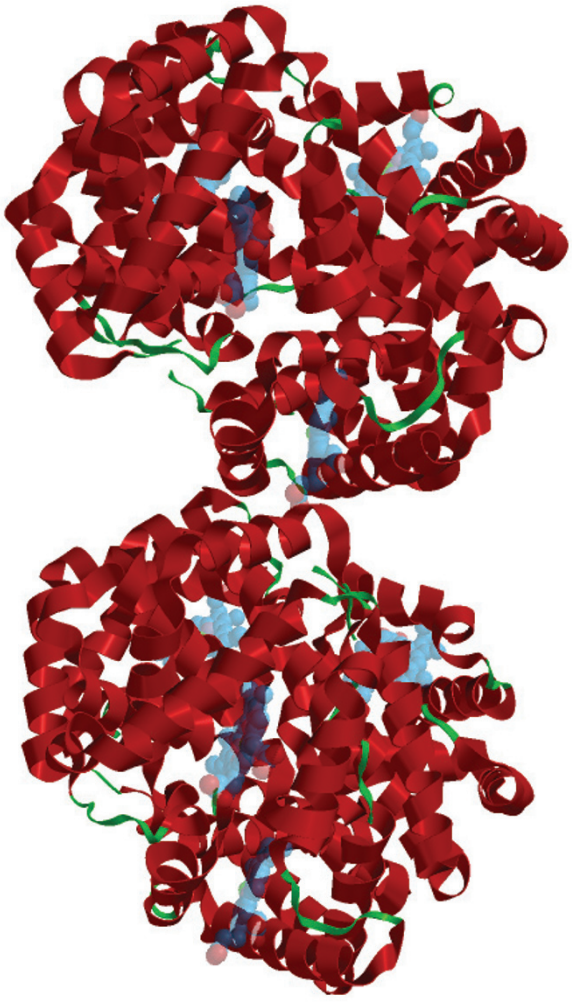
Sickle Cell Hemoglobin

In some people, glutamate 6 of the β chain has undergone a mutation to valine. This mutation changes the charge on the surface of hemoglobin. The mutant protein is called sickle cell hemoglobin, HbS. Valine residue 6 of the β chain of deoxy HbS lies on the surface of the protein. This hydrophobic residue, present in each β chain, forms a hydrophobic contact with a pocket in a neighboring β chain of another hemoglobin molecule. The mutation that replaces a glutamate residue by a valine residue decreases the solubility of deoxy-HbS.

	1	2	3	4	5	6	7	8
Hemoglobin A	Val-	His-	Leu-	Thr-	Pro-	Glu-	Glu-	Lys-
Hemoglobin S	Val-	His-	Leu-	Thr-	Pro-	Val-	Glu-	Lys-

The concentration of hemoglobin in red blood cells is high, and even in normal hemoglobin, it is near the limit of its solubility. The lower solubility of deoxy-HbS shifts the balance toward precipitation. The interaction of the valine residues leads to the formation of a polymeric fiber that forms when hemoglobin releases oxygen (Figure 27.21). The formation of the fibrous hemoglobin leads to abnormally shaped red blood cells. The cells tend to be sickle shaped, and as a result, their passage through the blood vessels is restricted. The associated circulatory problems are known as **sickle cell anemia**. That is why the mutant protein is called HbS.

Figure 27.21 Structure of Deoxyhemoglobin Dimer.
The β subunits of hemoglobin interact by van der Waals contact between the isopropyl side chains at residue 6 of sickle cell hemoglobin (HbS). Since each HbS has two β subunits on opposite sides of the tetramer, a fibrous polymer forms. HbS polymerizes when HbS releases O_2, which disorts the red blood cells into the shape of a sickle.



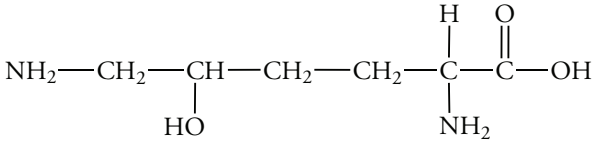
Exercises

Amino Acids

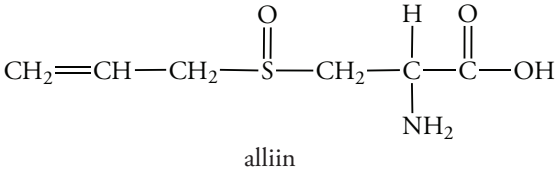
27.1 A D-Glutamic acid residue is found in some bacterial cell walls. Draw its Fischer projection formula.

27.2 Gramicidin S is a cyclic peptide antibiotic that contains a D-phenylalanine residue. Draw the projection formula of D-phenylalanine.

27.3 The following amino acid is present in collagen. From what amino acid is it derived?



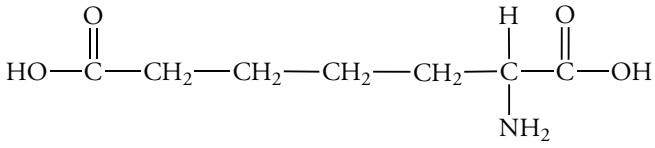
27.4 The following antibacterial agent, called allin, is present in garlic. From what amino acid might it be derived?



alliin

27.5 The following compound is an amino acid that acts as a neurotransmitter. Classify this amino acid and give its IUPAC and common name. (This neurotransmitter is universally known by its common name.)

27.6 The following compound is one of the amino acids formed in the biosynthesis of penicillin. Classify this amino acid and determine its common name.



Acid–Base Properties of Amino Acids

27.7 Draw the structures of alanine and glutamic acid at pH = 1 and pH = 12.

27.8 Draw the structures for the dipolar ions (zwitterions) of serine and valine.

27.9 How could you distinguish between aqueous solutions of asparagine and aspartic acid?

27.10 Would you expect an aqueous solution of lysine at pH 7 to be neutral, acidic, or basic? Explain.

27.11 One of the pK_a values of tyrosine is 9.11. What functional group is responsible for this acidic hydrogen atom?

27.12 One of the pK_a values of cysteine is 8.33. What functional group is responsible for this acidic hydrogen atom?

27.13 Explain why the pK_a for the —NH_3^+ group of tyrosine is slightly smaller than the corresponding pK_a of phenylalanine.

27.14 Explain why the pK_a for the side chain —CO_2H group of aspartic acid is smaller than the corresponding pK_a of glutamic acid.

27.15 Explain why the difference between the pK_a values of aspartic acid and asparagine is larger than the difference between the pK_a values of glutamic acid and glutamine.

27.16 Consider the amino and imino nitrogen atoms of the side chain of arginine. Which one would be protonated in acid solution? How can resonance stabilization account for the site of protonation?

Isoionic Points of Peptides and Proteins

27.17 Estimate the isoionic points of the following tripeptides.
(a) Ala-Val-Gly (b) Ser-Val-Asp (c) Lys-Ala-Val

27.18 Estimate the isoionic points of the following tripeptides.
(a) Glu-Val-Ala (b) Arg-Val-Gly (c) His-Ala-Val

27.19 Examine the structures of oxytocin and vasopressin in Section 27.7. Which one has the higher isoionic point?

27.20 Examine the structure of the enkephalin whose sequence is shown below and estimate its isoionic point.
Ala-Gly-Phe-Leu-Gly

27.21 The isoionic point of hen egg white lysozyme is 10.8. What does this value indicate about its amino acid composition?

27.22 The isoionic point of pepsin is 1.1. What does this value indicate about its amino acid composition?

Synthesis of Amino Acids

27.23 What haloalkane is required to synthesize isoleucine by the acetamidomalonate method? What side reaction might decrease the yield?

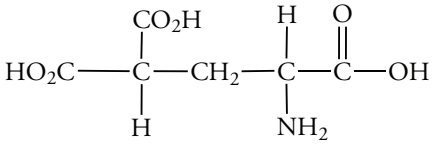
27.24 What reactants are required to synthesize phenylalanine by reductive amination?

27.25 3-Aminopropanoic acid, sometimes called β-alanine, is a nonsteroidal anti-inflammatory agent used in veterinary medicine. It is prepared by a conjugate addition reaction using ammonia and acrylonitrile (CH_2=CH—CN). The resulting nitrile is then hydrolyzed to give the product. Why is conjugated addition favored?

27.26 Methionine can be prepared from propenal in a multistep sequence. (a) Explain how is the thiomethyl group introduced? (b) Why is the carbon chain length increased by one carbon atom?

27.27 The structure of alliin is shown in Exercise 27.4. Propose a synthesis of alliin starting from an amino acid.

27.28 One of the amino acids in the blood-clotting protein prothrombin is shown below. It was difficult to detect because it decomposes under hydrolysis conditions. (a) What reaction occurs and (b) what is the product?



Peptides

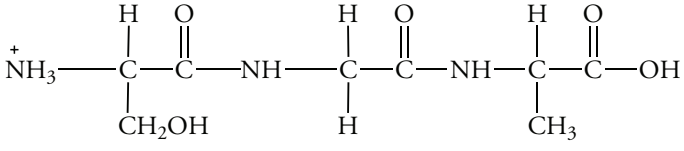
27.29 Write the bond line structure for alanylserine at pH 7.

27.30 How does glycylserine differ from serylglycine?

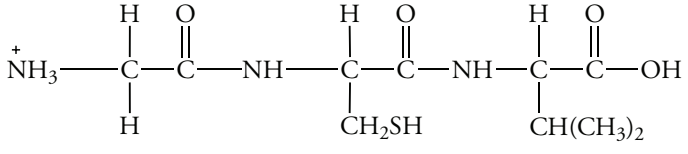
27.31 Which amino acids can form peptides with carboxylic acid groups or carboxylate groups at internal positions in the peptide chain?

27.32 Which amino acids can form peptides with amino groups or ammonium groups at internal positions in the peptide chain?

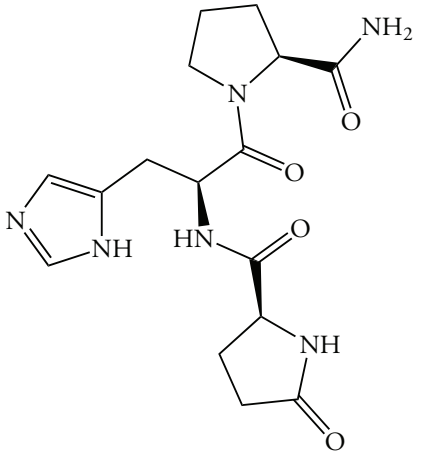
27.33 Identify the amino acids contained in the following tripeptide. Name the compound.



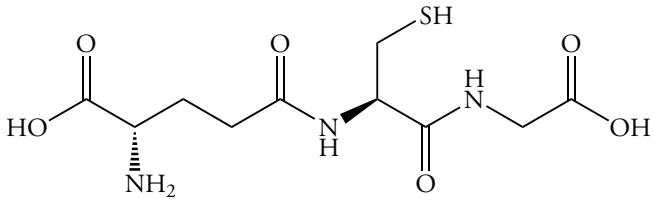
27.34 Identify the amino acids contained in the following tripeptide. Name the compound.



27.35 Thyrotropin-releasing hormone (TRH) causes the release of thyrotropin from the pituitary gland, which then stimulates the thyroid gland. Examine its structure and comment on one unusual structural feature.



27.36 The tripeptide glutathione, which is important in detoxifying metabolites, has an unusual structural feature. Identify it.



glutathione

27.37 How peptide many isomers with the composition Gly_2,Ala_2 are possible?

27.38 How peptide many isomers with the composition Gly_2,Ala,Leu are possible?

Peptide Hydrolysis and Primary Structure Determination

27.39 Assuming that only dipeptides are formed by partial hydrolysis, what is the minimum number that must be identified to establish the amino acid sequence of a pentapeptide?

27.40 Assuming that only tripeptides are formed by partial hydrolysis, what is the minimum number that must be identified to establish the amino acid sequence of an octapeptide?

27.41 The tetrapeptide tuftsin is hydrolyzed to produce Pro-Arg and Thr-Lys. Does this information establish the structure of tuftsin?

27.42 Partial hydrolysis of the octapeptide angiotensin II produces Pro-Phe, Val-Tyr-Ile, Asp-Arg-Val, and Ile-His-Pro. What is its amino acid sequence?

27.43 Treatment of somatostatin with the Edman reagent gives a derivative of alanine. Partial hydrolysis of the polypeptide gives the following oligopeptides. Write the structure of the polypeptide.
I: Phe-Trp II: Lys-Thr III: Thr-Ser-Cys IV: Thr-Phe-Thr-Ser-Cys
V: Asn-Phe-Phe-Trp-Lys VI: Ala-Gly-Cys-Lys-Asn-Phe

27.44 The amino acid composition of the peptide is (Arg_2, Gly, Phe_2, Pro_3, Ser). Treatment of bradykinin with the Edman reagent gives the PTC-derivative of arginine. Partial hydrolysis yields several fragments that include the following oligopeptides. What is the amino acid sequence of bradykinin?
I: Gly-Phe-Ser II: Arg-Pro-Pro-Gly III: Phe-Arg-Ser-Pro-Phe

Enzymatic Hydrolysis of Peptides

27.45 Which of the following tripeptides will be cleaved by trypsin? If cleavage occurs, name the products.
(a) Arg-Gly-Tyr (b) Glu-Asp-Gly (c) Phe-Trp-Ser (d) Ser-Phe-Asp

27.46 Which of the following tripeptides will be cleaved by trypsin? If cleavage occurs, name the products.
(a) Asp-Lys-Ser (b) Lys-Tyr-Cys (c) Asp-Gly-Lys (d) Arg-Glu-Ser

27.47 Indicate which of the tripeptides in Exercise 26.45 will be cleaved by chymotrypsin and name the products.

27.48 Indicate which of the tripeptides in Exercise 26.46 will be cleaved by chymotrypsin and name the products.

27.49 The tetrapeptide tuftsin is hydrolyzed by trypsin to produce Pro-Arg and Thr-Lys. Does this information establish the amino acid sequence of tuftsin?

27.50 The pentapeptide met-enkephalin is hydrolyzed by chymotrypsin to give Met, Tyr, and Gly-Gly-Phe. Does this information establish the amino acid sequence of met-enkephalin?

27.51 The nonapeptide known as the sleep peptide is hydrolyzed by chymotrypsin to produce Ala-Ser-Gly-Glu and Ala-Arg-Gly-Tyr and Trp. What two amino acid sequences are possible for the sleep peptide?

27.52 The sleep peptide is hydrolyzed by trypsin to produce Gly-Tyr-Ala-Ser-Gly-Glu and Trp-Ala-Arg. What is the amino acid sequence of the sleep peptide?

27.53 Feline gastrin, a hormone that stimulates secretion of gastric juice in cats, has the amino acid composition (Ala_2,Asp,Gly_2,$G1u_5$,Leu,Met,Phe,Pro,Trp2,Tyr).
End group analysis shows that the C-terminal and N-terminal amino acids are Phe and Glu, respectively. Hydrolysis with chymotrypsin yields the following four peptides. Write two possible amino acid sequences of feline gastrin.
I: Gly-Trp II: Met-Asp-Phe III: Glu-Gly-Pro-Trp IV: Leu-Glu-Glu-Glu-Glu-Ala-Ala-Tyr

27.54 Corticotropin, a pituitary hormone, stimulates the adrenal cortex. Hydrolysis by chymotrypsin yields six peptides:
I: Arg-Trp II: Ser-Tyr III: Ser-Met-Glu-His-Phe IV: Pro-Leu-Glu-Phe
V: Pro-Asp-Ala-Gly-Glu-Asp-Gln-Ser-Ala-Glu-Ala-Phe
VI: Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Pro-Val-Lys-Val-Tyr
Hydrolysis by trypsin produces lysine, arginine, and five peptides:
I: Trp-Gly-Lys II: Pro-Val-Gly
III: Pro-Val-Gly-Lys IV: Ser-Tyr-Ser-Met-Glu-His-Phe-Arg
V: Val-Tyr-Pro-Asp-Ala-Gly-Glu-Asp-Gln-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe
What is the amino acid sequence of corticotropin?

End Group Analysis

27.55 Edman degradation of tuftsin yields Thr as the N-terminal amino acid. Using the information in Exercise 27.49, what is the structure of tuftsin?

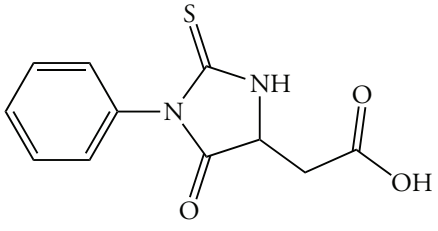
27.56 Hydrolysis of met-enkephalin with CNBr yields the homoserine lactone derivative of methionine and a tetrapeptide. Using the information in Exercise 27.50, what is the structure of met-enkephalin?

27.57 Explain why structure determination of insulin using the Edman method yields two phenylthiohydantoin products.

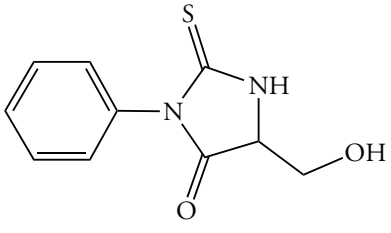
27.58 Cholecystokinin, a peptide that contains 33 amino acids, plays a role in reducing the desire for food, and its production is stimulated by food intake. Its N-terminal amino acid is lysine. Draw the structure of the phenylthiohydantoin product.

27.59 Reaction of angiotensin II with the Edman reagent yields the following product. What information has been established

27.60 Reaction of angiotensin II with the Edman reagent yields the following product. What is the N-terminal amino acid?



27.61 Reaction of corticotropin with the Edman reagent yields the following product. What information has been established?



Protein Structure

27.62 Which of the following amino acids are likely to exist in the interior of a protein dissolved in an aqueous solution?
(a) glycine (b) phenylalanine (c) glutamic acid (d) arginine

26.63 Which of the following amino acids are likely to exist in the interior of a protein dissolved in an aqueous solution?
(a) proline (b) cysteine (c) glutamine (d) aspartic acid

26.64 If a protein is embedded in a hydrophobic lipid bilayer of a biological membrane, which of the amino acids listed in Exercise 26.61 will be in contact with the interior of the bilayer?

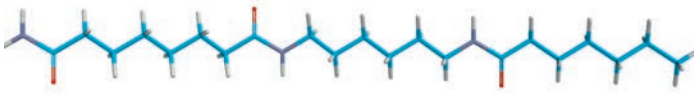
26.65 If a protein is embedded in a lipid bilayer, which of the amino acids listed in Exercise 26.62 will be in contact with the interior of the bilayer?

26.66 Noting that proline is a secondary amine, explain how proline can disrupt the a helix of a protein.

26.67 Examine the structures of valine and glutamic acid and suggest a reason why human hemoglobin is affected by the substitution of valine for glutamic acid at position 6 in the β chain.

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28 Synthetic Polymers



Nylon 66

28.1 NATURAL AND SYNTHETIC POLYMERS

In most of our study of organic chemistry, we have focused on the chemical reactions, structures, and physical properties of "small" molecules. We examined very large molecules, or macromolecules, in only two chapters. Repeated condensation reactions of small molecules called monomers form polysaccharides and proteins (polyamides), two classes of macromolecules found in living organisms.

Some naturally occurring macromolecules are important commercial products. For example, wood and cotton are carbohydrates; wool and silk are proteins. However, synthetic polymers far outstrip natural polymers in commercial importance. More than 130 million pounds of polymers are produced annually in the United States. A third of all funds for research and development are in polymer science in North America. The chemical industry has developed many synthetic macromolecules with diverse properties and a hundreds if not thousands of uses. These synthetic macromolecules are indispensable in a modern society. They include the rubber of tires, PVC of pipes and floor tiles, and synthetic fibers such as nylon.

Synthetic polymers have a wide range of properties. For example, certain transparent polymers can be molded into precise shapes in the manufacture of corrective lenses. The polymer rubber used in tires is not only flexible enough to be distorted from one shape to another but also capable of returning to its original shape. It is also durable and sufficiently stable to withstand exposure to extremes of weather conditions. Synthetic fibers used for clothing feel good against the body and are able to hold a dye. The range of physical properties of polymers is expanding rapidly, and they are used in every part of everyday life.

28.2 PHYSICAL PROPERTIES OF POLYMERS

The physical properties of synthetic macromolecules result from the number and kind of monomer units, as well as resulting intermolecular interactions and intramolecular interactions such as London forces and dipole–dipole forces. We recall that the properties of proteins and other natural macromolecules result from intermolecular interactions. For example, the strength of structural proteins such as collagen and cellulose is due to the many intermolecular hydrogen bonding. Hydrogen bonding can also be an important feature to consider in designing synthetic macromolecules.

Primary Structure and Physical Properties

By synthesizing appropriate monomers and learning how to polymerize them, organic chemists can prepare macromolecules to meet required specifications. The number of monomer units—ranging from a few hundred to several thousand—in a polymer affects its physical properties. However, no synthetic polymerization process can be stopped precisely after a specific number of monomers have been incorporated in the polymer. All polymerization reactions give mixtures of polymer molecule a range of molecular weights. Therefore, we refer to the average molecular weight of a polymer. The average molecular weight of synthetic polymers is in the 10^5–10^6 range.

Nylon, for example, must have a molecular weight of at least 10,000 to function well as a fiber. Below that molecular weight, the polymer is a brittle solid with no commercial value. The unique properties of polymers are also related to interactions between polymer chains. Therefore, a minimum size is required to give a material with useful properties. However, as the molecular weight increases, properties of a polymer often change. For example, if the molecular weight nylon is greater than 100,000, it does not form a fiber. However, it can be used in products that require high mechanical strength.

The types of monomers incorporated in a polymer strongly influence the flexibility and shape of the polymer. For example, polymers whose monomers contain aromatic rings are less flexible than those whose monomers are acyclic. In some polymers, the chains are cross-linked by covalent bonds. Cross-linking creates larger macromolecules with more rigid structures. Cross-links are also important in naturally occurring polymers. For example, the proteins in wool fiber are cross-linked by many disulfide bonds.

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As in the case of proteins, the intermolecular and intramolecular interactions of polymer chains are extremely important in determining physical properties. London forces are largely responsible for the folded or coiled conformations of a polymer. Intermolecular London forces between individual chains help to hold them together. Both intramolecular and intermolecular London forces increase with the polarizability of functional groups in the polymer. Only London forces affect the properties of polyethylene. This molecule, which can be produced as a linear polymer, resembles a giant alkane (Figure 28.1). We know that as the size of an alkane increases, the number of sites for intermolecular attractions increases. For example, the boiling points of alkanes increase as the number of hydrogen–hydrogen interactions between individual molecules increases. The attractive forces between pairs of hydrogen atoms on adjacent chains of a polymer may be only 0.5 kJ/mole. However, thousands of those interactions exist in a polymer producing a total interaction energy as large as that of covalent bonds.

The linear polymer of ethylene is called high-density polyethylene (HDPE). It has a high density and is high melting (135 °C) because parts of the molecules "line up" in a tightly packed, orderly array. HDPE is used to make materials as simple as bottle caps for milk containers and as complex as cabinets for televisions and computers. Ethylene can also be polymerized with branches of the main chain (Figure 28.2). The resulting polymer is called low-density polyethylene (LDPE). LDPE is less dense than HOPE because the branches prevent the main chains from pad closely. The more open structure not only is less dense but also has smaller London forces. Because the intermolecular forces between chains are smaller, LDPE has a lower melting point (120 °C) and is a more flexible material. It is used to make plastic bags and flexible bottles for consumer products such as soft drinks and bleach. Containers made of LDPE are also used for windshield wiper fluid, antifreeze, engine oil.

Structural units such as aromatic rings have polarizable electrons that create strong London forces. Hence, polymers with aromatic rings have higher ten strength than polymers with alicyclic units because there are strong London forces between aromatic rings in neighboring polymer chains. The aromatic rings reduce the flexibility of the polymer chain and the number of possible conformations. Chains of sp^3-hybridized carbon atoms in polymers such as polyethylene nylon 66 are more flexible. They can exist in gauche and *anti* conformations around each carbon–carbon bond. The allowed motions of the chains affect the properties of the polymer (Figure 28.3). One form of polyethylene, called ultra-high-molecular-weight polyethylene (UHMH) has molecular weight ranging from 2 to 6 million. It is remarkably resistant to abrasion and is commonly used in artificial joints such as artificial hips, shoulders, and knees.

Figure 28.1 London Forces in Polyethylene

The closely packed, all-*anti* conformation of the alkyl chains results in many London attractive forces.

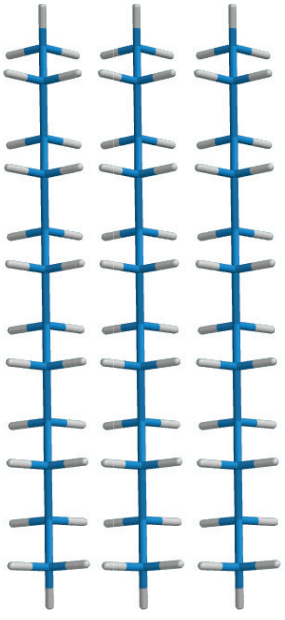


Figure 28.2 Branching in Low-Density Polyethylene

The branched chains of the alkanes prevent close packing and results in a lower-density polymer than polyethylene.

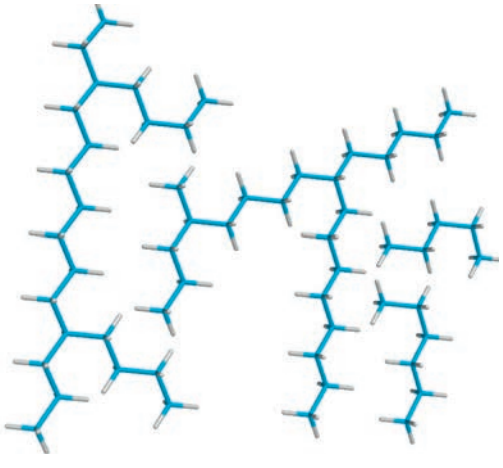


Figure 28.3 Nylon 66

Rotation around the planar amide bonds is highly restricted, but the conformations around the σ bonds between methylene groups allows for great flexibility.

All *anti* conformations around σ bonds of methylene groups



Rigid conformation around each planar amide bond

Hydrogen Bonding and Polymer Properties

We noted that intermolecular hydrogen bonding dramatically affects the properties of naturally occurring macromolecules such as structural proteins and cellulose. Some synthetic polymers also have extensive hydrogen bonding between polymer chains. The substantial strength of polyamides such as nylon 66 and Kevlar results from hydrogen bonding. The amount of hydrogen bonding in nylon 66 is affected by the flexibility of the chain and the conformation around the carbon–carbon bonds. The maximum number of hydrogen bonds is formed only if nylon 66 is in the all-*anti* conformation (Figure 28.4). Kevlar, used in bulletproof vests, is extensively hydrogen bonded because the aromatic ring and the amide bond restrict the conformation to the one best suited to form the maximum number of hydrogen bonds (Figure 28.5).

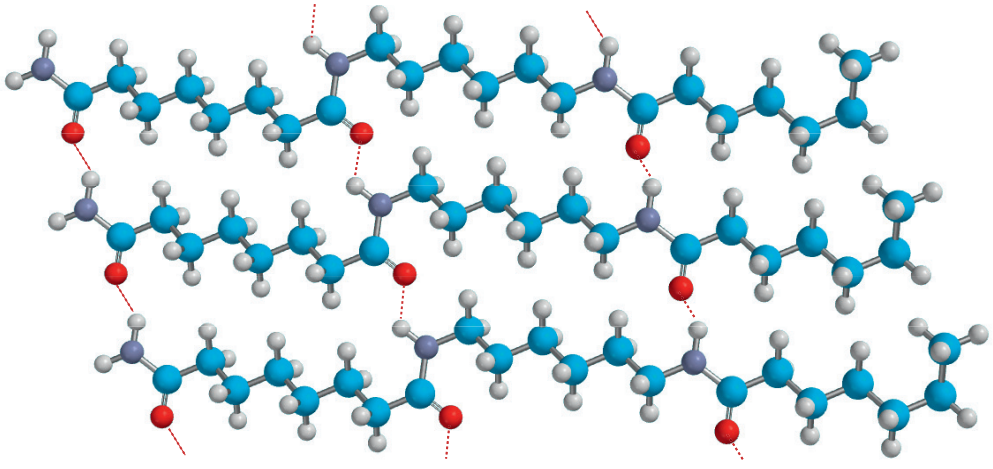


Figure 28.4 Hydrogen Bonding in Nylon 66
In the all-*anti* conformation, hydrogen bonds form between amide hydrogen atoms and carbonyl oxygen atoms.

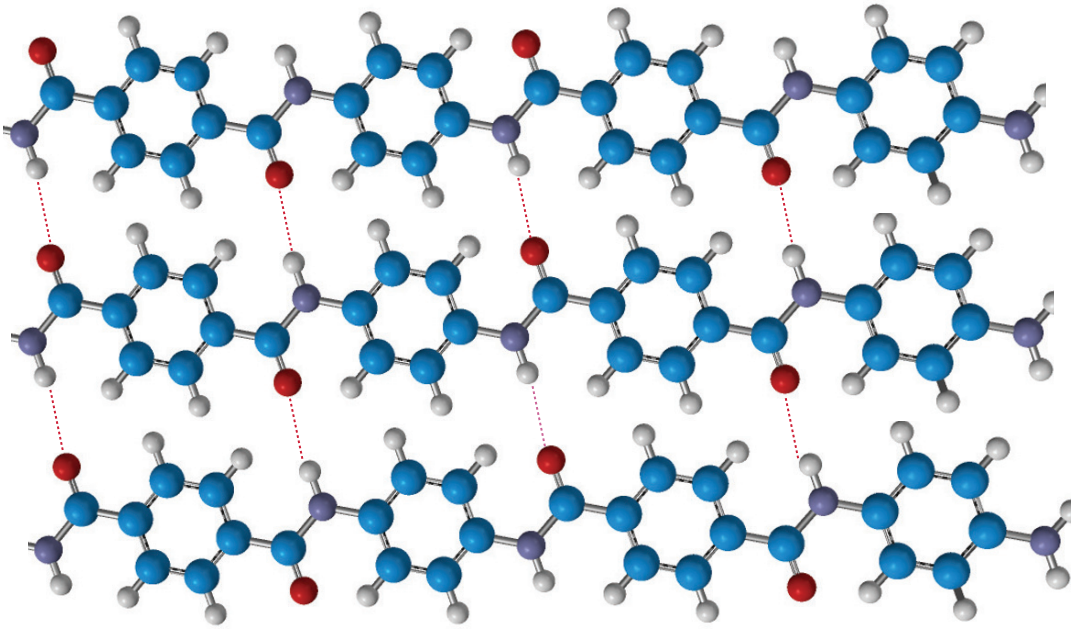


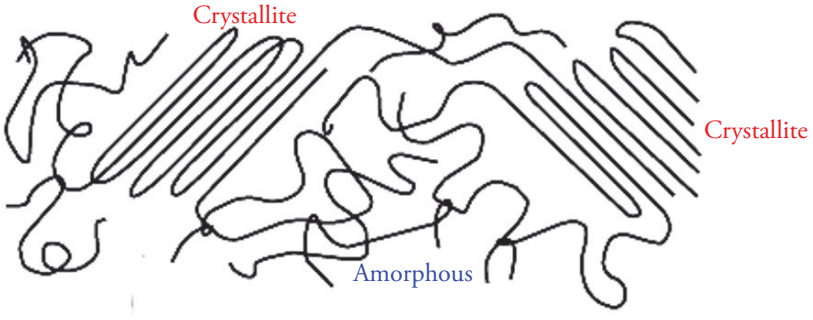
Figure 28.5 Hydrogen Bonding in Kevlar

Crystallinity

Crystalline structures are a common characteristic of ionic and covalent compounds. In these crystals, identical species are arranged in a precise, repeating manner. Polymers are not pure samples of a single molecular species. Since they are mixtures of high-molecular-weight molecules, they do not form true crystalline solids. An accumulation of intermolecular interactions within regions of a polymer causes a phenomenon known as crystallinity. The number and arrangement of such crystalline domains affect the properties of polymers. Crystalline regions—called crystallites—are dispersed between amorphous, noncrystalline areas (Figure 28.6).

Crystalline regions can form when portions of the chains oriented allow intermolecular hydrogen bonds. The crystallinity of a polymer is also influenced by dipole–dipole interactions among polar functional groups. Even hydrocarbon chains can form crystallite regions. In this case, many relatively weak London forces provide the cumulative attractive forces that maintain the crystallite structure.

Figure 28.6 Crystallinity in Polymers



Problem 28.1

How would the properties of an addition polymer formed from 3-methyl-1-pentene differ from those of a polymer formed from propene?

Problem 28.2

There are three isomeric benzenedicarboxylic acids. Which one should produce the most crystalline polymer in a reaction with ethylene glycol to give a polyester?

Sample Solution

The polymer of 3-methyl-1-pentene has large branched *sec*-butyl groups off the main chain, whereas propene has relatively small methyl groups as branches. As a result, the polymer of 3-methyl-1-pentene has a more open structure. The bulkier chains cannot pack closely, and the intermolecular forces between chains are smaller. The polymer of 3-methyl-1-pentene should have a lower melting point and be a more flexible material.

28.3 CLASSES OF POLYMERS

Polymers can be classified by macroscopic physical properties. The three major classes are elastomers, plastics, and fibers.

Elastomers

Elastomers are elastic materials that regain their original shape if they are distorted. Some common elastomers are rubber, a naturally occurring polymer of isoprene, and neoprene, a synthetic polymer of 2-chloro-1,3-butadiene. These elastomers contain carbon–carbon double bonds separated by intervening units containing two sp^3-hybridized carbon atoms (Figure 29.6). An elastomer's properties depend on both the groups bonded to the sp^3-hybridized carbon atoms and the geometry of the polymer chain around the double bond.

Elastomers are amorphous materials. The individual chains of the polymers are random coils that are tangled in an irregular way. The coils "straighten out" when they are stretched. When the force is released, the elastomer returns to its coiled state because the intermolecular forces are greatest in this arrangement.

The flexibility of an individual chain of an elastomer depends on the structure of the intervening unit of sp^3-hybridized carbon atoms. Some rotation can occur around the σ bonds. The

double bonds provide rigidity because they prevent rotation around π bonds. Polymer chains of *E* and *Z* configurations are both known. For example, natural rubber has a *Z* configuration. Natural rubber has a "bent" chain similar to that of an unsaturated fatty acid. This arrangement of atoms gives a more open, less regular relationship among polymer chains. As a result, the polymer chains are not closely packed, and they can slide past one another as the elastomer is distorted.

In contrast, gutta–percha, an industrial polymer of isoprene, has an *E* configuration. This stereochemical difference is reflected in the properties of the two polymers. Rubber is an elastomer, but gutta–percha is less flexible. In polyisoprene, the *trans* double bonds have a "zigzag" arrangement. The regularity of the zigzag chains allows them to pack tightly, resulting in large London forces (Figure 28.7).

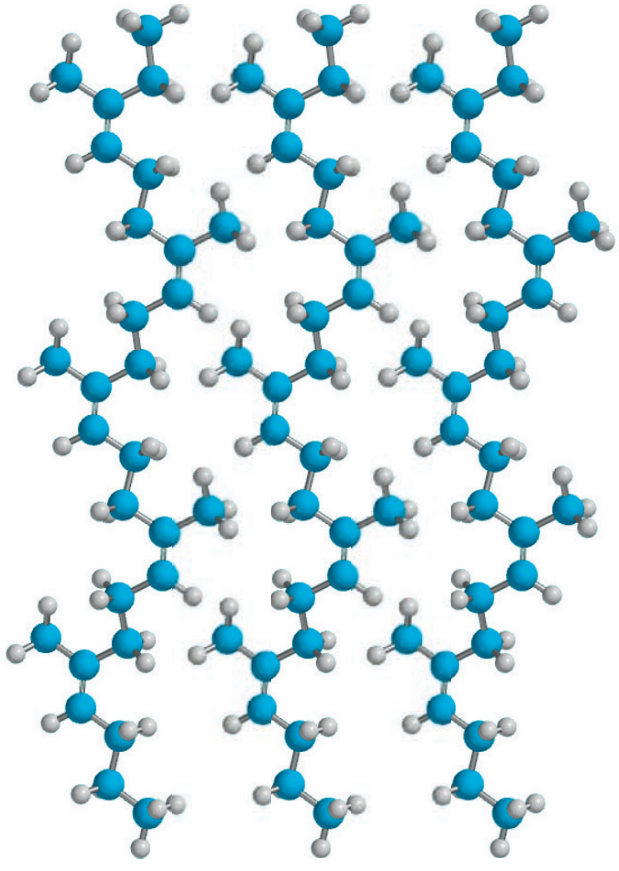


Figure 28.7 Polyisoprene
The double bonds in polyisoprene are all *trans*. Rotation around the planar double bonds cannot occur, and the conformations around the σ bonds allow close packing of the polymer chains giving a relatively hard, rigid structure.

Plastics

Perhaps the first thing we think of when we hear the word "plastic" is a social connotation of inauthenticity. In polymer chemistry, however, the term plastic is used for those polymers that harden upon cooling. They can be molded or extruded into shapes that remain after cooling (Gr. *plastikos* "fit for molding"). **Thermoplastics** are polymers that reversibly soften when heated, becoming sufficiently fluid to be molded. **Thermosetting polymers** can be molded when they are first prepared. However, after being heated, they "set" hardening irreversibly. If heated to a high temperature, thermosetting polymers decompose rather than melt. The difference between thermoplastics and thermosetting polymers is related to cross-linking. The polymer chains of thermoplastics are not cross-linked.

When a thermoplastic is heated, the kinetic energy of the polymer chains increases, overcoming the intermolecular forces and causing the polymer to melt. Polyethylene is a thermoplastic in which the London forces between hydrocarbon chains are the only intermolecular forces. Thermosetting polymers have extensive cross-links between polymer "chains" that result in much larger polymer molecules. Bakelite is a thermosetting polymer (Section 28.6). The only way that the structure of this material can be disrupted is by cleaving covalent bonds. This process irreversibly decomposes the material.

Fibers

Some thermoplastics are prepared as thin filaments that can be spun into fibers similar to natural fibers. The length of the polymer molecule must be at least 500 nm, which corresponds to a minimum average molecular weight of 10^4. The structure of the polymer chains must also provide sufficiently strong intermolecular forces to give the fiber an adequate tensile strength.

Filaments of thermoplastics are prepared by two methods. If the thermoplastic is stable in the molten state, it may be passed through tiny pores in a dye called a spinneret and then cooled. For less stable thermoplastics, the polymer is dissolved in a volatile solvent and forced through the spinneret. The solvent evaporates and a filament precipitates. Regardless of the method of formation, the fiber is then drawn out to several times its length after it has cooled. The cold drawing orients the molecules along the axis of the fiber. The resultant intermolecular forces between polymer molecules increase the tensile strength of the fiber.

Problem 28.3

(a) What type of plastic is best suited to make the handles for cooking utensils for the home?
(b) What type of plastic is most likely to be used for the frames of eyeglasses?

Problem 28.4

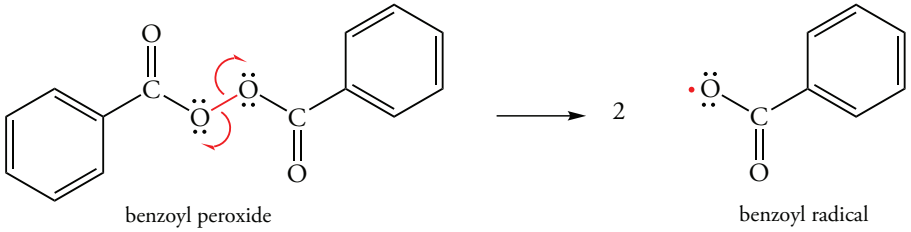
Assign the polymer represented by the following structure to one of the three classes of polymers. Identify a compound whose physical properties it most closely resembles.

Sample Solution

The polymer is an elastomer. The sp^3-hybridized carbon atoms between double bonds provide some flexibility to the elastomer. However, the *trans* arrangement of the double bond, which resembles that of gutta–percha, allows chains to pack efficiently and leads to less flexibility in the elastomer.

28.4 POLYMERIZATION METHODS

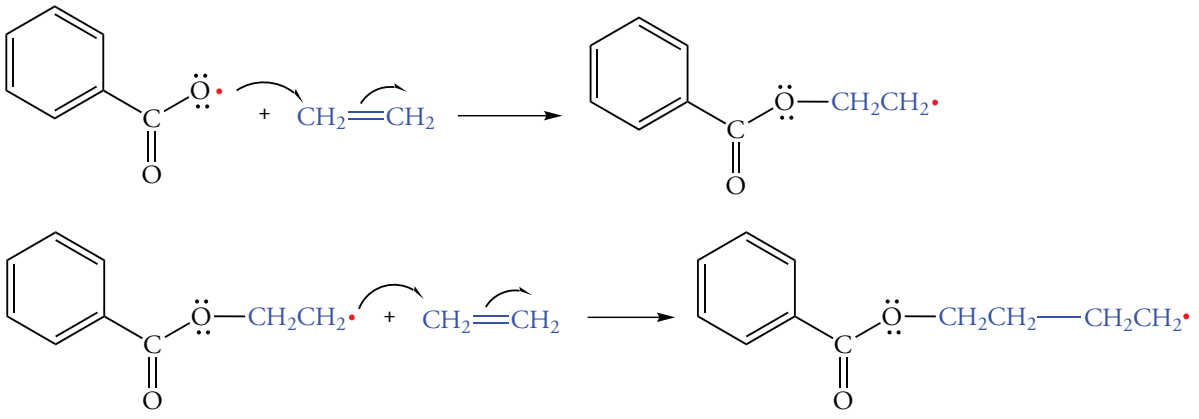
Polymers can be divided into two broad classes called **addition polymers** and **condensation polymers**. Addition polymers result from the successive addition reactions of one alkene or a mixture of alkenes by radical, cationic, or anionic mechanisms. Condensation polymers result from condensation reactions of monomers that contain two or more functional groups such as an alcohol and a carboxylic acid or an amine and a carboxylic acid. These functional groups react in condensation reactions to eliminate a small molecule such as water. Condensation polymerization reactions are often carried out at high temperatures so that the eliminated molecule evaporates, helping drive the reaction to completion. Addition polymers are also called **chain growth polymers**. The polymer chain grows when the reactive intermediate formed in an initiation step adds to another monomer unit. The initiating species may be a radical, carbocation, or carbanion. For example, dibenzoyl peroxide yields a benzoyl radical.



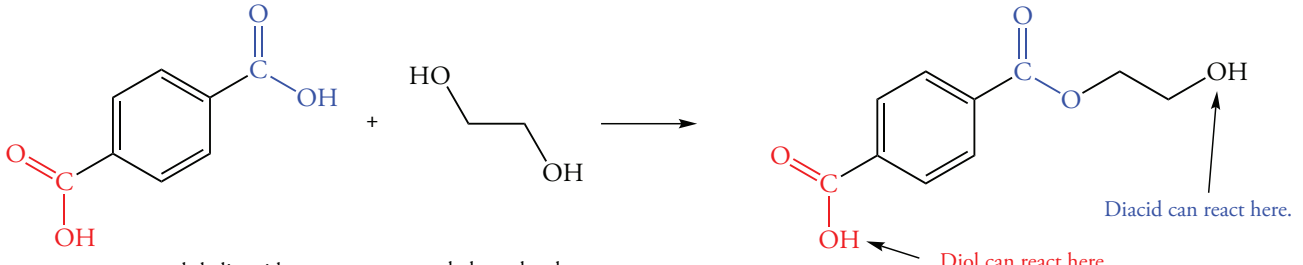
benzoyl peroxide — benzoyl radical

This radical reacts with a monomer to give another radical that then reacts with another unit of monomer.

The successive additions of monomers give a growing chain that always has a reactive end. The number of polymer chains formed therefore depends on the concentration of intermediates initially formed. A monomer cannot react until it encounters one of the growing chains with a reactive site.



Condensation polymers are also called **step-growth polymers**. In reactions between two units, such as a diol and a diacid, a stable ester forms between one alcohol site and one acid site. The new ester still has an alcohol site and an acid site at the ends of the molecule. Monomers can continue to react in condensation reactions with this product.



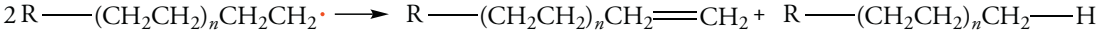
However, subsequent condensation reactions are not restricted to the ends of the growing polymer chain. The monomers in the reaction mixture can continue to react with each other randomly to start additional chains. Thus, the monomers in a step-growth polymerization generate many low-molecular-weight oligomers rather than a smaller number of steadily growing, high-molecular-weight chains. Formation of true polymers occurs only after the monomer is used up. At this point large increases in the chain length result from the reaction of the ends of the oligomers with each other. In step-growth polymerization, the polymer forms in "blocks" that result in substantially higher-molecular-weight products than an addition polymer.

28.5 ADDITION POLYMERIZATION

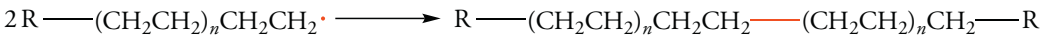
Addition polymerization occurs by a chain reaction in which one carbon–carbon double bond adds to another. For free radical polymerization, an initiation step forms a radical that adds to the alkene to give the intermediate required in the chain propagation step. Now let's consider chain termination.

Termination Steps

The monomer continues to react with the end of the growing polymer chain throughout an addition polymerization reaction until the reactive intermediate is destroyed in a termination reaction. Disproportionation and dimerization are two possible termination reactions. In disproportionation, a hydrogen atom at a carbon atom α to the radical center is abstracted by a radical in another chain. This produces a double bond in one polymer molecule, and the other polymer molecule becomes saturated. Because no new radical intermediates are formed, the propagation steps are terminated.



In the dimerization reaction, two radicals combine to form an even longer polymer chain. Again, the destruction of radicals prevents propagation.

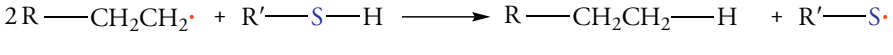


The probability that the reactive sites of two growing polymer chains will react in either of these bimolecular termination reactions is very small. A bimolecular reaction of one chain with a monomer molecule, which is present in higher concentration and consumed throughout the reaction, is more likely.

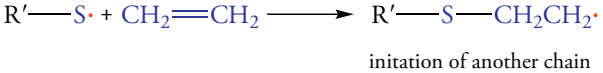
Regulation of Chain Length

The average molecular weight of the addition polymer is controlled by the number of times the propagation steps occur before the chain is terminated. However, the length of the chain can also be controlled by using either chain-transfer agents or inhibitors.

Chain transfer agents control the chain length of a polymer by interrupting the growth of one chain and then initiating the formation of another chain. Thiols are common chain transfer agents.



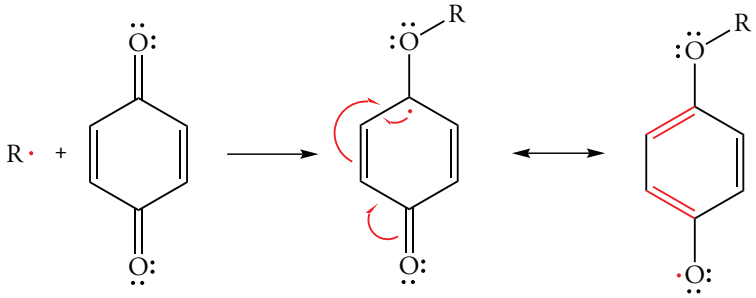
a terminated chain



initation of another chain

A chain transfer reagent must be reactive enough to transfer a hydrogen atom, but the resulting radical must be reactive enough to add to a double bond. The polymerization continues, and monomer continues to be consumed. However, the average molecular weight of the product is smaller because more chains are formed by the chain transfer process.

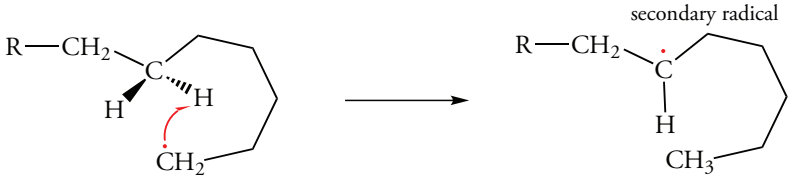
Inhibitors react with the radical site of a growing polymer chain to give a less reactive radical. Benzoquinone is a typical inhibitor used in free radical polymerization reactions.



benzoquinone

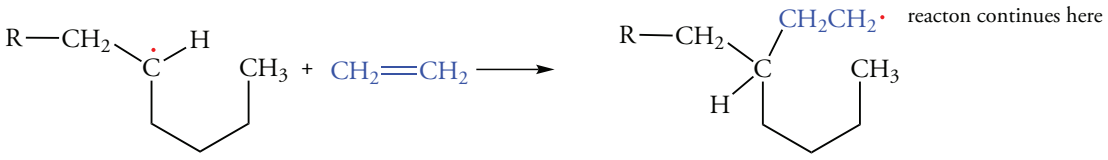
Chain Branching

In practice, the linear polymer we might expect for alkenes is not the major product of the free radical process. (Cationic polymerization is generally used to prepare linear addition polymers of alkenes.) The product chains have many alkyl branches, which most often are the four-carbon-atom butyl groups produced by short chain branching. These products are the result of intramolecular hydrogen abstraction by way of a six-membered transition state that generates a secondary radical from a primary radical.



primary radical

The polymerization continues at the new radical site, and a butyl group branch is located on the chain.



Large chain branching occurs by a random process. Intermolecular hydrogen atom abstraction can occur between the terminal radical of one chain and any of the hydrogen atoms located in another chain. In this case, one chain is terminated and the polymerization continues at a site within the other chain. The length of the resulting branch depends on the site of hydrogen abstraction. Short chain branching is more common than long chain branching because intramolecular reactions are more probable than intermolecular reactions. We recall that the ΔS_{rxn} is more negative for a bimolecular process than for an intramolecular process. Chain branching also occurs for other polymers, such as polypropylene or polystyrene.

Problem 28.5

Draw a structure of the reacting end of a polystyrene. What structural feature should exist in a chain terminated by a dimerization reaction?

28.6 COPOLYMERIZATION OF ALKENES

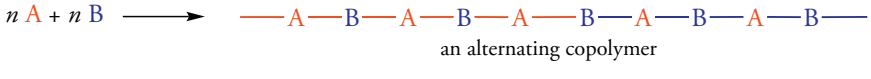
The addition polymers that we've discussed are homopolymers made up of repeating units derived from a single unsaturated monomer. Copolymers incorporate two different monomers in the polymer chain. They are formed in reactions of a mixture of two monomers. Copolymerization of various combinations of monomers provides many more possible structures and a greater variety of materials that might have desirable physical properties than homopolymerization. The structure of a copolymer depends on the structure of the radical at the end of the chain and the structure of the monomer that might add. The polymer formed results from kinetically controlled processes. Let's consider each of the following possible kinetic results for combinations of alkenes A and B.

1. A adds A at a rate significantly faster than it adds B; B adds B significantly faster than it adds A.
2. A adds B at a rate significantly faster than it adds A; B adds A at a rate significantly faster than it adds B.
3. A can add either A or B at comparable rates; B can add either A or B at comparable rates.

For the first case, no copolymer forms, and a mixture of homopolymers results. This process has no commercial application. For example, although styrene and 2-methyl-1,3-butadiene (isoprene) each readily polymerize to form homopolymers, they do not form a copolymer.



For the second case, a chain containing an alternating sequence of monomers results.

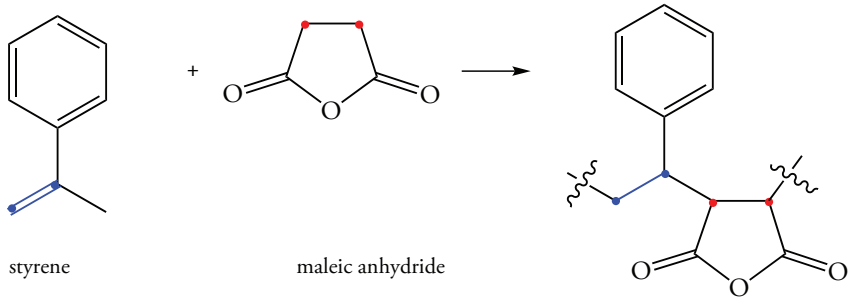


an alternating copolymer

For the third case, random polymers form. The exact composition depends on the reaction conditions and on the concentrations of the two monomers.

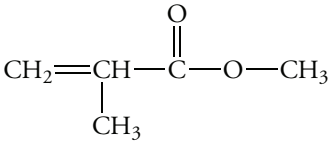


Few pairs of monomers give totally random copolymers. In fact, monomers are usually selected to avoid random copolymers. Monomers are chosen so that one monomer at the end of growing polymer chain prefers to react with the other monomer in the mixture, and vice versa. In short, it is desirable to have a monomer at the end of a chain that reacts preferentially with the other monomer in the reaction mixture. Nevertheless, some random distribution of monomers always occurs. It is difficult to form perfect alternating copolymers. However, the reaction of styrene with maleic anhydride produces a nearly perfect alternating copolymer.



styrene maleic anhydride

Maleic acid reacts with itself very slowly, and its homopolymer is difficult to form. Styrene readily reacts to form a homopolymer. However, a styrene group at the end of a growing polymer chain reacts faster with maleic anhydride than with itself. After the addition of styrene to maleic anhydride, a radical is produced that does not react with maleic anhydride. As a result, the next alkene that is added is styrene. Monomers that provide perfect alternating copolymers are highly desirable because the product can be reproduced. The amount of alternation compared to random sequencing in copolymers depends on two selectivity ratios. Consider the copolymerization of styrene and methyl-2-methylpropenoate.



methyl-2-methylpropenoate

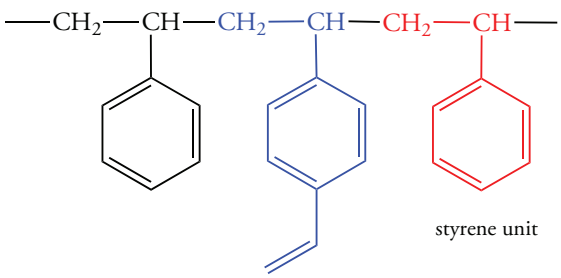
When styrene is at the end of the chain, it reacts with methyl 2-methylpropenoate rather than another styrene by about a 2:1 ratio. When methyl-2-methylpropenoate is at the end of the chain, it reacts with styrene rather than methyl-2-methylpropenoate by about a 2:1 ratio. These selectivity ratios tend to give an alternating copolymer. However, some repetition of one monomer or the other is still likely.

Problem 28.6

Styrene and acrylonitrile (CH_2=CH—CN) form an alternating copolymer that is used in the lenses of automobile headlights. Draw the structure of two units of the copolymer.

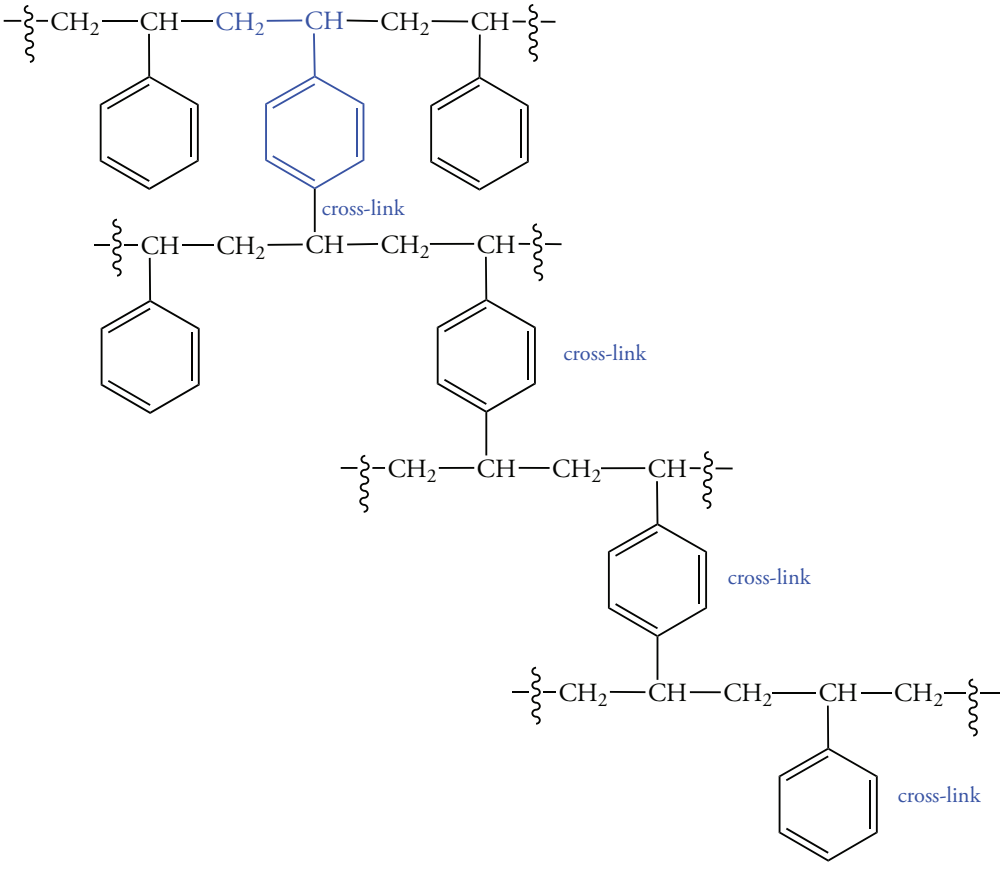
28.7 CROSS-LINKED POLYMERS

Atoms bonded between polymer chains are called cross-links. They form during polymerization of the monomers or in separate reactions after formation of the polymer. *p*-Divinylbenzene has two alkene functional groups, each of which can become part of a different polymer chain by an addition polymerization reaction. One alkene group of *p*-divinylbenzene is incorporated in a chain whose major components are styrene units.



At some point in the reaction, the other alkene group reacts in a chain propagation process that develops a second chain. Thus, divinylbenzene becomes part of each polymer chain and forms a link between the two chains (Figure 28.8). The degree of cross-linking and the space between the divinylbenzene units depend on the amounts of two monomers used. The importance of cross-links in determining the properties of a polymer was accidentally discovered by Charles Goodyear in his study of the properties of rubber. Natural and synthetic rubbers can be used to make rubber bands but are too soft and tacky for many applications such as tires. The resilience of rubber decreases when it is heated because the polyisoprene chains slide past each other more easily when stretched at higher temperatures. When tension is released, natural rubber does not regain its original structure.

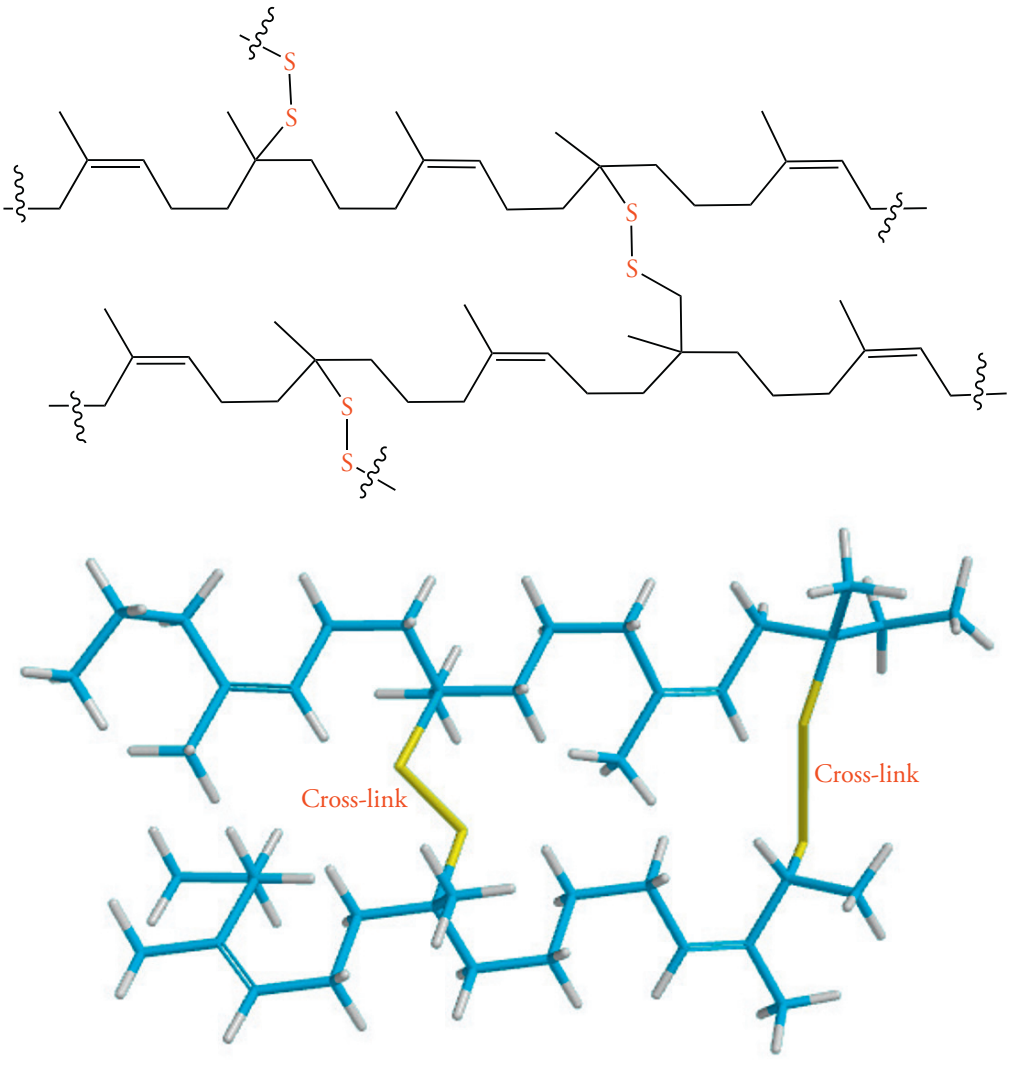
Figure 28.8 Cross-Links in Addition Polymerization



In 1839, Charles Goodyear found that heating natural rubber with a small amount of sulfur produces a material with new properties. He called this process **vulcanization**. (Vulcan is the fire good in ancient Roman mythology—not to mention the extraterrestrial creatures in Star Trek who dwell on the planet Vulcan.)

The sulfur reacts with polyisoprene to replace some C—H bonds with disulfide bonds. As a result, the polymer chains become connected by cross-links that may contain one, two, or more sulfur atoms (Figure 28.9). These cross-links increase the rigidity of the rubber because most of the chains are linked into a larger molecule. The freedom of movement of one chain relative to another is diminished. After distortion, the vulcanized rubber returns to its original molded shape. The amount of sulfur—3–10% by weight—controls the flexibility of the rubber.

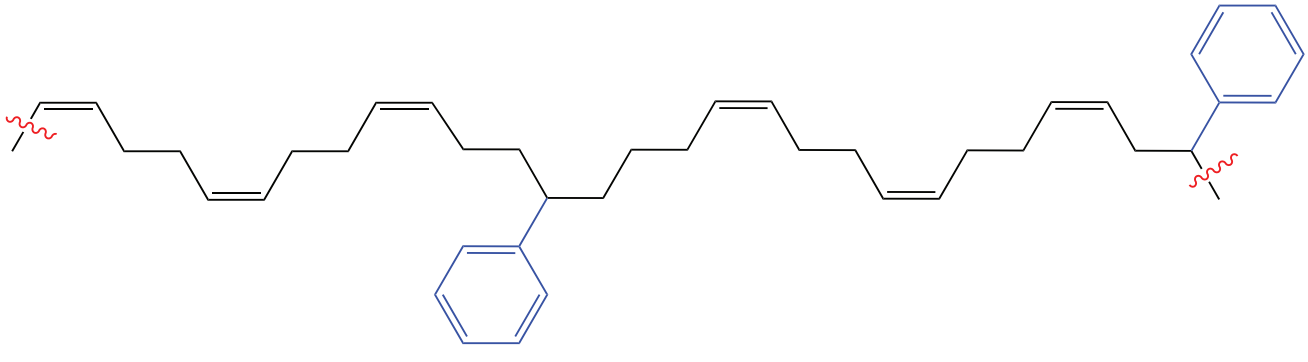
Figure 28.9 Cross-Links in Vulcanized Polyisoprene



Copolymers in Automobiles

The most important synthetic rubber produced in the United States is a copolymer of styrene and butadiene called SB. About 1.5 million tons of SB are produced annually for use in automobile tires. The elastomer with the best properties has a 1:3 ratio of styrene to butadiene. The remaining double bond in the butadiene unit of the polymer can be cross-linked by vulcanization.

A copolymer of three monomers—acrylonitrile, butadiene, and styrene—known as ABS can be molded to form many different products. Millions of tons are produced annually in the United States. Besides the large quantities used to make tires, they are present in instrument panels, grills, and exterior trim for automobiles.



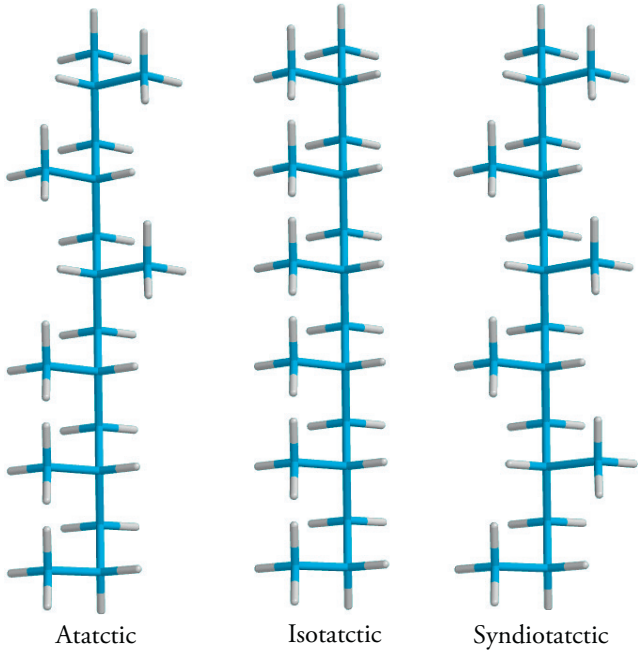
representation of an SB polymer (1:3) ratio

28.8 STEREOCHEMISTRY OF ADDITION POLYMERIZATION

Addition polymerization of some alkenes generates stereogenic centers along the entire backbone of the polymer. The relationship of these centers to one another affects the physical properties of the polymer. Consider the polymer formed from propene. If the methyl groups are all on the same side of the backbone of the zigzag chain, the polymer is **isotactic**. If the methyl groups are in a regular alternating sequence on opposite sides of the backbone, the polymer is **syndiotactic**. If the methyl groups are randomly oriented, the polymer is **atactic** (Figure 28.10).

The regularity of structure of isotactic and syndiotactic polymers is responsible for substantial areas of crystallinity. Both types of polymers have high melting points, so they can be used to manufacture objects that will be exposed to boiling water. Atactic polymers form from radical chain polymerization. These polymers have branches that result from hydrogen abstraction processes. Both isotactic and syndiotactic forms of polymers are produced with catalysts designed by K. Ziegler of Germany and G. Natta of Italy. These catalysts yield polymers with no chain branching. The development of methods to form stereochemically regular linear polymers revolutionized polymer science. The Ziegler–Natta catalysts are organometallic compounds that contain a transition metal and a cocatalyst. For example, triethylaluminum and titanium(III) chloride combine to give such a catalyst. The catalyst forms coordination complexes with alkene monomers. A series of rearrangements occur that resemble the catalytic reactions we discussed in Chapter 17. The reaction mechanism is remarkably complex and, despite years of study, is still only incompletely understood. The catalyst sits on a solid support such as magnesium chloride, which makes it difficult to study the mechanism. Figure 28.11 shows a schematic diagram of the steps in the catalytic reaction.

Figure 28.10 Atactic, Syntactic, and Syndiotactic Polymers



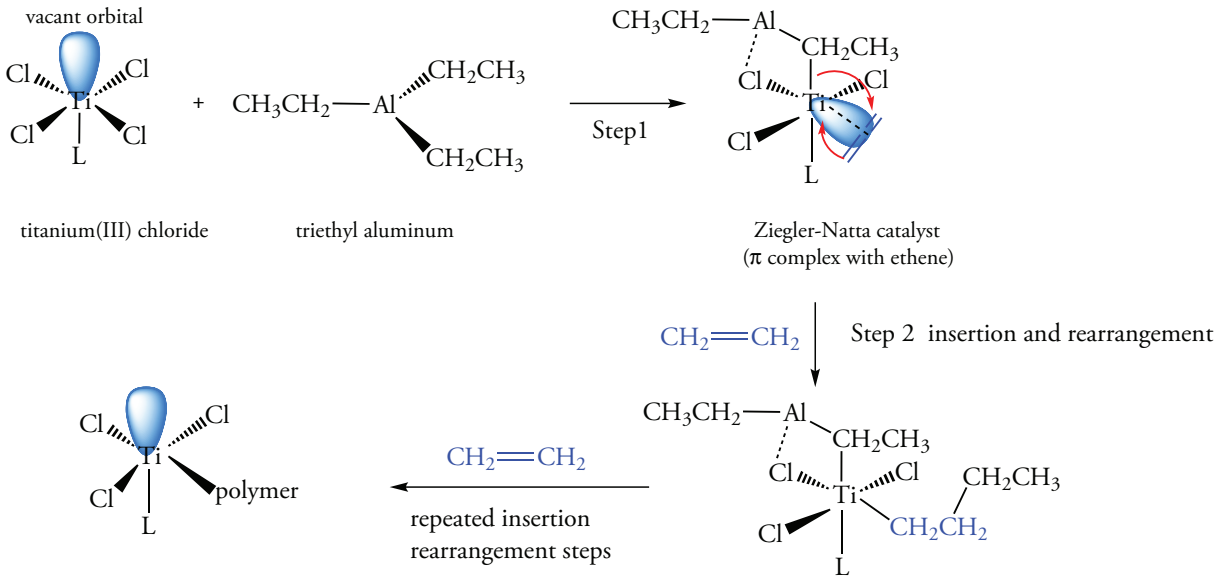
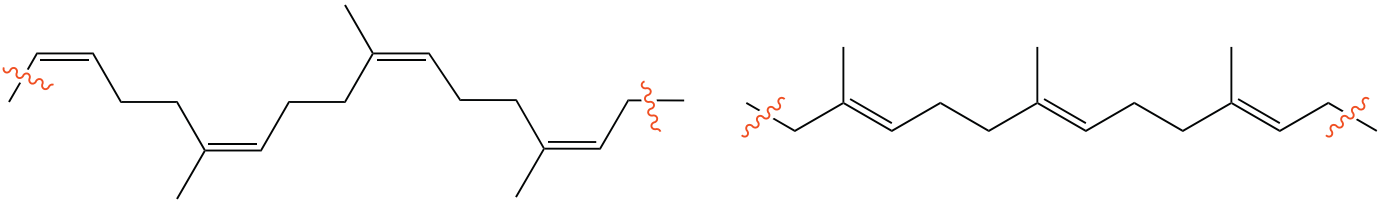


Figure 28.11 Schematic Diagram of Steps in Ziegler-Natta Catalysis

Diene Polymers

Conjugated dienes can form addition polymers by a 1,4-addition reaction. The remaining double bond of each monomer unit occurs at every fourth carbon atom along the chain. Natural rubber, for example, is a polymer of 2-methyl-1,3-butadiene (isoprene) with *cis* geometry at all of the double bonds. The polymer is obtained from the latex synthesized under the bark of some trees that grow in southeast Asia. The isomeric gutta–percha is a *trans* isomer of natural rubber that is produced by trees of a different genus. As usual, biosynthetic reactions yield products formed in stereospecific reactions. Both species use isopentenyl pyrophosphate as a starting material, but the enzyme catalysts differ.

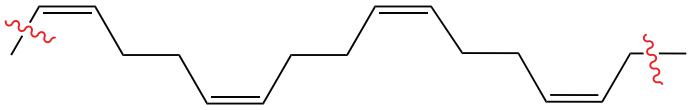


natural rubber (polyisoprene, all *cis*)

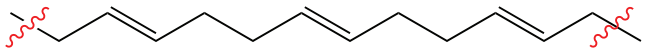
gutta–percha (all *trans*)

The different properties of natural rubber and gutta–percha reflect both the geometries around the double bonds and their molecular weights. The molecular weight of natural rubber is about 100,000, whereas that of gutta–percha is less than 10,000. As a result of the *cis* arrangement of the chain in natural rubber, the adjacent molecules cannot fit close to one another. Natural rubber has random coils that can be stretched out when the material is pulled. After the tension is released, the material returns to its original structure. Gutta–percha molecules, on the other hand, can pack closer because the *trans* arrangement of the double bonds and the favored *anti* conformation around the saturated carbon atoms provide a chain with a regular zigzag arrangement. So gutta–percha is a highly crystalline, hard, inflexible material. It was once used in golf ball covers. Early attempts to polymerize isoprene in industrial processes to prepare synthetic rubber were not successful because the reactions were not stereospecific. However, a variety of Ziegler–Natta catalysts are now available. One catalyst that contains titanium stereospecifically gives polyisoprene with *cis* double bonds, and another catalyst containing vanadium gives polyisoprene with *trans* double bonds.

1,3-Butadiene can also be stereospecifically polymerized to give either of two isomeric polymers. The stereochemistry depends on the conditions of the reaction and the Ziegler–Natta catalyst used.

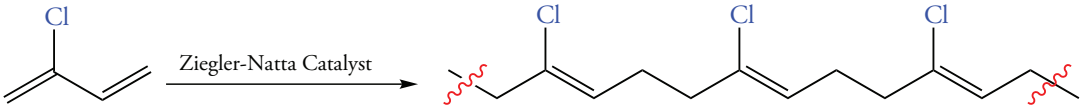


cis-poly(1,3-butadiene)



trans-poly(1,3-butadiene)

The polymerization of 2-chloro-1,3-butadiene was one of the reactions considered by U.S. industry to replace rubber made from natural sources located in areas of the world that could be cut off in a crisis such as war. This diene structurally resembles isoprene, with a chlorine atom replacing the methyl group of isoprene. Free radical polymerization gives a mixture of *cis* and *trans* double bonds as well as a mixture of 1,2 and 1,4-addition products. Polymerization of 2-chloro-1, 3-butadiene using a Ziegler-Natta catalyst yields neoprene, a compound with *trans* double bonds.



Neoprene

Neoprene resists oxidizing agents better than natural rubber because the electronegative chlorine atom of neoprene reduces the availability of electrons to oxidizing agents, and the large chlorine atom reduces the accessibility of the C—H bonds to oxidizing agents. Neoprene is therefore used to manufacture materials such as gaskets and industrial hoses.

Problem 28.7

The free radical polymerization of 1.3-butadiene yields some sections of the polymer that contain a vinyl group. Explain the origin of this group.

Sample Solution

The presence of a vinyl group bonded to the main chain means than the other vinyl group of 1,3-butadiene is incorporated in the chain. Thus, the polymerization of this unit occurs by a 1,2-addition reaction similar to that of a simple alkene.

Problem 28.8

Draw the structure of the product of ozonolysis of *trans*-poly(l,3-butadiene) under oxidation work-up conditions.

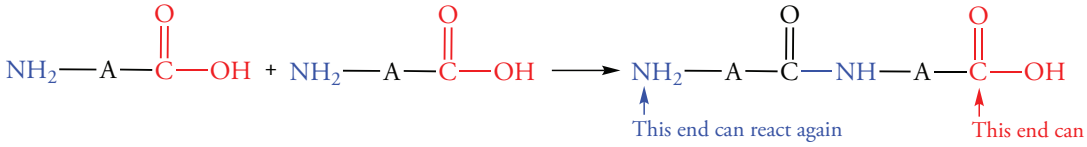
28.9 CONDENSATION POLYMERS

A condensation reaction is a reaction between two reactants that yields one larger product and a second, smaller product such as water. This type of reaction has been illustrated in the reactions of many functional groups containing oxygen or nitrogen. Products of condensation reactions include ethers, acetals, esters, imines, and amides.

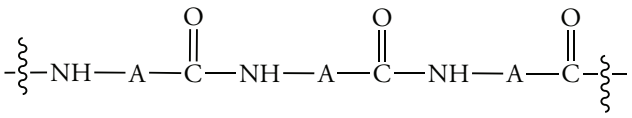
Types of Monomers

We now consider condensation reactions that yield polymers. Two functional groups are required in a monomer so that after one functional group reacts, the other is available to link to another monomer. The functional groups in monomers may be arranged in two ways for condensation polymerization.

A single compound can contain two different functional groups such as an amino group and a carboxylic acid group. Reaction of the amino group of one molecule with the carboxylic acid of another molecule gives an amide that still has a free amino group and a free carboxylic acid group, which can continue to react to form a polymer. The general reaction is shown below.

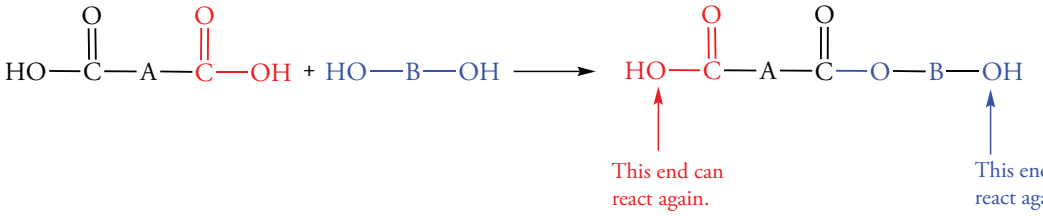


Continued reaction of the carboxylic acid end with the amino group of another monomer or of the amino group end with the carboxylic acid group of another monomer yields a homopolymer.

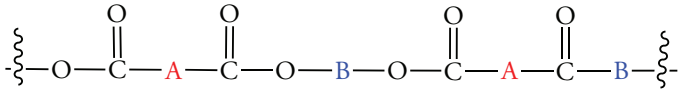


(homopolymer of an amino acid)

Condensation reactions also result from the copolymerization of two monomers. Each monomer contains two of the same functional group. Examples include the reaction of a monomer that is a dicarboxylic acid with a monomer that is a diol. The functional groups on one monomer can only react with the functional groups on the other monomer. The general reaction is shown below.



Continued reaction of the carboxylic acid end with the hydroxyl group of the diol monomer or of the hydroxyl group end with the carboxylic acid group of the dicarboxylic acid monomer yields a copolymer.

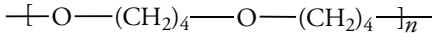


(an alternating copolymer)

A monomer can contain two different functional groups, but such monomers are not widely used. First, these monomers are more difficult to prepare without uncontrolled polymerization during their synthesis. Second, the monomer can only be used in one possible polymerization reaction. Condensation polymers formed from two different monomers are more common. The synthesis of each monomer is usually straightforward and less expensive. Each monomer can be used in reactions with other monomers. For example, any of a series of dicarboxylic acids can react with any of another series of diols. The reactants and the condensation reaction selected must give high yields of a product with few side reactions. The experimental conditions must also allow the reaction to be carried out on a large scale in a continuously operating industrial plant without "workup" conditions. We recall that an ester can be prepared in the laboratory using an acid chloride and an alcohol or by the Fischer esterification method. Each process has limitations when used in industrial laboratories. Although acid chlorides give high yields, they are very reactive compounds and are difficult to handle. The Fischer esterification is an equilibrium process that requires "driving" the reaction to completion by using excess reagent or by removing products.

Problem 28.9

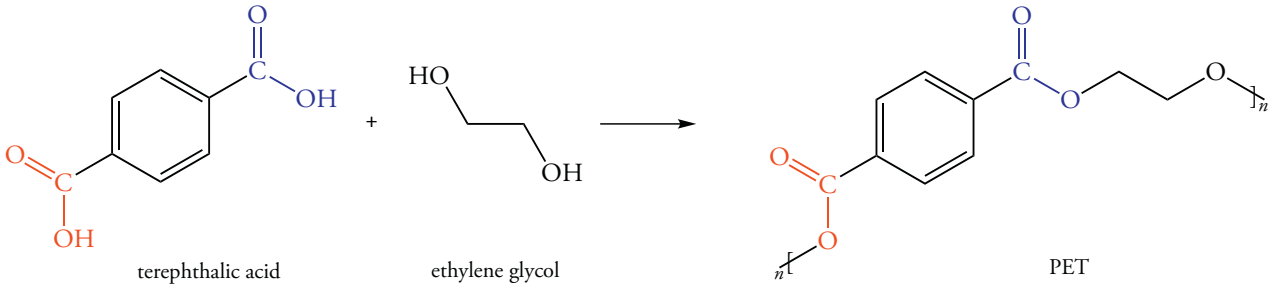
Can the disodium salt of 1,4-butanediol be used with 1,6-dibromohexane to yield a polyether represented by the following formula?



28.10 POLYESTERS

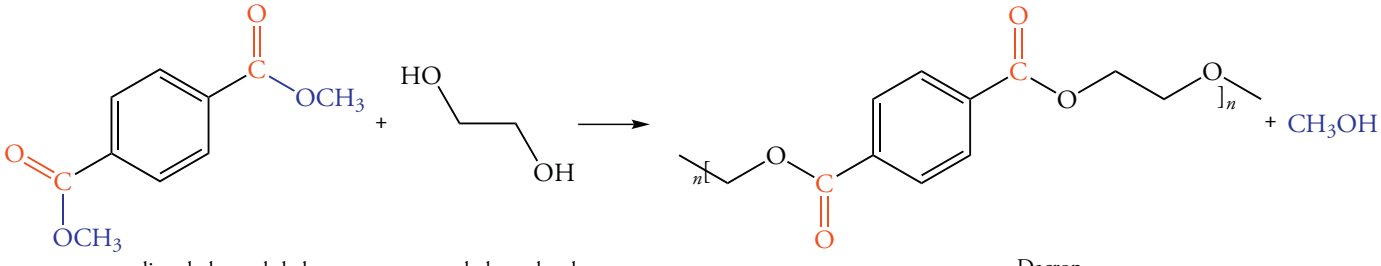
Polyesters account for approximately 40% of the synthetic fibers produced in the United States. Poly(ethylene terephthalate), also known as PET, is the major polyester. It is a copolymer of ethylene glycol and terephthalic acid.

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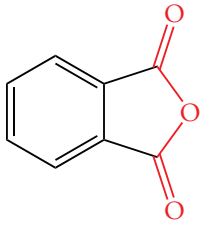
terephthalic acid ethylene glycol PET

PET and all other polyesters are produced industrially by transesterification reactions. PET is prepared by the reaction of dimethyl terephthalate with ethylene glycol at 150 °C. Neither reactant is volatile at this temperature, but the second product is methanol, which boils at 65 °C. As methanol forms, it is continuously vaporized from the reaction mixture, driving the polymerization reaction to completion.



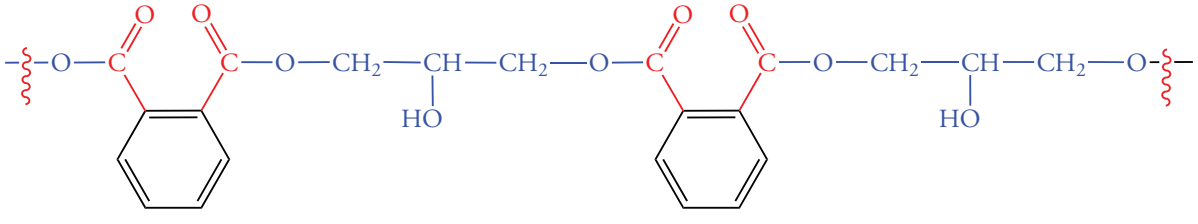
dimethyl terephthalate ethylene glycol Dacron

PET is produced as a fiber known as Dacron, which is used in products as common as clothing and as esoteric as tubes used to replace blood vessels. Human tissue can grow into and around Dacron, incorporating the polymer as part of the structure of the human body. PET is also used to form a film called Mylar, which can be produced in thin sheets. It is used to make magnetic recording tape. Thicker versions of Mylar are used in compact discs. Cyclic anhydrides such as phthalic anhydride and maleic anhydride also react with glycols to form polyesters. The anhydride is a bifunctional molecule that reacts with the bifunctional glycol to give linear, alternating copolymers.



phthalic anhydride

However, when a triol reacts with an anhydride, a cross-linked polymer results. For example, the reaction of phthalic anhydride with 1,2,3-propanetriol (glycerol) initially occurs regioselectively with the primary hydroxyl groups to give a linear polymer.



Reaction of phthalic anhydride with the secondary hydroxyl groups is so slow that continued polymerization can be carried our as a second step. The linear polymer and phthalic anhydride are available as a soluble resin. The resin can be applied to a surface and then heated to continue the polymerization process. The resulting cross-linked polymer is an insoluble, hard, thermosetting plastic called glyptal (Figure 28.12).

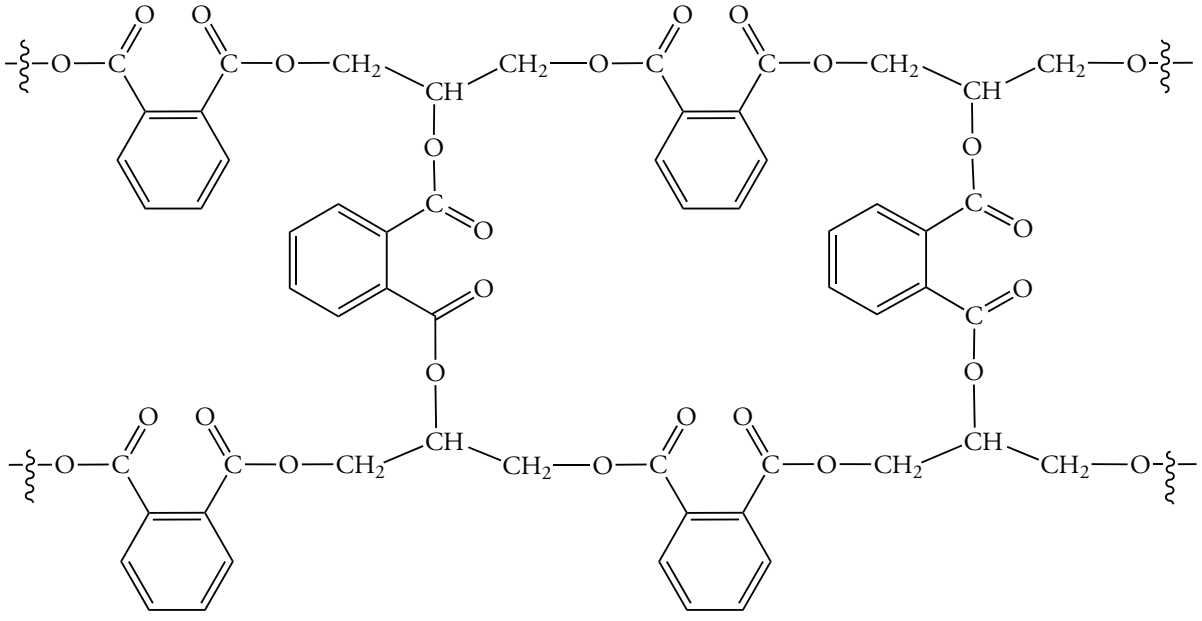
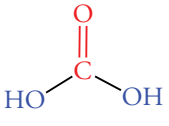


Figure 28.12 Cross-Links in a Condensation Polymer
The reaction of 2 moles of 1.2,3-propanetriol and 3 moles of phthalic anhydride gives a cross-linked polymer called a glyptal.

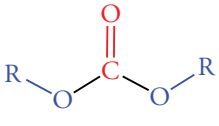
Problem 28.10
Poly(ethylene terephthalate) is melted and spun into fibers at 270 °C. Explain why the surrounding air must be "dry" while the polymer is hot.

28.11 POLYCARBONATES

Carbonates are esters of carbonic acid. However, because carbonic acid is unstable, carbonates cannot be produced from carbonic acid and an alcohol.

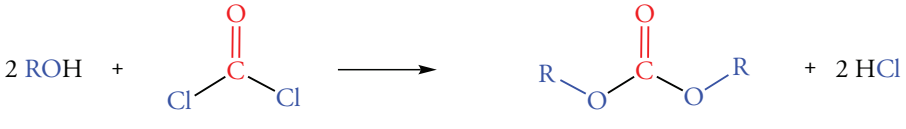


carbonic acid



(a dialkyl carbonate)

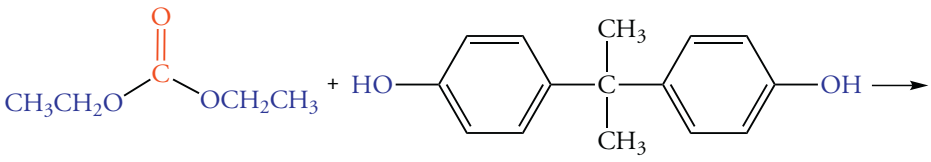
Dialkyl carbonates can be made from the reaction of alcohols with phosgene, a highly toxic gas. The second chlorine atom of phosgene increases the electrophilicity of the carbonyl carbon atom. As in the reaction of an alcohol with an acid chloride, a base is required to neutralize the HCl by-product.



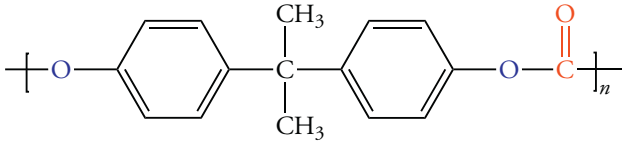
phosgene

(a dialkyl carbonate)

Although a polymeric carbonate could be produced in the reaction of a diol with phosgene, these products are usually obtained by a transesterification reaction with a dialkyl (or diaryl) carbonate. The reaction of diethyl carbon with a phenol called bisphenol A gives a polycarbonate known as Lexan.



bisphenol A



Lexan

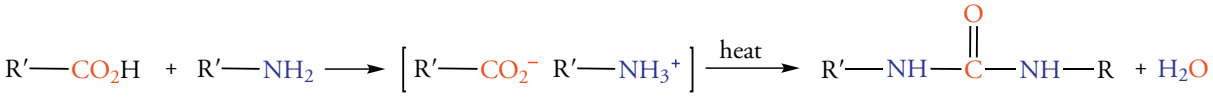
Lexan has very high impact strength and is strong enough to be used in crash helmets. It is also used to manufacture telephone housings. Because Lexan can be produced as a clear colorless polymer, it is used in bulletproof windshields and in the visors of astronauts' helmets.

Problem 28.11

Lexan can be prepared by using diphenyl carbonate rather than diethyl carbonate. Which reaction is thermodynamically more favorable?

28.12 POLYAMIDES

We recall that amides are best made by the reaction of acid chlorides and amines. Therefore, polyamides can be made by reaction of a monomer with two acid chloride functional groups and a monomer with two amine groups. However, the high reactivity of acid chlorides with nucleophiles such as water requires special precautions to preserve this reagent. Thus, these compounds are not much used in industrial laboratories. An alternate method for the synthesis of amides is the direct heating of an amine with a carboxylic acid. The first product is an ammonium salt, which loses water when heated to form the amide.

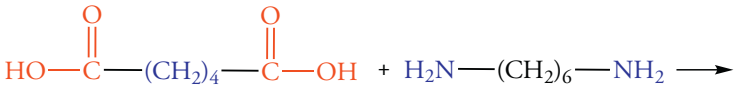


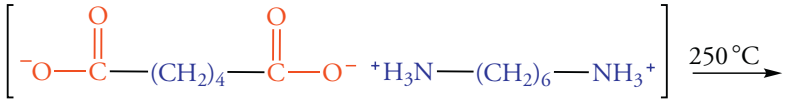
(an ammonium salt of a carboxylic acid)

This nylon is called nylon 6,6 (or nylon 66) to indicate that the polyamide is made by the reaction of a six-carbon diamine and a six-carbon diacid.

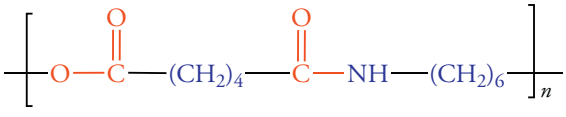
A polyamide can be produced from a single monomer containing both an amine and a carboxylic acid. However, a related cyclic structure called a lactam can also be converted into a polyamide. When the lactam ring is hydrolyzed, an amino acid is produced that can be polymerized.

6-Aminohexanoic acid lactam (ε-caprolactam) is obtained in two steps starting from cyclohexanone. The ketone is converted into an oxime. Then, the oxime is converted into ε-caprolactam by treatment with sulfuric acid. The second step, called the Beckmann rearrangement, proceeds through a series of cationic intermediates and a skeletal rearrangement.

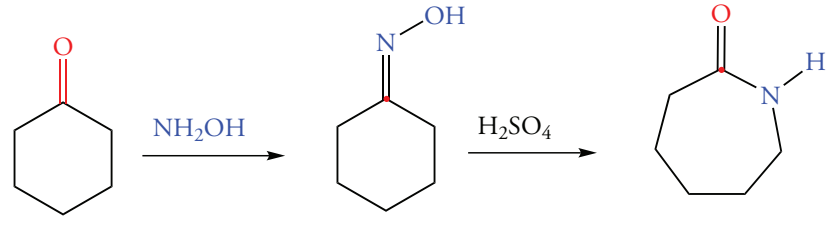




nylon salt

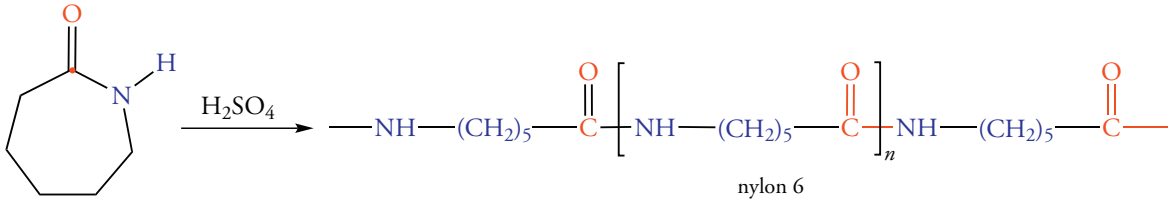


nylon 6,6



cyclohexanone | cyclohexanone oxime | ε-caprolactam

When ε-caprolactam is heated with a catalytic amount of a nucleophile such as water, the nucleophile attacks the carbonyl carbon atom and opens the ring. The amino group of the resulting amino acid is nucleophilic and reacts with another molecule of the lactam. Subsequent reaction of the amino group of the dimer with the lactam yields a trimer. Continued reaction yields a six-carbon homopolymer called nylon 6. The molecular weight of the polymer formed is approximately 6000.



nylon 6

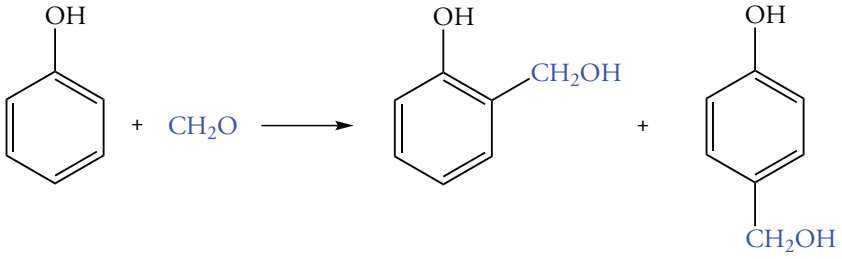
Nylons are used in many products. As a fiber, nylon is used in clothing, rope, tire cord, and parachutes. Because nylon has a high impact strength and resistance to abrasion, it can even be used to make bearings and gears.

Problem 28.12

Nylon 6,10 is prepared by reaction of a diamine and a diacid chloride. Draw the structures of the reactants.

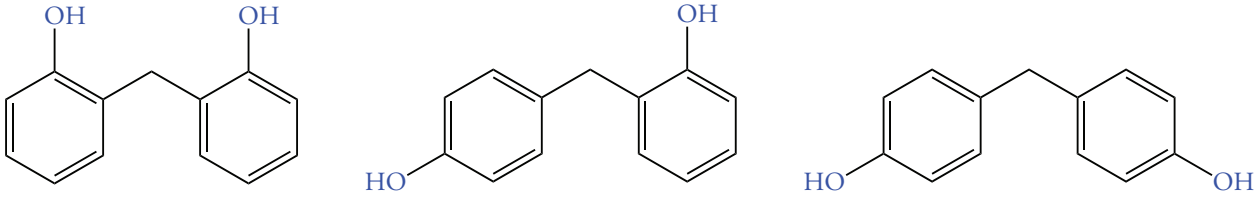
28.13 PHENOL–FORMALDEHYDE POLYMERS

Bakelite, a copolymer of phenol and formaldehyde, was the first commercial polymer. It was prepared in 1907 by Leo Bakeland. The chemistry of this reaction was described in Section 24.6. The first step is an addition reaction of a phenolate to formaldehyde to give either of two isomeric hydroxymethylphenols.



hydroxymethylphenols

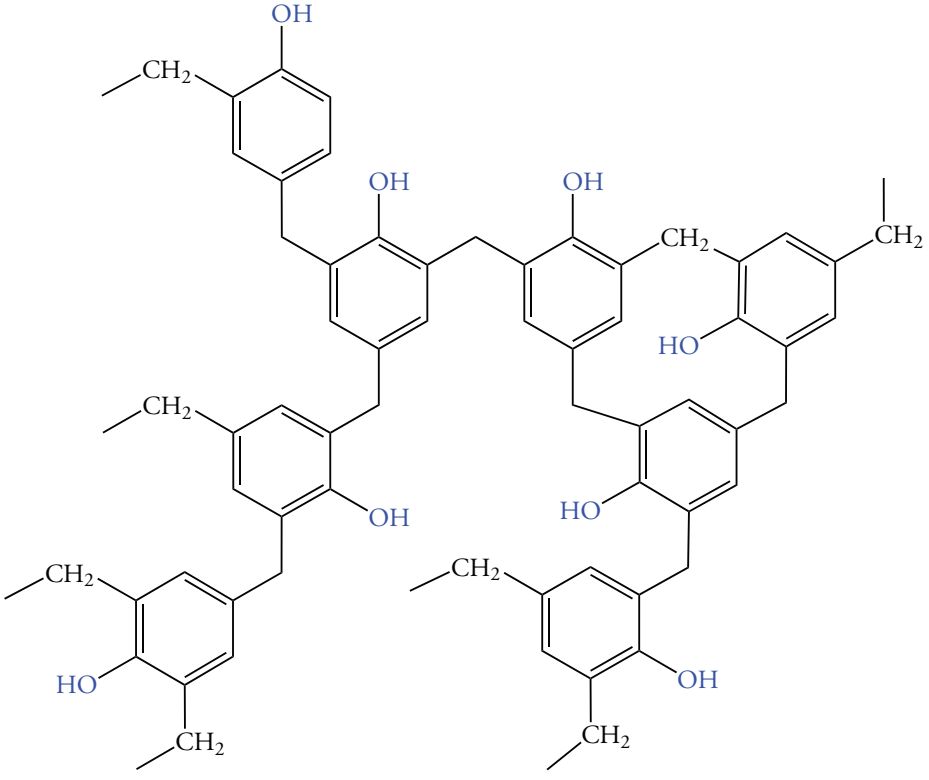
Subsequent alkylation of phenol by the benzylic carbon atom gives several possible bis(hydroxyphenyl) methanes that have a methylene group bonded between two *ortho* positions, two *para* positions, or an *ortho* and a *para* position. Addition of the carbanion to the carbon–oxygen double bond of formaldehyde gives a hydroxymethyl derivative, which can dehydrate to give a conjugated ketone, which can undergo conjugate addition reactions that resemble the aldol reaction. The reaction results in an elimination of water and thus is a condensation process.



bis(hydroxyphenyl)methanes

Continued condensation yields a branched oligomer that is produced as a Bakelite resin (Figure 28.13). This low-melting oligomer is then heated in a mold to give a thermosetting polymer with many more cross-links.

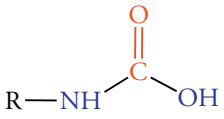
Figure 28.13 Cross-links in Thermosetting Plastic Bakelite



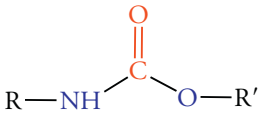
Problem 28.13
Explain why phenol and acetone do not react to give a condensation polymer.

28.14 POLYURETHANES

A urethane is an ester of a carbamic acid. We recall that a carbamic acid, the intermediate in a Hofmann rearrangement, is unstable and decomposes to an amine and carbon dioxide. Therefore, urethanes cannot be made by esterification of a carbamic acid.

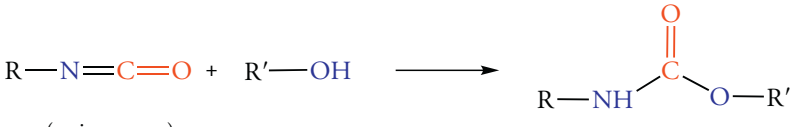


carbamic acid



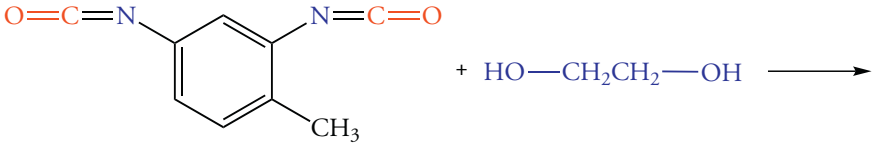
(a urethane)

We recall that an isocyanate intermediate forms in the Hofmann rearrangement and that it is trapped by reaction with an alcohol to give a urethane (Section 23.9). Isocyanates can also be prepared by other methods. They react quantitatively and rapidly with an alcohol or phenol to give carbamate esters.

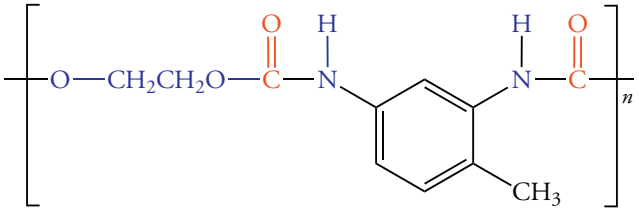


(an isocyanate) (a urethane)

Polyurethane can be prepared by the reaction of a diisocyanate with a diol. The major diisocyanate used is toluene diisocyanate, which has the isocyanate groups at positions *ortho* and *para* to the methyl group. When ethylene glycol is added to the diisocyanate, a typical condensation polymerization occurs to give a polyurethane.



(toluene isocyanate)

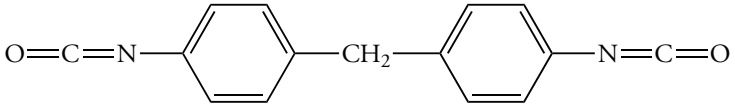


(a polyurethane)

The major use of polyurethanes is in foams. Gases are blown into the liquid polymer to produce bubbles that are trapped as the material cools. When the resulting material is spongy, it is used for cushions. If monomers are selected to give cross-links, the more rigid foams that form are used for thermal insulation in building construction. Fibers of polyurethanes can be made by using oligomeric ethers with a terminal hydroxyl group. The oligomer located between the ester linkages makes the polymer an elastomer. Polyurethane fibers are used in Spandex and Lycra.

Problem 28.14

Methanediphenyl diisocyanate (MDI) is used to prepare a polyurethane. Draw the structure of a polyurethane prepared from MDI and ethylene glycol.



MDI

EXERCISES

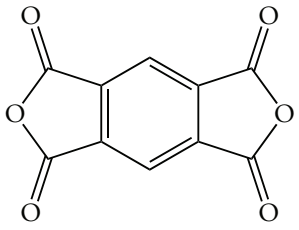
Properties of Polymers

28.1 Explain why the polymer of 2-methylpropene is a sticky elastomer with few crystalline domains.

28.2 How would the properties of the polymer of the following diamine and adipic acid differ from those of nylon 6,6?

$$CH_3—NH—CH_2)_6—NH—CH_3$$

28.3 Explain how 1,2,4,5-benzenetetracarboxylic acid dianhydride could be used to make a thermosetting polyester.



1,2,4,5-benzenetetracarboxylic acid dianhydride

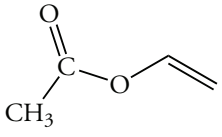
28.4 How would the properties of the copolymer of l ,4-butanediol with terephthalic acid differ from those of PET?

28.5 Why is neoprene less susceptible to oxidation than polyisoprene?

28.6 Explain why Teflon, a polymer of tetrafluoroethylene, is not sensitive to oxidation.

Addition Polymers

28.7 Vinyl acetate is used to make a polymer used in chewing gum. Draw a bond-line representation of the polymer.



vinyl acetate

28.8 Draw a bond-line structure of polyvinyl alcohol. Explain why the polymer is prepared by the hydrolysis of polyvinyl acetate.

28.9 What monomer is required to prepare the following polymer?

$$—CFCl—CF_2—CFCl—CF_2—CFCl—CF_2—CFCl—CF_2—$$

28.10 Hexafluoropropene is a monomer used to prepare a polymer called Yiton. Draw a representation of the polymer.

28.11 Draw the structure of the ozonolysis product of natural rubber under oxidative workup conditions.

28.12 The polymer formed from a compound with molecular formula C_6H_{10} undergoes ozonolysis to give 2,5-hexane-dione. What is the structure of C_6H_{10}?

Chain Transfer Reactions

28.13 Draw the structure of the branch formed by a short chain transfer reaction in the formation of polystyrene.

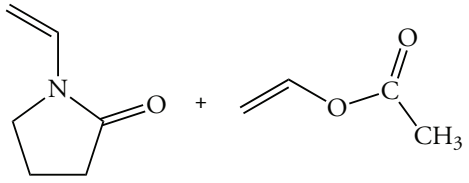
28.14 Explain why formation of a polymer of l-hexene under free radical conditions would produce some molecules with methyl groups bonded to the main chain.

Copolymers

28.15 Draw a representation of an alternating polymer of isoprene and 2-methylpropene.

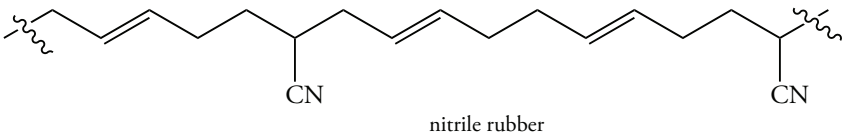
28.16 Styrene and 1,3-butadiene form a random polymer. What is the probability that a 1,3-butadiene unit will react with a growing polymer chain with styrene at its end?

28.17 Some hair sprays contain a solution of a copolymer made from the following monomers. Draw a representation of the polymer. Why does the copolymer hold hair in place?



28.18 Saran is a copolymer of vinylidene chloride ($CH_2{=}CCl_2$) and a smaller amount of vinyl chloride. Draw a representation of the polymer.

28.19 Nitrile rubber, which is used to make automotive hoses, has the following structure. What monomers are used to produce the polymer?



nitrile rubber

28.20 Draw a section of a copolymer of acrylonitrile, styrene, and 1,3-butadiene, which is used as a synthetic rubber.

Cross-Linked Polymers

28.21 What is the difference between the number of cross-links in the rubber used in tires and the rubber used in gloves?

28.22 Draw a representation of the polyester formed from butenedioic anhydride (maleic anhydride) and 1,2-propane-diol. Explain how this polymer could be cross-linked by reacting it with styrene.

Stereochemistry of Polymerization

28.23 Which of the following alkenes can be polymerized to give isotactic and syndiotactic structures?
(a) 1-chloroethene (b) 1,1-dichloroethene (c) 2-methylpropene (d) styrene

28.24 Are syndiotactic or isotactic forms of polypropylene optically active?

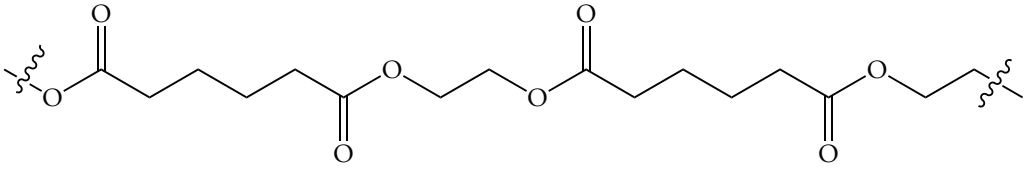
28.25 *S*-Methyl-1-pentene reacts with a Ziegler-Natta catalyst to give an isotactic polymer. What relationship exists between the alkyl groups on the polymer chain?

28.26 Ethylene and *cis*-2-butene form a syndiotactic copolymer in a reaction catalyzed by a vanadium catalyst. Draw a representation of the polymer.

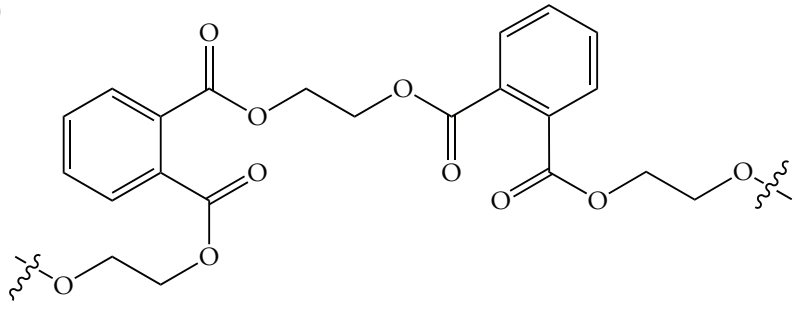
Condensation Polymers

28.27 What monomers are required to prepare the following polymers?

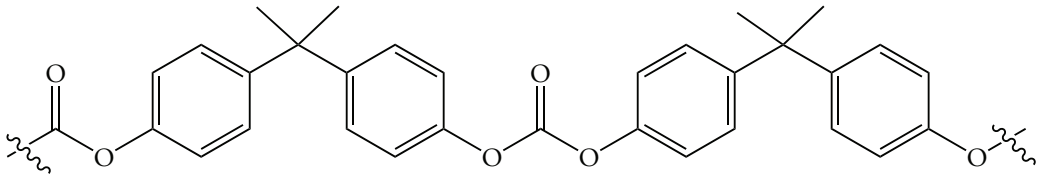
(a)



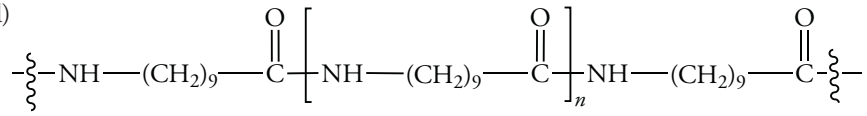
(b)



(c)

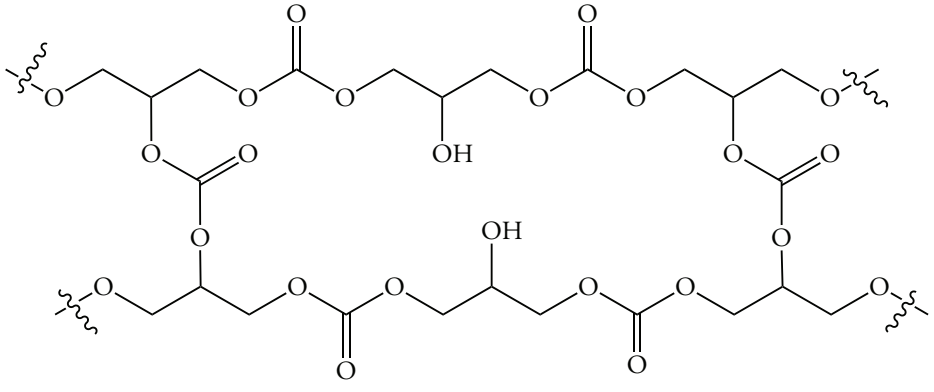


(d)

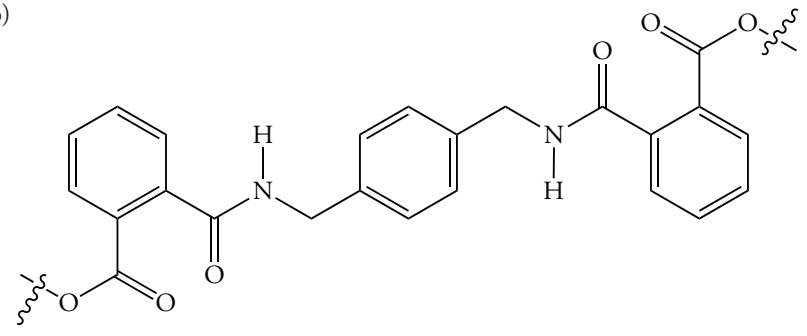


28.28 What monomers are required to prepare the following polymers?

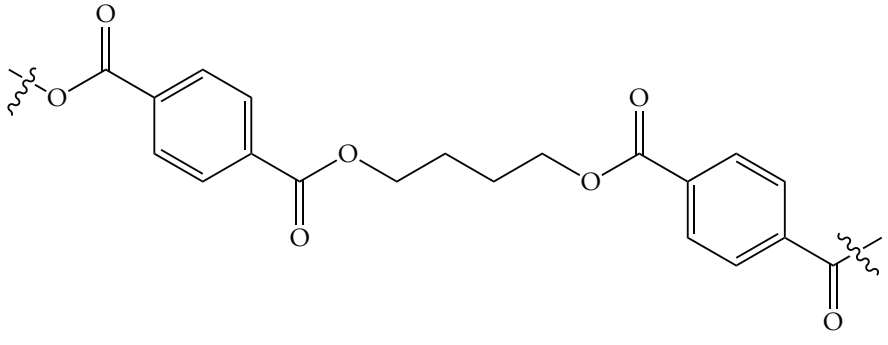
(a)



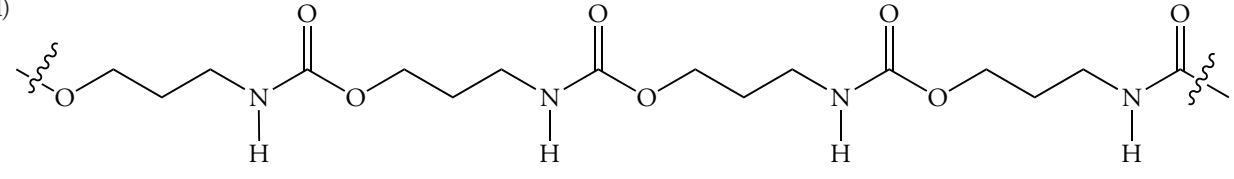
(b)



(c)



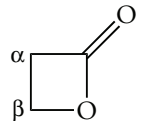
(d)



Polyesters

28.29 A homopolymer of lactic acid can be used to make body implants. Write a bond-line representation of the polymer.

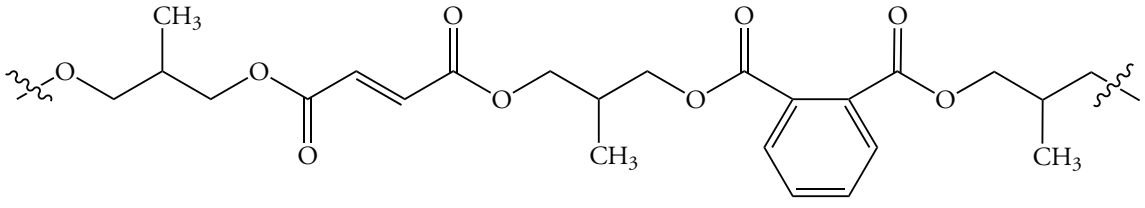
28.30 A polymer of β-propiolactone is obtained by using a catalytic amount of hydroxide ion. Draw the structure of the polymer. Why does the polymerization reaction continue?



β-propiolactone

28.31 Kodel is a polymer of terephthalic acid and *trans*-di-1,4-(hydroxymethyl)cyclohexane. Draw a representation of the polymer.

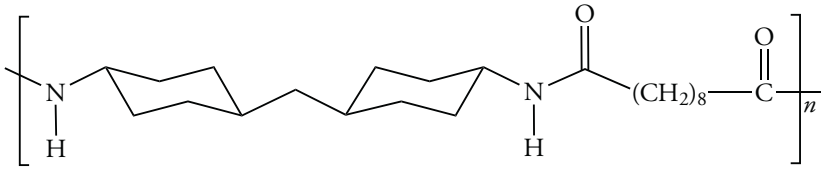
28.32 What monomers are used to prepare the following polyester? Identify an unusual feature of this polyester.



Polyamides

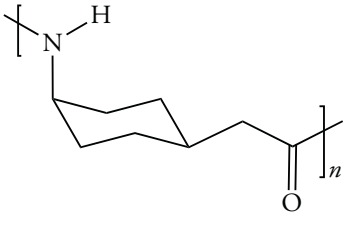
28.33 Draw a representation of each of the following polymers.
(a) nylon 6,10 (b) nylon 11 (c) nylon 4,6

28.34 The following structure represents a group of polyamides called Qiana. The value of *x* is 8, 10, or 12. What are the component monomers? What is the significance of the value of *x*?



28.35 Is it likely that nylon 11 could be prepared from a lactam?

28.36 A polyamide contains the following structural unit, which is prepared from the reaction of a lactam. Draw the structure of the lactam.

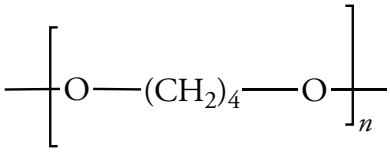


Polyethers

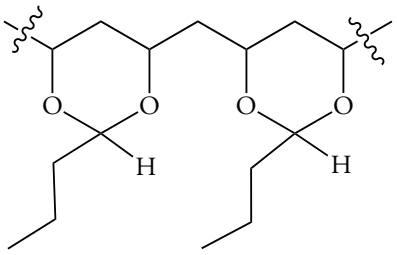
28.37 Carbowax is a polyether named polyethylene glycol. Why is ethylene oxide used to prepare this polymer?

28.38 Polymerization of (*S*)-2-methyloxirane catalyzed by a Lewis acid in ether yields an optically inactive polymer.

28.39 A polyether oligomer of tetramethylene glycol is produced by an acid-catalyzed ring opening of tetrahydrofuran. Write the steps that account for the formation of the oligomer.



28.40 Poly(vinylbutyral) is used in automobile windshield glass. How is this polymer prepared starting from polyvinyl acetate

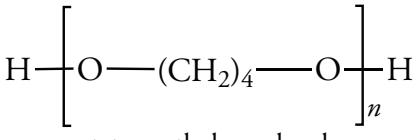


poly(vinyl butyral)

Polyurethanes

28.41 Explain why the addition of glycerol to the polymerization of toluene diisocyanate and ethylene glycol produces a stiffer foam.

28.42 An oligomer of tetramethylene glycol reacts with toluene diisocyanate to form a polyurethane called Lycra. Draw a representation of the polyurethane.



tetramethylene glycol

Appendix pK_a Values

Inorganic Acids	pK_a
Arsenic (H_3AsO_4)	2.25, 6.77, 11.6
Boric (H_3BO_3)	9.14, 12.7, 13.8
Carbonic (H_2CO_3)	6.37, 10.25
Hydrobromic (HBr)	–9
Hydrochloric (HCl)	–7
Hydrocyanic (HCN)	9.31
Hydrofluoric (HF)	3.45
Hydrogen sulfide (H_2S)	7.04, 12.0
Hypochlorous (HOCI)	4.53
Nitric (HNO_3)	–1.3
Nitrous (HNO_2)	3.37
Phosphoric (H_3PO_4)	2.12, 7.21, 12.7
Pyrophosphoric ($H_4P_2O_7$)	0.85, 1.49, 5.77, 8.22
Sulfuric (H_2SO_4)	–5.2, 2.0
Sulfurous (H_2SO_3)	1.81, 6.91

Acyclic Carboxylic Acids	
HCO_2H	3.75
CH_3CO_2H	4.72
$CH_3CH_2CO_2H$	4.87
$CH_3(CH_2)_2CO_2H$	4.82
$(CH_3)_2CHCO_2H$	4.84
$CH_3(CH_2)_3CO_2H$	4.81
$(CH_3)_3CCO_2H$	5.03
$HC{\equiv}CCO_2H$	1.9
$CH_3C{\equiv}CCO_2H$	2.6
$CH_2{=}CHCO_2H$	4.2

Substituted Acetic Acids	
FCH_2CO_2H	2.59
$ClCH_2CO_2H$	2.86
$BrCH_2CO_2H$	2.90
ICH_2CO_2H	3.18
Cl_2CHCO_2H	1.22
Cl_3CCO_2H	0.64
F_3CCO_2H	0.23
$NO_2CH_2CO_2H$	1.3
$NCCH_2CO_2H$	3.5
$HSCH_2CO_2H$	3.5
$HOCH_2CO_2H$	3.7
$CH_3OCH_2CO_2H$	3.6

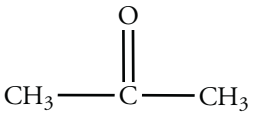
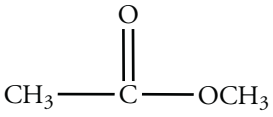
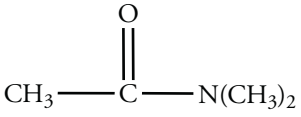
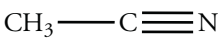
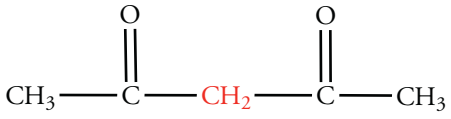
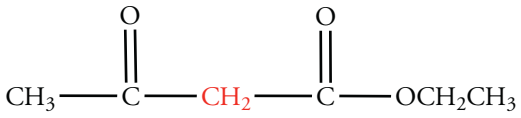
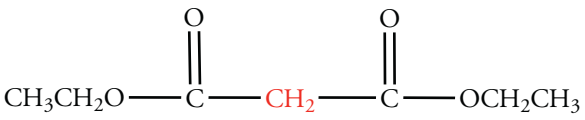
Benzoic Acids	pK_a
Benzoic	4.2
m-Aminobenzoic	4.8
p-Aminobenzoic	4.9
o-Bromobcnzoic	2.8
m-Bromobcnzoic	3.9
o-Chlorobenzoic	2.9
m-Chlorobenzoic	3.8
p-Chlorobenzoic	4.0
o-Nitrobenzoic	2.2
m-Nitrobenzoic	3.5
p-Nitrobenzoic	3.4
o-Methylbenzoic	3.9
m-Methylbenzoic	4.3
p-Methylbenzoic	4.4
o-Methoxybenzoic	4.1
o-Methoxybenzoic	4.1
o-Methoxybenzoic	4.5

Diarboxylic Acids	
Oxalic	1.27, 4.27
Malonic	2.85, 5.7
Succinic	4.20, 5.64
Glutaric	4.35, 5.42
Adipic	4.41, 5.41
Pimelic	4.51, 5.42
Suberic	4.52, 5.41
Azeleic	4.54, 5.41
Sebacic	4.55, 5.40

Alcohols	
Methanol	15.5
Ethanol	15.9
Isopropyl alcohol	18.0
tert-Butyl alcohol	19.0
2-Chloroethanol	14.2
2,2-Dichloroethanol	12.9
2,2,2-Trifluoroethanol	12.4
3,3,3-Trifluoropropanol	14.6
Benzyl alcohol	15.4

Phenols	pK_a
Phenol	10.0
o-Bromophenol	8.4
m-Bromophenol	8.9
p-Bromophenol	9.2
o-Chlorophenol	8.4
m-Chlorophenol	9.0
p-Chlorophenol	9.4
2,4-Dichlorophenol	7.8
2,4,6-Trichlorophenol	6.2
p-Cyanophenol	8.0
o-Methoxyphenol	10.0
m-Methoxyphenol	9.6
p-Methoxyphenol	10.2
o-Methylphenol	10.3
m-Methylphenol	10.1
p-Methylphenol	10.3
o-Nitrophenol	7.2
m-Nitrophenol	8.4
p-Nitrophenol	7.2
3,4-Dinitrophenol	3.5
2,4-Dinitrophenol	4.1
2,4,6-Trinitrophenol	0.3
p-Trifluoromethylphenol	8.7

Sulfur Compounds	
Methanesulfonic acid	–1.8
Thiophenol	6.6
Methanethiol	10.3
Dimethyl sulfoxide	35
Dimethyl sulfone	28

α-Hydrogen Atoms	pK_a
	19
	25
	30
	25
	19
	11
	19

Hydrocarbons	
Ethane	50
Ethene	44
Ethyne	25
Benzene	43
Toluene	41
Diphenylmethane	34
Triphenylmethane	32
Cyclopentadiene	15

Appendix A: Heats of Formation (kJ mole^{-1})

Alkanes

Methane	–74.48
Ethane	–83.85
Propane	–104.68
Butane	–126.78
2-Methylpropane	–134.18
Pentane	–146.94
2-Methylbutane	–153.55
Hexane	–166.94
2-Methylpentane	–174.68
3-Methylpentane	–172.0
Heptane	–187.65
2-Methylhexane	–194.72
3-Methylhexane	–191.3
Octane	–208.82
2-Methylheptane	–215.35
3-Methylheptane	–212.5
Nonane	–228.86
2-Methyloctane	–235.85
3-Methyloctane	–233.7
Decane	–249.55
2-Methylnonane	–256.52
3-Methylnonane	–254.4

Cyclolkanes

Cyclopropane	+53.3
Cyclobutane	+28.4
Cydopentane	–77.10
Cyclohexane	–123.19
Cycloheptane	–118.1
Cyclooctane	–124.4
Cyclononane	–132.6
Cyclodecane	–154.3
Cycloundecane	–179.4
Cyclododecane	–230.1
Cyclotridecane	–246
Cyclotetradecane	–301
Cyclopentadecane	–323

Substituted Cyclolkanes

Methylcyclopentane	–105.8
Methylcyclohexane	–154.7
Ethylcyclohexane	–171.4
trans-1,2-Dimethylcyclopropane	–3.2
cis-1,2-Dimethylcyclopropane	+0.7
trans-1,2-Dimethylcyclopentane	–32.7
cis-1,2-Dimethylcyclopentane	–31.0
trans-1,3-Dimethylcyclopentane	–31.9
cis-1,3-Dimethylcyclopentane	–32.5
trans-1.2-Dimethylcyclohexane	–171.6
cis-1,2-Dimethylcyclohexane	–179.5
trans-1.3-Dimethylcyclohexane	–184.2
cis-1.3-Dimethylcyclohexane	–176.2
trans-1.4-Dimethylcyclohexane	–176.2
cis-1,4-Dimethylcyclohexane	–184.2

Alkenes

Ethene	+52.5
Propene	+20.0
trans-2-Butene	–11.4
2-Methylpropene	–l6.9
cis-2-Pentene	–27.6
trans-2-Pentene	–31.9
2-Methyl-1-butene	–35.3
2-Methyl-2-butene	–41.8
3-Methyl-1-butene	–27.6

Cycloalkenes

Cyclopentene	+33.9
Cyclohexene	–5.0
1-Methylcyclohexene	–43.1
Cyclooctene	–27.2

Dienes

Propadiene	+190.5
1,2-Butadiene	+162.3
1,3-Butadiene	+110.3
2-Methyl-1,3-butadiene	+75.5
cis-1,3-Pentadiene	+81.4
trans-1,3-Pentadiene	+76.1
1,4-Pentadiene	+105.6
1 3-Cyclopentadiene	+133

Alkynes

Propyne	185.0
1-Butyne	165.7
2-Butyne	147.7
1-Pentyne	144.0
2-Pentyne	128.6
3-Methyl-1-butyne	136.1
1-Hexyne	123.4
1-Heptyne	102.8
1-Octyne	82.2
1-Nonyne	61.7
1-Decyne	41.1

Aromatic Hydrocarbons

Benzene	+82.6
Toluene	+50.4
o-Xylene	+19.1
m-Xylene	+17.3
p-Xylene	+18.0
Ethylbenzene	+29.9
Styrene	+147.9
Naphthalene	+150.3
Anthracene	+230.9
Phenanthrene	+207.5

Alcohols

Methanol	–201.5
Ethanol	–235.2
1-Propanol	–255.1
2-Propanol	–272.8
1-Butanol	–275.0
2-Butanol	–292.9
2-Methyl-1-propanol	–283.9
2-Methyl-2-propanol	–312.5
Cyclopentanol	–242.4
Cyclohexanol	–285.9

Ethers

Dimethyl ether	–184.1
Diethyl ether	–252.1
Ethylene oxide	–52.6
Tetrahydrofuran	–184.2
Furan	–34.9

Aldehydes and Ketones

Methanal	–108.6
Ethanal	–166.1
Propanal	–185.6
Propanone	–217.3
Butanal	–204.8
2-Methylpropanal	–215.8
2-Butanone	–238.7
Cyclopentanone	–192.1
Cyclohexanone	–225.7
Benzaldehyde	–36.7
Acetophenone	–86.7

Acids and Esters

Methanoic acid	–378.7
Ethanoic acid	–432.8
Methyl methanoate	–355.5
Methyl ethanoate	–411.9
Ethyl ethanoate	–444.1

Amines

Methylamine	–23.0
Ethylamine	–47.4
Propylamine	–70.2
Isopropylamine	–83.8
Butylamine	–92.0
Isobutylamine	–98.7
tert-Butylamine	–120.9
Pyrrole	+108.3
Pyrrolidine	–3.4
Pyridine	+140.4
Piperidine	–47.2

Sulfur Compounds

Thiophene	+115.4
Methanethiol	–22.9
Ethanethiol	–46.3
Dimethyl sulfide	–37.5
Dimethyl disulfide	–23.4
Dimethyl sulfoxide	–150.9

Appendix IR Absorptions (cm^{-1})

Hydrocarbons

C—H stretching	
Alkane	2850–3100
Alkene	3000–3100
Alkyne	3300
C—H stretching	
Alkene	
Monosubstituted	995–985, 910–905
cis	690
Disubstituted	895–885
trans	980–965
Trisubstituted	840–790
Aromatic	
5 adjacent hydrogens	770–730
4 adjacent hydrogens	770–735
3 adjacent hydrogens	810–750
2 adjacent hydrogens	860–800
1 hydrogen	900–860
C—C stretching	
Alkene (unconjugated)	1670–1630
Alkyne	2140–2100

Ketone Carbonyl Stretch

Acyclic	1715–1710
α,β-Unsaturated	1685–1665
Aryl conjugated	1700–1680
Cyclic	
6-Membered ring	1710
5-Membered	1745
4-Membered ring	1780

Aldehyde Carbonyl Stretch

Saturated	1725–1720
α,β-Unsaturated	1705–1680
Aryl conjugated	1715–1695

Ester Carbonyl Stretch

Saturated	1750–1735
α,β-Unsaturated	1730–1715
Cyclic	
6-Membered ring	1750–1700
5-Membered ring	1780–1760
4-Membered ring	1820

Carboxylic Acid Carbonyl Stretch

Saturated	1725–1700
α,β-Unsaturated aryl	1715–1690
Conjugated	1700–1680

Carboxylic Acid Derivatives

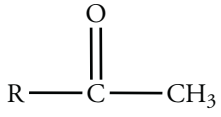
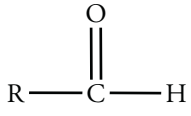
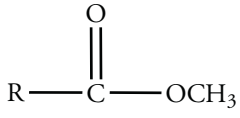
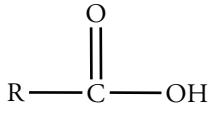
Acyl chloride (carbonyl)	1800
Amide (carbonyl)	1655
Nitriles (C≡N)	2250–2200

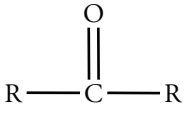
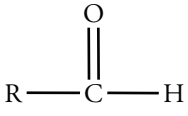
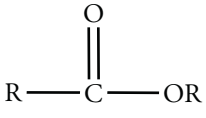
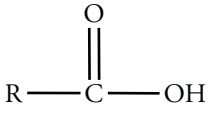
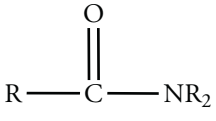
O—H, N—H, and S—H Groups

Alcohols	3400–3200
Carboxylic acids	3600–2400
Thiols	2600–2550
Amines	3375–3200

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Appendix ^{1}H NMR and ^{13}C NMR Chemical Shifts (ppm)

^{1}H	δ
$(CH_3)_4Si$	0
ROH	1.0–6,0
RNH_2	1.0–3.0
RCH_3	0.8–1.0
R_2CH_2	1.2–1.4
R_3CH	1.4–1.7
$R_2C{=}CRCH_2R$	1.6–1.9
$RC{\equiv}CCH_3$	1.9–2.1
$RC{\equiv}CH$	2.5–3.1
$ArCH_3$	2.2–2.5
Ar—H	6.5–8.5
	2.0–2.5
	9.4–9.8
	3.4–3.8
	10–12
RCH_2OH	3.3–4.0
RCH_2—Cl	3.6–3.8
RCH_2—Br	3.4–3.6
RCH_2OCH_3	3.3–3.9

^{13}C	δ
$(CH_3)_4Si$	0
R_3CH	0–40
R_2CH_2	15–55
$R_2C{=}CR_2$	100–150
$RC{\equiv}CR$	65–85
ArH	110–160
RCH_2—Cl	35–80
RCH_2—Br	25–65
	190–210
	190–210
	160–190
	160–190
	150–185

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Glossary

A

absolute configuration The spatial arrangement of atoms at a stereogenic center.

absolute specificity The ability of an enzyme to catalyze the reaction of only one substrate.

absorption spectroscopy A measure of the light absorption of a molecule as a function of wavelength, wavenumber, or frequency.

acetal A product formed from the reaction of 1 mole of an aldehyde and 2 moles of an alcohol, as in $RCH(OR)_2$.

acetoacetic ester synthesis Synthesis of substituted acetone derivatives by alkylation of acetoacetic esters followed by hydrolysis and decarboxylation.

acetyl coenzyme A Acetyl derivative of coenzyme A (a thiol); a central intermediate for metabolic processes.

acetylene The simplest alkyne, C_2H_2, also commonly used to designate the class of alkynes.

acetylide The conjugate base (anion) of a terminal alkyne.

achiral compound A compound that can be superimposed on its mirror image.

acid A substance that is a proton donor (Brønsted–Lowry acid). A substance that is an electron pair acceptor (Lewis acid).

acid anhydride A compound formed by loss of water in the reaction of two molecules of an acid.

acid derivative Compound derived from carboxylic acids with atoms or groups of atoms replacing the —OH group.

acid dissociation constant, K_a Equilibrium constant for dissociation of a weak acid that is a measure of the acidity of an acid in a reaction with water to produce the hydronium ion.

acid halide A carboxylic acid derivative in which a halogen atom replacing the hydroxyl group of a carboxylic acid.

acidic amino acids Amino acids that have more than one carboxyl group, e.g., aspartic and glutamic acids.

activating group A substituent on an aromatic ring that makes the ring more susceptible to attack by electrophiles.

activation energy The energy difference between reactants and the transition state that is the minimum required for a reaction to occur.

active site The region in an enzyme that has a unique arrangement of amino acid side chains required for catalytic activity.

active transport The movement of material across membranes from low concentration to high concentration.

acyclic compound A compound not containing any cyclic structure.

acylation Reaction attaching an acyl group to another structural unit.

acyl carrier protein The carrier of acyl groups in fatty acid biosynthesis.

acyl chloride (acid chloride) Carboxylic acid derivative with an RCOCl functional group.

acyl group The carbonyl-containing portion of a compound such as an ester or amide.

acylium ion A reactive intermediate that is produced in Friedel–Crafts acylation reactions.

acyl transfer Reaction converting one acyl derivative into another.

1,2-addition An addition of two groups of atoms to adjacent carbon atoms as in an alkene, alkyne, or carbonyl compound.

1,4-addition An addition of two groups of atoms to carbon atoms with a 1,4 relationship, usually in a conjugated system of double bonds or carbonyl groups.

addition–elimination reaction A two-step mechanism for nucleophilic aromatic substitution or in the formation of an imine from a carbonyl compound.

addition polymer Polymer that forms from the addition of monomers to each other, usually involving double bonds.

addition reaction The incorporation of two groups of atoms into a molecule with a multiple bond such as an alkene or carbonyl compound; reaction in which two reactants combine to give a single product.

adenine A purine base found in both RNA and DNA.

adenosine diphosphate (ADP) Hydrolysis product of adenosine triphosphate consisting of ribose, adenine, and two phosphoryl groups.

adenosine monophosphate (AMP) Hydrolysis product of adenosine triphosphate consisting of ribose, adenine, and one phosphoryl group.

adenosine triphosphate (ATP) Energy-rich phosphoanhydride consisting of ribose, adenine, and three phosphoryl groups.

adipose tissue Another name for depot fat found in connective tissue.

aglycone The group bonded to the anomeric carbon atom of a glycoside.

alcohol A compound containing a hydroxyl group bonded to a saturated carbon atom.

alcohol dehydrogenase The enzyme that catalyzes the oxidation of ethanol to acetaldehyde and acetic acid in living cells.

aldaric acid A dicarboxylic acid prepared by oxidation to carboxylic acid groups at each end of a monosaccharide.

aldehyde A carbonyl compound whose carbonyl carbon atom is bonded to one hydrogen atom and either an alkyl or aryl group.

alditol A poly alcohol formed by reduction of an aldose or ketose.

aldol condensation Formation of an α-hydroxy aldehyde or ketone or the related α,β-unsaturated carbonyl compound by reaction of two equivalents of carbonyl compounds.

aldonic acid A carboxylic acid obtained by oxidation of the aldehyde of an aldose.

aldose A carbohydrate containing an aldehyde group.

alkadiene A hydrocarbon containing two carbon–carbon double bonds.

alkali metals The elements of Group IA of the periodic table.

alkaline earth metals The elements of Group IIA.

alkane Hydrocarbon having only carbon–carbon single bonds and the molecular formula C_nH_{2n+2}.

alkene Hydrocarbon having a carbon–carbon double bond.

alkoxide ion Anion (RO^-) produced by loss of a proton from an alcohol.

alkoxy group A group, represented as RO^-, present in ethers.

alkoxymercuration The addition of a mercuric salt to an alkene in an alcohol solution.

alkyl ammonium ion Derivative of ammonium ion in which one or more alkyl groups replace hydrogen, as in RNH_3^+.

alkyl group A group of carbon and hydrogen atoms that is derived from an alkane but has one less hydrogen atom.

alkyl halide A derivative of an alkane of the type R—X.

alkyloxonium ion Positively charged species of the type ROH_2^+.

alkyne Hydrocarbon having a carbon–carbon triple bond.

allene The compound CH2=C=CH, or a compound containing two cumulated double bonds.

allosteric effect A change in conformation at one site caused by a change in conformation at a second, spatially separated site.

allosteric regulation The noncompetitive inhibition causing conformational changes.

allyl group The CH_2=CH—C_H2— group

allylic The saturated bonds at an atom adjacent to a carbon–carbon double bond.

alpha carbon atom The carbon atom immediately adjacent to the carbonyl carbon atom.

alpha elimination An elimination reaction in which the two groups of atoms eliminated are located on the same carbon atom.

amide The functional group with a nitrogen atom bonded to a carbonyl carbon atom.

amine derivative of ammonia in which one or more hydrogen atoms are replaced by alkyl or aryl groups.

amino group The functional group —NH_2.

amino acid An amino-substituted carboxylic acid. In proteins, the amino group is at the α-position.

amino acid residue Amino acyl components of a peptide or protein.

aminopeptidase Enzyme that sequentially hydrolyzes a peptide from the end that has the free amino group.

ammonium salt A tetravalent nitrogen species with a positive charge formed by protonation or alkylation of an amine.

amylopectin A component of starch that has branched chains of glucose.

amylose A component of starch that has a linear arrangement of glucose.

anabolic steroids Synthetic substances, related to testosterone, that promote muscle development.

androgens Male sex hormones; testosterone is one example.

angle strain The strain associated with bond angles that deviate from those associated with a particular type of hybrid bond.

angular (bent) molecule A planar molecule with three atoms arranged at an angle other than 180°.

anhydride An acid derivative containing an oxygen atom bridging two carbonyl carbon atoms.

anion Negatively charged ion that results from the gain of one or more electrons.

anomeric carbon atom The original carbonyl carbon atom of an aldose or ketose as contained in the cyclic acetal form of the sugar.

anomers Stereoisomers that differ in configuration at the anomeric carbon atom.

antagonist Drug that opposes the effect of another compound.

***anti* addition** Addition of two groups to the opposite faces of a molecule.

antibonding molecular orbital A molecular orbital that is of higher energy than the isolated atomic orbitals used to form the orbital.

antibody Protein that recognizes and combines with a foreign substance.

***anti* conformation** A conformation with a 180° dihedral (torsional) angle.

***anti* coplanar (*anti* periplanar)** Groups having a 180° dihedral angle.

anti-Markovnikov addition Addition reaction with reagents that occurs with regioselectivity opposite that of Markovnikov addition.

annulene Acyclic compound containing a closed cycle of alternating single and double bonds.

aprotic solvent Solvent lacking easily exchangeable protons.

arene Hydrocarbon with an aromatic ring.

aromatic compound A benzene-like compound represented by a Lewis structure containing alernating single and double bonds and having $4n+2$ pi electrons.

aromaticity Stability associated with electron delocalization in an aromatic compound.

aryl group The part of an aromatic hydrocarbon remaining after a hydrogen atom is removed.

aryl halide A benzene (or other aromatic ring) derivative with one or more halogen atoms bonded to the ring carbon atoms.

asymmetric carbon atom Older term indicating a carbon atom bonded to four different atoms or groups of atoms.

atomic number A number equal to the number of protons in the nucleus of an atom of the element.

atomic orbital A region in space about a nucleus in which one or two electrons may be located.

atomic radius The radius of an atom, given in nanometers.

axial position A bond position that is perpendicular to the average plane of a molecule and parallel to the "axis" of the molecule.

B

base A proton acceptor or electron pair donor.

base dissociation constant A measure of the basicity of a base in a reaction with the hydronium ion giving the conjugate acid of the base.

basic amino acid Amino acid that has an extra amino group.

basic solution A solution with a lower concentration of hydronium ions than exists in pure water.

Benedict's solution An alkaline solution of cupric ion as a complex ion used as a test reagent for aldehydes or reducing sugars.

benzene Aromatic compound with the molecular formula

benzyl carbon atom The carbon atom directly bonded to a benzene ring.

benzyl group The carbon group remaining after a hydrogen is removed from the methyl group of toluene.

benzyne A reactive intermediate derived from benzene with two hydrogen atoms removed from adjacent carbon atoms.

beta (β) elimination An elimination reaction in which the two groups of atoms eliminated are on adjacent atoms.

bilayer See lipid bilayer.

bimolecular A reaction with two structural units involved in the transition state.

biochemistry The study of the composition, structure, and reactions of substances in living systems.

boiling point The temperature at which the vapor pressure of a liquid equals atmospheric pressure.

bond angle The angle between two covalent bonds at a common atom in a molecule.

bond dissociation energy Energy required for homolytic bond cleavage in a molecule.

bonding A description of how atoms are held or fastened together in a molecule.

bonding electrons The electrons in covalent bonds.

bonding molecular orbital A molecular orbital that is of lower energy than the isolated atomic orbitals from which it is formed

bond length Distance between nuclei of two covalently bonded atoms.

bond-line structure A formula showing connections between atoms but not showing individual carbon or hydrogen atoms.

bond moment A measure of the polarity of a specific bond in a molecule.

branched alkane An alkane with an alkyl group bonded to a parent alkane.

branched chain A sequence of bonded atoms that have additional atoms attached to points within the chain.

bridged bicyclic compound A compound sharing two rings that are joined at nonadjacent atoms.

bridgehead atom An atom that is shared by two or more rings.

bromonium ion A halonium ion in which bromine is the halogen.

Brønsted–Lowry theory Acid–base theory describing acids as proton donors and bases as proton acceptors.

C

carbanion A negative carbon ion with three bonds and an electron pair on a carbon atom.

carbene A divalent uncharged carbon-containing molecule such as CH_2.

carbocation A carbon ion with three bonds that has a positive charge on a carbon atom.

carbohydrate A polyhydroxy aldehyde or ketone or a compound that can be hydrolyzed to produce a polyhydroxy aldehyde or ketone.

carbonyl group A group consisting of a carbon atom and an oxygen atom joined by a double bond.

carboxylate group The anion formed by loss of a proton from a carboxylic acid, represented by RCO_2^-.

carboxylation Preparation of a carboxylic acid as in the reaction of carbon dioxide with a Grignard reagent.

carboxyl group The —CO_2H group that is the functional group of carboxylic acids.

carboxylic acid Organic compound with the general molecular formula RCO_2H.

carboxypeptidase Enzyme that sequentially hydrolyzes a peptide from the end that has the free carboxyl group.

catalysis The increase in the speed of a reaction in the presence of a substance called a catalyst.

catalyst A substance that increases the speed of a chemical reaction.

catalytic site Position within an enzyme that provides the catalytic function.

cation Positively charged atomic particle that results from the loss of one or more electrons.

cellulose A polysaccharide of glucose with [3-1,4] linkages.

cephalin A phosphatidylethanolamine.

ceramide Amide of fatty acid and sphingosine.

cerebroside Glycosphingolipid, containing only glucose or galactose, found in the brain.

chain reaction A repeated series of reactions in which a reactive intermediate formed in one step reacts in a subsequent step that in turn generates a reactant for the previous step.

chair–chair interconversion A process described as a “flipping” of one chair conformation into another in which the equatorial and axial positions are interchanged.

chair conformation The most stable conformation of cyclohexane.

chemical bond Attractive force that holds atoms together in compounds.

chemical equilibrium Condition in which the rate of the forward reaction equals the rate of the reverse reaction.

chemical reaction The process in which one compound is converted to another.

chemical shift The difference, in parts per million (ppm), between the resonance of a nucleus and that of a reference nucleus such as the methyl groups of tetramethylsilane (TMS).

chirality The property of an object that cannot be superimposed on its mirror image.

chiral molecule A molecule that cannot be superimposed on its mirror image.

chlorohydrin Halohydrin in which chlorine is the halogen atom.

chromosomes Units contained in cells that possess genetic information.

cis On the same side of a ring or double bond.

***cis* isomer** An isomer that has two groups of atoms oriented on the same side of a structural feature such as a cycloalkane ring.

citric acid cycle A series of reactions that oxidize an acetyl group to carbon dioxide and water and save stored energy in NADH, $FADH_2$, and ATP.

Claisen condensation reaction Reaction of two ester molecules to give a β-keto ester.

Clemmensen reduction Reduction of a carbonyl group of an aldehyde or ketone using zinc amalgam and hydrochloric acid.

coenzyme A cofactor that is an organic molecule.

coenzyme A A thiol ester that transfers acyl groups in acetyl CoA.

cofactor A nonprotein material that is an essential part of some enzymes.

collagen Protein component of connective tissue.

combustion A rapid chemical reaction of a substance with oxygen.

common names Historically derived names of compounds that are unrelated to composition, also known as trivial names.

competitive inhibitor Compound similar to a substrate that binds to the active site of an enzyme.

complementary shapes Two structures that fit together to form a unit.

complex lipid Lipid that can be hydrolyzed by base.

compounds Pure substances composed of elements joined together by covalent bonds.

concerted reaction A reaction with all bonds broken and formed simultaneously in a single step.

condensation polymer A polymer made by reacting monomers to give a polymer and some small molecule such as water.

condensation reaction Reaction combining two molecules and forming water as a second product.

condensed structural formula A simplified structural formula in which some of the bonds are not shown but implied.

configuration The spatial arrangement of atoms.

configurational isomers Isomers with atoms bonded in the same order but with different orientations in space.

conformational analysis The description of the conformations of a molecule and their associated energy.

conformations Structures of a compound that result from the rotation about single bonds.

conformers Different spatial arrangements of atoms in space as a result of rotation about single bonds.

conjugate acid The acid formed when a base gains a proton.

conjugate addition Another term for 1,4-addition reaction.

conjugate base The base formed when an acid loses a proton.

conjugated double bonds A series of alternating single and double bonds.

connectivity Order of connection of atoms in a molecule.

conrotatory Description of rotation of bonded atoms in the same sense in a stereochemical pathway.

constitutional isomers Isomers that differ in the bonding sequence or order of atoms, also called structural isomers.

constructive bond overlap The overlap of lobes of orbitals having the same sign.

coordinate covalent bond The bond between two atoms formed by the contribution of a pair of electrons from just one of the atoms (also sometimes called a **dative** bond).

corticosteroids Steroids produced by the adrenal cortex, include glucocorticoids and mineralocorticoids.

coupled reactions Reactions that occur together. One is energy releasing, and the other is energy consuming.

coupling constant The distance between adjacent components of a multiplet given in Hertz (Hz).

covalent bond A bond formed by the sharing of a pair of electrons between two atoms.

covalent compound Compound of discrete molecules joined by covalent bonds.

cumulated diene Diene with a C=C=C unit.

curved arrow formalism A method of keeping track of electrons in a description of a reaction mechanism.

cyano group The —CN functional group of a nitrile.

cyanohydrin The addition product of HCN and a carbonyl compound having a cyano group and a hydroxyl group on the same carbon atom.

cyclic compound A structure containing a ring of atoms.

cycloaddition The addition of two alkenes or polyenes to give a cyclic product having two fewer multiple bonds.

cycloalkane A hydrocarbon that contains a ring of carbon atoms bonded by single covalent bonds.

cyclohexadienyl cation Intermediate formed in electrophilic aromatic substitution.

D

D stereoisomer Compound with a configuration related to D-glyceraldehyde.

deactivating group A substituent on an aromatic ring that decreases the reactivity of the ring toward electrophilic reagents.

deamination The loss of an amino group from a molecule such as an amino acid.

Debye unit Unit used to express dipole moments.

decarboxylation The loss of carbon dioxide from a carboxyl group as in carboxylic acid.

decoupling An experimental method to eliminate the coupling between nuclei.

degenerate orbitals Orbitals that have identical energy.

degree of substitution The number of alkyl groups bonded to an atom such as carbon.

degree of unsaturation A measure of the degree of reduction of hydrogen atoms in a molecule due to rings or multiple bonds.

dehalogenation The elimination of a halogen molecule from a compound, usually from adjacent carbon atoms.

dehydration The removal of H and OH from adjacent atoms in a molecule, usually in an acid-catalyzed reaction.

dehydrogenation The elimination of a hydrogen molecule from a compound, usually from adjacent carbon atoms

dehydrogenation reaction Reaction in which the reactant loses hydrogen.

dehydrohalogenation The elimination of hydrogen and halogen atoms, usually from adjacent carbon atoms.

delocalized electrons Bonding electrons associated with more than two atoms.

delocalized orbital A molecular orbital resulting from combination of atomic orbitals to encompass more than two atoms.

demercuration The removal of mercury or mercury-containing groups from a molecule such as the product of an oxymercuration reaction.

denaturation The loss or destruction of the native conformation of a protein.

deoxyribonucleic acid (DNA) A polynucleotide containing deoxyribose; phosphate; and a mixture of adenine, thymine, guanine, and cytosine.

deoxyribose Aldopentose in which the —OH group attached to the C-2 atom of ribose is replaced by hydrogen.

deoxy sugar A carbohydrate with a hydrogen atom replacing a hydroxyl group.

deshielded Effect on a molecule causing the spectrum to shift to lower field.

destructive overlap The overlap of lobes of orbitals of opposite signs.

detergent Synthetic compound with polar and nonpolar groups that can form micelles.

dextrorotatory Capable of rotating the plane of polarized light in a clockwise direction.

diastereomers Stereoisomers that are not minor images of each other. See also enantiomers.

diastereotopic atoms Nuclei that, when replaced, would give diastereomeric compounds.

1,3-diaxial repulsion The steric hindrance between two axial hydrogen atoms or other groups of atoms located in a 1,3 relationship in a cyclohexane compound.

diazo coupling The reaction of an aryldiazonium ion with an aromatic compound in an electrophilic substitution reaction.

diazonium ion The R—N_2^+ ion formed in reaction of a primary amine with nitrous acid.

dicarboxylic acid Compound with two carboxylic acid groups such as succinic acid.

Dieckman reaction An intramolecular Claisen condensation.

dielectric constant A measure of the ability of a substance to separate oppositely charged ions.

Diels–Alder reaction The cycloaddition reaction of a diene and an alkene to give a six-membered ring.

diene An unsaturated compound with two carbon–carbon double bonds.

dienophile A reactant containing a double bond that reacts with a diene in the Diels–Alder reaction.

dihedral angle The angle between two groups in a Newman projection formula.

dimer A compound formed from two smaller compounds called monomers.

dipeptide Two amino acids combined by a peptide (amide) linkage.

dipole A pair of opposite charges of equal magnitude at a distance from each other.

dipole–dipole attractive forces Intermolecular attractive forces between the partial positive and partial negative sites of polar molecules.

dipole moment Product of the two opposite charges located at sites within a structure and the distance separating them.

disaccharide A sugar (carbohydrate) formed by two monosaccharides joined by an acetal or ketal bond.

displacement reaction Reaction in which an atom or group of atoms replaces an atom or group of atoms in a reactant.

disrotatory Description of the rotation of bonded groups of atoms in the opposite sense in a stereochemical pathway.

disulfide A group represented by R—S —S —R.

double bond The bond formed by the sharing of two pairs of electrons between two atoms.

E

E1 reaction A multistep elimination reaction in which the leaving group departs in the slow ionization step.

E2 reaction A bimolecular concerted elimination reaction that usually occurs via a coplanar transition state.

eclipsed conformation A conformation with a 0° dihedral angle between two groups in a Newman projection formula.
elastomer A polymer that has elasticity.

electrocyclic reaction A pericyclic reaction that forms a cr bond between ends of a pi system.

electron A subatomic particle with a mass of 9.109×10^{-28} g and a charge of -1.06×10^{-19} coulomb (represented by a negative charge of –1).

electron configuration A description of the arrangement of the electrons in the atom by shells, subshells, and orbitals.

electron density The probability of finding electrons in a region of space.

electron-dot structure Structures using dashes for covalent bonds and pairs of dots for lone pair electrons.

electron-dot symbol A symbol giving the number of valence electrons as dots located around the elemental symbol.

electronegativity Number that indicates the electron-attracting tendency of an atom.

electron shell A name for principal energy levels designated by integers 1 to *n*.

electron spin A property of the electron, may be either clockwise or counterclockwise.

electrophile An electron pair acceptor in a chemical reaction.

electrophilic addition Mechanism of addition reaction of an electrophile to a site containing a multiple bond.

electrophilic aromatic substitution Substitution reaction of a hydrogen atom on an aromatic ring by an electrophilic intermediate usually generated using a Lewis acid.

electrophilicity The reactivity of an electrophile.

element Pure substance that cannot be decomposed into any simpler substance(s) by ordinary chemical reactions.

elimination The loss of two atoms or groups of atoms, usually from adjacent atoms and giving a π bond.

elimination–addition mechanism Two-step mechanism of a nucleophilic aromatic substitution reaction.

enantiomeric excess The excess of one enantiomer over another in a mixture.

enantiomers Stereoisomers that are mirror images of each other. See also diastereomers.

enantiotopic Property of two atoms in a molecule whose environment allows formation of enantiomers by replacement of either atom.

endergonic Energy-absorbing process that yields products of higher free energy than reactants; $\Delta G^\circ > 0$, endothermic reaction A process requiring heat energy from the surroundings.

enediol rearrangement A base-catalyzed rearrangement that interconverts α-hydroxy carbonyl compound and interchanging the hydroxyl and carbonyl functional groups.

energy of activation The minimum energy required in a molecular collision to initiate reaction between reactants.

enol An alcohol with the —OH group bonded to one of two double-bonded carbon atoms.

enolate ion The resonance-stabilized conjugate base formed by deprotonation of the carbon atom.

enolizable hydrogen The acidic hydrogen atom at the carbon atom that is lost or gained in keto–enol tautomerization.

enthalpy A quantity symbolized by ΔH°; ΔH° is the energy difference between two states or substances.

entropy A quantity symbolized by ΔS°; ΔS° is a measure of the change in the degree of disorder in a system.

envelope conformation One of the conformations of cyclopentane.

enzyme A biochemical catalyst that is predominantly protein.

epimers Diastereomers that differ in configuration at one chiral center.

epoxidation A reaction, using an oxidizing agent, that forms a three-membered ring containing an oxygen atom.

epoxide A three-membered ring containing one oxygen atom.

equatorial position A bond that is directed out from the average plane of the cyclohexane ring.

equilibrium A state in which opposing processes are in balance.

equilibrium constant A numerical quantity reflecting the relationship between the concentrations of reactants and products at equilibrium.

essential fatty acids Unsaturated fatty acids that cannot be synthesized by the body and must be obtained in the diet.

ester A compound containing an —OR or —OAr group bonded to a carbonyl group in place of the —OH group of a carboxylic acid.

esterase An enzyme that catalyzes the hydrolysis of esters.

esterification Ester formation as in the reaction of an alcohol and a carboxylic acid.

estrogens Female sex hormones; examples are estrone and estradiol.

ether Compound with C—O—C structural unit.

exergonic reaction An energy-releasing reaction that yields products of lower free energy than the reactants, $\Delta G^\circ < 0$.

exhaustive methylation Reaction of an amine with a methyl halide to form a quaternary ammonium ion.

exothermic reaction A process that releases heat energy to the surroundings.

***E,Z* notation** A system to assign double bond configuration based on priority of substituents.

F

fats Esters of glycerol and long-chain saturated carboxylic acids.

fat-soluble vitamins Nonpolar vitamins such as vitamins A, D, and E.

fatty acid A long-chain carboxylic acid containing an even number of carbon atoms.

fatty acid biosynthesis A series of reactions occurring in the cytoplasm of the cell that convert two-carbon-atom acetyl units into fatty acids.

Fehling's solution An alkaline solution of cupric ion as a complex ion used as a test reagent for aldehydes.

Fischer esterification The formation of an ester from a carboxylic acid and an alcohol in the presence of an acid catalyst.

Fischer projection A method of representing chiral molecules in two dimensions with a carbon chain arranged along a line and substituent bonds directed perpendicular to the axis.

Flavin adenine dinucleotide (FAD) Reducing agent that accepts two hydrogen atoms in biochemical reactions.

formal charge A charge calculated for an atom in a molecule as represented by a particular Lewis structure.

free energy change A quantity symbolized by $\Delta G°$ that measures the spontaneity of a chemical reaction.

free radical Reactive species containing one unpaired electron.

frequency The number of wave cycles of light per second (expressed in Hz with units of s^{-1}).

Friedel–Crafts acylation Formation of an acyl aromatic compound using an acyl derivative and a Lewis acid as with an acyl chloride and aluminum trichloride.

Friedel–Crafts alkylation Formation of an alkyl aromatic compound using an alkyl derivative and a Lewis acid as with an alkyl halide and an aluminum trihalide.

frontier molecular orbital The highest occupied molecular orbital used to describe pericyclic reactions.

fructose Ketohexose found in fruits.

functional group An atom or group of atoms in a molecule.

furan A five-membered ring containing one oxygen atom and two carbon–carbon double bonds.

fused-ring compound A compound in which two (or more) rings are joined through two (or more) adjacent carbon atoms.

G

Gabriel synthesis The steps forming a primary amine by alkylation of a phthalimide ion followed by hydrolysis.

galactose An aldohexose that is a component of lactose.

galactosemia A genetic disease that prevents the affected individual from converting galactose into glucose.

ganglioside A glycosphingolipid containing a higher hexose as the sugar unit.

gauche conformation A conformation with a 60° dihedral angle in the Newman projection formula.

geometric isomers Isomers that have the same sequence of atoms, but different orientations in space. See also *cis* isomer and *trans* isomer.

geminal Location of two atoms on the same carbon atom.

geminal dihalide A dihalide with both halogen atoms bonded to the same carbon atom.

geminal diol The hydrate of an aldehyde or ketone.

glucocorticosteroids Steroids produced by the adrenal cortex and involved in the control of glucose levels in the body.

glucose Aldohexose that is a component of starch, cellulose, lactose, and sucrose.

glucoside A glycoside of glucose.

glycogen A storage form of glucose in animals.

glycol A diol that has hydroxyl groups on adjacent carbon atoms.

glycolipid A covalent molecule containing both a sugar and a lipid unit.

glycolysis The conversion of glucose into pyruvic acid.

glycoside An acetal or ketal of a carbohydrate.

glycosidic linkage Acetal or ketal formed between the anomeric carbon atom and a hydroxyl group of a second monosaccharide.

glycosphingolipid A substance consisting of sphingosine, fatty acids, and a carbohydrate.

Grignard reagent A compound containing a bond to a —MgX group where X is chlorine, bromine, or iodine.

H

haloform reaction Conversion of a methyl group of a methyl ketone into CHX_3 and forming a carboxylate salt by reaction with halogen under basic conditions.

halogenation The reaction of an alkane with a halogen to replace one or more hydrogen atoms by halogen atoms.

halogens The elements of Group VIIA.

halohydrin An alcohol with a halogen located on the adjacent carbon atom.

halonium ion A positively charged, three-membered ring containing a halogen atom.

Hammond postulate Reactive species represented on a reaction coordinate diagram that are similar in energy are similar in structure. The transition state structure may resemble the structure of either reactant or product, whichever it is closer to in energy.

heat of combustion The heat released by one mole of a compound when burned to form carbon dioxide and water, expressed as ΔH°_c.

heat of hydrogenation The energy difference between related unsaturated and saturated compounds as determined by a hydrogenation reaction.

heat of reaction The energy difference between the products and the reactants.

Hell–Volhard–Zelinsky reaction Reaction of a carboxylic acid with bromine and PBr_3 to give an α-bromo acyl bromide.

hemiacetal A compound formed by the reaction of 1 mole each of an aldehyde and an alcohol and having one hydroxyl and one alkoxy group on the former carbonyl carbon atom.

hemiketal A compound formed by the reaction of 1 mole each of a ketone and an alcohol.

heteroatom Any atom in a molecule other than carbon or hydrogen, usually nitrogen, oxygen, or sulfur.

heterocyclic compound A compound having one or more atoms other than carbon in a ring.

heterogeneous catalysis A reaction with the catalyst in a separate phase from the substrate.

heterolytic cleavage Breaking a bond so that each atom retains one of the two bonding electrons.

Hofmann elimination Elimination reaction of a quaternary ammonium ion to give the less substituted alkene.

Hofmann product The less substituted alkene product of an elimination reaction.

Hofmann rearrangement Reaction converting an amide into a primary amine with the loss of one carbon atom.

HOMO The highest occupied molecular orbital of a conjugated system.

homogeneous catalysis A reaction with the catalyst in the same phase as the reactants.

homologous series A series of compounds that differ from adjacent members by a repeating unit.

homologs Compounds that differ only by one or more —CH— units.

homolytic cleavage Bond cleavage giving species each retaining one electron.

hormones Chemical messengers that are produced by endocrine glands. Some hormones are proteins.

Huckel's rule A cyclic compound is aromatic if it has a continuous series of overlapping atomic orbitals containing $4n + 2$ π electrons.

Hund's rule Electrons tend to avoid the same orbital so that electrons of equal energy locate singly in different orbitals before pairing occurs.

Hunsdiecker reaction Decarboxylation reaction replacing the carboxyl group with a halogen atom.

hybridization Combination of two or more atomic orbitals to form orbitals for bonding.

hybrid orbitals The result of mixing of two or more orbitals such as s and p to form directional orbitals suitable for bonding.

hydrate A geminal diol formed by addition of water to a carbonyl group.

hydration Addition of water to a molecule.

hydrazone Compound formed by the addition–elimination reaction of a carbonyl group with a hydrazine derivative.

hydride reagents A compound with hydrogen with a formal negative charge such as $NaBH_4$ or $LiAlH_4$ used as reducing agents. Also simple hydrides such as NaH used as bases.

hydride shift The movement of a hydrogen atom with its bonding pair of electrons from one atom to another—usually adjacent to one another.

hydroboration An addition reaction of a compound containing a boron–hydrogen bond to an unsaturated compound.

hydrocarbon A compound containing only carbon and hydrogen.

hydrogenation Reaction converting a multiple bond into a single bond by reaction with hydrogen.

hydrogen bond An intermolecular attraction between an electropositive hydrogen atom and a nonbonded electron pair of an electronegative atom of a neighboring molecule.

hydrolysis Heterolytic cleavage of a bond with water.

hydronium ion The principal form in which protons are found in aqueous solution, the ion H_3O^+.

hydrophilic Water-attracting. A term used to describe the surface of lipid bilayers and micelles.

hydrophobic Water-repelling. A term used to describe the interactions in the interior of lipid bilayers and micelles.

hydrophobic interaction A term describing the London forces between nonpolar hydrocarbon chains.

hydroxylation An addition reaction placing hydroxyl groups on adjacent carbon atoms of an unsaturated compound.

hydroxyl group A group represented by —OH.

I

imine A compound with a carbon–nitrogen double bond.

induced dipole A separation of charge within a molecule caused by a temporary dipole in the vicinity.

inductive effect Either electron donation or withdrawal from a site through sigma bonds.

inhibitors Compounds that deactivate enzymes.

initiation step First step in a free radical mechanism.

integral membrane proteins Proteins that extend from the surface into the interior of a membrane.

integration The measurement of the area of an NMR peak, which is proportional to the number of atoms giving rise to the signal.

intermediate A species formed from a reactant in a chemical reaction that exists for a short time before reacting further.

intermolecular forces Forces of attraction between separate molecules.

inversion of configuration The formation of a product with opposite configuration from the reactant.

ion An electrically charged atom or molecular particle in which the number of electrons is not equal to the number of protons.

ionic bond The bond resulting from the transfer of electrons from a metal to a nonmetal.

ionic compound A neutral collection of oppositely charged ions.

irreversible reaction A reaction that does not proceed appreciably in the reverse direction.

isoionic point The pH at which there is no net charge on an amino acid or protein.

isolated diene Diene in which two double bonds are separated by at least one sp^3-hybridized carbon atom.

isomerism The existence of two different compounds with the same molecular formula.

isomers Substances having the same molecular formula but different structures.

isotope effect The change in the rate of a chemical reaction resulting from isotopic substitution as in the case of deuterium for hydrogen.

IUPAC Acronym for the International Union of Pure and Applied Chemistry.

IUPAC rules Set of rules for naming compounds.

J

Jones oxidation The oxidation of alcohols using chromic acid in acetone as solvent.

K

Kekule structure A structure with alternating single and double bonds used to represent aromatic compounds.

ketal A compound formed from the reaction of 1 mole of a ketone and 2 moles of an alcohol, $R_2C(OR)_2$.

ketone A carbonyl compound whose carbonyl carbon atom is bonded to two alkyl or aryl groups or an alkyl group and an aryl group.

ketose A carbohydrate with a ketone functional group.

kinetically controlled reaction The products are controlled by the relative rates of two competing reactions.

kinetics The study of the rates of chemical reactions.

Knoevenagel reaction Condensation of a 1,3-dicarbonyl compound with an aldehyde or ketone.

Kolbe reaction Conversion of a phenolate into an orthohydroxy aromatic carboxylic acid using a high pressure of carbon dioxide.

L

lactam A cyclic amide

lactase An enzyme that catalyzes the hydrolysis of lactose.

lactone A cyclic ester.

lactose Disaccharide containing galactose and glucose.

leaving group The charged or uncharged atom or group of atoms that departs in a substitution or elimination reaction.

Le Chatelier's principle If a stress is applied to a system at equilibrium, the system will adjust to reduce the stress.

lecithin A phosphatidylcholine.

levorotatory Capable of rotating the plane of polarized light in a counterclockwise direction.

Lewis octet rule A rule referring to the eight electrons in the valence shell of an atom or ion in a compound.

Lewis structure Chemical formula showing valence electrons as dashes for bonds and dots for lone pair (nonbonding) electrons.

Lindlar's catalyst A heterogeneous catalyst containing palladium that forms *cis* alkenes from alkynes in a hydrogenation reaction.

linear combination of atomic orbitals (LCAO) The addition of wave functions of orbitals of two or more atoms to give wave functions of more complex molecular orbitals.

linear molecule A molecule in which all the atoms are arranged along a common axis.

lipid bilayer Two layers of lipid molecules arranged to form a membrane.

lipids A class of biomolecules that includes fats.

lock-and-key theory A model that pictures an enzyme as conformationally rigid.

London attractive forces Intermolecular forces from the attraction of temporary dipoles in adjacent molecules.

London forces Intermolecular forces involving temporary and induced dipoles.

lone pair electrons Valence-shell electrons associated with an atom but not involved in bonding.

LUMO The lowest unoccupied molecular orbital.

M

malonic ester synthesis Formation of substituted acetic acids by alkylation of malonate esters followed by hydrolysis and decarboxylation.

maltose A disaccharide containing two units of glucose.

Markovnikov's rule Rule predicting the product of addition to a double bond.

mass number A number equal to the sum of the number of protons and neutrons in the nucleus of the atom.

MCPBA An abbreviation for *meta*-chloroperoxybenzoic acid, a reagent used in epoxidation reactions.

mechanism A description of the pathway by which bonds break and form in a chemical reaction.

mercaptan A compound containing the sulfhydryl group, —SH.

***meso* compound** A compound with chiral centers that is symmetrical and is not optically active.

meta Prefix specifying the 1,3 relation of substituents on a benzene ring.

metabolites Intermediate and final compounds in metabolism.

meta director A deactivating substituent on an aromatic ring that deactivates the *ortho* and *para* positions and thus favors attack of electrophiles at the *meta* position.

methide shift Movement of a methyl group and its bonding electron pair from one atom to another, usually an adjacent atom.

methine The C—H unit resulting when three of the other bonds are to carbon atoms.

methylene group The —CH,— unit resulting when carbon is bonded to two other atoms.

methyl group The —CH, unit.

micelle An aggregate of molecules or ions assembled so that hydrophobic portions are in the interior and hydrophilic portions are on the surface.

Michael addition The conjugate addition (1,4) of a nucleophile to an α,β-unsaturated carbonyl compound.

microscopic reversibility The principle connecting forward and reverse reactions with common intermediates and transition states. The mechanisms of the forward and reverse reactions are the same.

miscible Term describing liquids that can dissolve in each other in all proportions.

molecular dipole moment A measure of the polarity of a molecule that derives from the vector sum of the bond dipole moments.

molecular formula A representation of a molecule indicating the number and type of each atom present in the molecule.

molecular orbital A region of space about two or more atoms where pairs of electrons are shared.

molecule A combination of atoms in discrete units.

monomer Small molecule that combines with similar small molecules to give a polymer.

monoprotic acid An acid that can transfer only one proton.

monosaccharide A simple carbohydrate that cannot be further hydrolyzed.

multiple bond Bond with more than one pair of electrons shared.

multiplet The number of peaks when an NMR absorption is split.

mutarotation The change in optical rotation due to equilibrium between anomeric forms.

N

NAD^+ (nicotinamide adenine dinucleotide) An oxidized coenzyme used in catabolic reactions.

NADPH (nicotinamide adenine dinucleotide phosphate) A reduced coenzyme used in biosynthesis.

neutral amino acid An amino acid containing only one amino group and one carboxyl group.

Newman projection formula A representation of a molecule looking along the axis between two carbon atoms.

nicotinamide adenine dinucleotide (NAD) A biological reducing agent that is converted to NADH

nitration Replacement of a hydrogen ion of an aromatic molecule by a nitro (—NO_2) group.

nitrile A functional group described by —C≡N.

nitronium ion The intermediate (NO_2^+) involved in aromatic nitration.

N-nitrosoamine A compound with an N—N=0 group formed by reaction of secondary amines with nitrous acid.

nodal plane A planar region of space with zero electron density.

node A region in an orbital with zero electron density.

nonbonding electrons Valence-shell electrons associated with an atom but not involved in bonding.

nonbonding molecular orbital Molecular orbitals that have the same energy as the isolated atomic orbitals.

nonpolar bond Covalent bond in which electrons are shared equally.

nonpolar molecule Molecule in which any polarity of bonds cancels out.

nonspontaneous reaction A reaction requiring continuous addition of energy to occur.

normal hydrocarbon A hydrocarbon molecule without branches.

nuclear magnetic resonance A spectroscopic method that measures the absorption of energy by nuclei in the presence of a magnetic field.

nucleophile An atom or groups of atoms that is an electron pair donor in a chemical reaction.

nucleophilic acyl substitution Substitution reaction at the carbonyl carbon atom replacing a leaving group by a nucleophile.

nucleophilic addition Addition reaction initiated by the attack of a nucleophile at an electrophilic center such as the carbonyl carbon atom.

nucleophilic aromatic substitution Replacement of a negatively charged leaving group such as a halide ion on an aromatic ring by a nucleophile.

nucleophilicity Measure of the reactivity of a nucleophile in a substitution reaction.

nucleophilic substitution The replacement of a leaving group by a nucleophile resulting in a substituted product.

nylon A polyamide made from a diamine and a dicarboxylic acid.

O

octane number A rating scale of the burning efficiency of hydrocarbons.

octet rule Rule stating that atoms tend to have eight outer-shell electrons about them in compounds.

oil A triglyceride containing a high percentage of unsaturated fatty acids.

olefin An older name for an alkene.

open chain sugar Noncyclic form of a monosaccharide.

optical activity The ability of a substance to rotate plane-polarized light.

optical isomers Compounds that are nonsuperimposable minor images of each other.

optical purity The specific rotation expressed as a fraction of the specific rotation of a single enantiomer.

optical rotation The amount and direction of rotation of plane-polarized light caused by a chiral compound.

orbital A region in space about the nucleus of an atom or about atoms of a molecule where no more than two electrons may be found.

orbital overlap The interpenetration of one atomic orbital by another to form a molecular orbital.

organolithium reagent An organic compound with a polar covalent or ionic bond to lithium.

ortho Prefix specifying the 1,2 relationship of substituents on a benzene ring.

***ortho*, *para* director** A substituent on an aromatic ring that activates the *ortho* and *para* positions toward attack by an electrophile.

oxetane A four-membered heterocyclic compound containing one oxygen atom.

oxidation Loss of electrons. Often described as loss of hydrogen or gain of oxygen in an organic molecule.

oxidation number A positive or negative integer assigned to describe an element as a free atom, an ion, or as part of a polyatomic ion or molecule.

oxidation–reduction reaction A reaction in which the oxidation numbers of two or more atoms are changed. Also referred to as redox reaction.

oxidative cleavage The cleavage of a carbon–carbon multiple bond in an oxidation reaction.

oxidizing agent The substance that gains electrons and is reduced in a redox reaction.

oxime A compound with a C=N—OH group formed by reaction of a carbonyl compound with hydroxylamine.

oxonium ion Trivalent oxygen species with a positive charge on the oxygen atom.

oxymercuration An addition reaction of a mercuric salt to an alkene along with a nucleophile derived from either the salt or solvent.

ozonolysis The reaction of ozone with an unsaturated compound such as an alkene or alkyne.

P

P_i A representation of inorganic phosphate ions in biochemical reactions.

paired electrons Two electrons of opposite spin in the same orbital.

para Prefix specifying the 1,4 relationship of substituents on a benzene ring.

pepsin An enzyme that cleaves peptides at the nitrogen end of the aromatic amino acid groups.

peptidase An enzyme that catalyzes the hydrolysis of peptide bonds.

peptide bond The amide bond in a polypeptide or protein.

pericyclic reaction Reactions that occur with the concerted reorganization of bonds via electrons through a cyclic transition state.

period A horizontal row in the periodic table.

periodic table An arrangement of elements, with elements of similar properties grouped together.

peripheral membrane proteins Proteins attached by ionic forces to the surface of a bilayer.

peroxyacid A carboxylic acid with an O—O—H group in place of an O—H group.

perspective formulas Structural formulas written in two dimensions that impart some three-dimensional aspects to the representation.

phenol A compound that has the hydroxyl group bonded to a carbon atom of an aromatic ring.

phenyl Substituent derived by removal of a hydrogen atom from benzene and abbreviated as $C_6 1H_5$—.

phosphoglycerides Molecules consisting of one unit each of glycerol, phosphate, and alcohol and two units of fatty acids.

photochemical reaction Chemical reaction that occurs via an excited state intermediate formed by absorption of light energy.

pi (π) bond A bond formed by the side-by-side overlap of two p orbitals.

pinacol rearrangement The loss of water from a vicinal diol to give a ketone and resulting in migration of a carbon group to an adjacent atom.

pK_a A measure of the acidity of an acid, equal to –log K. plf, A measure of the basicity of a base, equal to –log Kb.

plane of symmetry A plane that bisects a molecule into two mirror images.

plane-polarized light Light consisting of waves vibrating in a single plane.

polar covalent bond A bond formed by sharing electrons between two atoms of unequal electronegativity.

polarimeter An instrument used to measure the optical activity of molecules.

polarizability The ease with which an electron cloud can be distorted by nearby charges.

polarizable electrons Electrons in bonds that can be displaced toward a positive site.

polar molecule Molecule in which the bond polarities do not cancel.

polyamide A polymer of units joined by amide bonds.

polycyclic hydrocarbon Hydrocarbon with at least two carbon atoms shared in common with two or more rings.

polymer Large molecule made up of repeating units called monomers.

polymerization Process forming a polymer from monomers.

polynuclear aromatic compound Two or more fused aromatic rings as in naphthalene.

polypeptides Molecules consisting of α-amino acids linked by peptide (amide) bonds.

polysaccharides Polymers consisting of many monosaccharides linked by glycosidic bonds.

primary alcohol A carbon compound with a hydroxyl group bonded to a primary carbon atom.

primary amine An amine with a single hydrocarbon group in place of one hydrogen atom of ammonia.

primary carbon atom A carbon atom that is directly bonded to only one other carbon atom.

primary structure The linear sequence of amino acids in a polypeptide or protein.

products The substances produced in a chemical reaction.

progesterone A female sex hormone responsible for maintaining pregnancy.

propagation steps Repeating consecutive steps in a free radical reaction.

prostaglandins Biological derivatives of arachidonic acid that occur in low concentrations in body tissue and have a wide range of physiological activities.

protecting group A temporarily formed group that transforms a functional group into a less reactive functional group so that reactions can transform other unprotected functional groups.

protein A polymer of amino acids joined by peptide bonds.

protic solvent A solvent with easily exchangeable protons.

pyran A six-membered ring containing one oxygen atom and two carbon–carbon double bonds.

pyranose Cyclic form of a sugar containing six atoms in the ring.

pyridinium chlorochromate (PCC) An oxidizing agent that is made from CrO_3, pyridine, and HCl.

pyrimidine bases Cytosine, thymine, and uracil, components of nucleic acids.

Q

quaternary ammonium ion An ammonium ion having four hydrocarbon groups bonded to nitrogen and bearing a positive charge.

quaternary carbon atom Carbon bonded to four other carbon atoms.

quaternary structure The manner in which protein subunits (chains) are assembled to give the whole protein.

R

racemic mixture An equimolar mixture of enantiomers.

racemization A process in which a chiral substance is converted into a racemic mixture of products.

radical A species with an unpaired electron.

Raney nickel A finely divided form of nickel used as a hydrogenation catalyst.

rate-determining step The slowest step in a sequence of reactions. This step has the highest activation energy.

rate equation A mathematical relationship giving the order of the reactants in a rate law.

reactants The substances that enter into a chemical reaction.

reaction coordinate diagram A plot of potential energy on the vertical axis that corresponds to the energy associated with molecular changes that occur in a chemical reaction.

reaction mechanism Description of the sequence of steps of bond formation and cleavage in a chemical reaction.

reagent A compound or mixture of compounds used to carry out a chemical reaction.

rearrangement reaction Intramolecular migration of an atom or group of atoms from one site to another.

reducing agent A substance that loses electrons and is oxidized in a redox reaction.

reducing sugar A carbohydrate that causes the reduction of Benedict's solution (or Tollens's reagent).

reductase An enzyme that catalyzes a reduction reaction, usually with NAD or NADP as a coenzyme.

reduction The gain of electrons by a substance.

reductive amination Synthesis of an amine by reduction of an imine formed by reaction of a carbonyl compound with an amine.

Reformatskii reaction Reaction of an aldehyde or ketone with an α-halo ester using zinc.

regioselective reaction A reaction that gives predominately one of several possible compounds with a specific orientation of substituted or added groups.

regiospecific reaction A reaction that gives a single compound with a specific orientation of substituted or added groups.

resolution The separation of a racemic mixture into its enantiomeric constituents.

resonance energy The calculated stabilization energy resulting from the delocalization of electrons relative to a reference localized structure.

resonance structure Two or more plausible Lewis structures used when no single structure can accurately represent the molecule.

retention of configuration Formation of a product with the same configuration as the reactant.

retrosynthetic analysis A reverse thought process starting from products and going to reactants to develop a synthesis.

reversible reaction Reaction that proceeds in both forward and reverse directions.

ribose A pentose present in ribonucleic acids.

ring strain The strain associated with a ring compound that is composed of both angle strain and torsional strain.

Rosenmund reduction The reduction of an acid halide to an aldehyde using a deactivated transition metal catalyst.

S

Sandmeyer reaction Substitution of a diazonium ion of an aryl compound by a nucleophile by means of a copper(I) salt.

saponification The hydrolysis of a carboxylate ester by a strong base.

saturated fat Fat consisting of saturated fatty acids.

saturated hydrocarbon A hydrocarbon that has only carbon–carbon single bonds.

Saytzeff elimination An elimination reaction that gives the more highly substituted alkene.

s character The fraction or percent that the s orbital contributes to a hybridized orbital.

s-*cis* conformation A conformation about a single bond in a conjugated system that resembles the *cis* orientation of geometric isomers.

secondary alcohol A hydrocarbon compound with a hydroxyl group bonded to a secondary carbon atom.

secondary amine An amine with two hydrocarbon groups in place of two hydrogen atoms of ammonia.

secondary carbon atom A carbon atom bonded to two other carbon atoms.

secondary structure The spatial arrangement of amino acid residues in regularly repeating conformations in α-helices and β-pleated sheets in polypeptide chains.

semicarbazone A compound formed by the addition—elimination reaction of a carbonyl compound and semicarbazide.

sequence rule Procedures to rank substituents in the Cahn–lngold–Prelog nomenclature system.

sex hormones Steroids produced predominantly by the gonads (ovaries in females and testes in males).

shell A description of the electrons in a space about the nucleus. The shells are designated by integers.

shielded The result that atoms have on a nucleus causing the absorption to occur at a higher field.

side chain A group of atoms appended to a main chain as in hydrocarbons or peptides.

sigma (σ) bond A cylindrically symmetrical bond with its electron density oriented along the internuclear axis.

sigmatropic rearrangement Migration of a bond from one end of a conjugated system to the other end.

Simmons–Smith reaction The formation of a cyclopropane compound from an alkene using a carbenoid species containing zinc.

simple lipids Lipids that cannot be hydrolyzed by a base.

single bond A covalent bond with a pair of electrons between atoms.

skew conformation Any conformation that does not have groups at either 0° or 60° dihedral angles.

soap Salt of long-chain carboxylic acids.

space-filling models Models representing relative volumes of atoms in a molecule.

specificity The selectivity of enzymes for the individual substrates and reactions that they catalyze.

specific rotation A standard method of compiling the optical activity of chiral substance.

sphingophospholipids Lipids that consist of one unit each of sphingosine, an amide of a fatty acid, phosphate, and choline.

sp hybrid orbital One of two orbitals produced by mixing one s and one p orbital.

sp^2 hybrid orbital One of three orbitals produced by mixing one s and two p orbitals.

sp^3 hybrid orbital One of four orbitals produced by mixing one s and three p orbitals.

spin decoupling An experimental technique removing the effect of spin–spin splitting on the NMR spectrum.

spin–spin splitting The interaction of the spins of two or more nuclei usually connected by a small number of bonds.

spirocyclic compound A bicyclic compound that shares only one common atom between two rings.

spontaneous reaction Reaction that occurs without an outside source of energy.

staggered conformation Any conformation with 60° dihedral angles.

starch A polymer of glucose containing a linkages between glucose units.

stereochemistry The description of the three-dimensional arrangement of atoms in molecules.

stereogenic center An atom with four nonequivalent atoms or groups of atoms bonded to it.

stereoisomers Isomers with the same structure but different configurations.

stereoselective reaction A reaction in which stereoisomeric reactants give a predominance of stereoisomeric products.

stereospecific reaction A reaction in which stereoisomeric reactants give stereoisomeric products.

steric hindrance Interactions that result when two groups are close enough so that their electrons repel each other as given by the van der Waals radius.

steric strain Van der Waals strain.

steroids Lipids containing a characteristic system of four fused rings of carbon atoms.

straight chain A sequence of carbon atoms bonded to each other without side chains or heteroatoms.

s-*trans* conformation A conformation about a single bond in a conjugated system that resembles the *trans* orientation of geometric isomers.

structural formula Formula representing the spatial arrangement of atoms and bonds using lines to represent bonds.

structural isomers Isomers that differ in the bonding sequence of their atoms, also called constitutional isomers.

structure The arrangement of the components of a substance.

subshell A part of a shell characterized by a shape according to type. The subshells are labeled s, p, d, and f

substituent An atom or group of atoms attached to a skeleton of carbon atoms.

substitution reaction Reaction in which one atom or group of atoms replaces another atom or group of atoms in a molecule.

substrate A reactant in an enzyme-catalyzed reaction.

sucrose A disaccaride containing glucose and fructose.

sulfa drug Antibacterial drug derived from sulfanilamide.

sulfhydryl group A group represented by —SH.

sulfide Compound with C—S—C structural unit.

sulfonation Replacement of a hydrogen atom of an aromatic ring by a sulfonic acid group (—SO_3H)

superimposition The simultaneous blending of all atoms in a model with atoms in another model to show identity.

symmetry-allowed Concerted reactions that can occur because the process involves the appropriate overlap of orbitals of like sign.

symmetry-forbidden Reactions that cannot occur by a concerted process because the symmetry of the interacting orbitals would lead to destructive interference.

syn The addition or elimination of groups on the same face of a molecule.

***syn* coplanar (syn periplanar)** Groups having 0° dihedral angle.

systematic name IUPAC name containing information about the composition of a substance.

T

tautomerism Isomerism of keto and enol forms by migration of a hydrogen atom from the α-carbon atom to the carbonyl oxygen atom.

tautomers Isomers that differ by the shift of a hydrogen atom from one site to another.

temporary dipole A separation of charge produced momentarily in an otherwise nonpolar substance

terminal alkyne Alkyne of the type R—C≡C—H. termination The conclusion of synthesis of the protein chain.

terpene A class of compounds that can be dissected into units derived from isoprene.

tertiary alcohol A hydrocarbon compound with a hydroxyl group bonded to a tertiary carbon atom.

tertiary amine An amine with hydrocarbon groups in place of all three hydrogen atoms of ammonia.

tertiary carbon atom A carbon atom bonded to three other carbon atoms.

tertiary structure The three-dimensional conformation of a polypeptide chain.

testosterone A male sex hormone.

tetrahedral intermediate Intermediate formed by nucleophilic addition to a carbonyl carbon atom.

tetrahedral molecule A molecule that has an atom located in the center of a tetrahedron and four atoms bonded to the central atom located at the corners of the tetrahedron.

thermodynamic control Reactions that give product distributions controlled by their relative stabilities which are the result of an equilibrium process.

thermodynamics The science of the energy changes accompanying physical and chemical changes.

thioesters Esters of thiols and carboxylic acids containing a carbonyl carbon–sulfur single bond.

thiol A compound containing a sulfhydryl group (—S—H) bonded to a carbon atom.

tissue lipids Lipid materials in cell membranes (in contrast to triacylglycerols, see below).

Tollens's reagent An alkaline solution of [Ag(NH3),]+ that is used as a test for aldehydes.

torsional energy The energy associated with bonding electrons of two groups on adjacent atoms.

tosylate ester An ester of toluenesulfonic acid and an alcohol, also known as a tosylate.

trans On the opposite sides of either a ring or double bond.

transamination An interconversion process between keto compounds and amino compounds.

***trans* diaxial** An *anti* coplanar arrangement of atoms at adjacent carbon atoms—usually in cyclohexane compounds.

transesterification Substitution of one alkoxyl group of an ester by another under either acid- or base-catalyzed conditions.

***trans* isomer** An isomer that has two groups of atoms oriented on opposite sides of a structural feature such as a cycloalkane ring.

transition state The state of highest energy between reactants and products shown as a maximum on a reaction coordinate diagram.

transmembrane proteins Proteins that extend across the membrane.

triacylglycerols A newer name for triglycerides.

tricarboxylic acid (TCA) cycle The citric acid cycle.

triglycerides Esters of glycerol and fatty acids.

trigonal planar molecule A molecule with three atoms arranged around a central atom, with all atoms in a common plane and all bond angles at 120°.

trigonal pyramidal molecule A molecule with the central atom bonded to three other atoms so that a three-sided pyramid is formed. The three atoms bonded to the central atom are in a common plane.

triple bond A bond formed by the sharing of three pairs of electrons between two atoms.

t**riprotic acid** An acid that can transfer three protons, e.g., H_3PO_4.

U

ultraviolet Region of the electromagnetic spectrum with wavelengths of 200–400 nm.

unsaturated hydrocarbon A hydrocarbon that has double, triple bonds or both.

unshared electron pair (lone pair) A pair of valence-shell electrons associated with an atom but not involved in bonding.

urethane An ester of a carbamic acid.

V

valence The number of bonds normally formed by an atom in a neutral molecule.

valence-shell electron-pair repulsion (VSEPR) theory A theory relating the shape of molecules to the distribution of electron pairs about a central atom.

valence-shell electrons Electrons of the s and p subshells in the highest occupied energy level.

van der Waals radius A measure of the size of an atom or group of atoms in a molecule.

van der Waals strain Steric strain resulting from close approach of two atoms or groups of atoms bonded at two sites in a molecule.

vicinal Location of two substituents on adjacent carbon atoms.

vicinal dihalide A dihalide with halogen atoms on adjacent carbon atoms.

vinyl group The $CH_2{=}CH{—}$ group, also known as the ethenyl group.

vinyl halide A halogen-containing compound with halogen bonded to the sp^2-hybridized carbon atom.

W

wave function A mathematical description of an orbital. The square of the wave function gives the electron density.

wavelength The distance between corresponding points on a wave.

wavenumber The number of wavelengths per unit of distance, e.g., cm^{-1} in infrared spectroscopy.

wax An ester of a fatty acid and a long-chain alcohol.

Williamson ether synthesis The reaction of an alkoxide ion and a primary alkyl halide or alkyl tosylate.

Wittig reaction Formation of an alkene by reaction of a carbonyl compound with a phosphorus ylide.

Wolff–Kishner reduction Deoxygenation of an aldehyde or ketone converting a carbonyl group to a methylene group using hydrazine and a strong base.

Woodward–Fieser rules A set of rules giving additive structural components that predict the λ_{max} of the ultraviolet absorption of an unsaturated compound.

Woodward–Hoffmann rules A set of rules that determine whether a reaction is symmetry-allowed or symmetry-forbidden.

Z

zwitterion An electrically neutral, dipolar ion resulting from transfer of a proton from an acidic to a basic site in a molecule.

zymogen An inactive storage form of an enzyme.

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A Brief Overview of Thermodynamics

Die Energie der Welt ist konstant,
Die Entropie der Welt strebt ein Maximum zu.[1]
Clausius

Clausius's couplet summarizes the vast range of experience that is canonized in thermodynamics, a subject that lies at the heart of chemistry, biochemistry, and indeed to all of nature. The power of thermodynamics lies in its ability to provide a quantitative measure of the energy changes that occur in physical, chemical, and biological processes. Chemical reactions of metabolism, the transport of material across cell membranes, the assembly of membranes, and the assembly of other types of macromolecular complexes all obey these laws. Nothing overrides the laws of thermodynamics: they are the decrees of fate.

Since an energy change accompanies virtually every process, the importance of thermodynamics in cannot easily be exaggerated. Thermodynamics provides us with a way to determine how much energy is released or absorbed in a process. It also leads us from the concentrations of reactants and products in a chemical reaction or to the equilibrium constant for the reaction. And, from the equilibrium constant, we can determine the magnitude of the "force" that "drives" a process to equilibrium. Thermodynamics also reveals how this force (the free energy) is partitioned between a potential energy change—the enthalpy—and a change in the molecular order—the entropy—of the system.

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1 FIRST LAW OF THERMODYNAMICS

Thermodynamic Systems and Surroundings

The universe is bigger than our laboratories, and it is convenient to divide the world into **thermodynamic systems** and their surroundings. A thermodynamic system is that part of the universe in which we are studying a process. It can be almost anything you like, a reaction vessel in which a chemical reaction occurs, a cell, or a star. Everything else constitutes its surroundings. If matter cannot cross the boundaries between the system and its surroundings, the system is closed. A chemical reaction is one example of a process that can be carried out in a *closed* system. If, however, matter can be exchanged between the system and the surroundings, in many chemical reactions, and in all living systems, the system is *open*. If neither matter nor energy can be exchanged with the system, it is *isolated*.

Once we have defined the thermodynamic system, we must specify its **state**. In a chemical reaction, for example, we need to specify whether the reactants and products are solids, liquids, or gases. The state of the system depends upon the thermodynamic variables, called **state functions**. These include the temperature, pressure, and the number of moles of each component in the system. When we analyze a system from a thermodynamic perspective, are only interested in changes in thermodynamic variables. *A change in state of a system, and thus the change in all of the thermodynamic variables, depends only upon the difference between the initial and final states and is independent of the pathway by which the process is carried out.*

1. The energy of the universe is constant,
The entropy of the world increases to a maximum.

Temperature and the Zeroth Law of Thermodynamics

We commonly use the word "temperature" intuitively to describe whether an object is "hot" or "cool." This outlook can be defined more systematically by considering temperature in "thermodynamic" terms. Everyday experience teaches us that when we bring a hot object into contact with a cool one, the hotter object cools and the cooler object warms until a point is reached after which no more change occurs. At this point, the two objects are in thermal equilibrium. We say that the two objects—which are thermodynamic systems—have the same temperature when they are in thermal equilibrium. Now, we'll add a third object and allow all three objects to come into thermal equilibrium. When two objects are each in thermal equilibrium with a third object, they are in thermal equilibrium with each other, and they all have the same temperature. The preceding sentence is called the zeroth law of thermodynamics. If one of the three objects is an instrument calibrated to measure the temperature, that is, a thermometer, then we can measure the temperature quantitatively.

We started by saying that heat flows from a warm object to a cool one. We can now define "heat" in terms of temperature: The temperature of an object is the condition that determines whether heat spontaneously flows to it or away from it. Heat flows spontaneously from a body of higher temperature to a body of lower temperature.

The First Law of Thermodynamics

The **first law of thermodynamics** states that the total energy of the universe is conserved in every process. This is a remarkable statement and it is true whether we look across the entire know universe or at a single chemical reaction. We'll only consider chemical reactions. Thus, we will divide the universe into a thermodynamic system—the vessel in which a chemical reaction occurs—and its surroundings, which means everything else. Now we can rephrase the first law of thermodynamics slightly and say that the total energy of the system—the reaction vessel—and its surroundings—everything else—is a constant.

We can apply this statement to a chemical reaction.

$$\text{energy} + a\text{A} + b\text{B} \rightleftharpoons c\text{C} + d\text{D} \qquad (1)$$

The energy absorbed in reaction (1) in the forward reaction is exactly equal to the energy released in the reverse reaction. Energy is conserved in the process. The total energy change in reaction (1) is

$$\Delta U = Q - W \qquad (2)$$

where ΔU is the change in the internal energy for the process, Q is the heat absorbed by the reaction, and W is the work done by the system. When the system is a chemical reaction, as here, the change in internal energy ultimately depends on the change in the chemical bonds in the reactants and products so that energy in the form of heat either flows into or out of the system and the amount of work done by the system.

We don't often think of a chemical reaction doing work, but when you drive your car, the change in energy that results from burning gasoline does work by moving the engine's pistons and ultimately moving the car. If we burn the same amount of gasoline in a flask—not a clever idea—and the resulting gases (mostly carbon dioxide and water vapor) escape into the atmosphere, then the system doesn't do any work because the chemical reaction is not linked or coupled to another process. (In an automobile engine, the gases produced by combustion leave the engine through the exhaust, but they do mechanical work first.) If a chemical reaction generates electricity, as in a battery, then the energy stored in the battery can be used to drive an electronic device or an electrical car.

We said earlier that the energy change for a process depends only on the initial and final states of the system. Thus, the change in internal energy, ΔU, for reaction 1 (or any other reaction for that matter) is the same for the conversion of A and B to C and D whether the process requires many steps with many intermediates, or whether it occurs in a single step. We also picked two examples above in which a chemical reaction converts energy in one form—the energy stored in chemical bonds—to energy in another form, such as the electricity produce in a battery. In essence, the first law of thermodynamics tells us that different forms of energy—chemical, electrical, mechanical, and so forth—can be interconverted. Whenever energy is "lost" in one form, it reappears in exactly the same amount in another form.

There is another aspect of the formulation of the first law of thermodynamics expressed in Equation (2) that is almost completely counterintuitive. The term on the left-hand side , ΔU, the change in internal energy of the system, depends only on the difference between the initial and final conditions. However, the amount of heat, Q, released or absorbed by the reaction and the amount of work done by the system depends upon the way the process is carried out. It is the difference between Q and W that depends only on the initial and final conditions. A detailed analysis of this important but rather obscure result is beyond the scope of our introductory discussion.

Enthalpy Changes Under Standard Conditions

Many chemical processes, and almost all biochemical ones, occur at constant pressure. The work done by a system at constant pressure equals the product of the pressure and the change in volume that occurs during the process:

$$W = P\Delta V \qquad (3)$$

Substituting the term $P\Delta V$ in Equation (3) in for W in Equation (2) and rearranging we obtain

$$\Delta U = Q_p - P\Delta V \qquad (4)$$

Note that we have changed "Q" to "Q_p" to denote that the change in question takes place at constant pressure. Thus, Q_p is the heat released or absorbed in the process at constant pressure. Since U, P, and V are state functions, Q_p is also a state function. *The heat released or absorbed in the constant pressure process is called the* **enthalpy change** *for the reaction*. Thus, Equation (4) can be rewritten as

$$\Delta H = \Delta U + P\Delta V \qquad (5)$$

where ΔH is the symbol for the enthalpy change.

Heat is measured in either calories or joules. We will use joules (J) as the unit of heat in this text. 4.184 J is the amount of heat required to raise the temperature of 1 g of water from 14.5 to 15.5 °C at a pressure of 1 atmosphere atm. One kilojoule (kJ) is equal to 1000 J. The following conventions are used for enthalpy changes. In some fields, calories are used instead of joules (J); 1 cal = 4.184 J.

We often want to know whether heat is released by a chemical reaction so that the flask heats up; or whether heat is absorbed by a reaction, in which case the flask cools down. The following conventions are used for these possibilities.

$\Delta H < 0$ A reaction is **exothermic** when heat is evolved by the system and enters the surroundings.

$\Delta H > 0$ A reaction is **endothermic** when heat is absorbed by the system.

The enthalpy change for a chemical reaction depends upon the number of moles undergoing chemical change, and ΔH is expressed in terms of kJ/mol. To compare reactions under the same conditions, the following conventions are used. Since we are only interested in the difference in enthalpy between the initial state, the reactants, and the final state, the products, we need a reference point. We call this reference point the **standard state**.

1. The standard state of any element or compound is its most stable form at 298 K and 1 atm. pressure.
2. The standard state for a compound dissolved in a solution solute standard state is 1.0 molar (M).
3. The standard enthalpy of formation of any element in its standard state is 0 kJ/mol. The symbol for the stand enthalpy of formation is ΔH°_f.
4. The standard enthalpy of formation of a 1.0 M solution of hydronium ions is 0 kJ/mol.
5. The standard enthalpy of formation of a compound is the enthalpy change when 1 mole of the compound is formed in its standard state from its elements in their standard states.

The standards heats of formation of thousands of compounds have been determined, so in many cases it is possible to obtain very good information about enthalpy changes for common chemical reactions.

The magnitude of the standard enthalpy of formation tells us nothing about the path or reaction mechanism by which the compound is formed. It depends only on the difference in enthalpy between the final state (the products) and the initial state (the reactants, which in this case are elements). This path independence is true for the enthalpy change of every chemical reaction. Let's consider the following general reaction:

$$a\text{A} + b\text{B} \rightleftharpoons c\text{C} + d\text{D} \qquad (6)$$

To determine the standard enthalpy change for a reaction, we add the standard enthalpies of formation for all the products; then we subtract the sum of the standard enthalpies of the reactants. The standard enthalpy change for reaction (6) is therefore given by the following equation:

$$\Delta H^\circ_{\text{reaction}} = \sum \Delta H^\circ_f(\text{products}) - \sum \Delta H^\circ_f(\text{reactants}) \qquad (7)$$

That is, for reaction (6) we have to include the number of moles of each reactant and product in the balanced equation, and if the reaction takes place in solution, the molar concentration of each reactant and product must be included as shown in Equation (8):

$$\Delta H^\circ_{\text{reaction}} = \{c\Delta H^\circ_f(c)[\text{C}] + d\Delta H^\circ_f(d)[\text{D}]\} - \{a\Delta H^\circ_f(a)[\text{A}] + b\Delta H^\circ_f(b)[\text{B}]\} \quad (8)$$

We have to remember that the standard enthalpy of formation for each component of the reaction mixture refers to one mole. That is why we have to include not only the stoichiometric coefficients but also the concentrations of all reactants and products.

Heats of Combustion

The heat of combustion of any substance can be determined from its standard enthalpy of formation and from the standard enthalpies of formation of the oxidation products, such as carbon dioxide and water. Let us consider the oxidation of glucose (reaction 9). Glucose has a rather complicated structure, but for the moment we'll just use its empirical formula:

$$C_6H_{12}O_6 + 6CO_2 \text{ -> } 6CO_2(g) + 6H_2O(g) \qquad (9)$$

The standard enthalpy change for this reaction is identical to the heat of combustion, as shown in Equation (10). Note that the physical state of each reactant is indicated. The heat of combustion depends upon the physical states of all reactants and products. Since the reaction is combustion, we replace add the subscript "f" with "c" for the standard enthalpy change:

$$\Delta H^\circ_c(\text{glucose}) = \{6\Delta H^\circ_f((CO_2(g)) + 6\Delta H^\circ_f(\text{water(g)}\} - \{\Delta H^\circ_f(\text{glucose})\} \quad (10)$$

When we look up the data for the reactants and products in Equation (10), we find that the heat of combustion is –2552 kJ/mol (Equation 11):

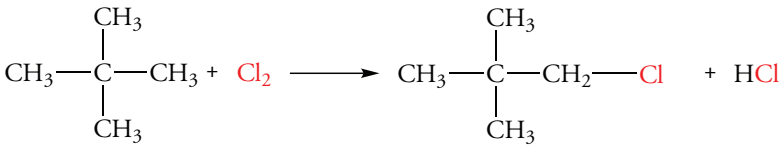
$$\Delta H^\circ_c(\text{glucose}) = [6(-394.1)\text{ kJ/mol} + 6(-241.8)\text{ kJ/mol}] - (-1267)\text{ kJ/mol} \quad (11)$$

$$\Delta H^\circ_c(\text{glucose}) = -2552\text{ kJ/mol}$$

Since the enthalpy of combustion is independent of the path by which the process is carried out, converting one mole of glucose to carbon dioxide and water by aerobic metabolism releases the same amount of heat as burning the glucose in a laboratory experiment. That's why food companies and nutritionists can provide the number of calories in a given serving of their products.

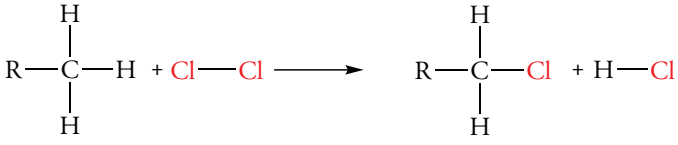
2 ESTIMATING ΔH°_{rxn} FROM BOND ENERGIES

We can obtain an approximate value for the standard enthalpy change for a chemical reaction, ΔH°_{rxn}, by considering the energy of the bonds that are cleaved or formed in the process. The exact bond energies are not known for complex molecules, but average bond energies can be estimated based on simple, strucurally analogous compounds. Consider the substitution reaction of 2.2-dimethylpropane with chlorine.



2,2-dimethylpropane 1-chloro-2,2-dimethylpropane

In this reaction, a C—H bond is broken in a part of a molecule that resembles CH_4. Therefore, we approximate the $\Delta H°$ for the C—H bond in the compound by using the bond dissociation energy $\Delta H°$ for CH_3—H. Similarly, the C—Cl bond formed in the product resembles the C—Cl bond in CH_3—Cl, so we use the listed bond dissociation energy for CH_3—Cl. These approximations are summarized in the following equation, where the remainder of the molecule—the central carbon atom and its three attached CH_3 groups—is represented by R:



The net enthalpy change for a process that can be divided into two or more steps equals the sum of the enthalpy changes for the individual steps. This is **Hess's law**. The enthalpy changes for the individual bonds that are broken or formed are added as shown below.

Process	*$\Delta H°$ (kJ mole^{-1})*
Break C—H bond	428
Break Cl—Cl Bond	242
Make C—Cl bond	–349
Make H—Cl bond	–431
$\Delta H°_{rxn} = -100$	–100

Even though average bond dissociation energies are used in the calculation, the reaction is clearly predicted to be exothermic. The enthalpy change for the reaction is negative because the C—Cl and H—Cl bonds that form are collectively stronger than the C—H and C—Cl bonds that are broken. In general, reactions are favored enthalpically when the bonds made are stronger than the bonds broken. The actual enthalpy change for a reaction may be somewhat different from the value calculated because bond energies depend on structure. Thus, the C—H bond energy of ethane is 422 kJ mole^{-1} compared to 438 kJ mole^{-1} for methane.

3 SECOND LAW OF THERMODYNAMICS

The **second law of thermodynamics** states that the entropy of the universe is increasing. The elusive concept of entropy is related to the order, or structure, of the system, and even more precisely it is related to our knowledge about the system. So, in the end we can relate entropy to information. We'll begin, however, with a less sophisticated, if also less precise point of view. In a physical, chemical, or biochemical change, if the final state is more ordered than the initial state, the entropy change is negative. On the other hand, if the final state is less ordered than the initial state, the change in state occurs with a positive entropy change. Although every process occurs with a positive entropy change when we consider both the system and the surroundings, a negative entropy change in a system is possible if it is offset by a larger positive entropy change in the environment. Stating this slightly differently, processes with negative entropy changes are permitted since it is the entropy of the universe, including both the thermodynamic system and the surroundings, that must increase for any process (Equation 12):

$$\Delta S(\text{process}) = \Delta S(\text{system}) + \Delta S(\text{surroundings}) > 0 \qquad (12)$$

Therefore, ΔS(process) can be negative if ΔS(surroundings) is positive and if

$$|\Delta S(\text{surrounding}| > |\Delta S(\text{system})|.$$

In a system such as the flask in which a chemical reaction occurs, the order in the system may increase provided that disorder increases in the environment. For example, a living cell maintains its low entropy, highly structured state at the expense of increasing the entropy of the environment.

Like enthalpy changes, the change in entropy for a change in state is independent of the path by which the process occurs and depends only on the initial and final states of the system. For the reaction

$$a\mathrm{A} + b\mathrm{B} \rightleftharpoons c\mathrm{C} + d\mathrm{D}$$

$$\Delta S^\circ(\text{reaction}) = \sum \Delta S_f^\circ(\text{products}) - \sum \Delta S_f^\circ(\text{reactants}) \quad (14)$$

When we substitute the stand entropies of formation for all the reactants and products, using the same rules we described for enthalpy changes, we obtain the following (Equation 15):

$$\Delta S^\circ(\text{reaction}) = \{c\Delta S_f^\circ(c)[\mathrm{C}] + d\Delta S_f^\circ(d)[\mathrm{D}]\} - \{a\Delta S_f^\circ(a)[\mathrm{A}] + b\Delta S_f^\circ(b)[\mathrm{B}]\} \quad (15)$$

Entropy, Probability, and Information

"What never?" "No, never." "What never?" "Well, hardly ever!"
W.S. Gilbert and A.S. Sullivan, H.M.S. Pinafore

We said earlier that the entropy change for a process is related to our knowledge about the system before and after the process has taken place. That is, the entropy change is related to our information about the state of the before and after it has occurred. Let us now examine the relationship between entropy and probability. Consider a deck of 52 playing cards. The probability of drawing a spade is 1/4, and the probability of drawing an ace is 1/13. The probability of drawing an ace of spades is ($1/4 \times 1/13 = 1/52$).

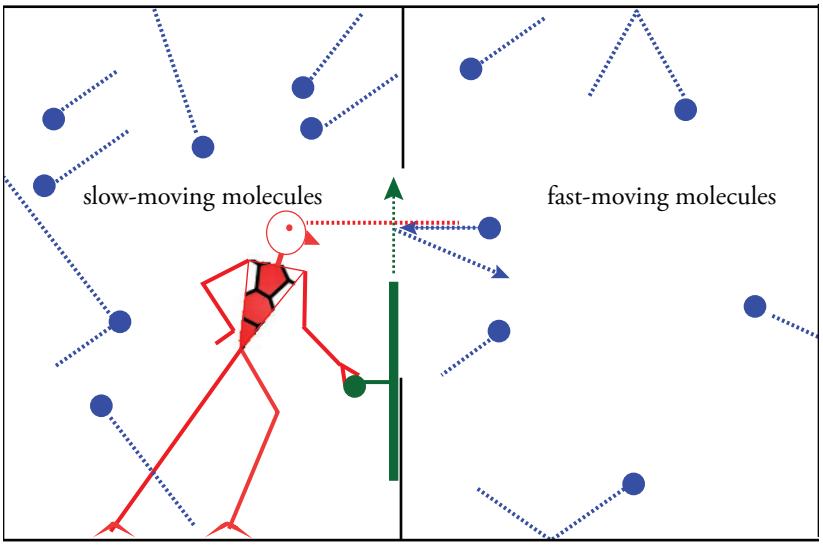
Probabilities are multiplicative. Additive entropies and multiplicative probabilities are related by a logarithmic function (Equation 16):

$$S = k \ln W \quad (16)$$

In equation (16), S is the entropy, k is the Boltzmann constant (13.8×10^{-24} J K^{-1}, or the ideal gas constant per molecule), and W is the probability that an event will occur. Since entropy in this formulation is a purely statistical law, it can be applied only to large numbers of particles or events.

James Clerk Maxwell (1831–1879), whose monumental achievement in physics was the unification of electricity and magnetism, invented, in a letter to Boltzmann, one of the most significant fantasies in the history of science. Suppose that we appoint a microscopic being, named Maxwell's demon, to guard a gate between two flasks containing equal numbers of molecules at the same temperature (Figure 1). By letting only fast molecules pass through the gate, the demon (who deserves his appellation) can cause one flask to heat up and the other one to cool down with no expenditure of energy. The entropy of the system would thus decrease (in a spontaneous change to a less probable state) in violation of the second law of thermodynamics. In Equation (16), S is the entropy, k is the Boltzmann constant (13.8×10^{-24} J K^{-1}, or the ideal gas constant per molecule), and W is the probability that an event will occur. Since entropy in this formulation is a purely statistical law, it can be applied only to large numbers of particles or events.

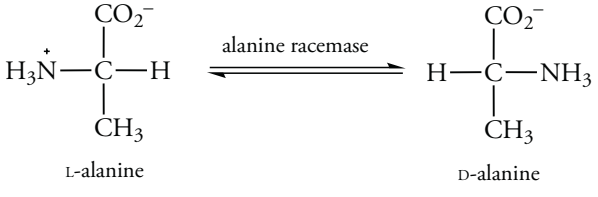
Figure 1 Maxwell's Demon
Maxwell's demon is able to separate fast and slow moving molecules, but not without expending energy in the form of information.



Over 50 years elapsed before the demon was deprived of his paradoxical and magical powers. In 1929, Leo Szilard pointed out that the demon must be endowed with memory to separate "hot" and "cold" molecules, an idea that was altered slightly by L. Brouillon, who showed that Maxwell's demon must possess information to carry out his duties. The demon has two choices: he must either open or close the gate as a molecule approaches. The decision to open or close the gate requires energy equal to $-k \ln 2$. This fundamental quantity is called a bit (from binary digit). The loss of energy that accompanies making each decision exactly balances the gain to be had in separating hot and cold molecules.

Maxwell's demon was vanquished because of an explicit connection between information and entropy. Let us return to our deck of playing cards. When the cards are arranged by suit in ascending order from deuce through ace, the entropy of the system is defined as zero. The second law of thermodynamics says that shuffling the cards will abolish this order and eventually produce a random distribution of cards corresponding to the state of maximum entropy. Conversely, information is required to restore order to the chaos of the randomly shuffled deck. The information required to restore order is equal in magnitude and opposite in sign to the increase in entropy produced by shuffling the deck originally.

Let us consider a reaction that is driven by an entropy change in which the statistical concept of entropy comes directly into play. The bacterium *Pseudomonas putida* produces an enzyme called alanine racemase, that interconverts L- and D-alanine. From either pure enantiomer the enzyme produces a racemic mixture, that is, a mixture containing equal amounts of the D- and L-stereoisomers, as shown below.



L-alanine D-alanine

The enthalpy change for racemization is zero and the equilibrium constant is 1.0, confirming the notion that the isomers have the same thermodynamic stability. Since the enthalpy change for the reaction is zero, it must be driven by an entropy change. What is the origin of this entropy change? If the reaction begins with either pure isomer, converting the starting material into equal amounts of D- and L-alanine produces a more random state than the reactants. The probability that a Maxwell demon can pick out an L-alanine decreases from 1.0 to 0.5; the final state is therefore more disordered than the initial state consisting of pure enantiomer. The entropy change for the reaction is given by Equation (18):

$$\Delta S(\text{racemization}) = S(\text{products}) - S(\text{reactants}) \qquad (18)$$

We recall from Equation (16) that the entropy of a state can be expressed as $S = k \ln W$. For the products, a racemic mixture, $W = 2$ because there are two possible microscopic states: D-alanine

and L-alanine. For the reactant, $W = 1$ because there is only a single microscopic state consisting of a pure enantiomer. The Boltzmann constant can be converted to the gas constant R by multiplying it by Avogadro's number, $R = k_b N$. Therefore, the entropy change for racemization of 1 mole of D-alanine at room temperature (298 K) is given by Equation (19):

$$\Delta S(\text{racemization}) = R \ln 2 - R \ln 1 = 5.76 \text{ J K}^{-1} \text{ mol}^{-1} \qquad (19)$$

3 ENTROPY CHANGES IN CHEMICAL REACTIONS

We have seen that the concept of entropy is related to the order, or structure of the system. The standard entropy at 25 °C ($S°$) is determined relative to the entropy of the substance at absolute zero in its perfect crystalline state, where the entropy of the elements is defined as zero. The units of entropy of a substance are J mole^{-1} deg^{-1}.

In a physical or chemical change, the entropy change $\Delta S°$ is positive if the final state is less ordered than the initial state. Conversely, the entropy change is negative if the final state is more ordered than the initial state. Like the change in enthalpy, the change in entropy is independent of the path by which the process occurs, and depends only on the initial and final states of the system. Thus, the standard entropy change for a general equilibrium reaction may be written in the following general equation:

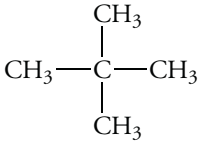
$$m\,A + n\,B \rightleftharpoons p\,X + q\,Y$$

$$\Delta S°_{rxn} = [pS°(X) + qS°(Y)] - [mS°(A) + nS°(B)]$$

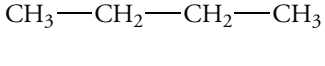
Entropies of Compounds

Several general trends for the entropy of various substances are useful in discussing chemical reactions:

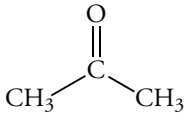
1. The entropy of a substance is lower in the solid state than in the liquid state, and much lower in the liquid state than in the gaseous state.
2. The entropy of a more symmetrical molecule is lower than the entropy of a less symmetrical molecule. For example, the entropy of 2,2-dimethylpropane, which has a spherical shape, is less than that of pentane, which has a cylindrical shape.
3. The entropy of a molecule in which free rotation around σ bonds is possible is larger than that of a molecule in which such rotation is restricted. For example, the entropy of acetone is larger than that of the isomeric molecule oxetane (trimethylene oxide). In acetone, the methyl group may rotate freely about the σ bond to the carbonyl carbon atom. In oxetane, the ring restricts both the movement of the ring atoms and the position of the hydrogen atoms.



2,2-dimethylpropane
$S° = 294$ J mole^{-1} deg^{-1}
highly symmetric



pentane
$S° = 338$ J mole^{-1} deg^{-1}
less symmetric



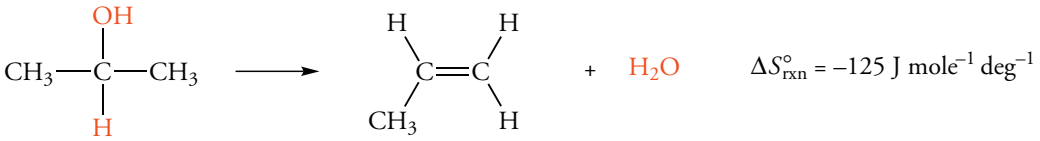
acetone
$S° = 295$ J mole^{-1} deg^{-1}
rotation around σ bonds



oxetane
$S° = 274$ J mole^{-1} deg^{-1}
no rotation around σ bonds

Stoichiometry and $\Delta S°_{rxn}$

Although the individual $S°$ values of the reactants and products contribute to the overall value of $\Delta S°_{rxn}$ for a reaction, the largest entropy changes are observed for chemical reactions in which the number of moles of product and reactant is different. For example, the number of moles of product is greater than the number of moles of reactant in an elimination reaction such as the dehydration of an alcohol.

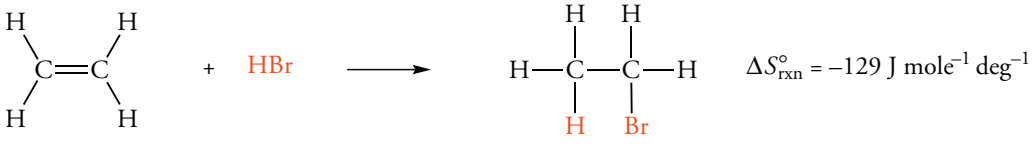


one mole of reactant

two moles of products

Since the number of moles of product is greater than the number of moles of reactant, there is more disorder in the distribution of atoms in the products than in the reactants, and we expect the entropy change for the reaction to be positive. An increase of 1 mole of product over reactant corresponds to a value of approximately +125 J mole^{-1} deg^{-1} for ΔS°_{rxn}.

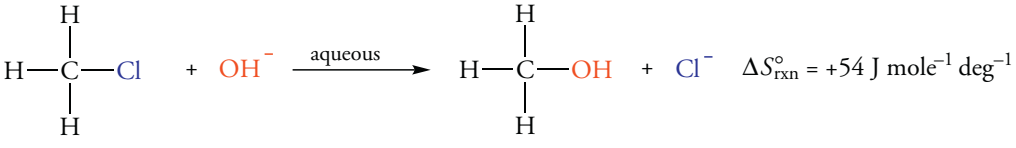
Now let's examine the addition reaction of HBr to ethylene, a reaction in which there are fewer moles of product than moles of reactants. The change in entropy for the reaction is expected to be approximately –125 J mole^{-1} deg^{-1}, based on a net decrease of 1 mole. The experimental value is –129 mole^{-1} deg^{-1}.



two moles of reactants

one mole of product

When we estimate the entropy change for a reaction, we must consider the effect of the solvent. Solvent molecules may solvate the reactants and products to a different degree. Consider the substitution reaction of chloromethane by hydroxide ion in aqueous solution.



The entropy change is positive even though the numbers of moles of product and reactant are equal. In the aqueous phase, ions are solvated, which corresponds to more order. In this case, the hydroxide ions, which form strong hydrogen bonds to water, are more strongly solvated than chloride ions. Thus, as the reaction proceeds, some solvent molecules are released to the bulk solvent, and the disorder of the system increases. The change in the order of the solvent molecules contributes to the positive entropy change.

3 FREE ENERGY

All physical processes occur with an increase in entropy when changes in both the system and the surroundings are considered. When no further spontaneous change is possible, the total entropy has increased to a maximum, and the system is at equilibrium (Figure 2).

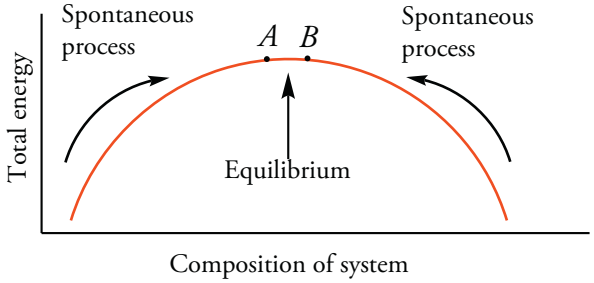


Figure 2 Composition of System
Relationship between entropy and composition of a system. When the entropy of the universe is maximum, no spontaneous change is possible, and the system is at equilibrium.

The ability of the system to do work decreases as equilibrium is approached, and at equilibrium there is no **free energy** available to do work. When an organism is at equilibrium with the surroundings, it is dead. The **Gibbs free energy** (G) is a thermodynamic state function that defines the equilibrium condition at constant temperature and pressure (Equation 20):

$$\Delta G = \Delta H - T\Delta S \qquad (20)$$

The Gibbs free energy determines both the direction and the magnitude of spontaneous change in systems held at constant temperature and pressure. Because most chemical reactions are carried out under these conditions, the Gibbs free energy is of enormous importance. *The change in free energy is the force that drives a process to equilibrium.*

By convention, if ΔG is negative, the process is spontaneous in the direction written and is called **exergonic** (from Greek *ergon*, meaning "work"). When ΔG is positive, the process is not spontaneous in the direction written and is said to be **endergonic**. If the free-energy change for a process is zero, the system is at equilibrium. These conventions are summarized below:

Conventions of the algebraic sign of ΔG and the direction of spontaneous change:

1. $\Delta G < 0$ The change in state is exergonic and spontaneous in the direction written.
2. $\Delta G = 0$ The reaction is at equilibrium, the system cannot undergo any spontaneous change, and there is no free energy available to do work.
3. $\Delta G > 0$ The change in state is endergonic and is not spontaneous in the direction written. (The reverse reaction is spontaneous.)

The sign of ΔG is controlled by the balance between ΔH and $T\Delta S$. For processes in which ΔH is negative and $T\Delta S$ is positive, the enthalpy and the entropy act in concert, and both terms favor the spontaneous change.

We have now defined two conditions for equilibrium:

1. The entropy of the universe is a maximum at equilibrium.
2. The Gibbs free energy of the system is a minimum at equilibrium.

Since the Gibbs free energy is a property of the system, it provides us with a measurable criterion of equilibrium in which enthalpy and entropy changes are balanced. Since the enthalpy change is a consequence of the first law of thermodynamics, and the entropy change is described by the second law of thermodynamics, the Gibbs free energy is a tremendous unifying principle. The relationship between the spontaneity of a given change in state and the enthalpy and entropy changes for a given change in state are summarized in Table 1.

Table 1
Relation Between Free Energy, Enthalpy, and Entropy

ΔH	ΔS	ΔG
+	+	The reaction is exothermic, but favored entropically. It may occur if the temperature is high enough.
+	–	The reaction is endothermic and not favored entropically. It will not be spontaneous at any temperature.
–	+	The reaction is spontaneous at all temperatures.
–	–	The reaction is exothermic, but not favored entropically. The process may be spontaneous at low enough temperatures for the $T\Delta S$ term to outweigh the enthalpic contribution to the free-energy change.

Standard Free-Energy Changes

The standard free energy of a compound is the free-energy change for formation of 1 mole in its standard state (298 K and 1.0 atm.) from its elements in their standard states. The standard free energy of formation of any element in its standard state is zero; the standard state for a solute in solution is 1.0 M; and the standard free energy of formation of a 1.0 M solution of hydronium ions is assigned a value of zero.

The free-energy change for a given process is independent of the pathway by which the change in state is brought about. Consider the general reaction shown below.

$$a\text{A} + b\text{B} \rightleftharpoons c\text{C} + d\text{D} \qquad (21)$$

The standard free-energy change for reaction (21) is given by Equation (22):

$$\Delta G^\circ(\text{reaction}) = \{c\Delta G_f^\circ(c)[\text{C}] + d\Delta G_f^\circ(d)[\text{D}]\} - \{a\Delta G_f^\circ(a)[\text{A}] + b\Delta G_f^\circ(b)[\text{B}]\} \qquad (22)$$

Standard Free-Energy Changes and the Equilibrium Constant

We have now discussed three related ideas: free-energy changes, standard free-energy changes, and the equilibrium condition. What is the relation among them? The free-energy content of a compound depends upon the number of moles present and is thus an extensive property of the system. The standard free energy of a compound is defined for 1 mole of the compound under specified conditions of constant temperature and pressure. It can be shown that the two are related by Equation (23):

$$G_A = G_A^\circ + 2.303RT\log[A] \qquad (23)$$

When the concentration of A is 1.0 M, G_A simply equals G_A°, but under all other conditions the standard free energy and the free energy have different values. The second term on the right side of Equation (23) is a "correction factor" that relates the actual free energy of the compound to the standard free energy. Let us consider our standard reaction again:

$$a\text{A} + b\text{B} \rightleftharpoons c\text{C} + d\text{D} \qquad (24)$$

The free-energy change (note *not* the standard free-energy change) is given by Equation (25):

$$\Delta G(\text{reaction}) = (cG_C + dG_D) - (aG_A + bG_B) \qquad (25)$$

Substituting a term of the form of equation 23 for each of the reactants and products into Equation (25) gives the result shown in Equation (26):

$$\Delta G^\circ(\text{reaction}) = [c\Delta G_C^\circ + d\Delta G_D^\circ] - [a\Delta G_A^\circ - b\Delta G_B^\circ] + 2.303RT\log\{[\text{C}]^c[\text{D}]^d\}/\{[\text{A}]^a[\text{B}]^b\} \qquad (26)$$

The term in parentheses in Equation (26) is simply the standard free-energy change for the reaction. Let us call the mantissa of the log term Q. Thus,

$$Q = \log\{[\text{C}]^c[\text{D}]^d\}/\{[\text{A}]^a[\text{B}]\}^b \qquad (27)$$

At equilibrium, Q is the equilibrium constant for the reaction. The free-energy change for the reaction is zero, and Equation (27) reduces to Equation (28):

$$0 = \Delta G^\circ(\text{reaction}) + 2.303RT\log K_{\text{equilibrium}} \qquad (28)$$

Equation (28) is one of the most useful in all of thermodynamics.

If we take the antilog of Equation (28), we obtain Equation (29):

$$K_{eq} = \exp(-\Delta G^\circ(\text{reaction})/RT \qquad (29)$$

Referring to Equation (26), we see why ΔG°(reaction) is related to the equilibrium constant rather than ΔG(reaction). *The log term represents the free-energy change that occurs when the reactants and products are brought from standard state concentrations to equilibrium concentrations.* The log

term exactly balances the standard free-energy change required to make ΔG(reaction) equal to zero. Thus, the standard free-energy change is not the criterion of spontaneity for chemical reactions. In many reactions, there are steps whose standard free-energy changes are positive, but which are nevertheless spontaneous. Referring again to Equation (26), this means that the value of Q determines the spontaneity. If the value of Q is less than 1.0 the log term is negative; if it is sufficiently negative, the process is spontaneous under the prevailing conditions even though the standard free-energy change for the reaction is positive. The numerical relationship between equilibrium constants and standard free-energy changes is shown in Table 2.

Table 2
Relationship Between $\Delta G°$ and the Equilibrium Constant for the Equilibrium Between Two Species, A and B, at 298 K

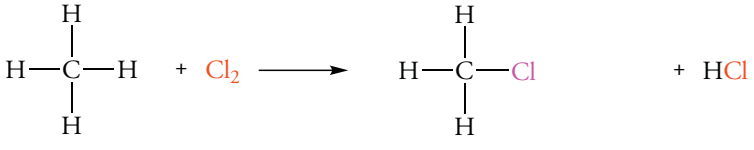
%B	*K*	*$-\Delta G°$ (J/mol)*
50	1.00	0
55	1.22	500
60	1.50	1000
65	1.86	1500
70	2.33	2100
75	3.00	2700
80	4.00	3400
85	5.67	4300
90	9.00	5450
95	19.0	7300
98	49	9650
99	99.0	1.1×10^4
99.9	999.0	1.7×10^4
99.99	9999.0	2.4×10^4

4 CONTRIBUTIONS OF $\Delta H°_{rxn}$ AND $\Delta S°_{rxn}$ TO $\Delta G°_{rxn}$

For most organic reactions, the value of $\Delta H°_{rxn}$ contributes more strongly to $\Delta G°_{rxn}$ than to $T\Delta S°_{rxn}$. For reactions in which the number of moles of reactants and products is the same and in which there is no significant change in the symmetry or rotational freedom, we know that $\Delta S°_{rxn}$ will be close to zero. Thus, the value $\Delta H°_{rxn}$ is often a close approximation of $\Delta G°_{rxn}$:

$$\Delta H°_{rxn} = \Delta G°_{rxn}$$

Consider the reaction of chlorine with methane, in which two molecules react to give two molecules of product. For this reaction, $\Delta S°_{rxn}$ = +2.9 J mole^{-1} deg^{-1}. The standard entropy change is a small value because the numbers of moles of reactant and products are equal. The $T\Delta S°_{rxn}$ term at 298 K is –860 J mole^{-1} deg^{-1}. Since $\Delta H°_{rxn}$ is –102 kJ mole^{-1}, $\Delta G°_{rxn}$ is –103 kJ mole^{-1}:



$$\Delta G°_{rxn} = \Delta H°_{rxn} - T\Delta S°_{rxn}$$

$$\Delta G°_{rxn} = -102{,}000 \text{ J mole}^{-1} - (298 \text{ K})(140 \text{ J mole}^{-1} \text{ deg}^{-1})$$

$$\Delta G°_{rxn} = -103{,}000 \text{ J mole}^{-1} = -103 \text{ kJ mole}^{-1}$$

The contributions of enthalpy and entropy changes to the free-energy change depend on temperature. The enthalpy component is more important at low temperature where the $T\Delta S^\circ_{rxn}$ term is small. On the other hand, the $T\Delta S^\circ_{rxn}$ term becomes more important at higher temperatures. Thus, if an increase in the degree of disorder is great, an endothermic process may be exergonic at a sufficiently high temperature. A reaction in which the products have greater order than the reactants has a negative entropy change and can occur only in an exothermic reaction. Such reactions become more favorable at a low temperature. To illustrate the effect of temperature on a reaction, consider the decomposition reaction of butane to give ethane and ethylene at 298 and 700 K. The reaction is endothermic, but occurs with a large positive entropy change:

$$CH_3CH_2CH_2CH_3 \longrightarrow CH_3CH_3 + CH_2{=}CH_2$$

$$\Delta H^\circ_{rxn} = 93.1 \text{ kJ mole}^{-1}$$

$$\Delta S^\circ_{rxn} = 140 \text{ J mole}^{-1} \text{ deg}^{-1}$$

At 298 K, the ΔH°_{rxn} term is more important than the $T\Delta S^\circ_{xn}$ term, and the standard free-energy change is positive:

$$\Delta G^\circ_{rxn} = \Delta H^\circ_{rxn} - T\Delta S^\circ_{rxn}$$

$$\Delta G^\circ_{rxn} = 93{,}100 \text{ J mole}^{-1} - (298 \text{ K})(140 \text{ J mole}^{-1} \text{ deg}^{-1})$$

$$\Delta G^\circ_{rxn} = 51{,}400 \text{ J mole}^{-1} = 51.4 \text{ kJ mole}^{-1}$$

An contrast, the $T\Delta S^\circ_{rxn}$ term dominates at 700 K, and the standard free-energy change is slightly positive.

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CHEMICAL KINETICS

1 PRACTICAL KINETICS

When we study a given chemical reaction, we would like to know (a) the equilibrium constant and hence the standard free-energy change and (b) the speed or velocity with which the reaction occurs. The first subject lies in the province of thermodynamics, and the second lies in the realm of chemical kinetics.

Rate Law for First-Order Reactions

The rates of chemical reactions play an important part in chemistry since we would like to carry out reactions in a reasonable period of time, but not explosively fast. We will begin with the simplest case. Consider the reaction in which a single reactant is converted to a single product:

$$A \rightarrow P \tag{1}$$

When A is converted to P, the rate of the reaction is given by Equation (2):

$$v = -\frac{d[A]}{dt} = +\frac{d[P]}{dt} = -k_1[A]^1 \tag{2}$$

Equation (2), which defines the algebraic relation between reaction velocity, v, and concentration, is called the **rate law** for the reaction. The exponent in the above equation in the term $[A]^1$ means that the rate depends upon the concentration of the reactant, [A], raised to the first power. Therefore, if the concentration of A is doubled, the rate also doubles. The exponent associated with the concentration of A, 1, is called the **order** of the reaction in A; that is the reaction is first order in A. In general, we do not know the order of a reaction in a given reactant until we have carried out a series of experiments to determine the relation between the rate of reaction and the concentration of reactants so that Equation (2) is strictly empirical. The term k_1 in Equation (2) is the first-order rate constant for the reaction, where the subscript means "first order."

What are the units of the first-order rate constant, k_1? To find out, let's look at Equation (2) again. The velocity is the change in concentration divided by time; i.e. $mol^{-1}\ L^{-1}\ s^{-1}$, and the units on the right side of Equation (2) are $mol^{-1}\ L^{-1}$. Thus,

$$\cancel{mol^{-1} \cdot L^{-1}} \cdot s^{-1} = k\ \cancel{mol^{-1} \cdot L^{-1}} \tag{3}$$

The terms for concentration on the right- and left-hand side of Equation (3) cancel, so the units of a first order rate constant are s^{-1}.

We can eliminate the term $-d[A]/dt$ in Equation (2) by integration. The term [A] is the concentration of A at any given time, t, during the reaction, and the term $[A]_0$ is the concentration at the beginning of the reaction, t_0:

$$v = -\frac{d[A]}{dt} = -\int_{[A]_o}^{[A]} \frac{d[A]}{[A]} = k\int_{t_o}^{t} dt \tag{4}$$

Solving this equation with $t_0 = 0$ gives the following result.

$$-\ln[A] + \ln[A_o] = kt \tag{5}$$

We can rewrite this as,

$$\ln\frac{[A_o]}{[A]} = kt \tag{6}$$

Taking the antilog gives,

$$[A] = [A_o]e^{-kt} \tag{7}$$

If we make a plot of the natural log (ln) of the concentration of A versus time for a first-order reaction, we obtain a straight line whose slope is $-k_1$ (Figure 1).

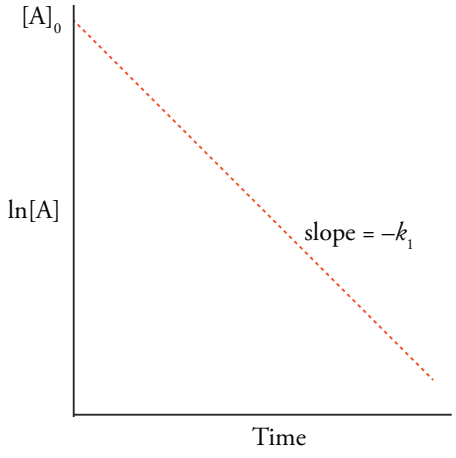


Figure 1 Plot of [A] vs. *t*.
If a reaction is first order, a plot of [A] vs. *t* gives a straight line whose slope equals the negative rate constant, $-k_1$, for the reaction. It is the negative of the rate constant because the concentration of A is decreasing.

Now let's consider a special case in which the initial concentration of A, $[A_0]$, has decreased by one-half. Substituting these values in Equation (6), we obtain

$$\ln\frac{[A_o]}{[0.5A]} = kt_{1/2} \tag{8}$$

So that,

$$\ln 2 = kt_{1/2} = 0.693 \tag{9}$$

The term $t_{1/2}$ is called the **half-life** of the reaction. The term $t_{1/2}$ is often given the symbol τ (tau). Note that for a first-order reaction the half-life, τ, is independent of the initial concentration of the reaction, A.

Second-Order Reactions

Many of the reactions we will consider in organic chemistry (and in biochemistry too) have two reacting species. Consider a reaction in which two reactants are converted to two products.

$$A + B \rightarrow C + D$$

If this reaction is first order in both A and B, then it is second order overall. The rate, or velocity, of this reaction is given by

$$v = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} + \frac{d[C]}{dt} + \frac{d[D]}{dt} \tag{10}$$

That is, the rate at which either A or B disappears is exactly equal to the rate at which C and D are produced. We can monitor the rate of reaction experimentally by picking the reactant or product that is easiest to detect. If experimental analysis reveals that the reaction is indeed first order in both A and B, then the rate of the reaction is given by,

$$v = k_2[A][B] \tag{11}$$

The term k_2 in Equation (1) is called a second-order rate constant (the subscript "2") is the moniker for second order. What are the units of k_2? As we saw earlier, we want to substitute the units for v, and for the concentrations of A and B into Equation (11):

$$\cancel{\text{mol}^{-1}}\ \cancel{\text{L}^{-1}}\ \text{s}^{-1} = k_2\ \cancel{(\text{mol L}^{-1})}(\text{mol L}^{-1}) \tag{12}$$

Two concentration terms cancel. Dividing Equation (12) by the remaining concentration term, we find that the units of a second-order rate constant are L mol^{-1} s^{-1}. The term L mol^{-1} is the *reciprocal* of the concentration, M^{-1}. Thus, the units of a second-order rate constant are often written as $\text{M}^{-1}\ \text{s}^{-1}$.

If we integrate the equation for a second-order reaction, we obtain Equation (13):

$$\frac{1}{[\text{B}_o]-[\text{A}_o]}\ln\frac{[\text{A}_o]\,[\text{B}_o - x]}{[\text{B}_o]\,[\text{A}_o - x]} = k_2 t \tag{13}$$

where A_0 and B_0 are the initial concentrations of A and B, respectively, x is the amount of A and B have reacted at time t, and k_2 is the second-order rate constant. This is a bit cumbersome. Suppose we begin the reaction with equal concentrations of A and B. The rate law for the reaction then becomes,

$$v = -\frac{\text{d}[\text{A}]}{\text{d}t} = k_2[\text{A}][\text{A}] = k_2[\text{A}]^2 \tag{14}$$

When we integrate Equation (14), we obtain,

$$\frac{1}{[0.5\text{A}_o]} - \frac{1}{[\text{A}_o]} = kt_{1/2} = k\tau \tag{15}$$

It is certainly much easier to work with Equation (15) than with Equation (14). What is the half-life for the second-order reaction defined in Equation (15)? To find out, we'll set the concentration of A to 0.5A_0:

$$\tau = \frac{1}{[\text{A}_o]k_2} \tag{16}$$

When we solve Equation (16) for τ, we find the relation of the half-life of a second-order reaction depends upon the concentration of A, which is quite unlike the behavior of a first-order reaction.

Pseudo First-Order Reactions

We have just seen that the rate law for a first-order reaction is simpler than the rate law for a second-order reaction. It turns out to be quite easy to set up reaction conditions for a second-order reaction so that its kinetics will resemble a first-order reaction. When this is the case, we say that the reaction is **pseudo first order.** This situation results if we pick one of the two reactants, say A, and make its initial concentration much greater than the concentration of B. Then, we will follow the reaction experimentally only until about 1% of B has reacted. At this time, the concentration of A will scarcely have changed at all. So the rate law reduces to

$$v = k_2[\text{A}_0][\text{B}] \tag{17}$$

where $k_{app}[\text{A}_0]$ is a pseudo first-order rate constant. We can obtain the true second-order rate constant by dividing k_{app} by A_0. We could, of course, have done the same kind of analysis by setting the initial concentration of B much greater than that of A:

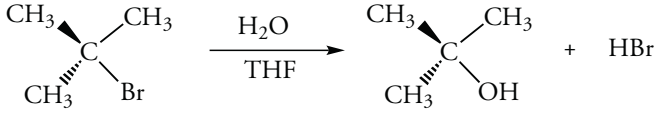
$$v = k_{app}[B] \tag{18}$$

By setting up experiments in this way, it is much simpler to establish the rate constant for the second-order rate constant than it would have been by using the rate law in Equation (13).

Order and Molecularity

When we study reaction mechanisms among the things we would like to discover are its regiospecificity, stereochemistry, and the number of chemical species that are present in the **transition state**, or **activated complex** of the of the reaction. The number of chemical species in the transition state is called the **molecularity** of the reaction. It is easy to fall into the trap of imagining that the molecularity of a reaction is correlated with the order of the reaction. However, we have just seen that the reaction conditions can be manipulated to turn a reaction with second-order kinetics into one that is pseudo first order. Thus, molecularity and the order of a given reaction are not deeply related.

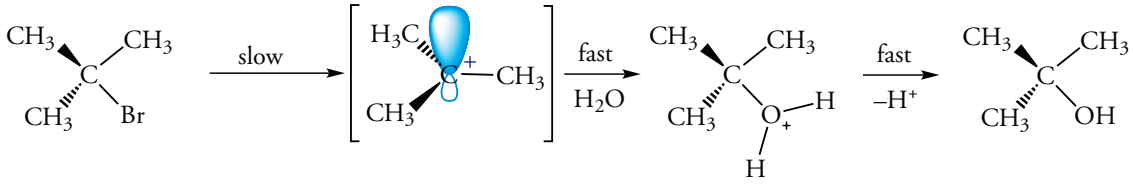
We can, however, use kinetic data to make inferences about the order of a chemical reaction. Consider the following process in which *tert*-butyl bromide reacts with water (in a solvent such as tetrahydrofuran) to give *tert*-butyl alcohol:



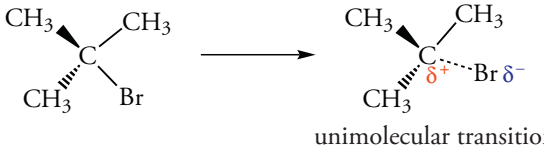
Kinetic studies show that this reaction is first order in *tert*-butyl bromide and zero order in water. The overall rate is determined by the slow step, so water does not appear in the rate law, which is

$$v = -\frac{d[t\text{BuBr}]}{dt} = +\frac{d[t\text{BuOH}]}{dt} = k_1[t\text{BuBr}] \tag{19}$$

This result might lead us to propose a mechanism in which a carbocation forms in a slow step—which is why the reaction is first order in the halide—and that the carbocation is captured in a subsequent fast step by water. This process is shown below.

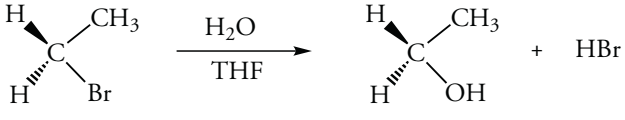


The kinetic result does not prove that a carbocation forms, but it is one piece of evidence supporting the existence of a carbocation. The above reaction is unimolecular because only one molecular species is present in the transition state for the slow, or rate-determining step of the reaction in which the carbocation forms.



unimolecular transition state

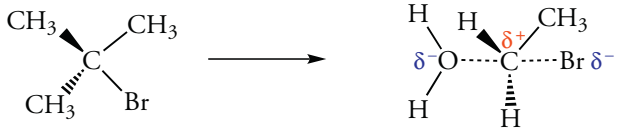
Next, let's consider a reaction in which bromoethane reacts with water to give ethanol.



This reaction is first order in both in the alkyl halide and in water. The rate law therefore is given by

$$v = +\frac{d[EtOH]}{dt} = k_2[EtBr][H_2O] \tag{20}$$

This rate law suggests that the transition state for the reaction has two molecular species so that it is a bimolecular reaction.



bimolecular transition state

Steady-State Approximation

We have just seen that the rate law for a first-order reaction is simpler than the rate law for a second-order reaction. It turns out to be quite easy to set up reaction conditions for a second-order reaction so that its kinetics will resemble a first-order reaction. When this is the case, we say that the reaction is **pseudo first order.** This situation results if we pick one of the two reactants, say A, and make its initial concentration much greater than the concentration of B. Then, we will follow the reaction experimentally only until about 1% of B has reacted. At this time, the concentration of A will scarcely have changed at all. So the rate law reduces to

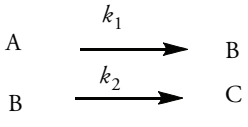
$$v = k_2[A_0][B] \tag{21}$$

where $k_{app}[A_0]$ is a pseudo first-order rate constant. We can obtain the true second-order rate constant by dividing k_{app} by A_0. We could, of course, have done the same kind of analysis by setting the initial concentration of B much greater than that of A:

$$v = k_{app}[B] \tag{22}$$

By setting up experiments in this way, it is much simpler to establish the rate constant for the second-order rate constant than it would have been by using the rate law in Equation (13).

Let us suppose that in the conversion of reactant A to product C occurs through the formation of an intermediate, B (Scheme I):



Scheme I

The first-order rate constants for the two steps are k_1 and k_2. If the magnitudes of the two rate constants are comparable, this is rather complicated, but if $k_2 >> k_1$, then we can write the rate law as shown below in Equation (23):

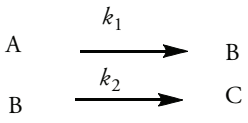
$$v = -\frac{d[A]}{dt} = +\frac{d[C]}{dt} = k_1[A] \tag{23}$$

Since $k_2 >> k_1$, $d[B]/dt = 0$. This is the steady-state approximation, Equation (24):

$$\frac{d[B]}{dt} = k_1[A] - k_2[B] = 0 \tag{24}$$

Therefore,

$$k_1[A] = k_2[B] \tag{25}$$



Scheme I

The first-order rate constants for the two steps are k_1 and k_2. If the magnitudes of the two rate constants are comparable, this is rather complicated, but if $k_2 >> k_1$, then we can write the rate law as shown in Equation (26):

$$v = -\frac{d[A]}{dt} = +\frac{d[C]}{dt} = k_1[A] \tag{26}$$

Since $k_2 >> k_1$, $d[B]/dt = 0$. This is the steady-state approximation, Equation (27):

$$\frac{d[B]}{dt} = k_1[A] - k_2[B] = 0 \tag{27}$$

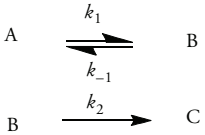
Therefore,

$$k_1[A] = k_2[B] \tag{28}$$

In other words,

$$v = \frac{d[C]}{dt} = k_1[A] = k_2[B] \tag{29}$$

Now let's make the situation more complex, and more realistic too, by making the first step reversible, Scheme II:



Scheme II

The form of the rate law for Scheme II depends upon the relative magnitudes of k_1, k_{-1}, and k_2. Suppose that $k_1 >> k_2$ and that $k_{-1} >> k_2$. In this case, the second step, in which B is converted to C is rate determining,

$$v = k_2[B] \tag{30}$$

However, since $k_1 >> k_2$ and that $k_{-1} >> k_2$, B is a transient intermediate (think of the carbocation in the reaction shown above, for instance), whose concentration is constant, that is, it exists in a steady state. That is,

$$\frac{d[B]}{dt} = 0 \tag{31}$$

The intermediate can form by one pathway, but it can disappear by two pathways. The rate law for the formation and disappearance of B is given by Equation (32):

$$\frac{d[B]}{dt} = +k_1[A] - k_2[B] - k_{-1}[B] = 0 \tag{32}$$

We can rewrite Equation (32) as,

$$k_1\,[A] = (k_{-1} + k_2)[B] \tag{33}$$

Solving for B yields,

$$[B] = \frac{k_1[A]}{(k_{-1} + k_2)} \tag{34}$$

This means that the rate law for Scheme II reduces to Equation (35):

$$v = \frac{k_1 k_2[A]}{(k_{-1} + k_2)} \tag{35}$$

The rate constants in Equation (35), which are not observed directly, are called **microscopic rate constants**. The combination of these constants (k_1, k_{-1}, and k_2) gives an apparent or observed first-order rate constant (Equation 36).

$$k_{\text{observed}} = \frac{k_1 k_2}{(k_{-1} + k_2)} \tag{36}$$

Interpretation of Rate Constants

What good is a rate constant? That is, once we have obtained the rate constant for a given reaction, how can interpret it? One of the first attempts to interpret rate constant is the Arrhenius equation, (Equation 37):

$$k_{\text{obs}} = A\text{e}^{-E_a/RT} \tag{37}$$

The parameter E_a in Equation (37) is called the **activation energy** for the reaction. This is the minimum energy required to allow the reaction to proceed. R is the ideal gas constant, T is the Kelvin temperature, k_{obs} is the observed rate, and the parameter A is called the preexponential factor. It is a statistical correction factor. We can rearrange the Arrhenius equation by dividing by A (Equation 38):

$$\frac{k_{\text{obs}}}{A} = \text{e}^{-E_a/RT} \tag{38}$$

Now let's take the natural logarithm (Equation 39):

$$\ln\frac{k_{\text{obs}}}{A} = -\frac{E_a}{RT} \tag{39}$$

Note that the activation energy, E_a, is independent of temperature. Solving for E_a gives Equation (40).

$$E_a = -RT \ln \frac{k_{obs}}{A} \tag{40}$$

The term k_{obs}/A is a dimensionless constant. So, we can write,

$$E_a = -RT \ln C \tag{41}$$

We also recall that the equilibrium constant for a reaction, K_{eq}, is also a dimensionless constant. The form of Equation (41) is familiar. We recall from an earlier appendix on thermodynamics that

$$\Delta G^\circ = -RT \ln K_{eq} \tag{42}$$

Equations having similar forms are always intriguing, and in the case we can ask whether we can give the activation energy a thermodynamic significance. The answer is "yes," as we shall see in the next section.

2 TRANSITION STATE THEORY

We recall that the transition state, or activated complex, for a chemical reaction is a transient configuration of atoms or molecules that lies at the point of maximum energy on the minimum energy pathway leading from reactants to products. By analogy, we can think of this maximum energy position as a saddle point, or the top of a mountain pass.

Consider the following equilibrium for the interconversion of a reactant A to a product B in a first-order reaction (Scheme III):

$$\mathrm{A} \xrightarrow{k_1} \mathrm{B}$$

Scheme III

We assert that reactant A is in equilibrium with an activated complex, $A^\ddagger$, with equilibrium constant, $K^\ddagger$, as shown in Scheme IV.

The rate constants in Equation (35), which are not observed directly, are called **microscopic rate constants**. The combination of these constants (k_1, k_{-1}, and k_2) gives an apparent or observed first order rate constant (Equation 36):

$$\mathrm{A} \overset{K^\ddagger}{\rightleftharpoons} \mathrm{A}^\ddagger \xrightarrow{k_1} \mathrm{B}$$

Scheme IV

By the usual conventions for defining an equilibrium constant, $K^\ddagger$ is written as

$$K^\ddagger = [A^\ddagger]/[A] \tag{43}$$

Since this is a first-order reaction, the rate law is

$$v = -\frac{d[A]}{dt} = k_1[A] \tag{44}$$

We next assert that

$$k_1[A] = k^\ddagger[A^\ddagger] \tag{45}$$

That is, the rate of the reaction depends only on (a) the concentration of the activated complex, $A^\ddagger$, and (b) on its absolute rate constant, $k^\ddagger$. The absolute rate constant, $k^\ddagger$, is the rate of passage over the potential energy barrier separating the reactants and products. $k^\ddagger$ is a constant,

$$k^{\ddagger} = \frac{k_b T}{h} \tag{46}$$

where k_b is the Boltzmann constant, T is the Kelvin temperature, and h is Planck's constant. When we substitute Equation (44) into Equation (42) we obtain,

$$k_1 = k^{\ddagger} K^{\ddagger} \tag{47}$$

Corresponding to equilibrium constant, $K^{\ddagger}$, there is a free energy of activation, $\Delta G^{\ddagger}$. Therefore, we can write,

$$k_1 = \frac{k_b T}{h} \exp\left(\frac{-\Delta G^{\ddagger}}{RT}\right) \tag{48}$$

where,

$$\Delta G^{\ddagger} = -RT \ln K^{\ddagger}$$

so that,

$$-\frac{\Delta G^{\ddagger}}{RT} = \ln K^{\ddagger} \tag{49}$$

and

$$K^{\ddagger} = \exp\left(\frac{-\Delta G^{\ddagger}}{RT}\right) \tag{50}$$

Furthermore, by analogy with equilibrium thermodynamics we can write a relation between the free energy of activation, $\Delta G^{\ddagger}$, and the enthalpy, $\Delta H^{\ddagger}$ and entropy of activation, $\Delta S^{\ddagger}$. Thus,

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \tag{51}$$

Therefore, Equation (47) can be rewritten as

$$k_1 = \frac{k_b T}{h} \exp\left(\frac{-\Delta H}{RT}\right) \exp\left(\frac{-\Delta S^{\ddagger}}{R}\right) \tag{52}$$

It can also be shown that there is a simple relation between the Arrhenius activation energy, E_a, and the enthalpy of activation, $\Delta H^{\ddagger}$:

$$\Delta H^{\ddagger} = E_a - nRT \tag{53}$$

where n is the order of the reaction.

We recall that the Arrhenius equation contains a preexponential term called the statistical factor, A. It is aesthetically very pleasing that the statistical term is related to the entropy of activation (Equation 54):

$$A = \frac{k_b T}{h} \exp\left(\frac{-\Delta S^{\ddagger}}{R}\right) \cdot e^{n} \tag{54}$$

where n is again the order of the reaction and $\Delta S^{\ddagger}$ is the order of the reaction. In sum

E_a is proportional to $\Delta H^{\ddagger}$

and

A is proportional to $\Delta S^{\ddagger}$

3 THE HAMMOND POSTULATE

We are now in a position to discuss the Hammond postulate in a slightly different context. We recall that the Hammond postulate states that the structure of transition state of an exothermic reaction resembles the reactants. This means that very little structural change is required to convert the reactants to the transition state. Therefore,

$$\left|-\Delta H_{\text{exothermic}-\text{reaction}}\right| >> \left|-\Delta H^{\ddagger}\right| \tag{55}$$

Similarly, the structure of transition state of an endothermic reaction resembles the products, which means that considerable structural change is required to convert the reactants to the transition state.

We will pursue these ideas qualitatively, without the mathematical formalism, throughout the text.

Summary of Synthetic Methods

Synthesis of Alkanes, Cycloalkanes, and Aromatic Hydrocarbons

1. Catalytic hydrogenation of alkenes (5.9, 17.7)
2. Catalytic hydrogenation of alkynes (7.5)
3. Catalytic hydrogenation of aromatic compounds (13.11)
4. Protonation of Grignard reagents (9.8)
5. Addition of carbenoids to alkenes (6.7)
6. Friedel–Crafts alkylation of aromatic compounds (13.2)
7. Wolff–Kishner or Clemmensen reduction of aldehydes or ketones (13.8, 18.5)
8. Reduction of aryldiazonium salts with hypophosphorous acid (13.8)
9. Catalytic reduction of aryl ketones (13.11)
10. Substitution reaction of alkyl halide with lithium dialkyl cuprates (9.8)
11. Reduction of thioacetals (19.9)
12. Gilman reagent alkylation of aromatic compounds (17.2)
13. Gilman reagent alkylation of allylic halides (17.2)
14. Heck reaction for synthesis of aryl alkenes (17.3, 17.5)
15. Suzuki coupling of aryl group and aryl halides (17.3, 17.4)
16. Sonogashira reaction for synthesis of aryl alkynes (17.3, 17.6)

Synthesis of Alkenes

1. Acid-catalyzed dehydration of alcohols (8.20)
2. Catalytic hydrogenation of alkynes (7.5)
3. Dehydrohalogenation of alkyl halides (9.18)
4. Hofmann elimination of quaternary ammonium hydroxides (23.9)
5. Wittig reaction of aldehydes or ketones (19.9)
6. Alkene coupling with the Grubbs metathesis reaction (17.9)
7. Heck reaction for synthesis of aryl alkenes (17.3, 17.5)
8. Gilman reagent alkylation of allylic halides (17.2)

Synthesis of Alkynes

1. β-Elimination of dihaloalkanes or vinyl halides (7.7)
2. Alkylation of alkynides with alkyl halides (7.7)
3. Sonogashira reaction for synthesis of aryl alkynes (17.3, 17.6)

Synthesis of Alkyl Halides

1. Polar addition of hydrogen halides to alkenes (7.2)
2. Addition of halogens to alkenes (7.6)
3. Reaction of alcohols with hydrogen halide (8.14)
4. Reaction of alcohols with thionyl chloride or phosphorus tribromide (15.3)
5. Allylic or benzylic halogenation (11.5)
6. α-Halogenation of aldehydes, ketones, or carboxylic acids (22.5, 22.14)
7. A halogenation of aldehydes, ketones, or carboxylic acids (23.5, 23.14)

Synthesis of Aryl Halides

1. Direct halogenation using Lewis acid catalyst (14.2)
2. Reaction of aryldiazonium salts with copper(I) halide (13.8)

Synthesis of Alcohols

1. Acid-catalyzed hydration of alkenes (6.5)
2. Oxymercuration–demercuration of alkenes (15.8)
3. Hydroboration–oxidation of alkenes (15.8)
4. Reduction of aldehydes or ketones (15.9, 18.4)
5. Reduction of carboxylic acids (20.7)
6. Reduction of esters (18.6)

7. Reaction of Grignard reagent with aldehydes or ketones (15.10)
8. Reaction of Grignard reagent with ethylene oxide (16.10)

Synthesis of Glycols

1. Ring opening of epoxides (17.10)
2. Reaction of atkenes with potassium permanganate or osmium tetroxide (6.9)

Synthesis of Ethers

1. Alkoxylation of alkyl halides with alkoxides or phenoxides (16.5, 24.5)
2. Alkoxymercuration–demercuration of alkenes (16.5)
3. Acid-catalyzed addition of alcohols to alkenes (16.4)
4. Acid-catatyzed dehydration of alcohols (16.4)
5. Acetal formation of aldehydes and ketones (19.5)
6. Aromatic ether by nucleophilic aromatic substitution (24.4)

Synthesis of Epoxides

1. Oxidation of alkenes with peroxy acids (6.8, 16.9)
2. Intramolecular Williamson synthesis from halohydrins (16.9, 17.9)

Synthesis of Alcohols

1. Oxidation of primary alcohols (15.4, 18.5)
2. Reduction of acid chlorides (15.6, 21.8)
3. Hydroboration–oxidation of alkynes (18.6)
4. Reduction of aldehydes or ketones (15.9. 18.4)
5. Ozonolysis of alkenes (6.10, 18.6)
6. Oxidative cleavage of glycols (15.5)
7. Reduction of nitriles (15.6)

Synthesis of Ketones

1. Oxidation of secondary alcohols (15.4)
2. Mercury(II)-catalyzed hydration of alkynes (7.6, 18.5)
3. Reaction of acid chlorides with lithium dialkyl cuprates (15.6, 17.2)
4. Friedel–Crafts acylation of aromatic compounds (13.2, 18.5)
5. Ozonolysis of alkenes (6.10, 18.6)
6. Oxidative cleavage of glycols (15.5)
7. Acetoacetic ester synthesis (22.16)
8. Hydroboration–oxidation of alkynes (15.6)
9. Reaction of organolithium reagents with carboxylic acids (15.6)
10. Acetoacetic ester synthesis (22.16)

Synthesis of Carboxylic Acids

1. Oxidation of primary alcohols (16.4, 18.5, 21.6)
2. Oxidation of aldehydes (18.5, 21.6)
3. Reaction of Grignard reagent with carbon dioxide (21.6)
4. Hydrolysis of esters (22.5)
5. Hydrolysis of amides (22.5)
6. Hydrolysis of acid chlorides (22.5)
7. Hydrolysis of nitriles (21.6, 22.5)
8. Ozonolysis of alkenes with oxidative workup conditions (7.10)
9. Ozonolysis of alkynes (11.5)
10. Haloform reaction of methyl ketones (21.6)
11. Malonic ester synthesis (22.16)

Synthesis of Esters

1. Acid-catalyzed esterification of carboxylic acid with alcohol (20.11)
2. Alkylation of carboxylate salts with alkyl halides (20.11)
3. Alkylation of carboxylic acids with diazomethane (20.11)
4. Reaction of acid chlorides with alcohols (21.6)
5. Reaction of anhydrides with alcohols (21.6)

Synthesis of Acid Chlorides

1. Reaction of carboxylic acid with thionyl chloride (20.10)

Synthesis of Carboxylic Acids

1. Oxidation of primary alcohols (16.4, 18.5, 21.6)
2. Oxidation of aldehydes (18.5, 21.6)
3. Reaction of Grignard reagent with carbon dioxide (21.6)
4. Hydrolysis of esters (22.5)
5. Hydrolysis of amides (22.5)
6. Hydrolysis of acid chlorides (22.5)
7. Hydrolysis of nitriles (21.6, 22.5)
8. Ozonolysis of alkenes with oxidative workup conditions (7.10)
9. Ozonolysis of alkynes (11.5)
10. Haloforn reaction of methyl ketones (21.6)
11. Malonic ester synthesis (22.16)

Synthesis of Anhydrides

1. Reaction of carboxylic acids with dehydrating agent (20.11)
2. Reaction of carboxylate salt with acid chloride (20.11)

Synthesis of Amides

1. Reaction of acid chloride with amines (21.7)
2. Reaction of amines with anhydrides (22. 7)
3. Reaction of esters with amines (21.7)

Synthesis of Nitriles

1. Reaction of alkyl halides with cyanide ion (9.7)
2. Reaction of aryldiazonium ion with copper(I) cyanide (13.7)

Synthesis of Amines

1. Reducton of amides (21.8, 23.8)
2. Reduction of nitriles (21.8, 23.8)
3. Alkylation of amines using alkyl halides (23.8)
4. Reductive amination (23.8)
5. Gabriel synthesis (23.7)
6. Hofmann rearrangement (23.13)
7. Reduction of nitro compounds (13.8, 23.8)

Synthesis of Thiols and Sulfides

1. Thiols from alkyl halides (9.8, 15.11)
2. Sulfides from alkyl halides (16.11)

Formation of Carbon–Carbon Bonds

1. Reaction of alkyl halide with cyanide ion (8.10)
2. Reaction of alkynide ions with alkyl halides (7.7, 8.9)
3. Reaction of alkenes with carbenoids (7.7)
4. Wittig synthesis (19.9)

5. Cyanohydrin formation (19.2)
6. Friedel–Crafts alkylation and acylation reactions (13.2, 18.5)
7. Reaction of Grignard reagent with aldehydes or ketones (15.10)
8. Reaction of Grignard reagent with ethylene oxide (16.10)
9. Reaction of Grignard reagent with carbon dioxide (21.6)
10. Reaction of Grignard reagent with esters (21.9)
11. Reaction of lithium dialkylcuprates with acid chlorides (17.2, 18.6, 22.10)
12. Aldol condensation (23.7)
13. Claisen condensation (23.14)
14. Malonic ester synthesis (22.16)
15. Acetoacetic acid synthesis (22.16)
16. Alkylation of ester enolates (23.6)
17. Alkylation of enamine (25.12)
18. Conjugate addition reactions of α,β-unsaturated carbonyl compounds (22.10)
19. Diels–Alder reaction (11.8, 24.5)
20. Electrocyclic reactions (25.4)
21. Gilman reagent alkylation of aromatic compounds (17.2)
22. Gilman reagent alkylation of allylic halides (17.2)
23. Heck reaction for synthesis of aryl alkenes (17.3, 17.5)
24. Suzuki coupling of aryl group and aryl halides (17.3, 17.4)
25. Sonogashira reaction for synthesis of aryl alkynes (17.3, 17.6)

Solutions to In-Chapter Problems

Chapter 1

Atomic Properties

Problem 1.1

A few proteins contain selenocysteine, which contains a selenium atom in place of the sulfur atom of the amino acid cysteine. Selenium is in the fourth period, just below sulfur. Is sulfur or selenium more electronegative?

Answer:

Sulfur, which is higher in Group VIA.

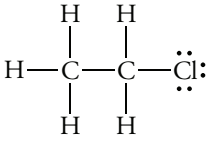
Lewis Structures

Problem 1.3

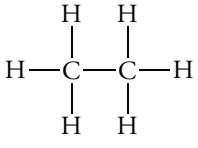
Chloroethane (CH_3CH_2Cl) is a topical anesthetic that boils at 12 °C. When liquid chloroethane is released from a pressurized spray can, it expands and cools rapidly, numbing the skin. Describe the bonding in this compound. (Refer to the structure of ethane.)

Answer:

Three nonpolar covalent C—H bonds to one carbon atom; two nonpolar covalent C—H bonds and a polar covalent C—Cl bond to the other carbon atom.



chloroethane

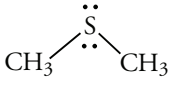


ethane

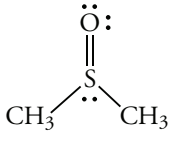
Problem 1.4

Dimethyl sulfoxide is a liquid that is readily absorbed through the skin. It was once considered as a possible solvent to deliver drugs by direct application to the skin, but turned out to be too toxic for this use. Write its structure and compare it to dimethyl sulfide.

Answers:



dimethyl sulfide

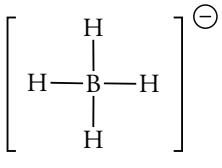


dimethyl sulfoxide

Problem 1.5

Sodium borohydride ($NaBH_4$) is a reducing agent used in organic chemistry. This ionic compound contains borohydride ion BH_4^-. Write the Lewis structure of borohydride.

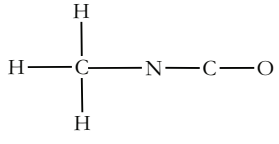
Answer:



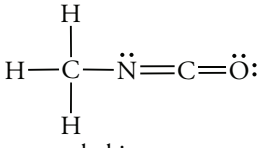
borohydride

Problem 1.7

Methyl isocyanate is an important industrial intermediate used to synthesize compounds such as Sevin, an insecticide. A massive leak of this compound occurred in Bhopal, India, in 1984 and caused the death of at least 2000 people. Using the following molecular framework, write a Lewis structure for methyl isocyanate.



Answer:



methyl isocyanate

Formal Charge

Problem 1.8

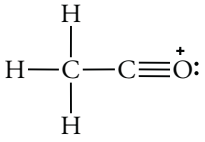
Consider the structure of dimethyl sulfoxide given in Problem 1.4, and calculate the formal charges of sulfur and oxygen.

Answer: The formal charger of oxygen is –1; it is +1 for sulfur.

Problem 1.9

The acylium ion is an intermediate in one of the substitution reactions of aromatic compounds. Calculate the formal charges of the carbon and oxygen atoms connected by a triple bond in the following structure. What is the charge of the ion?

Answer:



The formal charge of oxygen is +1.

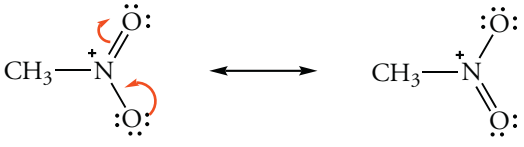
Problem 1.11

Consider the structure of nitromethane, a compound used to increase the power in some specialized race car engines. A nitrogen–oxygen single bond length is 136 pm; a nitrogen–oxygen double bond length is 114 pm. The nitrogen–oxygen bonds in nitromethane are equal and are 122 pm. Explain the data in terms of the electronic structure of nitromethane.

Answer:

There is an equivalent resonance structure interchanging the N—O and N=O bonds, and the bond length is intermediate between the single and double bond lengths.

Answer:



Dipole Moments

Problem 1.13

The bond moment of C=O in compounds such as formaldehyde is 2.3 D. The bond length is 1.22 Å. Determine the partial charge of the oxygen atom.

Answer:

The formula for calculating the dipole moment is $\mu = lqlr$. Substituting $\mu = 2.3$ esu Å, and $r = 1.22 \times 10^{-10}$ m, and solving for q gives a value of 0.53×10^{-10} esu. Since the charge of an electron is 4.8×10^{-10} esu/electron, dividing 0.53×10^{-10} esu/electron by 4.8×10^{-10} esu, gives a value of 0.11 electron. Therefore, the charge on oxygen is –0.11.

$$\frac{0.53 \times 10^{-10}\text{esu}}{4.8 \times 10^{-10}\text{esu/electron}} = 0.11 \text{ electron}$$

Hybridization

Problem 1.14

What type of overlap is present in the carbon–carbon single bond of propene? What is the C—C=C bond angle?

CH_3—CH=CH_2
propene

Answer:

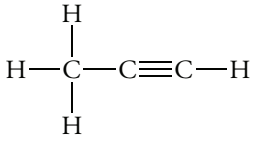
The carbon atom of the CH_3 group is sp^3 hybridized and the CH group is sp^2 hydridized, so there is a σ sp^3–sp^2 bond. The bond angle is 120°.

Problem 1.15

The carbon–carbon single bond length of propyne is 146 pm. Why is this value different from the carbon–carbon single bond length of ethane (154 pm)?

Answer:

Bonds involving an sp-hybridized carbon atom are always shorter than bonds involving only sp^3-hybridized carbon atoms.



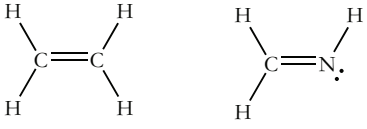
propyne

Problem 1.16

Compare the structures of ethylene and a simple compound with a C=N bond. What similarities and differences do you see between these two molecules? Where are the lone pair electrons of nitrogen located?

Answer:

Both have a double bond that consists of a sigma bond and a pi bond, and the shapes of the molecules are similar. The lone pair electrons are in an sp^2 orbital at a 120° angle to the C=N bond.



Problem 1.17

Compare the structures of propyne and cyanomethane (acetonitrile), a compound with a C≡N bond. What similarities and differences do you see between these two molecules? Where are the lone pair electrons of nitrogen located?

Answer:

Both have a triple bond that consists of a σ and two π bonds, and the shapes of the molecules are similar. In cyano methane, the lone pair electrons are in an sp orbital at a 180° angle to the C≡N bond.



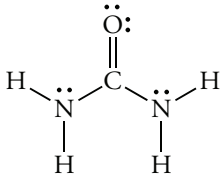
propyne cyanomethane

Problem 1.18

Urea, which contains carbon in its highest positive oxidation state, is a metabolic product excreted in urine. Based on the following Lewis structure, predict the hybridization of both the carbon and oxygen atoms.

Answer: Both carbon and oxygen are sp^2 hybridized.

Answer:



Solutions to In-Chapter Problems

Chapter 2

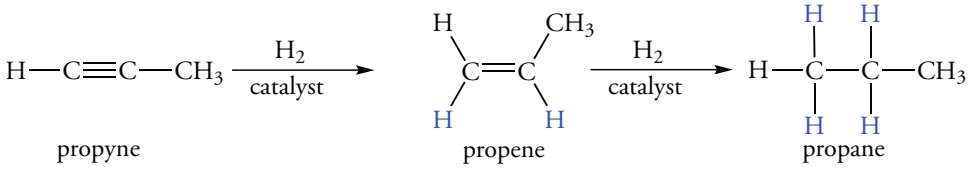
Functional Groups

Problem 2.2

Based on the reaction of hydrogen with ethene, draw the structure of the product of the reaction of excess hydrogen gas with propyne.

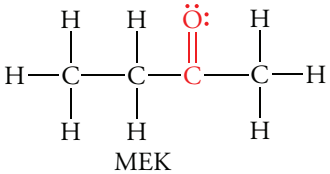
Answer:

Propyne reacts with two moles of hydrogen to give propane.



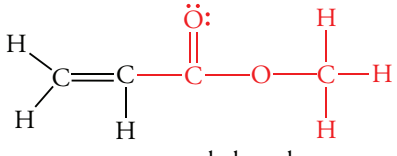
Problem 2.4 MEK is an inexpensive commercial solvent that is produced in large quantities by the chemical industry. Identify the functional group in MEK.

Answer: Ketone



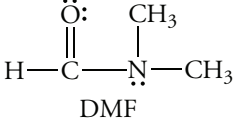
Problem 2.5 Methyl acrylate is used to produce poly(methyl acrylate), a transparent polymer found in windshields and shatter-proof glasses. Identify all functional groups in methyl acrylate.

Answer: Alkene (black), ester (red).



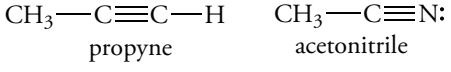
Problem 2.7 DMF is an excellent solvent for many classes of organic compounds. Identify the functional group in DMF.

Answer: Amide



Problem 2.8 Why is the carbon–nitrogen triple bond of acetonitrile (cyanomethane) shorter than the carbon–carbon triple bond of propyne?

Answer: Nitrogen is more electronegative than carbon. Therefore, the bond is more polar, and hence, shorter.

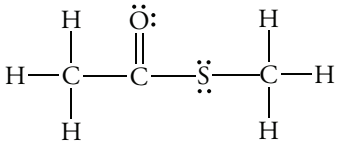


Problem 2.9

Acetyl coenzyme A is a substrate in many biochemical reactions. The structure of the simplest compound containing the functional group responsible for the activity of acetyl coenzyme A is given below. What functional group is similar to this sulfur-containing functional group? What is the O—C—S bond angle?

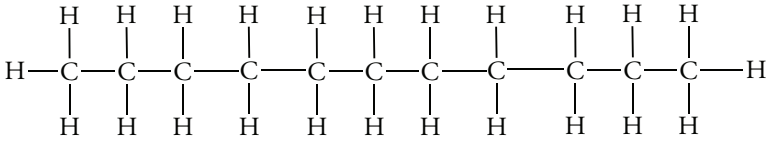
Answer:

The functional group is a thioester; the O—C—S bond angle is 120°.



Problem 2.10

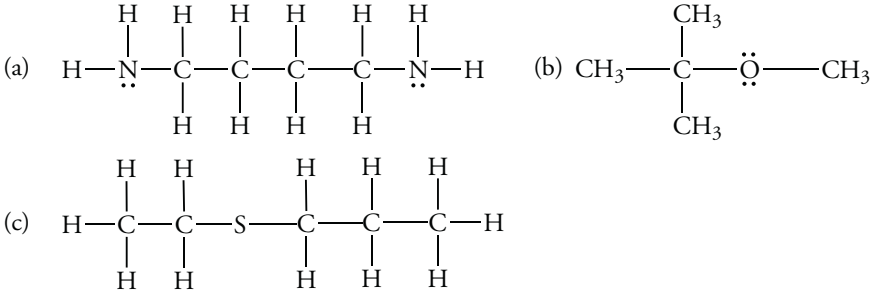
A species of cockroach secretes the substance shown below, which attracts other cockroaches. Write three condensed structural formulas for the substance.



Answers: (a) $CH_3—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3$
(b) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$
(c) $CH_3(CH_2)_9CH_2CH_3$

Problem 2.11

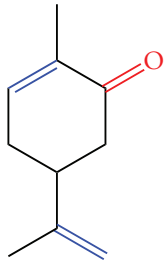
Write fully condensed formulas for each of the following structures.



Answers: (a) $NH_2(CH_2)_4NH_2$ (b) $C(CH_3)_3OCH_3$ (c) $CH_3CH_2S(CH_2)_2CH_3$

Problem 2.12 What are the functional groups of carvone, which is found in oil of caraway?

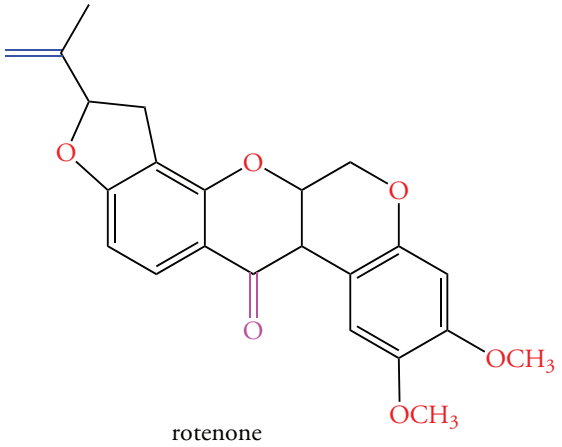
Answers: (a) ketone (red); (b) alkene (blue)



carvone

Problem 2.14 Rotenone is an insecticide used in home gardening. What oxygen-containing functional groups are in this molecule?

Answers: (a) ethers (red); (b) alkene (blue); ketone (magenta); benzene rings (black)



rotenone

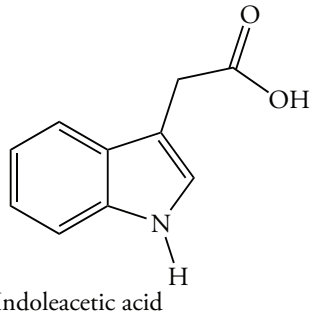
Problem 2.15 What is the molecular formula of each of the following plant growth hormones?

Answers:

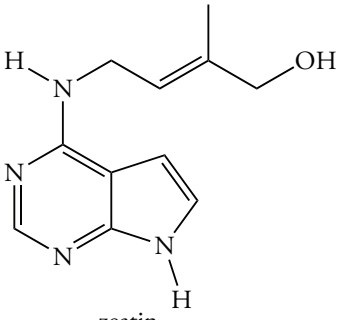
(a) Indole acetic acid, $C_{10}H_9NO_2$

(b) Zeaton, $C_{12}H_{16}N_4O$

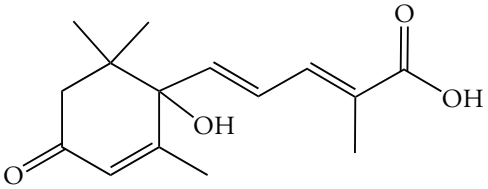
(c) Abscisic acid $C_{12}H_{20}O_4$



Indoleacetic acid
(promotes shoot growth)



zeatin
(promotes root growth)



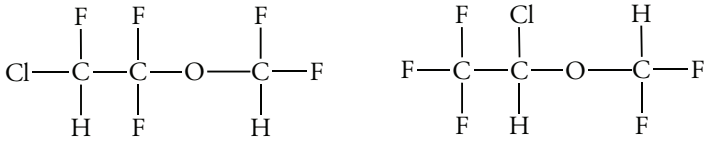
abscisic acid
(inhibits germination)

Problem 2.16

The structural formulas for two compounds used as general anesthetics are shown below. Are they isomers? How do they differ?

Answer:

They are isomers that differ in the locations of the hydrogen, fluorine, and chlorine atoms on the left most two carbon atoms. The CF_2H groups on the right-hand carbon are the same.

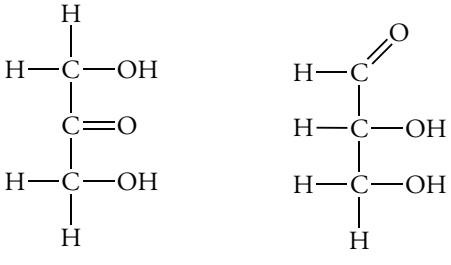


Problem 2.17

Compare the following structures of two intermediates in the metabolism of glucose. Are they isomers? How do they differ?

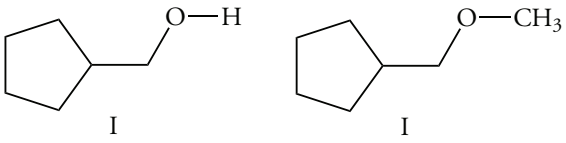
Answer:

They are isomers that differ in the locations of a hydroxyl and a carbonyl group. The compound on the left contains a ketone, and the one on the right contains an aldehyde.



Problem 2.20 Explain how you could distinguish between the following two compounds by infrared spectroscopy.

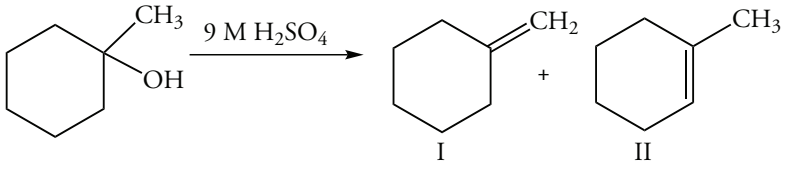
Answer: Compound I has an intense broad O—H stretching absorption in the 3400–3600 cm^{-1} region.



I I

Problem 2.21 Draw the structures of the two dehydration products of 1-methylcyclohexanol and describe how infrared spectroscopy can be used to establish their structures.

Answer: Compound I has an absorption in the 875–895 cm^{-1} region; compound II has an absorption in the 790–840 cm^{-1} region.



I II

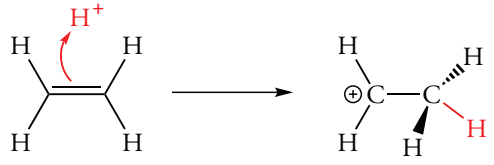
Solutions to In-Chapter Problems

Chapter 3

Acids and Bases

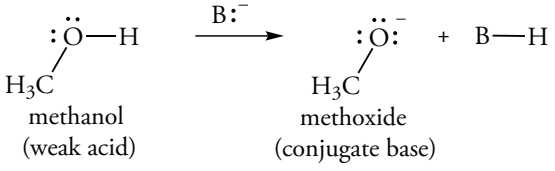
Problem 3.1 A hydrogen ion can react with ethylene to give a charged intermediate called a carbocation. Classify the reactants using Lewis acid–base nomenclature.

Answer: The π bond of the alkene is a Lewis base, and the carbocation, which has a vacant 2p orbital, is a Lewis acid.



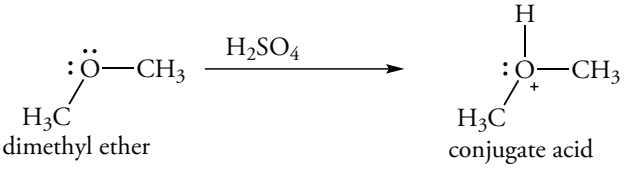
Problem 3.2 Methanol can act as either a Brønsted acid or a Brønsted base. Explain why this is the case. What is the conjugate base of methanol? What is the conjugate acid of methanol?

Answer: The hydroxyl group hydrogen is a weak Brønsted acid. If this proton is removed, the conjugate base, methoxide anion, (CH_3O^-), is a Brønsted base.



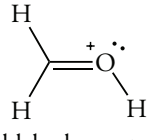
Problem 3.3 Write the structure of the cation formed by protonation of dimethyl ether (CH_3OCH_3) by sulfuric acid. What is the H–O–C bond angle? Which atom bears the formal positive charge?

Answer: The lone pair on oxygen is a Lewis base. Protonation gives the conjugate acid. The oxygen has a formal charge of +1.The oxygen is sp^3-hydridized, and the H—O—C bond angle is ~105°.



Problem 3.4 Formaldehyde reacts with acid such as HCl to form a protonated adduct. Draw the structure of the cation. What is the C–O–H Bond angle? (Note: lone pairs are not shown.)

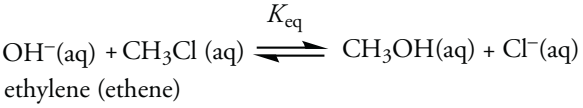
Answer: The oxygen is sp^2 hydridized, and the C—O—H bond angle is ~120°. The formal charge on oxygen is +1.



formaldehyde, protonated adduct

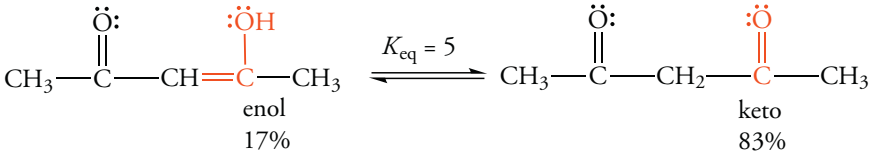
Problem 3.5 Chloromethane reacts in a substitution reaction with sodium hydroxide in aqueous solution to produce methanol and sodium chloride. Write the equilibrium constant expression for this substitution reaction. The equilibrium constant is 5×10^{16}. Is the reaction quantitative?

Answer: The equilibrium is overwhelmingly on the side of product; the reaction is quantitative.



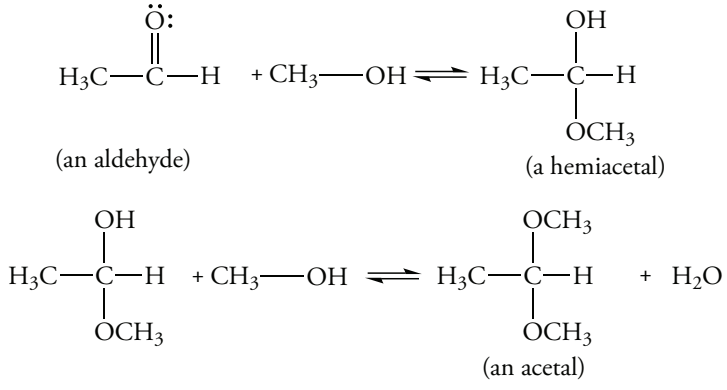
Problem 3.7 The equilibrium constant for the following rearrangement reaction, an enolization reaction, is 5. Calculate the percent composition of the equilibrium mixture.

Answer: Since the equilibrium constant is 5, there are five parts of the keto form and one part of the enol form, so the reaction mixture contains 17% of the enol form and 83% of the keto form.



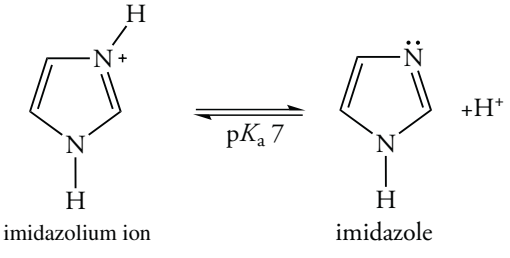
Problem 3.8 Aldehydes react with alcohols to give hemiacetals and acetals by two equilibrium reactions. What experimental conditions would increase the yield of the acetal derived from the aldehyde?

Answer: Increase the concentration of methanol and remove water from the reaction mixture.



Problem 3.9 The amino acid histidine contains an imidazole ring. The pK_a of the imidazolinium ion, the conjugate acid of imidazole, is 7.0. (a) What is the K_a of the imidazolinium ion? (b) What fraction of the conjugate acid exists as imidazole at pH 7?

Answer: Since pK_a = –log K_a, K_a = 10^{-7}. (b) Since pH = pK_a, the mixture contains 50% imidazole and 50% imidazolium ion.

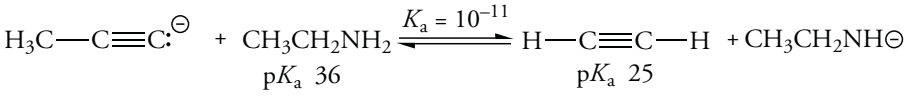


Problem 3.10 The pK_b values for diethylamine and triethylamine are 3.51 and 2.99, respectively. Which compound is the stronger base? What are the pK_a values for the related ammonium ions? Which ammonium ion is the stronger acid?

Answer: Triethylamine is a stronger base than diethyl amine. Since pK_a + pK_b = 14, the pK_a of triethyl ammonium ion is 10.49, and the pK_a value of diethyl ammonium ion is 11.01.

Problem 3.11 Given the pK_a values of acetylene (25) and amide anion (36), predict the position of the equilibrium for the reaction shown below. That is, is the equilibrium constant greater or less than 1.0?

Answer: Since the conjugate base of ethylamine is much stronger than the conjugate base of acetylene, the equilibrium constant lies far on the side of reactants. The equilibrium constant is ~10^{-11}.



Problem 3.13 The pK_a values of ethanol and 2,2,2-trifluoroethanol are 15.9 and 12.4, respectively. What is responsible for this difference?

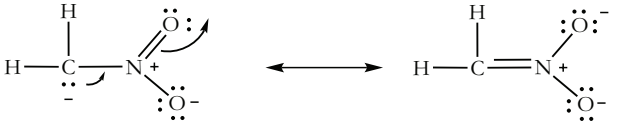
Answer: The three strongly electron-withdrawing atoms in 2,2,2-trifluoroethanol withdraw electron density from the O—H bond by an inductive effect, greatly increasing its acidity. The electron-withdrawing effect of the fluorine atoms also stabilizes the conjugate base.

$CH_3—CH_2—OH$	$CF_3—CH_2—OH$
ethanol	2,2,2-trifluoroethanol
pK_a = 15.9	pK_a = 12.4

Problem 3.14

The pK_a values of nitromethane and methane are 10.2 and approximately 49, respectively. What is responsible for this difference?

Answer: The conjugate base of nitromethane is resonance stabilized, greatly increasing its acidity.



resonance-stabilized conjugate base of nitromethane

Problem 3.15

Based on periodic trends and structurally similar compounds, predict which is the stronger acid, $CH_3O—H$ or $CH_3S—H$.

Answer: The S—H bond in methyl sulfide is longer and weaker than the O—H bond in methanol, so CH_3SH is a stronger acid.

Problem 3.17 The $\Delta G°_{rxn}$ for the addition reaction of HBr to ethylene at 25 °C is –50 kJ mole^{-1}. Calculate K_{eq} at this temperature.

$$\underset{\text{ethylene}}{CH_2=CH_2} + HBr \longrightarrow \underset{\text{bromoethane}}{CH_3—CH_2—Br}$$

Answer: Substituting the values of $\Delta G°_{rxn}$ and temperature (25 °C = 298 K) in the equation $\Delta G°_{rxn} = 2.3\ RT \log K_{eq}$, where R = 4.184 KJ mole^{-1}, gives a value for K_{eq} of 2.7×10^7.

Problem 3.18 Using the following $\Delta G°_{rxn}$ values for the addition of HBr to propene to give two possible bromoalkanes, determine which product is the more stable.

$$\underset{\text{propene}}{CH_3—CH=CH_2} + HBr \longrightarrow \underset{\text{1-bromopropane}}{CH_3—CH_2—CH_2—Br} \qquad \Delta G°_{rxn} = -31.9 \text{ kJ mole}^{-1}$$

$$\underset{\text{propene}}{CH_3—CH=CH_2} + HBr \longrightarrow \underset{\text{2-bromopropane}}{CH_3—CHBr—CH_3} \qquad \Delta G°_{rxn} = -36.6 \text{ kJ mole}^{-1}$$

Answer: 2-Bromopropane is more stable than 1-bromopropane, and the value of $\Delta G°_{rxn}$ is more negative for 2-bromopropane.

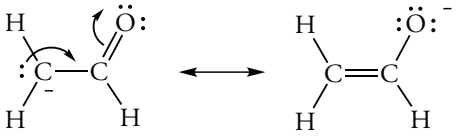
Problem 3.19

Trichloromethane ($CHCl_3$) is a stronger acid (pK_a = 25) than methane (pK_a = 49). Explain this difference based on the stability of the respective conjugate bases.

Answer: The three strongly electron-withdrawing atoms in trichloromethyl anion stabilize the conjugate base.

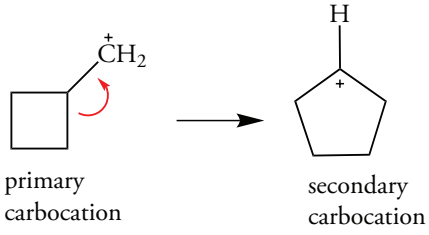
Problem 3.20
The conjugate base derived from ethanal (acetaldehyde) is more stable than the conjugate base of ethane. Explain why.

Answer: The conjugate base of ethanal is resonance stabilized, and the conjugate base of ethane is not.



Problem 3.21 Explain whether you expect the following carbocation rearrangement to be favorable based on the stabilities of the reactant and product.

Answer: The carbocation rearrangement is favorable because a primary carbocation is converted to a more stable secondary carbocation.



Problem 3.22 The rate constant for the nucleophilic substitution reaction of CH_3Br with °C is 6.6×10^{-4} L mole^{-1} s^{-1} at 310 K. Compare this value to the rate constant for the reaction of CH_3C1 with OH^- (Table 3.6). Which reaction is faster? What does this information indicate about the leaving group characteristics of Cl^- and Br^-?

Answer: The reaction with CH_3Br is faster, indicating that the bromide ion is the better leaving group.

Problem 3.23 Bromoethane reacts with cyanide ion according to the following equation. When the concentration of the cyanide ion is doubled, the rate of the reaction is doubled. When the concentration of bromoethane is tripled, the rate of the reaction is tripled. What is the kinetic order with respect to each reactant? What is the overall kinetic order of the reaction? Write the rate equation for the reaction.

Answer: The reaction is first order in each reactant, and second order overall. The rate expression is as follows: rate = k [CH_3CH_2Br][CN^-]

$$CH_3—CH_2—Br + :C{\equiv}N:^- \longrightarrow CH_3—CH_2—C{\equiv}N + Br^-$$

Problem 3.24 The rate constants for the nucleophilic substitution reaction with hydroxide ion with CH_3CI and CH_3Br at 310 K are 3.2×10^{-5} and 6.6×10^{-4} L mole^{-1} s^{-1}, respectively. Which reaction has the larger E_a?

Answer: The slower reaction has the higher activation energy.

Problem 3.25 The hydrolysis reaction of ethyl ethanoate (ethyl acetate) in basic solution occurs in three steps. How many transition states are there? How many intermediates form in this reaction?

Answer: The reaction has three transition states; there are two intermediates.

Solutions to In-Chapter Problems

Chapter 4

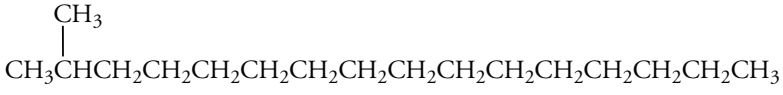
Problem 4.1 One of the components of the wax of a cabbage leaf is a normal alkane containing 29 carbon atoms. What is the molecular formula of the compound?

Answer: For $n = 29$, there must be $(2 \times 29) + 2$ hydrogen atoms. The molecular formula is $C_{29}H_{60}$.

Problem 4.2 Hectane is a normal alkane with 100 carbon atoms. What is the molecular formula of hectane?

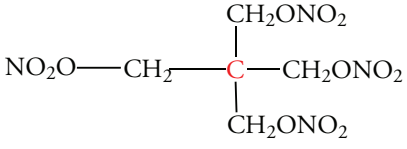
Answer: For $n = 100$, there must be $(2 \times 100) + 2$ hydrogen atoms. The molecular formula is $C_{100}H_{102}$.

Problem 4.3 The following compound is a sex attractant released by the female tiger moth. Classify the carbon atoms in this compound as primary, secondary, or tertiary.



Answer: The carbon atoms at the ends of the chain are primary; C-2 is tertiary; all the others are secondary.

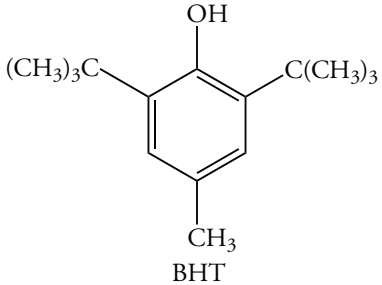
Problem 4.4 Pentaerythritol tetranitrate is used to reduce the frequency and severity of angina attacks. Classify the carbon atoms in this compound.



Pentaerythritol tetranitrate

Answer: The carbon atom shown in red is quaternary; all the others are primary.

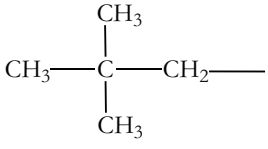
Problem 4.9 The food preservative BHT has the following structure. Identify the alkyl groups bonded to the benzene ring.



BHT

Answer: The CH_3— group is a methyl group, the $C(CH_3)_3$— group is a tertiary-butyl group.

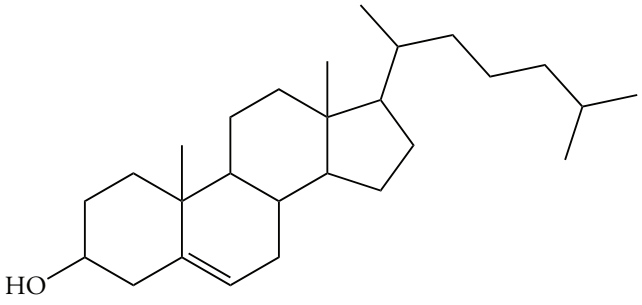
Problem 4.10 The common name for the five-carbon alkyl group with a quaternary carbon atom is neopentyl. What is its IUPAC name?



neopentyl

Answer: The IUPAC name for neopentyl is 2,2-dimethylpropyl.

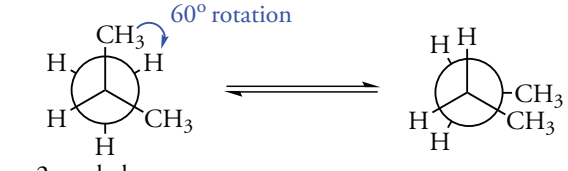
Problem 4.11 Name the eight-carbon alkyl group that is bonded to the five-membered ring of cholesterol.



cholesterol

Answer: The eight-carbon alkyl chain of cholesterol is a 1,5-dimethylhexyl group.

Problem 4.12 Predict the energy difference between the eclipsed and staggered conformations of 2-methylpropane around the C-1 to C-2 bond.

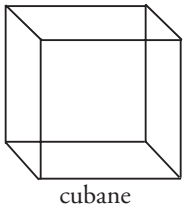


2-methylpropane (staggered conformation)

2-methylpropane (eclipsed conformation)

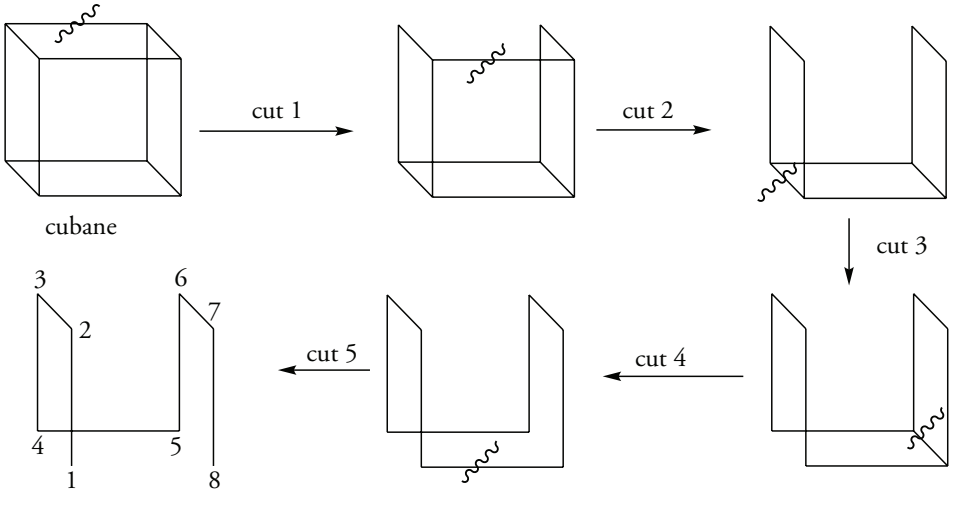
Answer: Rotation around the C-1 to C-2 bond is equivalent to rotation around the C-1 to C-2 bond of propane. The energy barrier is the same, 13.7 kJ $mole^{-1}$.

Problem 4.14 Cubane, classified as a pentacyclic compound, appears to have six rings. Apply the bond-cutting procedure to show that it really does have five rings.



cubane

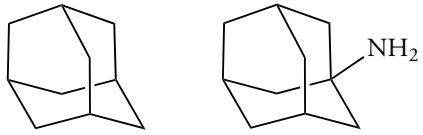
Answer: Cubane is a six-sided molecule, so cutting it in five places gives a single, noncyclic molecule, octane!



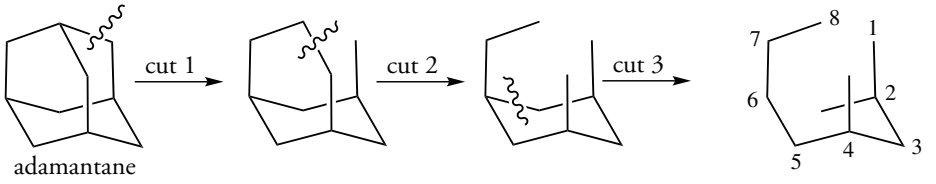
cubane

octane

Problem 4.15 Adamantane has a carbon skeleton also found as part of the structure of diamond. Amantadine, which has an amino group bonded to the adamantane structure, is useful in the prevention of infection by influenza A viruses. What are the molecular formulas of adamantane and amantadine? How many rings are in each structure?



Answer: The formulas of adamantane and amantadine are $C_{10}H_{16}$ and $C_{10}H_{17}N$; each molecule is tricyclic. The result of cutting admanantane in three places is 2,4-dimethyloctane



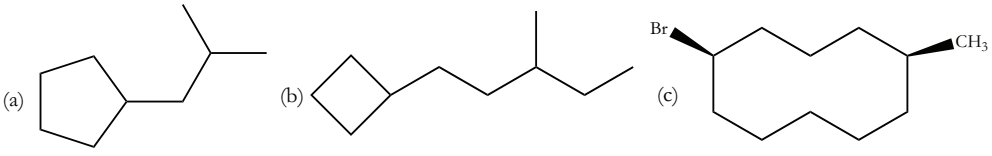
Problem 4.16 Disparlure, the sex attractant pheromone of the female gypsy moth, has the following general structure. Are geometric isomers possible for this molecule?



disparlure

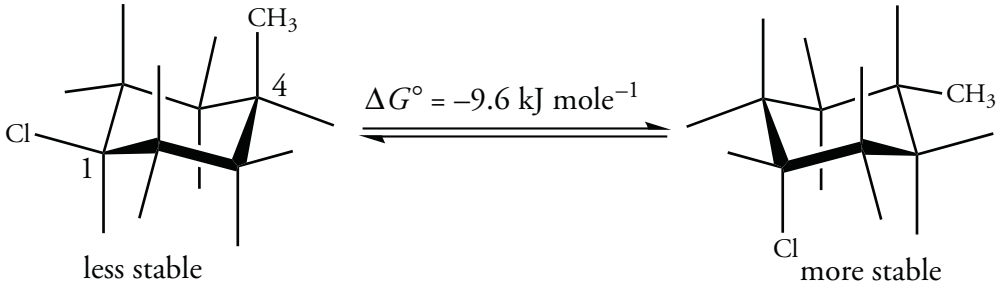
Answer: Yes, the two alkyl groups of the epoxide can be either *cis* or *trans* to each other.

Problem 4.17 What are the names of the following compounds?



Answers: (a) Isobutylcyclopentane, (b) 1-cyclobutyl-3-methylpentane, (c) *cis*-1-bromo-5-methyl-cyclodecane

Problem 4.18 Draw the chair conformations of *cis*-1-chloro-4-methylcyclohexane and determine the most stable conformation. Use the data in Table 4.6 to determine the energy difference for the two conformations.



cis-1-chloro-4-methylcyclohexane

Answers: The methyl group has a greater conformation preference (7.6 kJ per 1,3 diaxial interaction) than the chlorine atom (2.8 kJ per 1,3 diaxial interaction). Therefore, the predominant conformation has an axial chlorine atom and an equatorial methyl group.

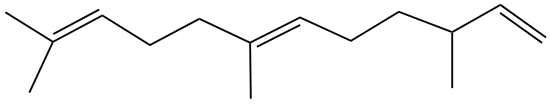
Solutions to In-Chapter Problems

Chapter 5

Problem 5.1 The C—Cl bond energy in chloroethane is 341 kJ mole^{-1}, for chloroethene (CH_2=CHCl) is 368 kJ mole^{-1}. Why is the bond in chloroethene stronger? The C—C1 bond length in chloroethane is 178 pm. Explain whether you expect the C—Cl bond length in chloroethene to be longer or shorter than the C—Cl bond in chloroethane.

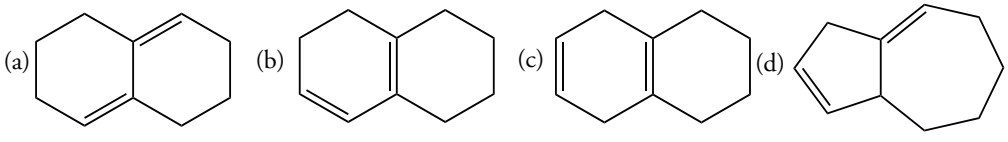
Answer: The carbon atom in chloroethene is sp^2 hybridized and forms shorter and stronger bonds than the sp^3-hybridized carbon atom of chloroethane. The C—C1 bond length should be about 2% shorter, or 175 pm.

Problem 5.3 Classify each of the three double bonds of farnesene, a compound found in the waxy coating of apples.



Answer: Farnesene contains a terminal double bond on the right with two hydrogen atoms bonded to it. Thus, it is monosubstituted. The double bond in the "middle" is disubstituted, and the double bond on the left is trisubstituted.

Problem 5.4 Classify each of double bond in the following isomeric dienes. Which compounds contain conjugated double bonds?



Answers: (a) Two conjugated trisubstituted double bonds. (b) The double bond on the left is disubstituted; the one in the center is tetra substituted. They are conjugated. (c) The double bond on the left is disubstituted; the one on the center is tetrasubstituted. They are *not* conjugated. (d) The double bond on the left is disubstituted; the one on the center is trisubstituted. They are *not* conjugated.

Problem 5.6 Based on its location in the periodic table, how should sulfur be treated in the calculation of the degree of unsaturation of a sulfur-containing organic compound?

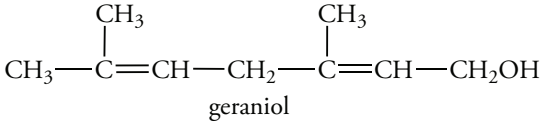
Answer: Sulfur is in the same group as oxygen. Thus, there is no effect on the degree of unsaturation calculation.

Problem 5.7 Calculate the unsaturation number for each of the following.

(a) $C_{10}H_{16}$ (b) $C_8H_{10}Br_2$ (c) $C_6H_6O_3$ (d) $C_5H_6N_2$

Answer: (a) 3 (b) 3 (c) 4 (d) 4

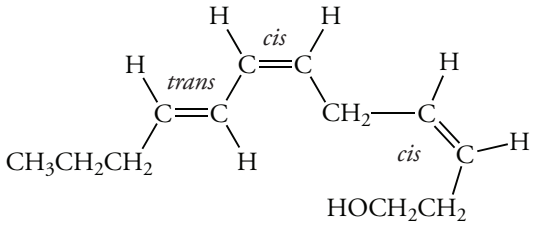
Problem 5.8 Is *cis-trans* isomerism possible around either of the double bonds of geraniol, a natural oil?



geraniol

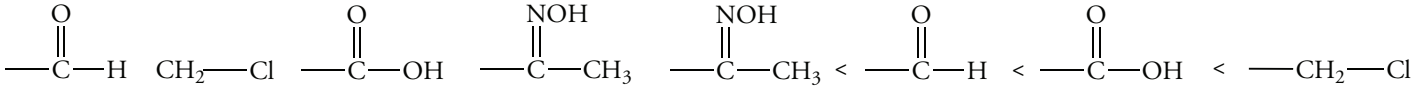
Answer: (a) The double bond on the left is bonded to two methyl groups; so *cis*/*trans* isomers are impossible. (b) The double bond on the right has two different substituents, so *cis*/*trans* isomers are possible.

Problem 5.9 Determine the *cis-trans* geometry around the double bonds in the following compound, a trail pheromone of termites. (The chain is numbered starting from the carbon atom with the hydroxyl group.) How many geometric isomers are possible for the structure?



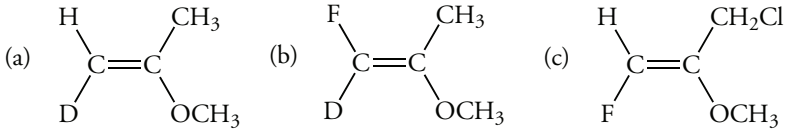
Answers: (a) The double bond on the left is *trans*; the other two are *cis*. There are a total of 2^3, or 8 possible geometric isomers.

Problem 5.10 Rank the following sets of substituents in the order of increasing priority according to the Cahn–Ingold–Prelog rules.



Answer:

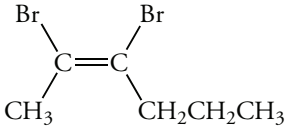
Problem 5.12 Assign *E* or *Z* to each of the following structures.



Answer: (a) *Z* (b) *E* (c) *Z*

Problem 5.13 Name the following compound.

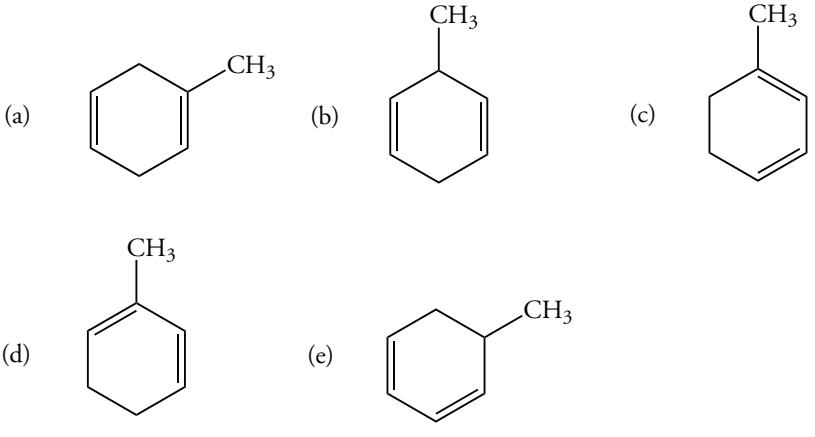
Answer: (*Z*)-2,3-dibromo-2-hexene



Problem 5.14 Draw the structures of the following isomeric compounds.

(a) 1-methyl-1,4-cyclohexadiene
(b) 3-methyl-1,4-cyclohexadiene
(c) 1-methyl-1,3-cyclohexadiene
(d) 2-methyl-1,3-cyclohexadiene
(e) 5-methyl-1,3-cyclohexadiene

Answers:

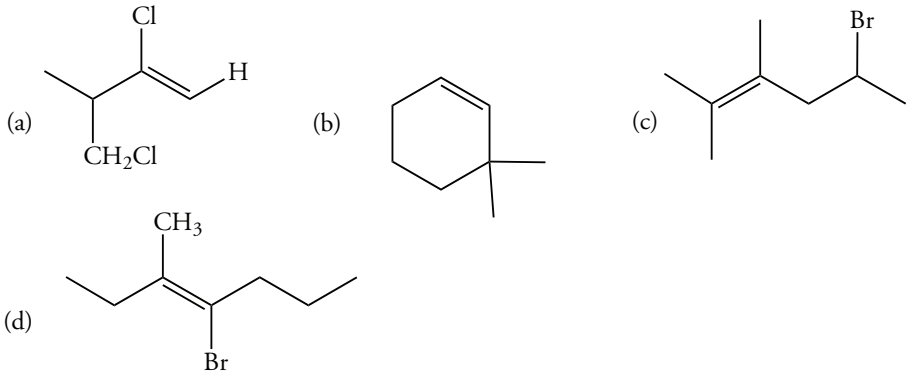


Problem 5.15 Draw the structure of each of the following compounds.

(a) (*E*)-1,3-dichloro-2-methy1-3-hexene (b) 3,3-dimethylcyclohexene

(c) 5-bromo-2,3-dimethyl-2-hexene (d) (*Z*)-4-bromo-3-methyl-3-heptene

Answers:

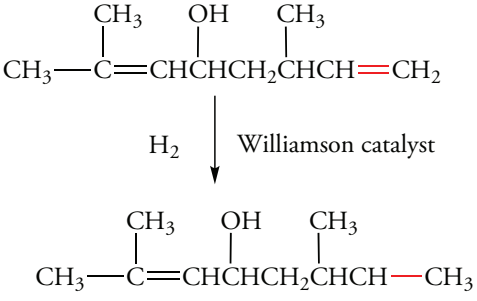


Problem 5.17 Explain why acetic acid (CH_3CO_2H) and ethyl acetate ($CH_3CO_2CH_2CH_3$) can be used as solvents for catalytic hydrogenation of alkenes.

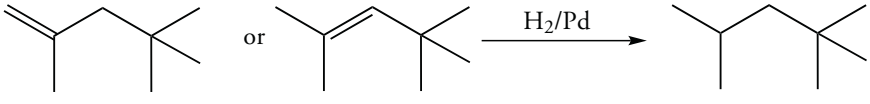
Answer: The carbonyl group of carboxylic acids and esters is not easily reduced.

Problem 5.18 Write the structure obtained by hydrogenation of ipsdienol, a pheromone of the Norwegian spruce beetle, using one equivalent of hydrogen gas and the Wilkinson catalyst.

Answer: The reaction is regioselective. Only the monosubstituted double bond is reduced.



Problem 5.19 A mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene is obtained in the commercial dimerization of 2-methylpropene. Hydrogenation of the mixture gives a single product. Draw the structures of the alkenes and the product. Explain why a single product forms.

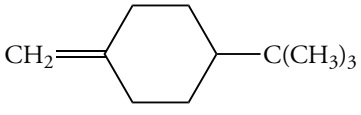


Answer: The isomers differ only in the position of the double bond; hydrogenation gives the same saturated product.

Problem 5.20 Squalene, an intermediate in the biosynthesis of steroids, has the molecular formula $C_{30}H_{50}$. Hydrogenation yields a compound with molecular formula $C_{30}H_{62}$. What is the unsaturation number of squalene? Does the compound contain any rings?

Answer: The unsaturation number is 6. Squalene does not have any rings.

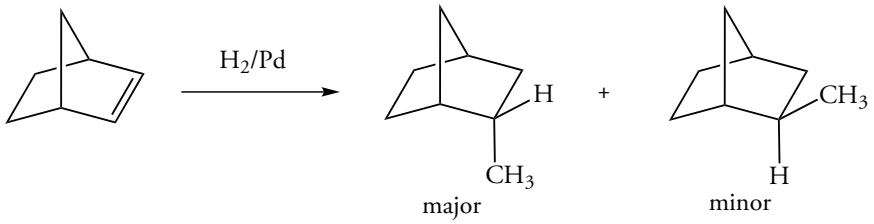
Problem 5.21 Catalytic hydrogenation of the following compound gives a mixture of *cis*- and *trans*-1-*tert*-buty1-4-methylcyclohexanes in a 7:1 ratio. Explain why.



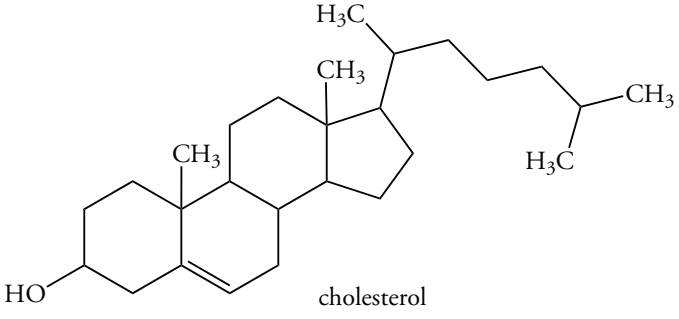
Answer: Approach of hydrogen from the "top" to give the equatorial methyl group is more hindered than the alternate approach to give the axial methyl group. The major product is the *cis* isomer.

Problem 5.22 Draw the structures of the two products obtained by hydrogenation of the following unsaturated bicyclic compound. Will they be obtained in equal amounts?

Answer:
Approach from the bottom side of the bicyclic ring is more sterically hindered than approach from the top.

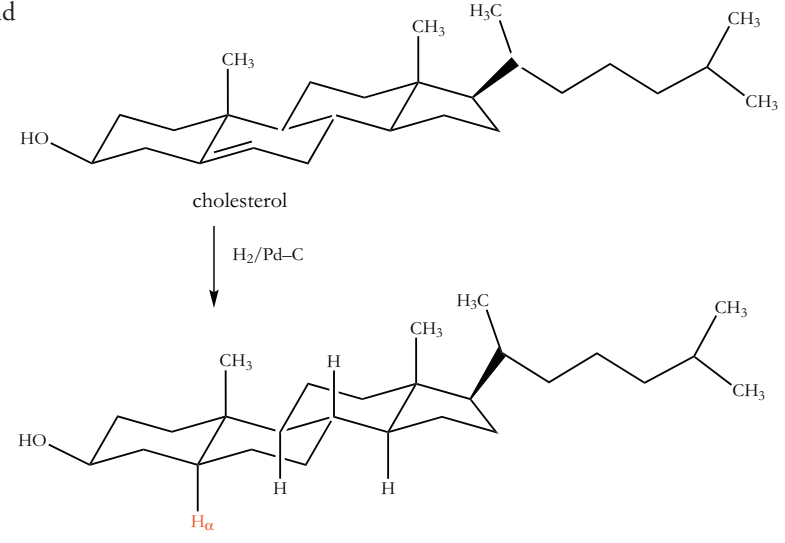


Problem 5.23 Predict the stereochemistry of the product obtained by catalytic hydrogenation of cholesterol. The six-membered rings are all in the chair conformation, and the methyl groups at the bridgehead positions are axial.



cholesterol

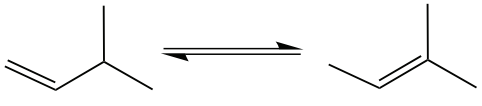
Answer: Hydrogen will add from "below" the AB ring, and give an axial C—H bond at C-5.



Problem 5.24 Explain why the stability of 2-methyl-l-propene can be compared to the stability of the isomeric butenes using heat of combustion data, but these stabilities cannot be directly compared using heat of hydrogenation data.

Answer: The products are the same in the combustion reaction regardless of the hydrocarbon skeleton. Hydrogenation of alkenes with different hydrocarbon skeletons does not give the same saturated product.

Problem 5.25 The heats of hydrogenation of 3-methyl-1-butene and 2-methyl-2-butene are 127 and 113 kJ mole^{-1}, respectively. Assuming that the following equilibrium reaction can be established, predict the $\Delta H^{\circ}_{\text{reaction}}$.

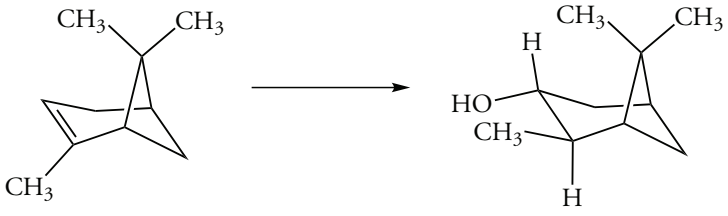


Answer: The enthalpy change for this equilibrium is simply the difference between the heats of hydrogenation of the reactant and products; that is, 14 kJ mole^{-1}.

Solutions to In-Chapter Problems

Chapter 6

Problem 6.1 In hydroboration–oxidation, a reaction sequence used to synthesize alcohols, α-pinene is converted to the alcohol shown below. What molecule has been added to the alkene? What is the stereochemistry of the addition reaction?

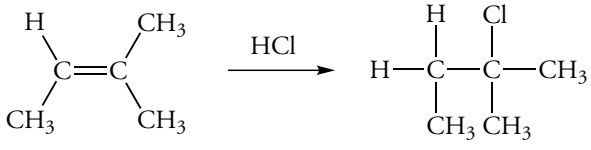


Answer: The net result of the reaction is *syn* addition of water; it is *anti*-Markovnikov.

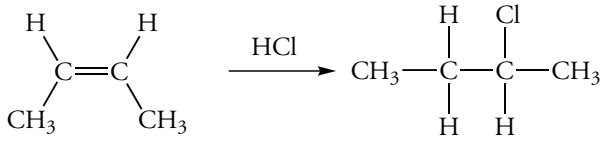
Problem 6.2 Predict the product(s) formed when HCl adds to each of the following.
(a) 2-methyl-2-butene (b) (*Z*)-2-butene (c) (*E*)-2-pentene

Answers:

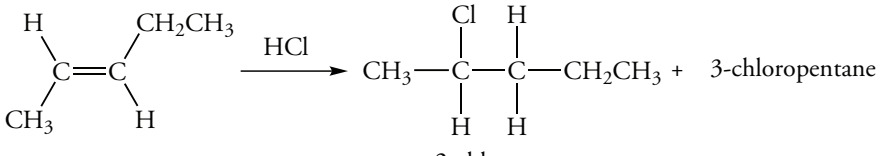
(a)



(b)



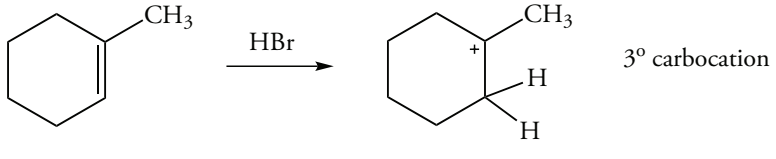
(c)



Problem 6.4 Write the structure of the carbocation formed in the addition reaction of HBr with each of the following alkenes.
(a) 1-methylcyclohexene (b) (*Z*)-2-butene (c) 4-methyl-1-pentene

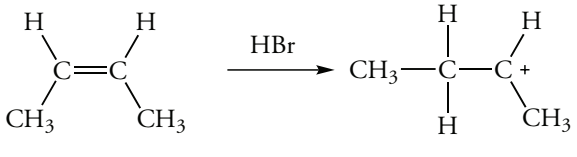
Answers:

(a)



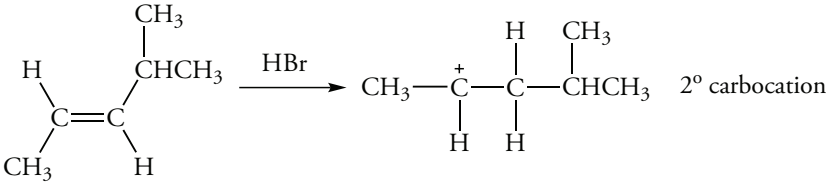
3° carbocation

(b)



2° carbocation

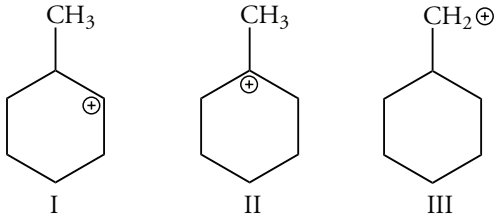
(c)



2° carbocation

Problem 6.5 Rank the following carbocations in the order of their stabilities.

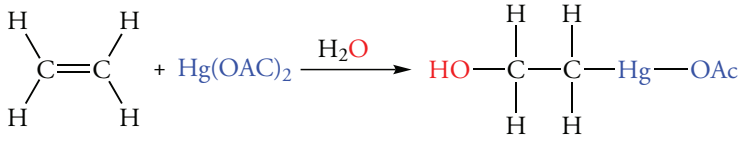
Answer: The order of stability is III < I < II; that is 1° < 2° < 3° carbocation.



Problem 6.6 Reaction of either 1-butene or 2-butene with HBr gives the same product, 2-bromobutane. The reaction of 1-butene is faster than the reaction of 2-butene, even though both reactions proceed via a common carbocation intermediate. What is responsible for the difference in the observed rates?

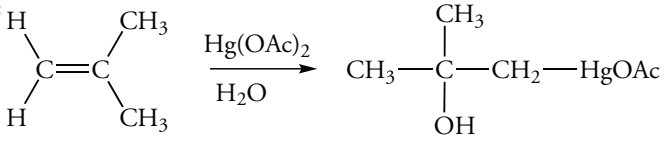
Answer: 1-Butene is less stable than 2-butene and is of higher energy. Thus, it is closer in energy to the transition state.

Problem 6.9 One of the steps in the indirect hydration of alkenes (Section 16.8) is the electrophilic addition of mercuric acetate, $Hg(OAc)_2$, a covalent compound, according to the following equation. What is the electrophile? Predict the structure of the product of the reaction of mercuric acetate with 2-methyl-1-propene.



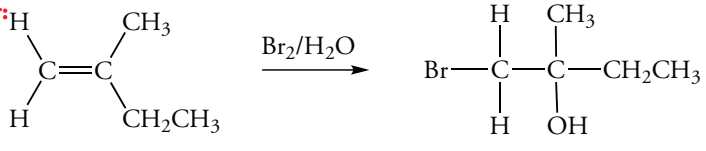
Answer: The electrophile is the oxymercurium ion, $^{+}Hg(OAc)$. The reaction occurs by Markovnikov addition of the oxymercurium ion. The product is shown below.

Answer:



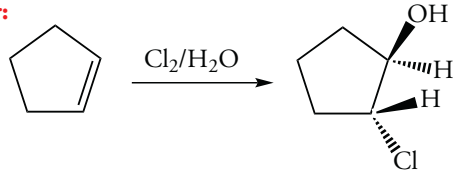
Problem 6.10 Give the structure of the product formed when 2-methyl-1-butene reacts with bromine in aqueous solution.

Answer:



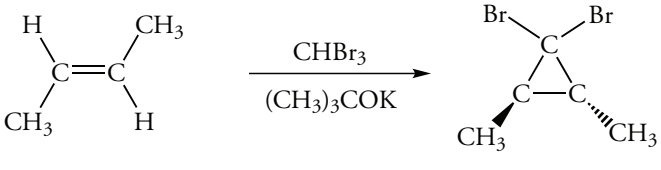
Problem 6.11 Give the structure of the product formed when cyclopentene reacts with chlorine in aqueous solution. What is the stereochemistry of the product?

Answer:

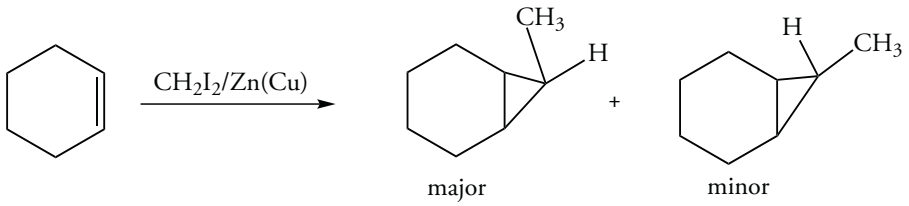


Problem 6.12 Write the expected product of the reaction of *trans*-2-butene with $CHBr_3$ and potassium *tert*-butoxide.

Answer:



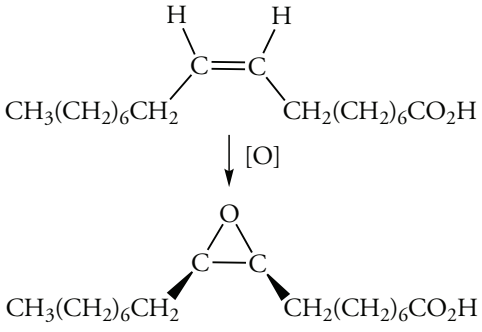
Problem 6.13 1,1-Diiodoethane and Zn(Cu) react with cyclohexene to give a mixture of two isomers with the formula C_8H_{14}. (a) What are their structures? (b) Why does one isomer predominate?



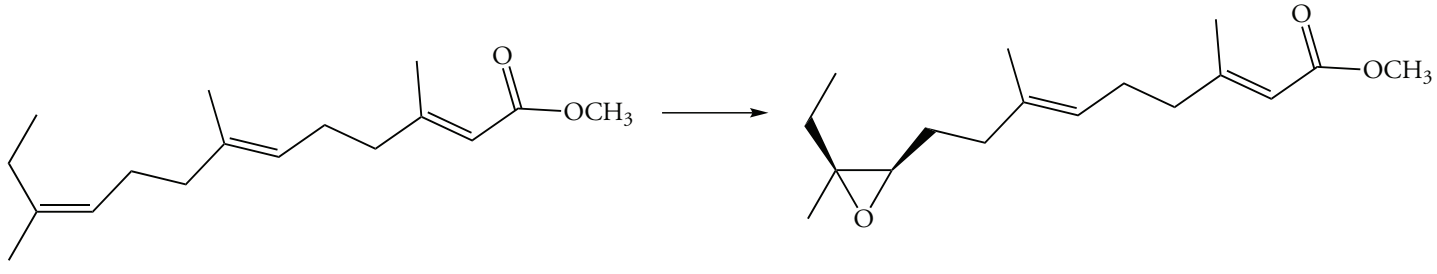
Answer: The ethylidene can approach so that the methyl group is over the cyclohexene ring or directed away from it.

Problem 6.14 Microbial oxidation of oleic acid yields an epoxide. Write the structure of the product.

Answer:



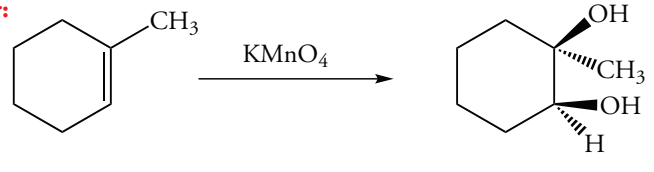
Problem 6.16 Epoxidation of the following compound in a laboratory synthesis gives a 40% yield of the juvenile hormone of insects. Explain why only a 40% yield is obtained.



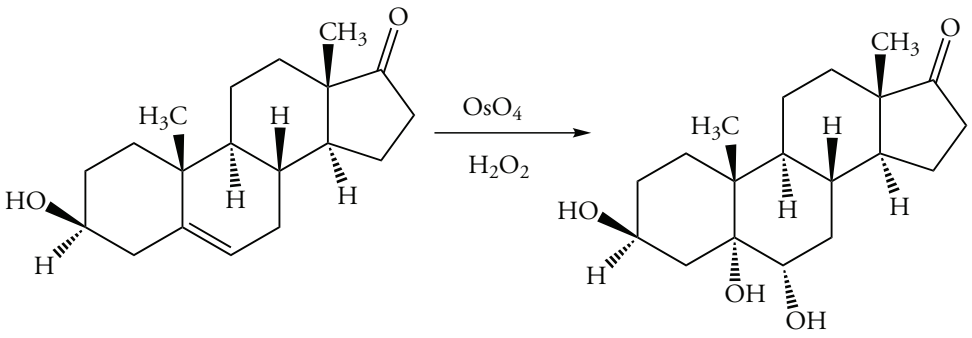
Answer: Any of the three trisubstituted double bonds can react. If all were identically reactive, there would be 33% of the desired product.

Problem 6.17 Write the product of the reaction of potassium permanganate with 1-methylcyclohexene under basic conditions.

Answer:

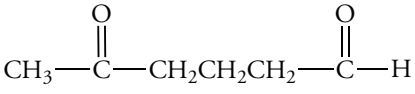


Problem 6.19 Dihydroxylation of the following steroid gives only the indicated product. Based on the mechanism of the reaction, and the stereochemistry of the product, explain why only one diol forms.



Answer: Approach of the reagent occurs from the "bottom" of the ring because the top face is sterically hindered by the axial methyl group.

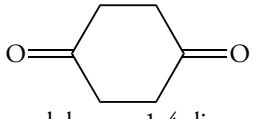
Problem 6.20 A hydrocarbon of molecular formula C_6H_{10} reacts with ozone followed by treatment with zinc and acetic acid to give 5-ketohexanal. Draw the structure of the hydrocarbon.



5-ketohexanal

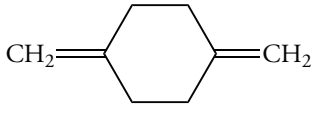
Answer: The two carbonyl carbons must have been linked by a carbon–carbon double bond. Since one of the carbonyl groups is part of an aldehyde and the other part of a ketone, the original compound was 1-methylcyclopentene.

Problem 6.21 A hydrocarbon of molecular formula C_8H_{12} reacts with O_3 followed by workup with $(CH_3)_2S$ to give formaldehyde and cyclohexane-1,4-dione. Draw the structure of the hydrocarbon.



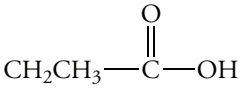
cyclohexane-1-4-dione

Answer:

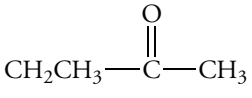


Answer: Since formaldehyde was produced along with the dione shown above, the original compound must have had two methylene groups rather than carbonyl groups.

Problem 6.23 A hydrocarbon of molecular formula C_7H_{14} reacts with O_3 followed by an oxidative workup to give propanoic acid and 2-butanone. Does this information unambiguously establish the structure of the hydrocarbon?



propanoic acid



2-butanone

Answer: No, because either the *E* or *Z* isomer of 3-methyl-3-hexene would give these products.

Solutions to In-Chapter Problems

Chapter 7

Problem 7.1 Based on hybridization considerations alone, predict the C-2 to C-3 bond length of 1-buten-3-yne.

$CH_2{=}CH{-}C{\equiv}C{-}CH_3$

1-buten-3-yne

Answer: Since the sp^2–sp^2 bond length in ethene is 105 pm and the sp–sp bond length in ethyne is 109 pm, based on hybridization effects alone we expect the C-2 to C-3 sp^2–sp bond length to be 142 pm.

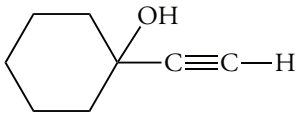
Problem 7.3 1,3,11-Tridecatriene-5,7,9-triyne is a compound found in safflowers and used as a chemical defense against nematode infestations. Write its structure.

Answer: $CH_2{=}CH{-}CH{=}CH{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}CH{-}CH_3$

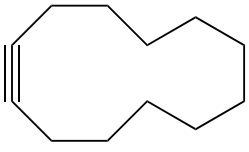
Problem 7.4 Write the structure of each of the following compounds.
(a) 1-ethynylcyclohexanol (b) cyclododecyne (c) 4-methyl-1,6-heptadiyne

Answers:

(a)



(b)



(c) $H{-}C{\equiv}C{-}CH_2CH(CH_3)CH_2{-}C{\equiv}C{-}H$

Problem 7.5 The heats of hydrogenation of 1-butyne and 2-butyne are 292 and 274 kJ $mole^{-1}$, respectively. Which compound is more stable? Why?

Answer: 2-Butyne because the multiple bond has more alkyl substituents.

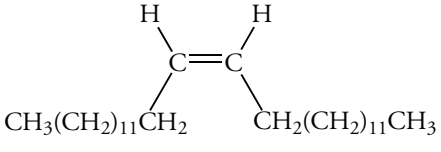
Problem 7.6 One of the intermediate compounds in the synthesis of the spruce budworm sex pheromone is (*E*)-11-tetradecen-1-ol. How can this compound be produced from a substituted alkyne? Name the alkyne.

Answer: Reduction of 11-tetradecyn-1-ol using sodium and liquid ammonia.

$$HO{-}CH_2(CH_2)_8CH_2{-}C{\equiv}C{-}CH_2CH_3$$

Problem 7.7 The IUPAC name of muscalure, the sex hormone of the housefly, is (*Z*)-9-tricosene. How can this compound be produced from a structurally related alkyne? Name the alkyne.

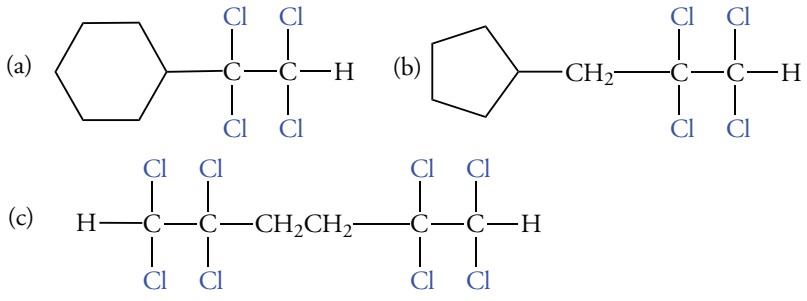
Answer: Reduction of 9-tricosyne using the Lindlar catalyst.



muscalure

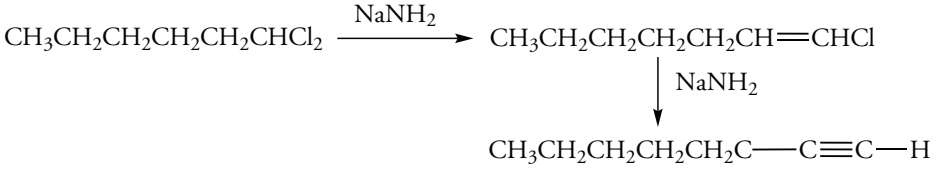
Problem 7.8 Write the structure of the product formed in the reaction of excess chlorine with each of the following compounds.
(a) ethynylcyclohexane (b) propargylcyclopentane (c) 1,5-hexadiyne

Answers:



Problem 7.10 The double dehalogenation of a geminal dihalide can be used to form alkynes. Write the steps for the reaction of 1,1-dichlorohexane and NH_2^-/N_3. What limitations might one encounter if the reaction were attempted with 2,2-dichlorohexane?

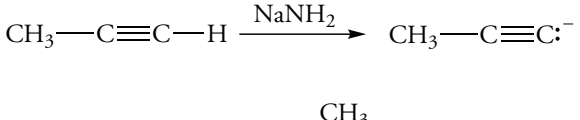
Answer: Both 1-hexyne and 2-hexyne can form as well as 1,2-hexadiene.

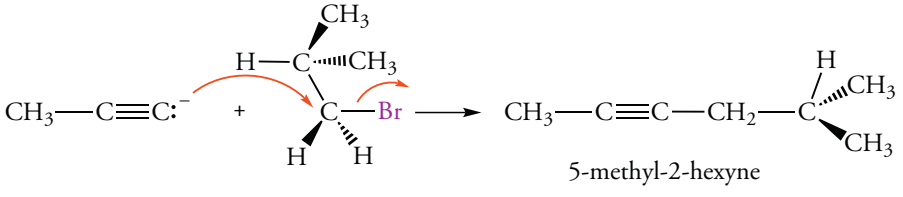


Problem 7.11 Sodium amide reacts with acetylene to give sodium acetylide. Removal of a second proton by the amide ion does not occur under ordinary conditions. Explain why.

Answer: The second ionization constant of an acid is always smaller than the first ionization constant. It is more difficult to remove a proton from a negatively charged substance, in this case the acetylide ion.

Problem 7.12 Suggest a method to prepare 5-methyl-2-hexyne using reagents containing no more than four carbon atoms.





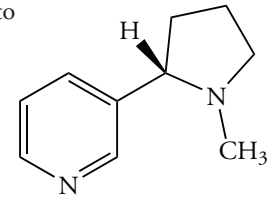
5-methyl-2-hexyne

Solutions to In-Chapter Problems

Chapter 8

Problem 8.1 The structure of nicotine is shown below. Is nicotine chiral?

Answer: Yes, the carbon atom bonded to the benzene ring is a stereogenic center.

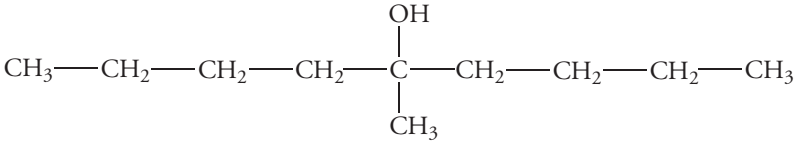


nicotine

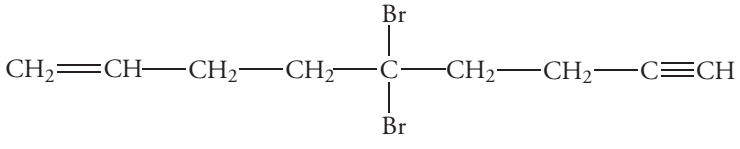
Problem 8.2 Which of the following structures can represent a chiral molecule? Why

Answer: Only (c) is chiral, (a) has two equivalent butyl groups, and (b) has two equivalent bromine atoms.

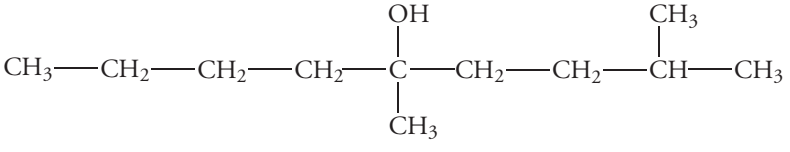
(a)



(b)



(a)



Problem 8.4 What is the $[\alpha]_D$ of the enantiomer of naturally occurring testosterone? (See Table 8.1) What is the name of this enantiomer?

Answer: Since the $[\alpha]_D$ of naturally occurring testosterone is +109°, its enantiomer has an $[\alpha]_D$ of –109°. Its name is (–)-testosterone.

Problem 8.5 A sample of a solution of 1.5 g of cholic acid, a bile steroid, in 10 mL of alcohol is placed in a 10.0-cm tube. The observed rotation is +5.5. Calculate $[\alpha]_D$ for cholic acid.

Answer: The $[\alpha]_D$ of cholic acid is 36.7°.

Problem 8.7

Write the Fischer projection formula of each of the following compounds.

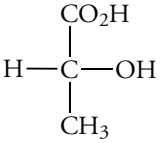
(a) D-lactic acid, $CH_3CH(OH)CO_2H$

(b) L-serine, $HOCH_2CH(NH_2)CO_2H$

(c) D-valine, $(CH_3)_2CHCH\ (NH_2)CO_2H$

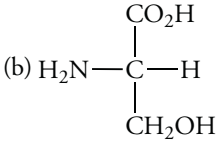
Answers:

(a)



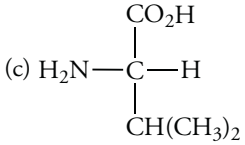
D-lactic acid

(b)



L-serine

(c)

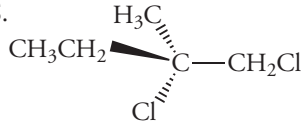


L-valine

Problem 8.8

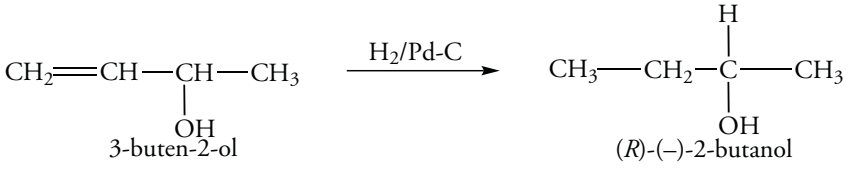
Assign the configuration of the following stereoisomer of 1,2-dichloro-2-methylbutane.

Answer: It is S.



Problem 8.10 Reduction of (–)-3-buten-2-ol with hydrogen over a palladium catalyst gives (–)-2-butanol. Does the same sign of rotation establish that the relative configurations of the two compounds are the same? Based on the mechanism of catalytic hydrogenation, can you establish the relative configuration of the two compounds? If (–)-3-buten-2-ol has the *R* configuration, what is the configuration of (–)-2-butanol?

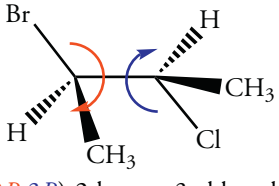
Answer: No, the sign of the rotation is unrelated to the configuration. The relative configurations are the same because the reaction does not occur at a stereogenic center. The configuration is (*R*).



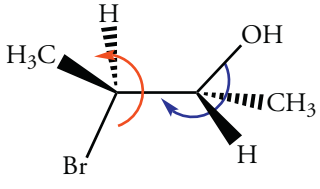
3-buten-2-ol (*R*)-(–)-2-butanol

Problem 8.12 Assign the configuration at the stereogenic centers of each of the following structures.

View C-2 from behind the page!



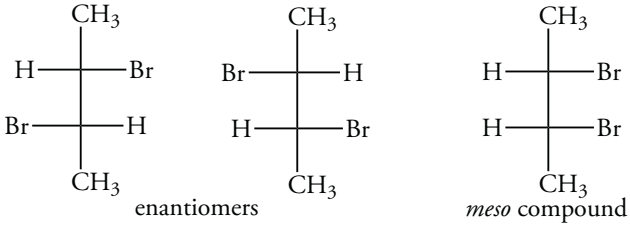
(2*R*,3*R*)-2-bromo-3-chloro-butane



(2*R*,3*S*)-3-bromo-2-butanol

Problem 8.13 Write the Fischer projection formulas of the stereoisomers of 2,3-dibromobutanes. What relationship should exist between the optical activities of these isomers?

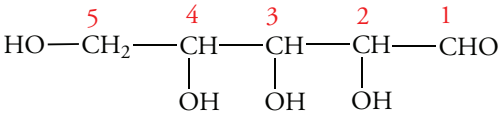
Answer: The enantiomers have equal and opposite optical rotations; the *meso* compound has no optical activity.



enantiomers *meso* compound

Problem 8.15 D-Ribose is a component of ribonucleic acids. Its name is 2,3,4,5-tetrahydroxypentanal. Using numbers and the symbols *R* and *S*, write the prefix designations of all of the possible stereoisomers.

Answer: (2*R*,3*R*,4*R*): (2*R*,3*R*,4*S*); (2*R*,3*S*,4*R*); (2*S*,3*R*,4*R*); (2*R*,3*S*,4*S*); (2*S*,3*R*,4*S*); (2*S*,3*S*,4*R*); (2*S*,3*S*,4*S*)



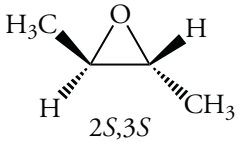
2,3,4,5-tetrahydroxypentanal

Problem 8.17 Write the structures of (1*R*,2*S*)- and (1*S*,2*S*)-1-bromo-2-chlorocyclopropane. Which is a *cis* and which is a *trans* isomer? Are the structures enantiomers or diastereomers?

Answer: The 1*R*,2*S* isomer is *cis*. The structures are diastereomers.

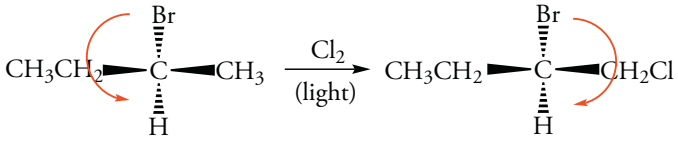


Problem 8.18
Assign the configuration of each stereogenic center in the following *trans*-2,3-dimethyloxirane. Write a structure of its enantiomer.



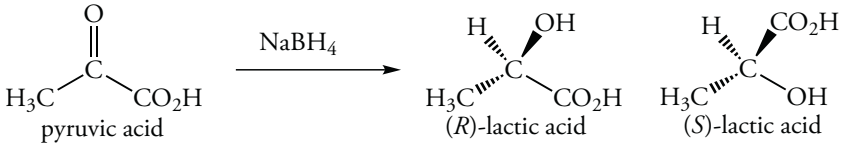
Problem 8.19 Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure of the 2-bromo-1-chlorobutane formed. Assign the configuration of the stereogenic center(s). Is the product optically active?

Answer: (*R*)-2-bromo-l-chlorobutane has no new stereogenic centers. However, the priority of the methyl group is lower than the priority of the CH_2C1, and that changes the assignment of the configuration.



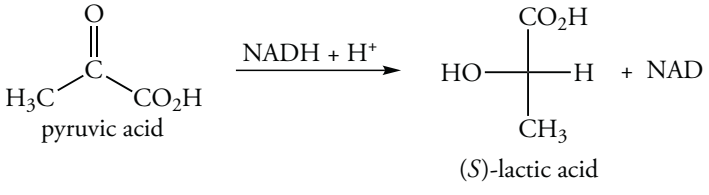
Problem 8.21 Sodium borohydride ($NaBH_4$) reacts with the C-2 carbonyl carbon atom of pyruvic acid to give lactic acid. What is the optical rotation of the product(s)?

Answer: The product is optically inactive because a racemic mixture is formed.



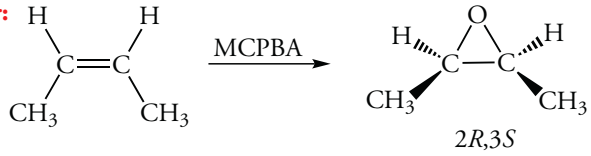
Problem 8.22 Reduction of pyruvic acid by NADH using the liver enzyme lactate dehydrogenase yields exclusively (*S*)-lactic acid. Write the Fischer projection of this product. Why does only a single product form?

Answer: The enzyme is chiral, and the reaction is stereospecific.



Problem 8.23 Write the structure of the oxirane (epoxide) that forms when (*Z*)-2-butene reacts with *m*-chloroperbenzoic acid? Assign the configurations of the stereogenic centers.

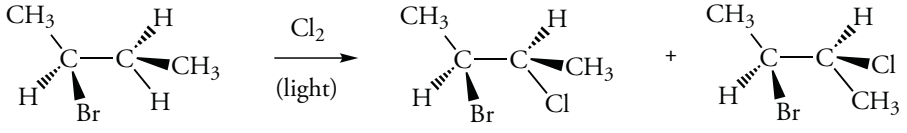
Answer:



2R,3S

Problem 8.24 Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure(s) of the 2-bromo-3-chlorobutane formed. Assign the configuration of the stereogenic center(s). Is the product optically active?

Answer: Unequal amounts of (2*S*,3*R*)-2-bromo-3-chlorobutane and (2*S*,3*S*)-2-bromo-3-chlorobutane, which are diastereomers, form in this reaction. There is a net optical rotation.



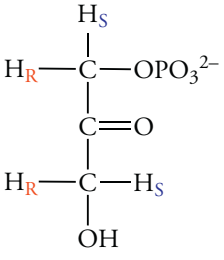
(*S*)-2-bromobutane

(2*S*,3*R*)-2-bromo-3-chlorobutane

(2*S*,3*S*)-2-bromo-3-chlorobutane

Problem 8.26 The structure of dihydroxyacetone phosphate, an intermediate in glycolysis, is shown below. Identify the prochiral hydrogen atoms and label them as H_R and H_S.

Answer:



dihydroxyacetone phosphate

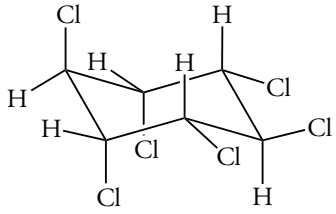
Problem 8.27 Is the face to which oxygen adds in the addition of water to oleic acid in the above example *si* or *re*?

Answer: Since $CH_2OPO_3^{2-}$ (at C-1) has a higher priority than CH_2OH, it is the *si* face.

Solutions to In-Chapter Problems

Chapter 9

Problem 9.2 Classify the carbon centers containing chlorine in the insecticide lindane.

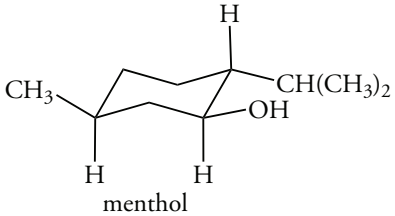


lindane

Answer: The chlorine atoms are all attached to secondary carbons; all are secondary halides.

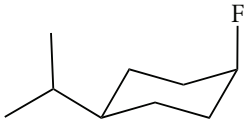
Problem 9.4 Menthol is the most stable stereoisomer of 2-isopropyl-5-methylcyclohexanol. Draw the chair conformation of this compound.

Answer: All of the substituents are equatorial.



menthol

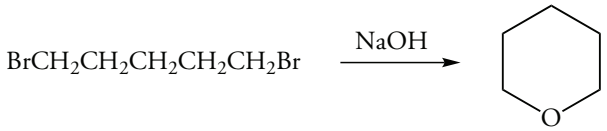
Problem 9.6 Assign the IUPAC name of the following cyclic, fluorine-containing compound.



Answer: There is a fluorine atom at C-1; it is *cis* to an isopropyl group at C-4. The name is *cis*-l-fluoro-4-isopropylcyclohexane.

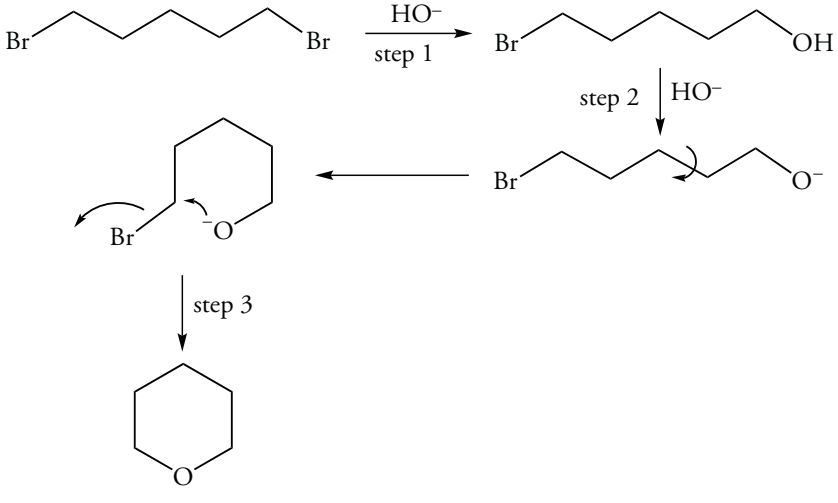
Problem 9.9

Write a sequence of steps that accounts for the following reaction of 1,5-dibromopentane to give tetrahydropyran.



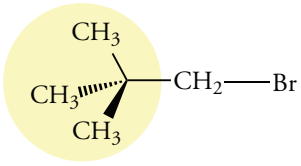
tetrahydropyran

Answer: In the first step OH^- displaces Br^- to give $BrCH_2CH_2CH_2CH_2CH_2OH$. Next, The OH group loses a proton to form an alkoxide that displaces the second bromide ion in an intramolecular reaction.



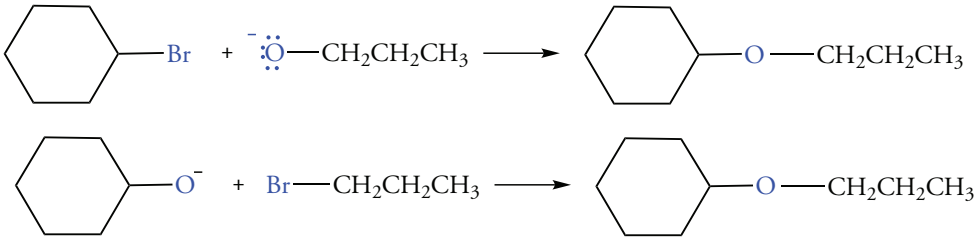
Problem 9.10 The rates of S_N2 reactions of primary haloalkanes can differ substantially. The rate of reaction of 1-bromopentane with a nucleophile is approximately 4×10^6 times faster than the reaction of 2,2-dimethyl-l-bromopropane. Explain why.

Answer: There is a *tert*-butyl group bonded to the primary carbon atom of 2,2-dimethyl-l-bromopropane (neopentyl bromide) that sterically hinders attack at the back side by the nucleophile.



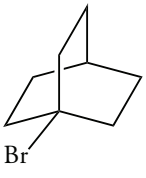
steric hindrance to backside attack by nucleophile

Problem 9. 11 Which of the following two possible reactions will produce the ether propoxycyclohexane at a faster rate?



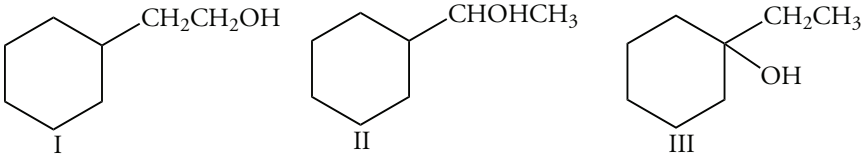
Answer: The second reaction with 1-bromopropane is faster because the site for attack by the nucleophile is primary.

Problem 9.13 Although 1-bromobicyclo[2.2.2]octane is a tertiary bromide, it cannot react via an S_N1 mechanism. Suggest a reason for its lack of reactivity.



Answer: First, attack by a nucleophile from the back side for an S_N2 mechanism is impossible. Second, a planar carbocation, required for an S_N1 mechanism, cannot form at the bridgehead carbon.

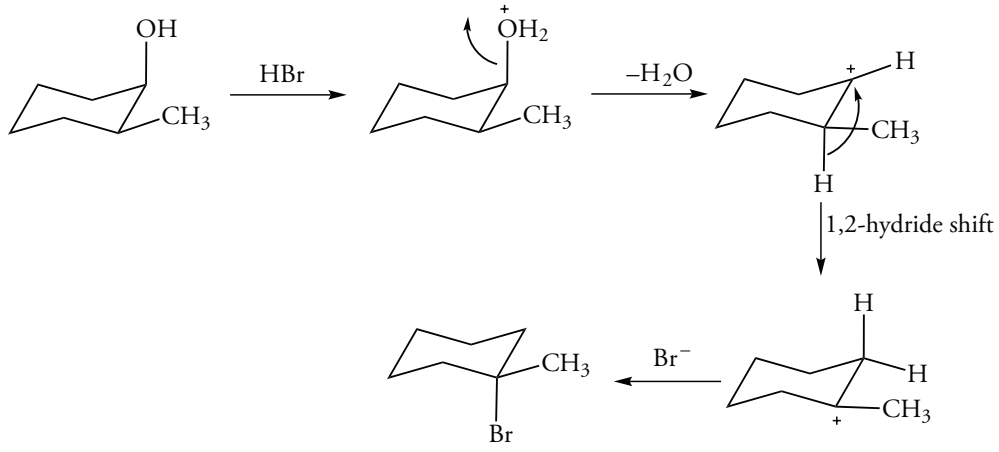
Problem 9.15 What is the most likely mechanism for the reaction of each of the following isomeric alcohols with HBr?



Answer: Compound I is a primary alcohol, so it reacts by an S_N2 mechanism. The secondary and tertiary alcohols in II and III react by an S_N1 mechanism.

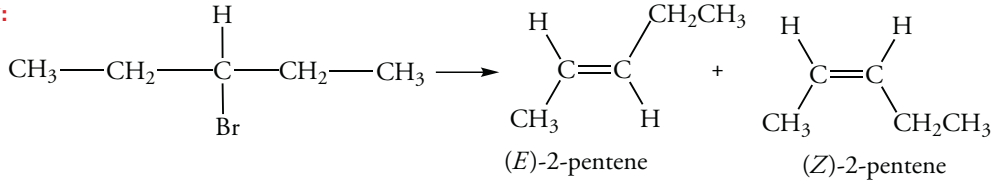
Problem 9.16 The reaction of *cis*-l-methylcyclohexanol with HBr yields 1-bromo-l-methylcyclohexane. Write a mechanism to explain the origin of this product.

Answer: In the first step, HBr protonates the alcohol to give an alkyloxonium ion. Loss of water gives a secondary carbocation. A 1,2 hydride shift produces a tertiary carbocation that reacts with bromide to give 1-bromo-1-methylcycohexane.



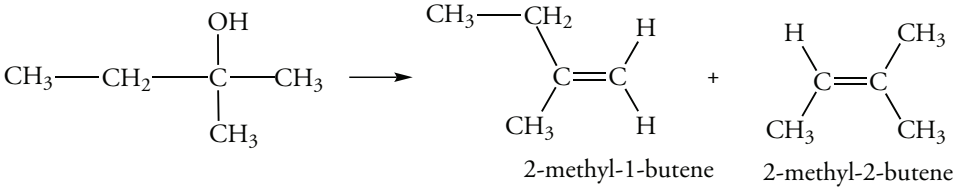
Problem 9.18 The C-2 and C-4 methylene units of 3-bromopentane are equivalent. However, the dehydrobromination of 3-bromopentane gives two products. Write their structures.

Answer:



Problem 9.19 Two alkenes are produced in the dehydration of 2-methyl-2-butanol, but three are produced in the dehydration of 2-pentanol. Write the structures of the products of both reactions.

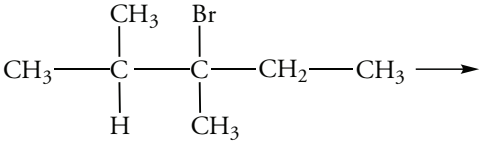
Answer:

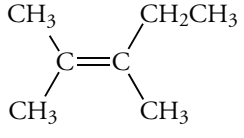


Problem 9.20 How many products can result from the dehydrobromination of 3-bromo- 2,3-dimethylpentane? Predict the major alkene product formed. Predict the alkene formed in the smallest amount.

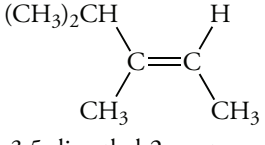
Answer:

The most substituted alkene is the major product. The minor product can exist in *E*- and *Z*-isomers.



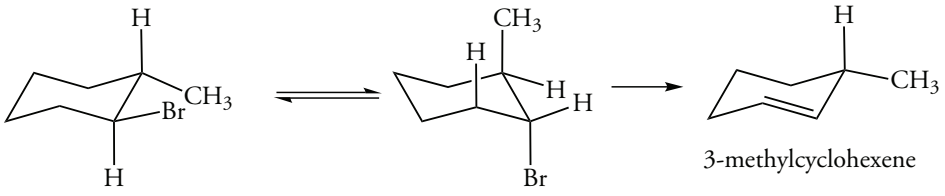


2,3-dimethyl-2-pentene
(major product)



3,5-dimethyl-2-pentene
(minor product)

Problem 9.21 The product of the dehydrobromination of *trans*-1-bromo-2-methylcyclohexane is not 1-methylcyclohexene, the Zaitsev product, but rather 3-methylcyclohexene. Explain why. (Hint: Remember that the ring-flipping process gives a mixture of two conformations.)



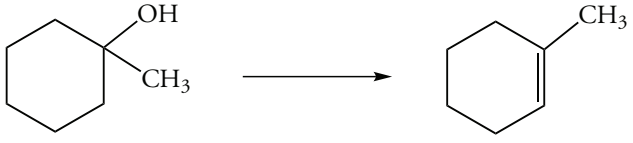
3-methylcyclohexene

Answer: The elimination occurs when the axial bromine in the less stable conformation is in an antiperiplanar relationship with the axial hydrogen at C-3.

Problem 9.22 Predict the major product formed in the dehydration of each of the following alcohols.
(a) l-methylcyclohexanol (b) 3-ethyl-2-pentanol (c) 1-isopropylcyclohexanol

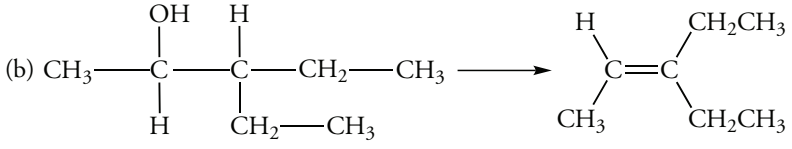
Answer:s

(a)



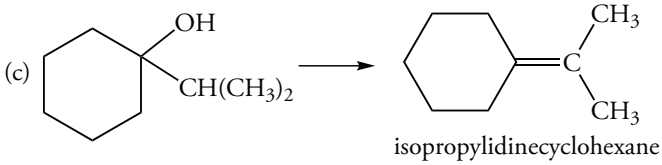
1-methyl-cyclohexene

(b)



3-ethyl-2-pentene

(c)

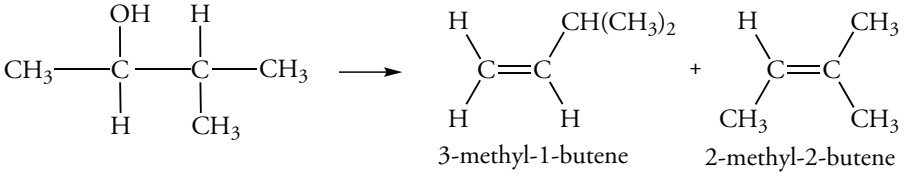


isopropylidinecyclohexane

Problem 9.24 Write structures of the products of the dehydration of 3-methyl-2-butanol.

Answer:

The most highly substituted alkene is the major product.



3-methyl-1-butene 2-methyl-2-butene

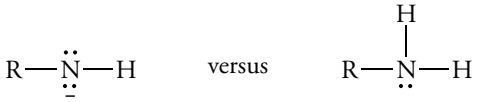
Solutions to In-Chapter Problems

Chapter 10

Problem 10.1 Trimethylamine, $(CH_3)_3N$, is a good nucleophile, but trimethylborane, $(CH_3)_3B$, is not. Explain the difference in the nucleophilicities of these two compounds.

Answer: The trimethylborane has an electron-deficient boron atom. There are no nonbonded electrons that can act as nucleophiles.

Problem 10.2 Which is expected to be the stronger base, an amide ion or an amine? Which is expected to be the better nucleophile?



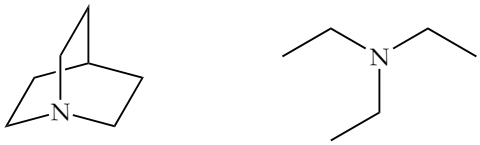
an amide ion an amine

Answer: The amide ion is the better nucleophile and stronger base.

Problem 10.3 Which is expected to be the better nucleophile, diethyl sulfide, $(CH_3CH_2)_2S$, or diethyl selenide, $(CH_3CH_2)_2Se$?

Answer: Diethyl selenide, which is in the same group of the periodic table as sulfur, but one period down, is more polarizable, and therefore more nucleophilic than diethyl sulfide.

Problem 10.4 Quinuclidine reacts about 50 times faster than triethylamine to displace iodide ion from iodomethane. Suggest a reason for the different nucleophilicities of these two compounds, which contain the same number of alkyl groups bonded to the nitrogen atom.

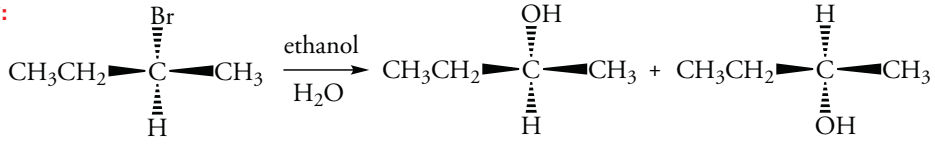


quinuclidine triethyl amine

Answer: The hydrocarbon groups of quinuclidine are "tied back" and do not sterically hinder the site of nucleophilicity.

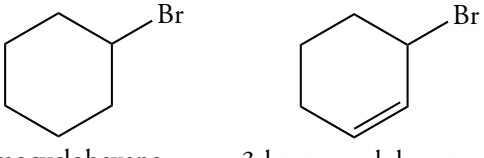
Problem 10.5 The reaction of (*S*)-2-bromobutane in ethanol and water proceeds via an S_N1 mechanism. Write the structures of the products.

Answer:



(*S*)-2-bromobutane (*S*)-2-butanol (*R*)-2-butanol

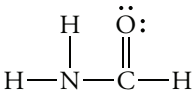
Problem 10.7 Explain why the reaction of 3-bromocyclohexene with methanol (CH_3OH) is faster than the reaction of bromocyclohexane with methanol.



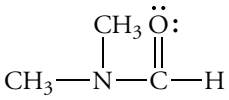
bromocyclohexane 3-bromocyclohexene

Answer: The bromine atoms in each compound are at secondary carbons, but in 3-bromocyclohexene, the bromine is also allylic. An S_N1 reaction therefore produces are resonance-stabilized allylic carbocation, which is more stable than a secondary carbocation.

Problem 10.8 The relative rates for the conversion of 1-iodobutane into 1-chlorobutane in methanol, formamide, and dimethylformamide are 1, 12, and 1.2×10^6, respectively. Explain the small rate difference between methanol and formamide and the large rate difference between formamide and dimethylformamide.



formamide



dimethylformamide (DMF)

Answer: Formamide and methanol are both protic solvents, and hydrogen bonding decreases the nucleophilicity of the chloride ion. Dimethylformamide is aprotic, so it does not solvate chloride ions, which become more nucleophilic as a consequence.

Problem 10.9 The ratio of elimination to substitution products for the reaction of 2-bromo-2-methylbutane depends on the concentration of the base. For 0.05 and 1.0 M sodium ethoxide, the percentages of elimination product are 56% and 98%, respectively. Explain these data.

Answer: The higher concentration of base gives the *E*2 product.

Problem 10.10 The amount of elimination product for the reaction of 1-bromooctadecane with an alkoxide in the corresponding alcohol solvent is about 1 % for methoxide ion and 85% for *tert*-butoxide ion. Explain these data.

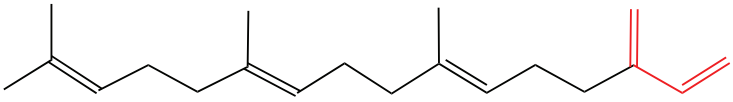
Answer: The sterically hindered *tert*-butoxide ion is a poorer nucleophile, and elimination is favored by default.

Solutions to In-Chapter Problems

Chapter 11

Problem 11.1 Classify the double bonds found in β-springene, a sex attractant secreted by the dorsal gland of the springbok, a South African gazelle.

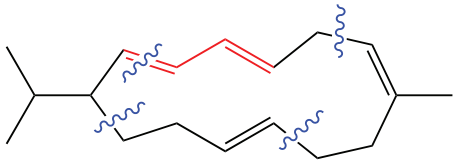
Answer: The double bonds shown in red are conjugated.



β-springene

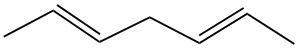
Problem 12.2 Classify the following terpene and indicate its division into isoprene units. Then, identify the conjugated double bonds.

Answer: (a) The compound is a diterpene.
(b)The double bonds shown in red are conjugated.

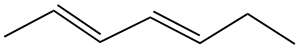


Problem 11.3 Estimate the total heats of hydrogenation of 2*E*,4*E*-heptadiene and of 2*E*,5*E*-heptadiene.

Answer: The heat of hydrogenation of 2*E*,5*E*-heptadiene is 230 kJ mole^{-1}, which is twice that of a disubstituted alkene; the heat of hydrogenation for 2*E*,4*E*-heptadiene, which is disubstituted, but is also conjugated, is 215 kJ mole^{-1}.



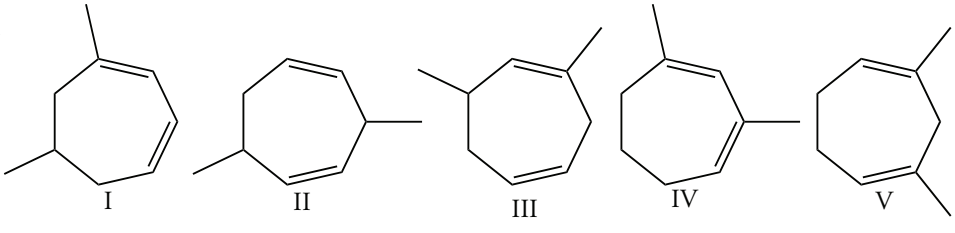
2*E*,5*E*-heptadiene



2*E*,4*E*-heptadiene

Problem 11.5 Arrange the following compounds in order of increasing heats of hydrogenation.
I 1,6-dimethyl-1,3-cycloheptadiene
II 3,6-dimethyl-l,4-cycloheptatdiene
III 2,7-dimethyl-1,4-cycloheptadiene
IV l,3-dimethyl-l,3-cycloheptadiene
V 2,4-dimethyl-1,4-cycloheptadiene

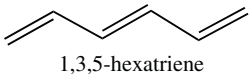
Answer:
II < III < V < I <IV



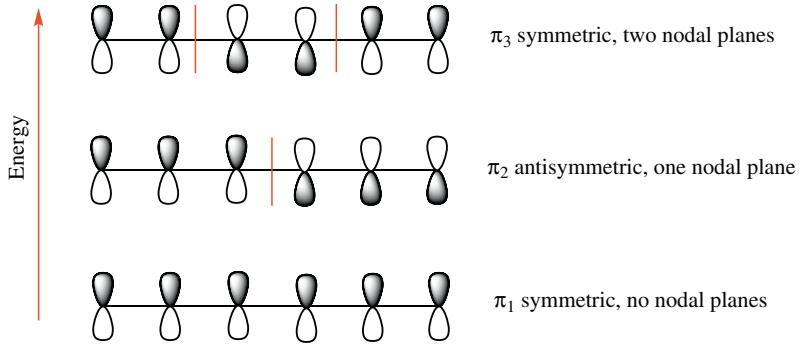
I II III IV V

Problem 11.6 How many molecular orbitals of 1,3,5-hexatriene contain bonding π electrons? Sketch each one, showing vertical nodal planes, and determine the symmetry of each wave function.

Answer: Each molecular orbital contains two electrons in bonding π orbitals.

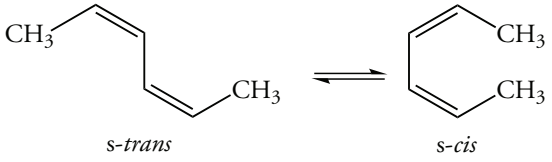


1,3,5-hexatriene



Problem 11.8 Draw the structure of the planar conformations of (2*Z*,4*Z*)-hexadiene and determine whether the equilibrium constant for conversion of the s-*trans* to s-*cis* conformation is larger or smaller than the same equilibrium for 1,3-butadiene.

Answer: The equilibrium constant is smaller because the s-*cis* conformation is sterically hindered.



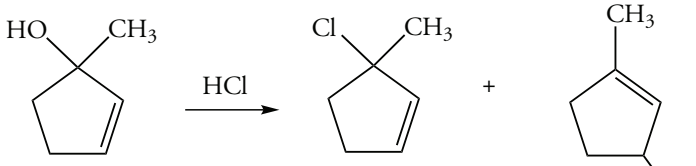
s-*trans* s-*cis*

Problem 11.9 How is the equilibrium constant for the s-*trans* to s-*cis* conversion affected by the size of alkyl groups in 2,3-dialkyl, disubstituted 1,3-butadienes?

Answer: The equilibrium constant is smaller because the s-*cis* conformation has eclipsed alkyl groups that cause greater steric hindrance. As the size of the alkyl groups increase, the steric hindrance also increases.

Problem 11.11 What substitution products should form by reaction of the following alcohol with HCl? Which one do you expect to be the major product?

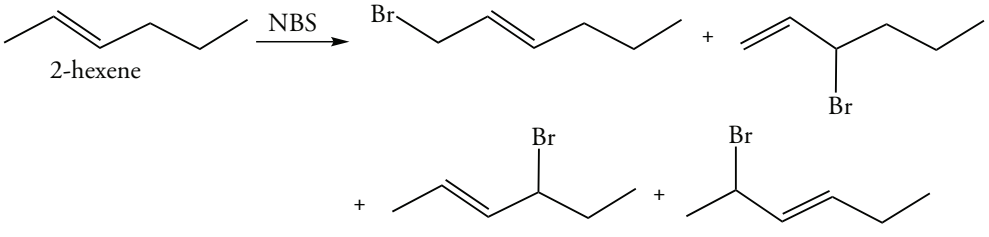
Answer: The more stable, trisubstituted alkene is favored.



3-methyl-cyclopenten-3-ol minor major

Problem 11.12 Write the structures of all products formed in the allylic bromination of 2-hexene, using one molar equivalent of NBS.

Answer:



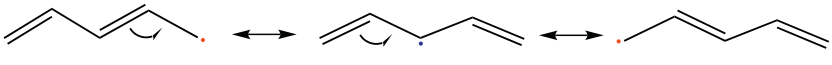
2-hexene

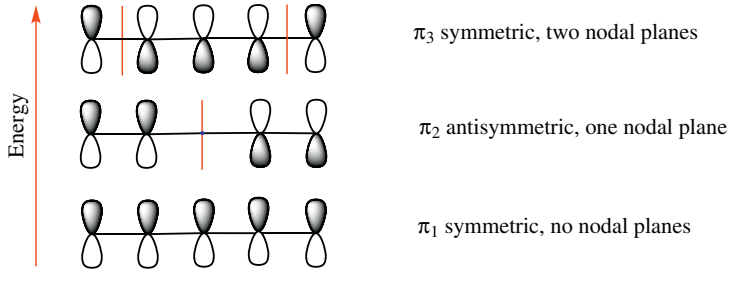
Problem 11.14 Consider the π_3 MO for the pentadienyl radical. How many vertical nodal planes does it have? The unpaired electron must be in π_3. Determine which atoms have radical character.

$CH_2{=}CH{-}CH{=}CH{-}CH_2\bullet$

1,3-pentadienyl radical

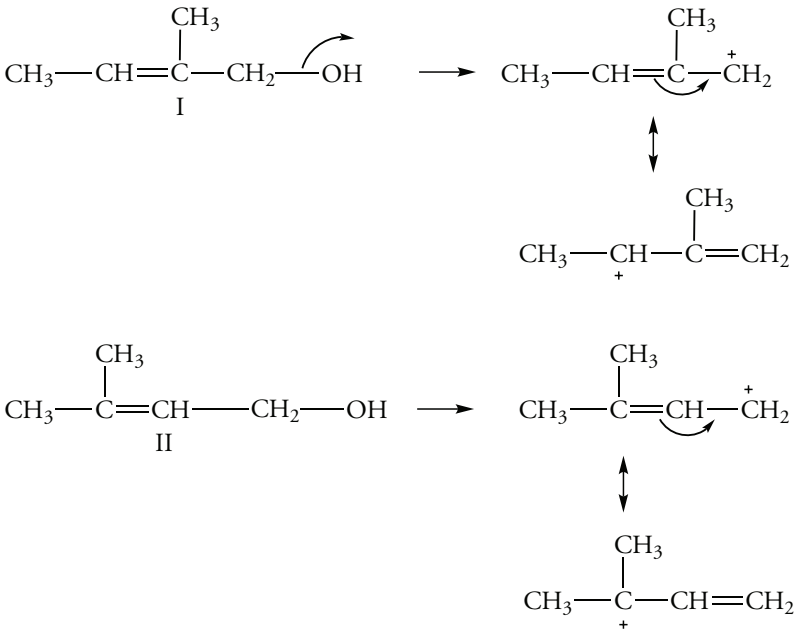
Answer: The π_3 MO has two nodes; atoms C-1, C-3, and C-5 have radical character.





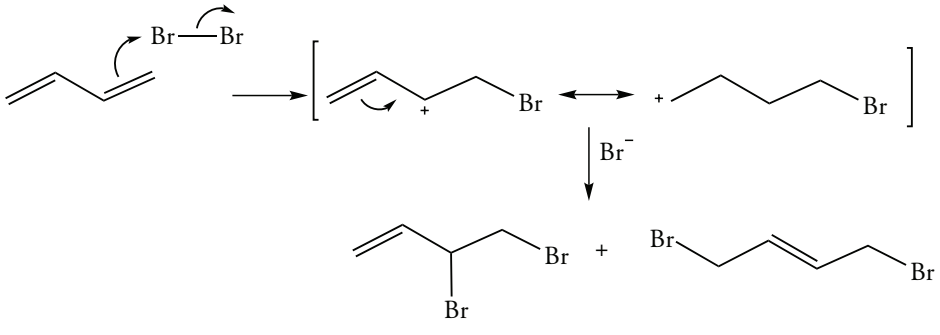
Problem 11.16 Based on molecular orbital theory, which of the following primary alcohols will react faster with HBr in a S_N1 reaction?

Answer: Compound II reacts faster because one terminal carbon atom of the allyl cation is disubstituted.



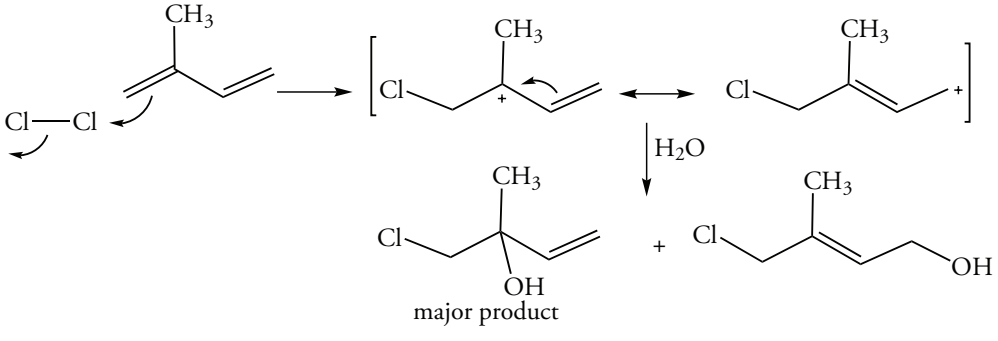
Problem 11.17 When bromine adds to a conjugated diene, a carbocation forms, not a bromonium ion. Explain why. One molar equivalent of bromine adds to 1,3-butadiene to give a mixture of two products. What are their structures?

Answer: The allylic carbocation is resonance stabilized, so it is more stable than a cyclic bromonium ion. The products are 3,4-dibromo-l-butene and 1,4-dibromo-2-butene



Problem 11.18 Reaction of 2-methyl-1,3-butadiene with chlorine in water gives a chlorine-containing tertiary alcohol. Draw its structure. Does 1,2- or 1,4-addition occur? What is the electrophile in the reaction?

Answer: The major product results from 1,2-addition to the tertiary center of the allyl carbocation.

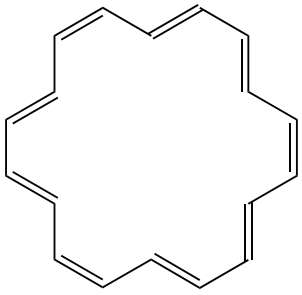


Solutions to In-Chapter Problems

Chapter 12

12. 1 Annulenes are large monocyclic, conjugated compounds. A prefix within brackets indicates the number of carbon atoms in the ring. Given the structure shown below, and based on the Hückel rule determine if [18]annulene is aromatic.

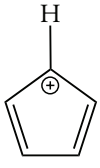
Answer: Yes, it is aromatic, $n = 4$.



[18]annulene

12.2 Consider the electronic structure of the carbocation that would result from the loss of a hydride ion from 1,3-cyclopentadiene; that is, cyclopentadienyl cation. How many electrons are in the π system? Are they all paired? Is this ion aromatic? What are the relative energy levels of this ion?

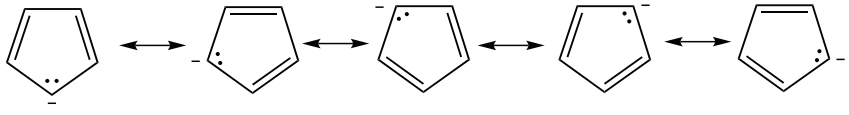
Answer: No, it is not aromatic because there are only four π electrons.



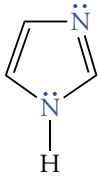
cyclopentadienyl cation

12.3 Write the resonance structures of the cyclopentadienyl anion to show how the negative charge can be delocalized over five carbon atoms.

Answer:



12.4 The heterocyclic ring in the drug cimetidine is imidazole. The lone pairs of the two nitrogen atoms are not shown. Which nitrogen atom contributes electrons to the aromatic sextet?

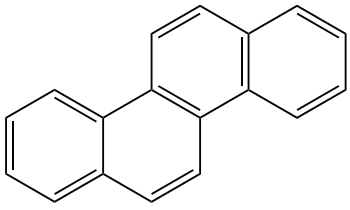


imidazole

Answer: The electron pair on the nitrogen at the bottom of the structure is part of the aromatic sextet. The electron pair on the nitrogen at the upper right is in the plane of the ring and is not part of the aromatic sextet.

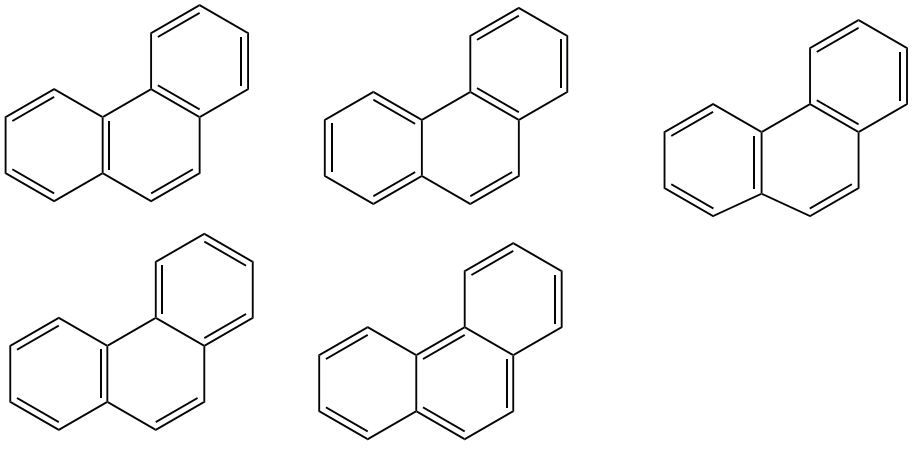
12.5 Determine the number of π electrons in chrysene. Is it aromatic?

Answer: The structure has nine double bonds, so it has 18 p electrons, $4n + 2 = 18$ for $n = 4$, so chrysene is aromatic.



chrysene

12.6 Draw the five contributing resonance forms of phenanthrene. Based on these structures, explain why the C-9 to C-10 bond behaves more like a double bond than the other bonds in the molecule.



Answer: Four of the five resonance forms have a double bond between C-9 and C-10.

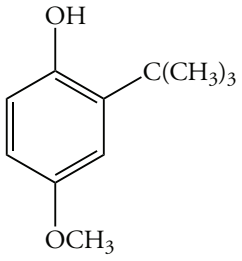
Solutions to In-Chapter Problems

Chapter 13

Problem 13.1

What is the name of the following trisubstituted compound?

Answer: 2-*tert*-butyl-4-methoxyphenol

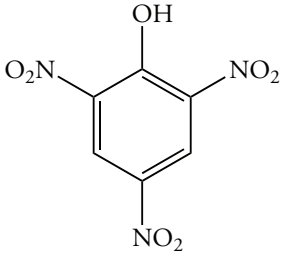


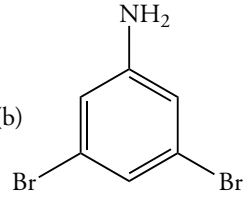
Problem 13.3

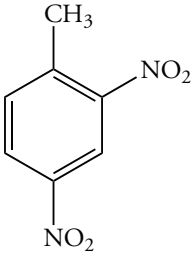
Write the structure of each of the following compounds.

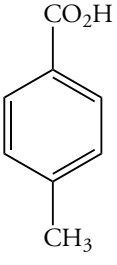
(a) 2,4,6-trinitrophenol (b) 3,5-dibromoaniline (c) 2,4-dinitrotoluene
(d) *p*-methylbenzoic acid (e) *p*-chloroanisole (f) *o*-methylacetophenone

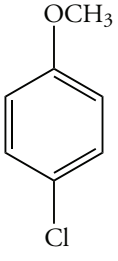
Answers:

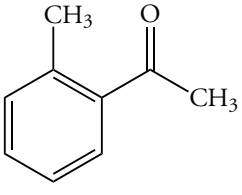
(a)


(b)


(c)


(d)


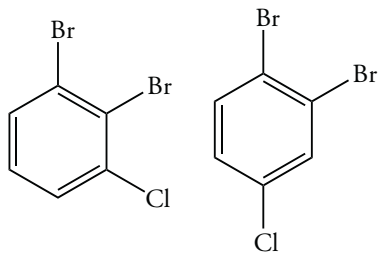
(e)


(f)


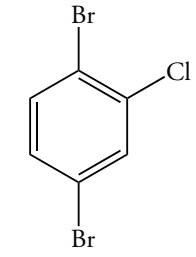
Problem 13.4

Draw the structures of all possible products formed by monosubstitution of o-dibromobenzene in a chlorination reaction. Do the same for *m*- and *p*-dibromobenzene.

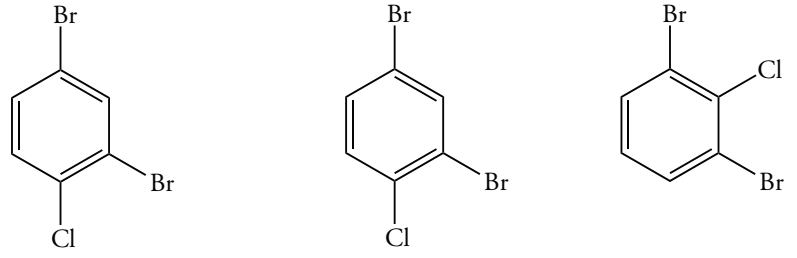
Answers:



from *o*-dibromobenzene



from *p*-dibromobenzene

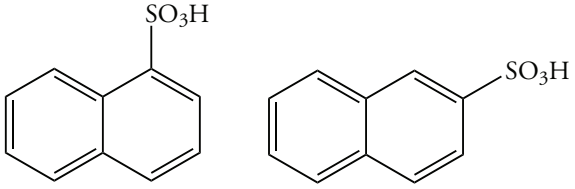


from *m*-dibromobenzene

Problem 13.6

Write the structures of the two possible products formed by sulfonation of naphthalene. At 80 °C, isomer I constitutes 96% of the reaction mixture. At 165 °C, isomer II is 85% of the reaction mixture. When isomer I is heated in sulfuric acid at 165 °C, it is converted into isomer II. Explain these observations. Based on steric considerations, which isomer is likely to be more stable?

Answer: Isomer II is more stable. Isomer I is the product of kinetic control. Isomer I is less stable than isomer II because the sulfonic acid group is sterically hindered by the adjacent aromatic ring.

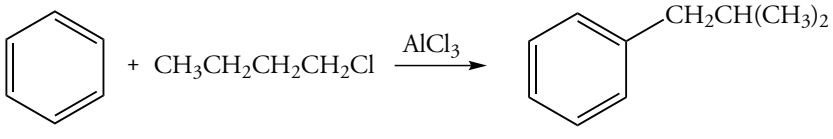


Isomer I Isomer II

Problem 13.8

Predict the structure of the major product formed in the Friedel–Crafts alkylation of benzene with 1-chlorobutane.

Answer: *sec*-Butylbenzene as a result of hydride shift from the C-2 atom of the butyl to give a secondary carbocation.



Problem 13.9

Reaction of 2-methylpropene with benzene in the presence of H_3PO_4 yields *tert*-butyl-benzene. Propose a mechanism for this reaction.

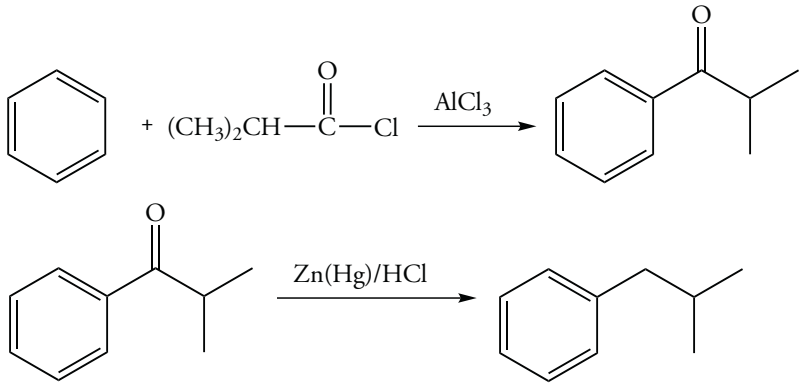
Answer: Protonation of 2-methylpropene gives the *tert*-butyl carbocation, which is the electrophile.



Problem 13.10

Outline a synthesis of 2-methyl-l-phenylpropane (iso-butylbenzene) starting from benzene using a Friedel–Crafts reaction.

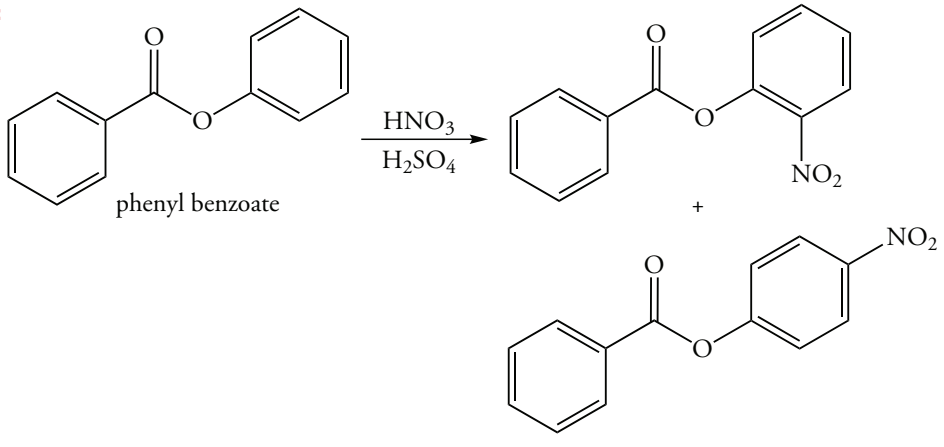
Answer: Friedel–Crafts acylation followed by Clemmensen reduction.



Problem 13.13

Which of the two aromatic rings of phenyl benzoate would be nitrated? Predict the structure of the product(s) formed.

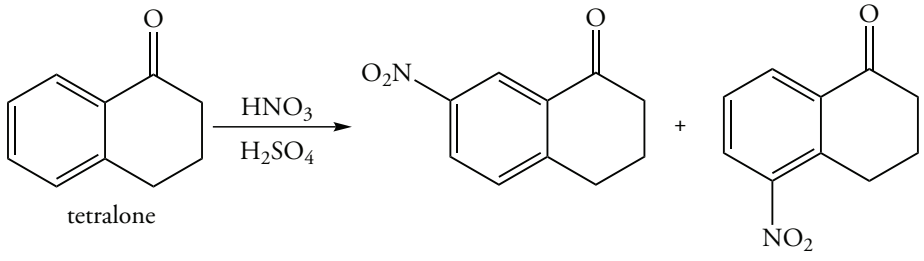
Answers:



Problem 13.14

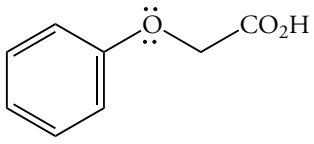
Which two of the four possible products should form in the nitration of tetralone?

Answers:



Problem 13.15

A selective herbicide that kills broad-leaf weeds is made by chlorinating phenoxyacetic acid. Is the substituent an activating or deactivating group?



phenoxyacetic acid

Answer: The oxygen atom is part of an ether and is an activating group.

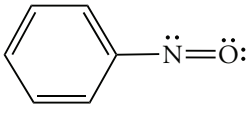
Problem 13.17

The major product of the nitration of phenylboronic acid is the *meta* isomer. Based on the electronic structure of boron, explain the *meta*-directing effect of the $—B(OH)_3$ group.

Answer: The boron atom is electron deficient and withdraws electrons from the aromatic ring.

Problem 13.18

Chlorination of nitrosobenzene by electrophilic aromatic substitution of yields a mixture of *ortho* and *para* products, but chlorination of nitrobenzene yields the *meta* product. Explain this difference.



nitrosobenzene

Answer: Methyl group is weakly activating, and chloro is weakly deactivating. Thus, the two groups have only small effects on the rate of reaction. The methyl group directs the electrophile to two possible positions *ortho* and *para* to it. The chloro group directs the electrophile to the other two possible positions. Therefore, four isomers result.

Problem 13.19

Nitration of *o*-chlorotoluene yields a mixture of four chloronitrotoluene isomers. Considering the directing influences of the chlorine atom and methyl group, and their effects on reactivity, explain why a mixture results.

Answer: The lone pair electrons of nitrogen in the nitroso group can be donated by resonance to the aromatic ring. It is an activating, *ortho*, *para*-directing group.

Problem 13.20

Nitration of isopropylbenzene gives a mixture containing 30% of the *ortho* product and 63% of the *para* product. In contrast, nitration of *tert*-butylbenzene gives a mixture containing 16% *ortho* and 73% *para* isomers. Why does the ratio of the amounts of the *ortho* and *para* isomers differ for these two alkylbenzenes?

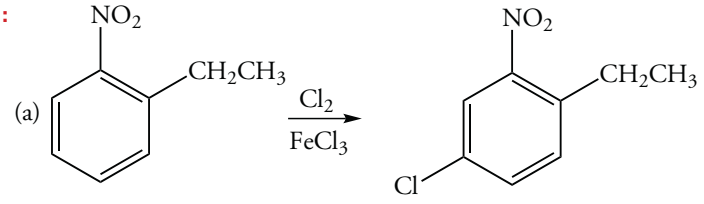
Answer: The *tert*-butyl group sterically hinders attack at the *ortho* position more than the isopropyl group.

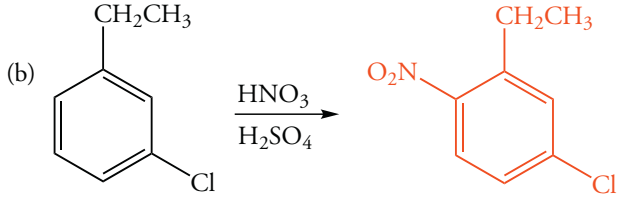
Problem 13.22

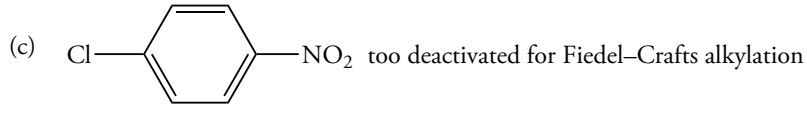
Which of the following procedures will yield 4-chloro-2-ethylnitrobenzene?
(a) chlorination of *o*-ethylnitrobenzene
(b) nitration of *m*-chloroethylbenzene
(c) Friedel–Crafts alkylation of *p*-chloronitrobenzene

Answer: Only (b) gives the desired isomer. The product in (a) is 5-chloro-2-ethylnitrobenzene. Compound (c) is too deactivated for a Friedel–Crafts reaction.

Answers:



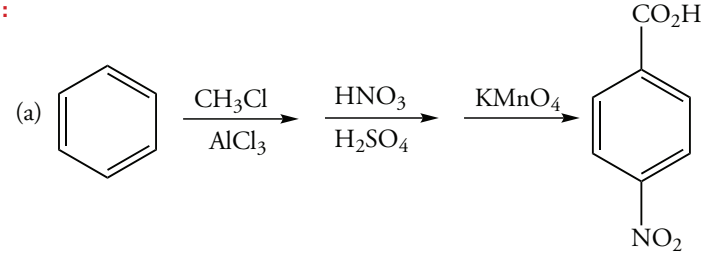


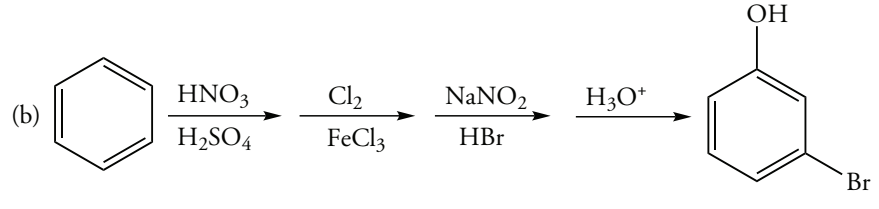


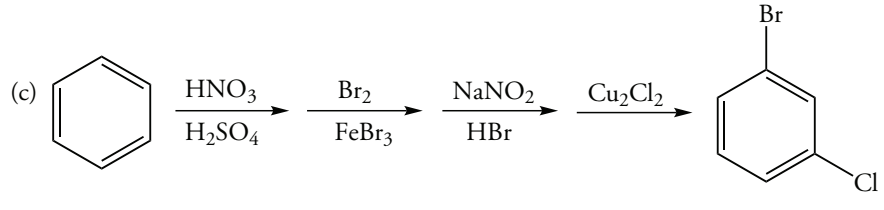
Problem 13.24

Devise a synthesis of each of the following compounds from benzene.
(a) *p*-nitrobenzoic acid (b) *m*-bromophenol (c) *m*-bromochlorobenzene

Answers:



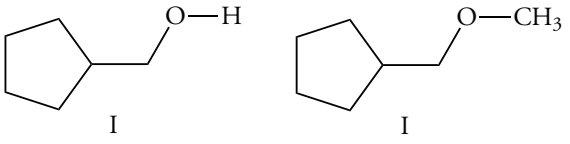




Solutions to In-Chapter Problems
Chapter 14

Problem 14.3 Explain how you could distinguish between the following two compounds by infrared spectroscopy.

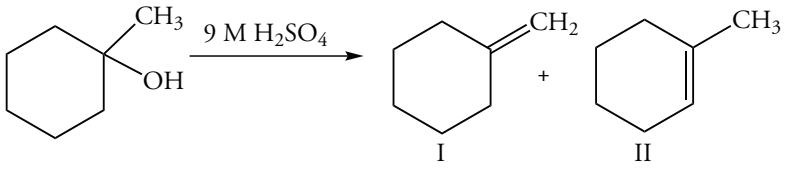
Answer: Compound I has an intense broad O—H stretching absorption in the 3400–3600 cm^{-1} region.



I I

Problem 14.4 Draw the structures of the two dehydration products of 1-methylcyclohexanol and describe how infrared spectroscopy can be used to establish their structures.

Answer: Compound I has an absorption in the 875–895 cm^{-1} region; compound II has an absorption in the 790–840 cm^{-1} region.



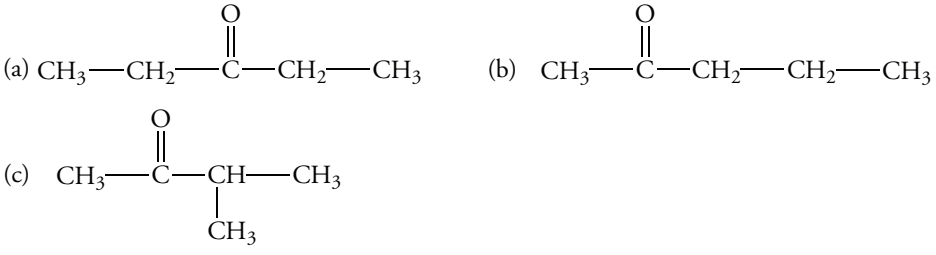
I II

Problem 14.5 The chemical shift of methylene chloride as measured with a 300 MHz instrument is 5.30 δ. What is the separation in Hz from TMS? What is the δ value when measured with a 400 MHz instrument?

Answer: A chemical shift of 1 ppm (1 δ) is 300 Hz in a 300 MHz instrument. Therefore, if the chemical shift is 5.3 δ, it is 1590 Hz. In a 400 MHz instrument, the chemical shift would still be 5.3 δ, but it would be 2120 Hz.

Problem 14.6 How many sets of nonequivalent hydrogen atoms are contained in each of the following ketones?

Answer: (a) 2 (b) 4, (c) 3

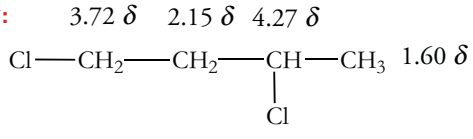


Problem 14.8 Explain why the chemical shift of the hydrogen atoms of $(CH_3)_4Sn$ appears at higher field than TMS.

Answer: Tin is below silicon in the periodic table, and is less electronegative. Therefore, tin deshields the protons of the methyl group less than silicon.

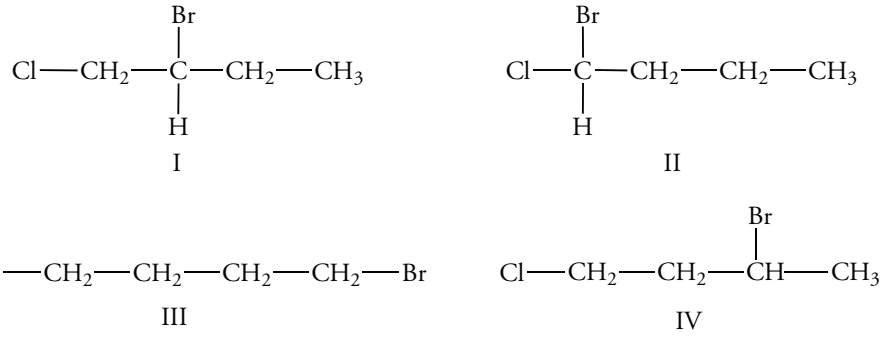
Problem 14.9 1,3-Dichlorobutane has resonances 1.60, 2.15, 3.72, and 4.27 ppm downfield from TMS. Assign each resonance to the individual hydrogen atoms.

Answer:



1,3-dichlorobutane

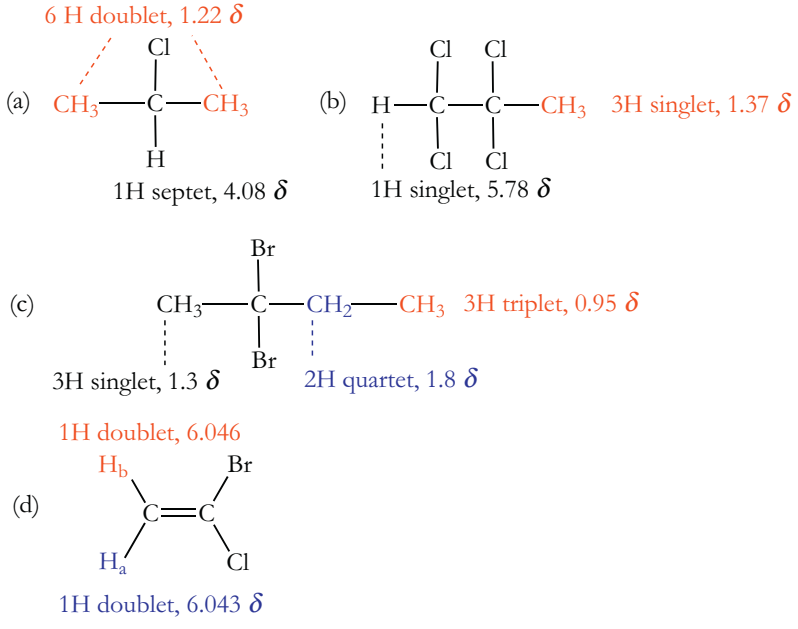
Problem 14.11 Which of the following isomers can be distinguished from the others solely on the basis of the number of NMR absorptions and their intensities?



Answer: All four compounds have four NMR absorptions. C-1 of compound II has a very low field resonance that integrates to one hydrogen. The remaining compounds have two low-field absorptions. Those due to hydrogen atoms on carbon bearing chlorine are at lower field than those due to hydrogen atoms on carbon bearing bromine. From low field to high field the intensities are: I (2:1), III (2:2), IV(2: I). Thus only compounds II and III can be distinguished by number and intensity of absorptions.

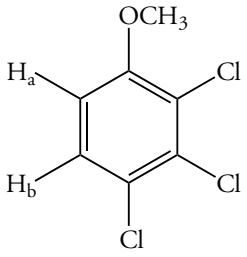
Problem 14.13 Describe the NMR spectrum of each of the following compounds.
(a) 2-chloropropane (b) 1,1,1,2-tetrachloropropane (c) 2,2-dibromobutane (d) 1-bromo-l-chloroethene

Answers: (a) 2-Chloropropane has two resonances: a high-field doublet that integrates to 6H and a low-field septet that integrates to 1H.
(b) 1,1,2,2-Tetrachloropropane has a high-field singlet that integrates to 3H and a low-field singlet that integrates to 1H.
(c) 2,2,-Dibrombutane has a singlet that integrates to 3H at C-1, a quartet of intensity 2H, and a triplet of intensity 3H;
(d) two doublets each of intensity 1H.

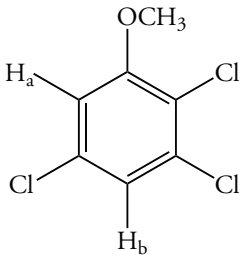


Problem 14.14 Explain how 2,3,4-trichloroanisole, 2,3,5-trichloroanisole can be established using the coupling constants of the two doublets in the NMR spectrum of each compound.

Answer: The coupling constant, J_{ab}, for 2,3,4-trichloroanisole is 8.23 Hz. The coupling constant, J_{ab}, for 2,3,5-trichloroanisole is 8.23 Hz.

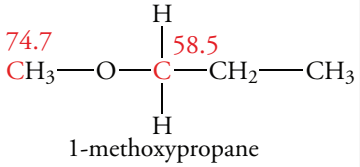


2,3,4-trichloroanisole

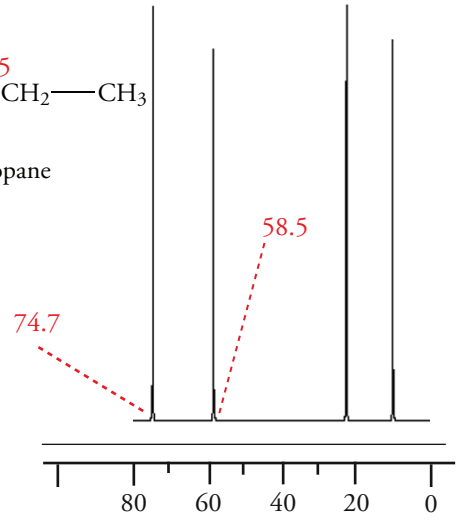


2,3,5-trichloroanisole

Problem 14.15 How can a compound of molecular formula $C_4H_{10}O$ be established as an ether or an alcohol using ^{13}C NMR spectroscopy?

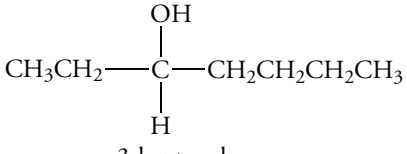


1-methoxypropane

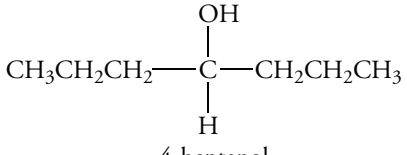


Answer: If we compare ^{13}C NMR spectra of an alcohol and an ether with the same formula, we find that the alcohol has one carbon with a high chemical shift (see Figure 14.24), but an ether has two low-field resonances, as shown above for 1-methoxypropane. This feature allows us to distinguish the two compounds.

Problem 14.16 The isomeric alcohols 3-heptanol and 4-heptanol cannot be easily distinguished by hydrogen NMR spectroscopy. Describe how ^{13}C NMR spectroscopy can be used to distinguish between these isomers.



3-heptanol



4-heptanol

Answer: 4-Heptanol, which is highly symmetrical, has only four nonequivalent carbon atoms, and therefore only four ^{13}C NMR resonances. In contrast, 3-heptanol has seven ^{13}C NMR resonances.

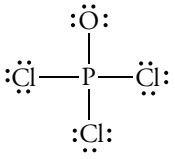
Solutions to In-Chapter Problems

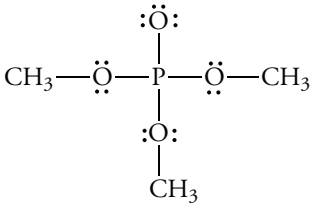
Chapter 15

Problem 15. 1

Write the Lewis structure of phosphorus oxychloride ($POCl_3$) the acid chloride of phosphoric acid. Write the structure of the product formed when excess methanol reacts with phosphorus oxychloride.

Answers:

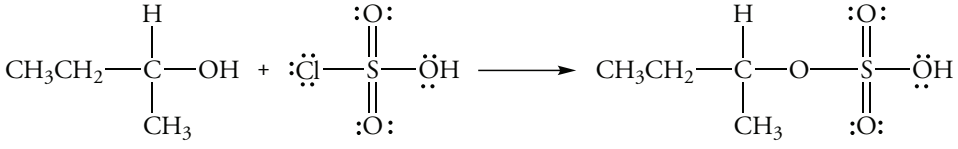




Problem 15. 2

Write the structure of the product formed in the reaction of chlorosulfonic acid with (*S*)-2-butanol. What is the configuration of this product?

Answer: The reaction occurs with retention of configuration. The product is *S*.

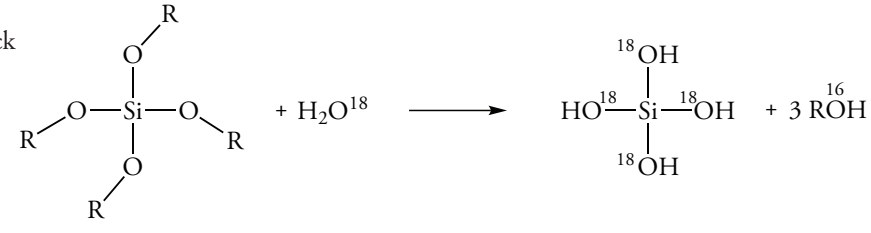


Problem 15. 3

Silicic esters, $(RO)_4Si$, form in the reaction of alcohols with $SiCl_4$. They react with water to form silica and an alcohol. Mechanisms for the hydrolysis can be written that involve S_N2 attack of water on silicon or at the carbon atom of the R group. Suggest an experiment using isotopes that would distinguish between these two possible mechanisms.

$$(RO)_4Si + 4H_2O \rightarrow 4ROH + Si(OH)_4$$

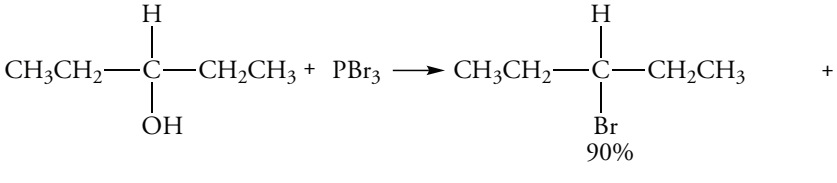
Answer: Use water containing O^{18}. Attack at silicon will give alcohol without the isotope. Attack at carbon will give alcohol containing the isotope.

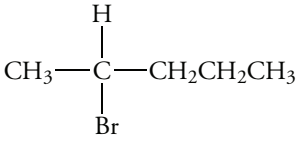


Problem 15. 5

The reaction of 3-pentanol with phosphorus tribromide yields a mixture of 3-bromopentane and 2-bromopentane in approximately a 9:1 ratio. Explain the source of each product.

Answer: A hydride shift from C-2 to C-3 occurs because the transition state develops some carbocation character.

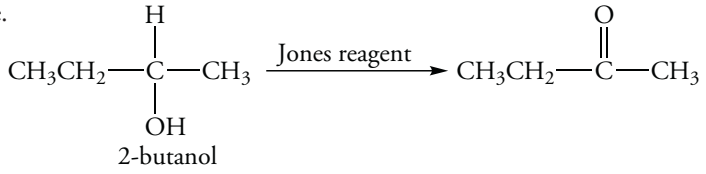




Problem 15. 7

Which of the isomeric C_4H_{10} alcohols reacts with the Jones reagent to produce the ketone C_4H_8O?

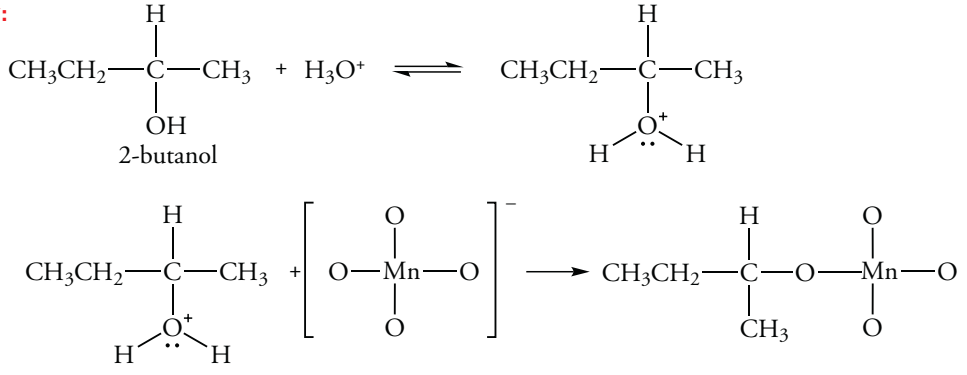
Answer: Only 2-butanol gives a ketone.

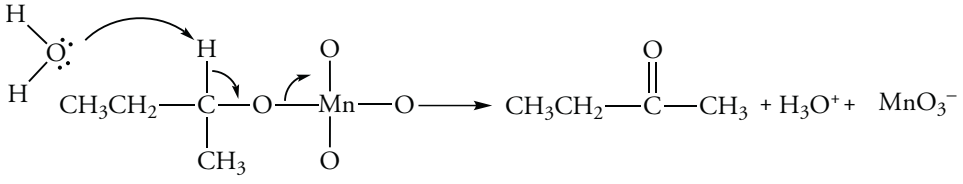


Problem 15. 8

Potassium permanganate ($KMnO_4$) oxidizes alcohols, but is a less selective reagent than chromium(VI) reagents. Write a reasonable multistep mechanism involving a manganate ester that accounts for the oxidation of a secondary alcohol to a ketone.

Answer:

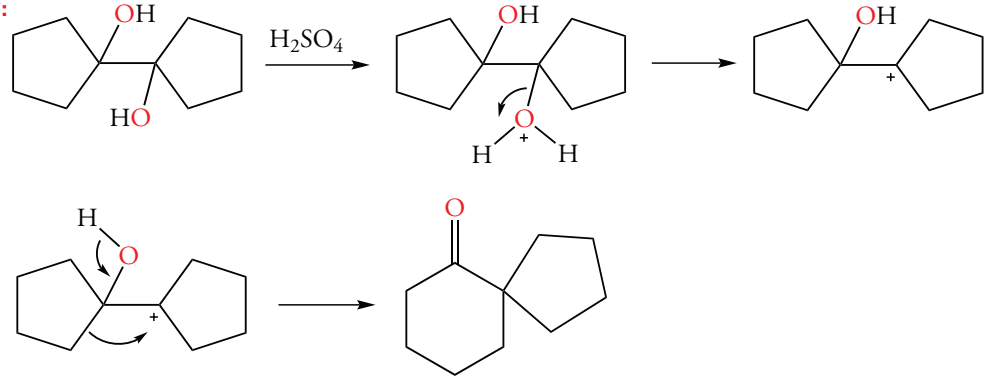




Problem 15. 10

Reaction of the following diol with sulfuric acid yields a ketone with the molecular formula $C_{10}H_{16}O$. Write the structure of the product.

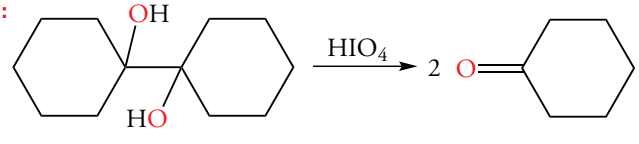
Answer:



Problem 15. 11

A compound with the formula $C_{12}H_{22}O_2$ reacts with periodic acid to give cyclohexanone. Write the structure of the reactant.

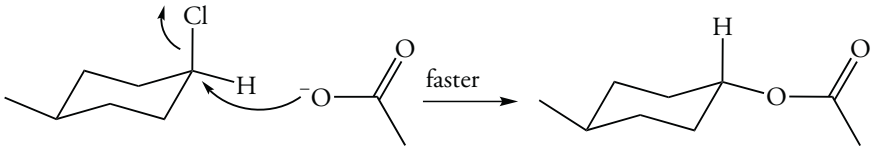
Answer:



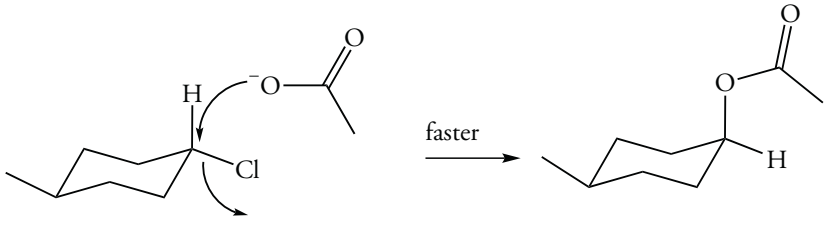
Problem 15. 13

Which of the two compounds should react faster with sodium acetate in DMF, *cis*- or *trans*-4-methyl-1-chlorocyclohexane?

Answer: The *cis* isomer, which has an axial chlorine atom, reacts faster than the *trans* isomer. Attack is easier from the equatorial position.



cis-1-chloro-4-methylcyclohexane

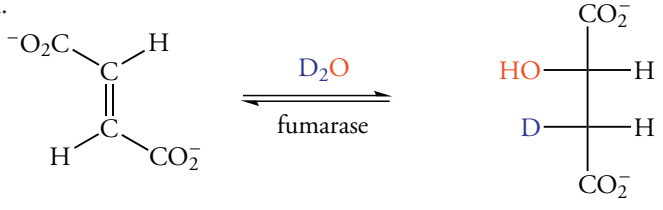


trans-1-chloro-4-methylcyclohexane

Problem 15. 14

Hydration of alkenes occurs stereospecifically in biological systems. Hydration of fumarate by D_2O catalyzed by fumarase yields (2*S*,3*R*)-3-deuteriomalate. Determine the stereochemistry of addition.

Answer: The product form by *anti* addition.

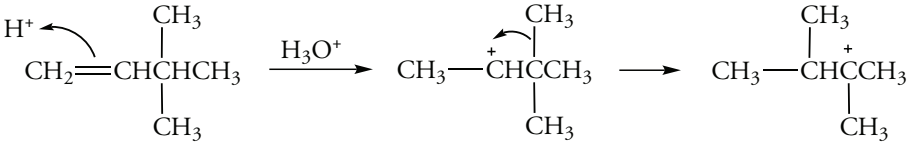


fumarate (2*S*,3*R*)-3-deuteromalate

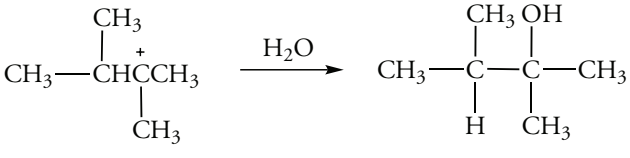
Problem 15. 16

Write the structure of the product of oxymercuration–demercuration of 3,3-dimethyl-l-butene. Is this product the same as would be obtained by the acid-catalyzed hydration of the alkene?

Answer: No, 3,3-dimethyl-1-butene rearranges to give 2,3-dimethyl-2-butanol. This rearrangement would not occur for oxymercuration–demercuration.



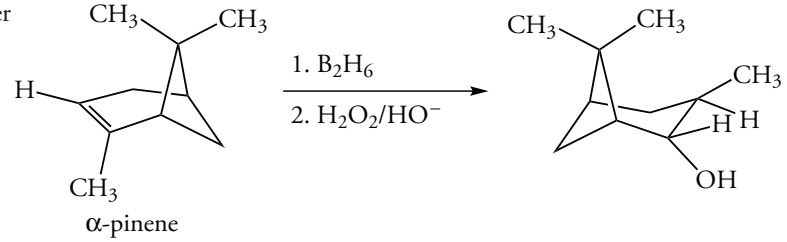
3,3-dimethyl-1-butene



Problem 15. 17

Write the structure, showing the stereochemistry, of the product of hydroboration-oxidation of 2,6,6-trimethyl-2-bicyclo[3.1.1]heptene (α-pinene).

Answer: Net *syn* addition of water occurs from the "bottom," the side away from the methyl groups.

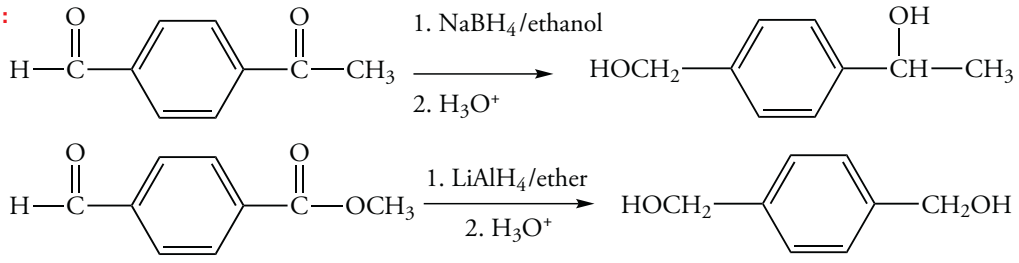


α-pinene

Problem 15. 18

Write the structure of the product of each of the following reactions, assuming an excess of each metal hydride.

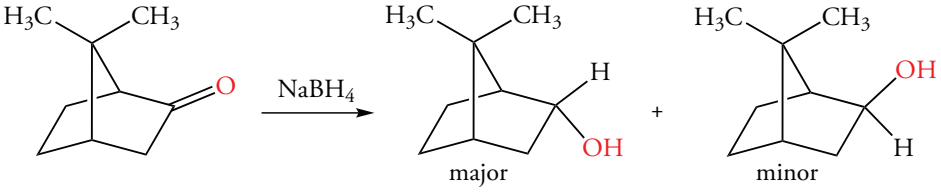
Answers:



Problem 15. 19

Reduction of 7,7-dimethylbicyc1o[2.2.1]heptan-2-one with sodium borohydride yields two isomeric alcohols in a 6:1 ratio. Considering the effect of the methyl groups, write the structures of the products.

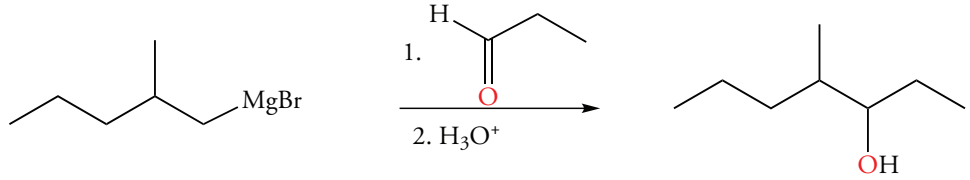
Answer: The major product arises from attack at the least sterically hindered side, away from the bridge methyl groups.



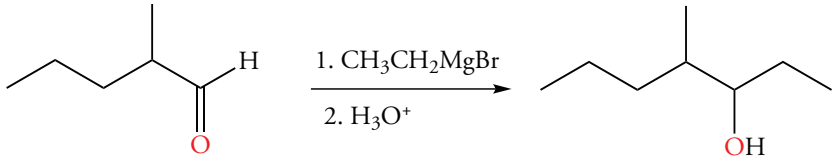
Problem 15.20

The European bark beetle produces a pheromone that causes beetles to congregate. Describe two ways that the compound could be synthesized by a Grignard reagent.

Answers:



4-methyl-3-heptanol

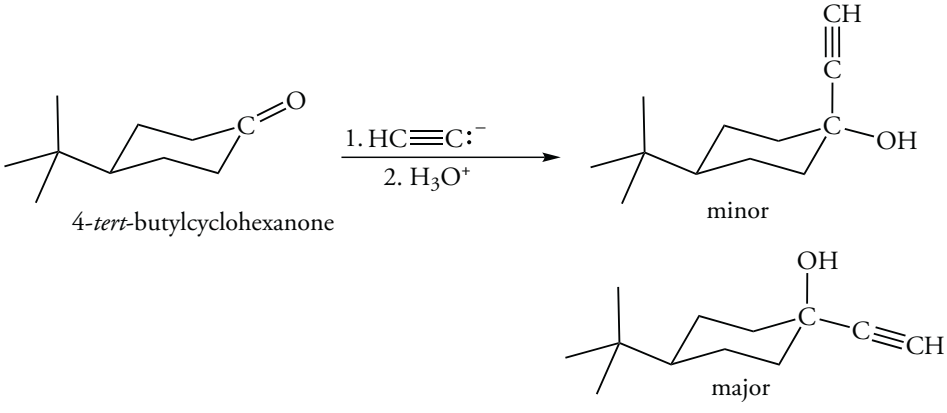


4-methyl-3-heptanol

Problem 15.21

Write the structures of the two products obtained by reaction of 4-*tert*-buty1cyclohexanone with sodium acetylide. Predict which one is obtained in the larger amount.

Answer:



4-*tert*-butylcyclohexanone

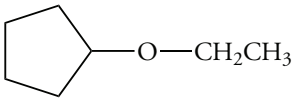
minor

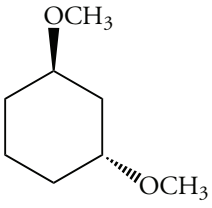
major

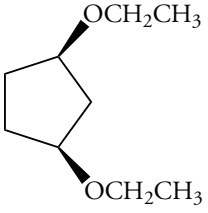
Solutions to In-Chapter Problems
Chapter 16

Problem 16. 1
What are the IUPAC names of the following compounds?

Answers:
(a) ethoxycyclopentane
(b) *trans*-1,3-dimethoxycyclohexane
(c) *cis*-1,3-diethoxycyclopentane

(a) 

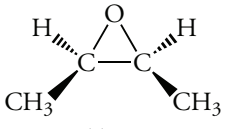
(b) 

(c) 

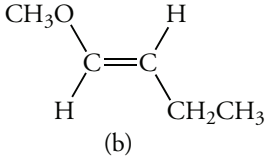
Problem 16. 2
Which of the following compounds can exist as pairs of enantiomers?
(a) 2-methoxytetrahydropyran (b) 4-methyltetrahydropyran
(c) 2-ethoxytetrahydrofuran (d) 3-methyltetrahydrofuran

Answers: (a), (c), and (d)

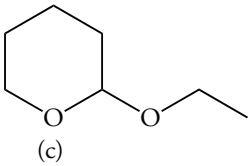
Problem 16. 3
Draw the structure of each of the following compounds.
(a) (2*S*,3*R*)-dimethyloxirane (b) (*Z*)-1-methoxy-1-butene
(d) 2-ethoxyoxane (c) *trans*-1,4-dimethoxycyclohexane



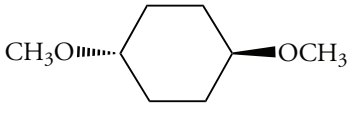
(a)



(b)

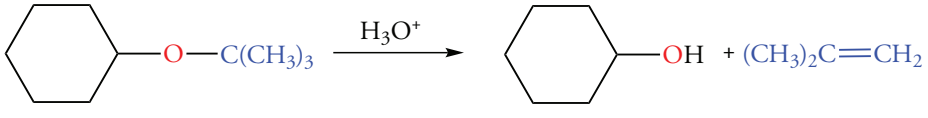


(c)



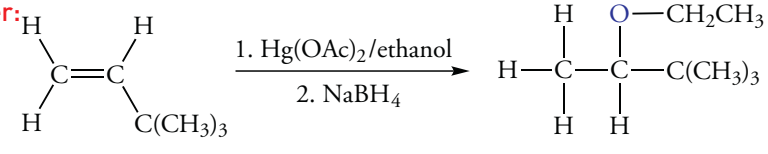
(d)

Problem 16. 4
Explain why both glyme and 1-4-dioxane are miscible with water.



Answer:
Both have a higher ratio of oxygen to carbon atoms than simple ethers. As a result, hydrogen bonding with water is more extensive.

Problem 16. 6
Write the structure of the product of a reaction of 3,3-dimethyl-l-butene with mercuric acetate in ethanol as solvent.

Answer:


Problem 16. 7

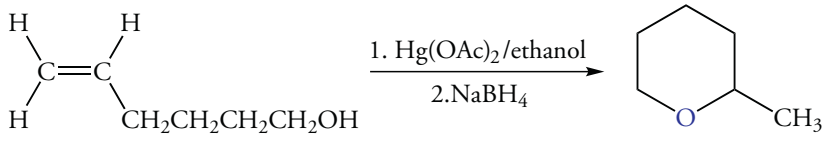
Select the reagents required to prepare each of the following compounds using alkoxymercuration–demercuration.
(a) ethoxycyclohexane (b) 1-propoxybutane (c) dicyclohexyl ether

Answers:
(a) cyclohexene in ethanol (b) 1-butene in 1-propanol (c) cyclohexene and cyclohexanol

Problem 16. 8

Reaction of 5-hexen-1-ol with mercuric acetate followed by demercuration gives a cyclic ether. The product is formed by an intramolecular alkoxymercuration reaction. Draw the structure of the product.

Answer:



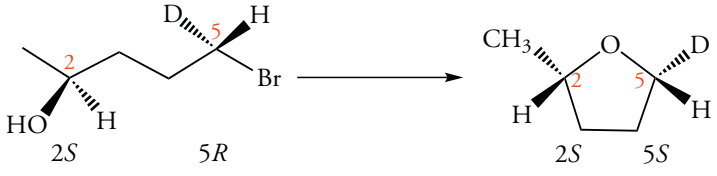
Problem 16. 10

Propose a synthesis of each of the following compounds using the Williamson ether synthesis.
(a) phenyl propyl ether (b) benzyl *tert*-butyl ether (c) 1,4-dimethoxybutane

Answers:
(a) phenoxide and 1-bromopropane (b) *tert*-butoxide and benzyl bromide (c) methoxide and 1 ,4-dibromobutane

Problem 16. 11

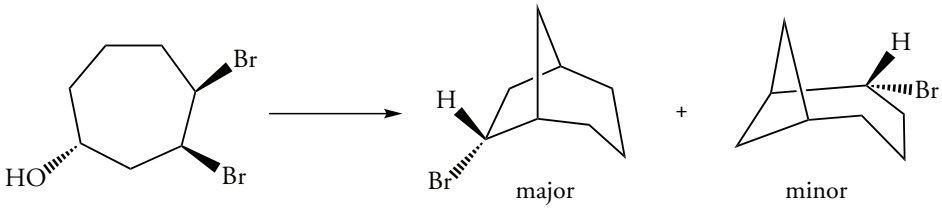
What is the configuration at each chiral center of the following bromo alcohol. Draw the structure of the tetrahydrofuran formed by an intramolecular Williamson ether synthesis or this compound and assign its configuration.



Answer:
The reaction occurs with inversion of configuration at C-5; the configuration at C-2 is unchanged.

Problem 16. 12

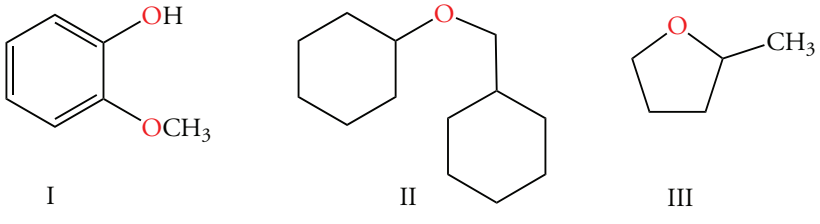
Draw the structures of two possible bicyclic ethers that could result from the intramolecular displacement of bromide by the alkoxide derived from the following dibromo alcohol. Which compound should predominate?



Problem 16. 13

Based on the mechanism of ether cleavage, what are the products of the reaction of HI with each of the following compounds.

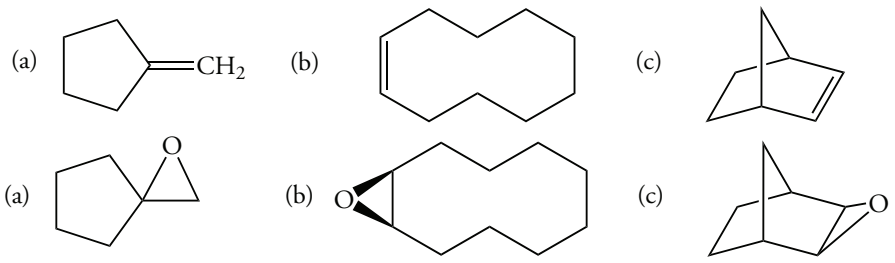
Answers:
I: CH_3I and *o*-dihydroxybenzene
II: bromomethylcyclohexane and cyclohexanol
III: 5-bromo-2-pentanol



Problem 16.16

Draw the structure of the epoxide formed in the reaction of each of the following compounds with MMPP in ethanol.

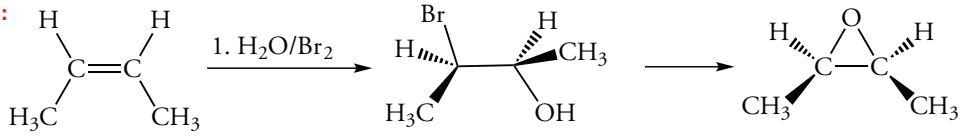
Answer:



Problem 16.17

Write the halohydrin product of the electrophilic addition of bromine in water to *cis*-2-butene. What is the stereochemistry of the epoxide formed from this bromohydrin?

Answer:

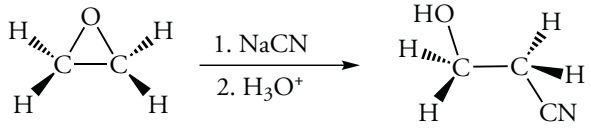


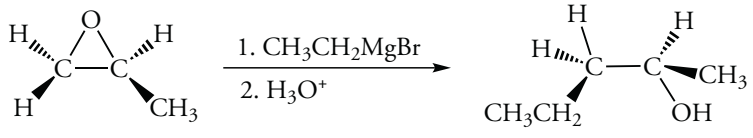
Problem 16.19

Predict the product of each of the following reactions.

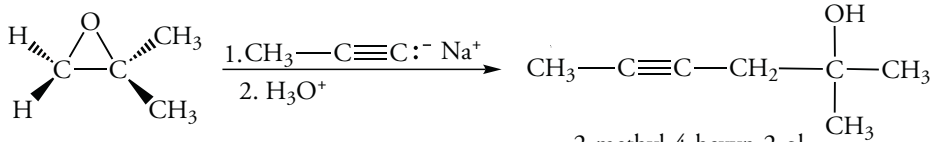
(a) sodium cyanide and ethylene oxide
(b) (*R*)-2-methyloxirane and the ethyl Grignard reagent
(c) propynyl sodium in liquid NH_3 and 2,2-dimethyloxirane

Answers:





(*R*)-2-pentanol

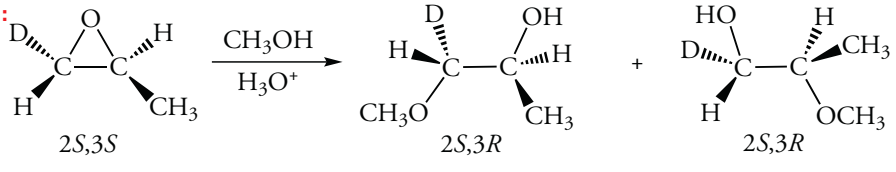


2-methyl-4-hexyn-2-ol

Problem 16. 21

Assign the configuration of both stereogenic centers of the following epoxide. Draw two possible products that could form in the reaction of the epoxide with methanol in an acid-catalyzed reaction. Assign the configuration at any stereogenic centers in both products.

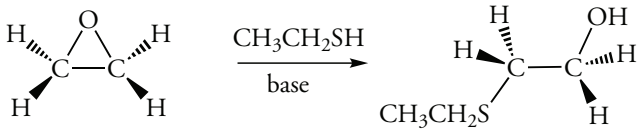
Answers:



2*S*,3*S* 2*S*,3*R* 2*S*,3*R*

Problem 16. 22

Write the product of the base-catalyzed reaction of CH_3CH_2SH and ethyloxirane. Explain why only a catalytic amount of base is required.

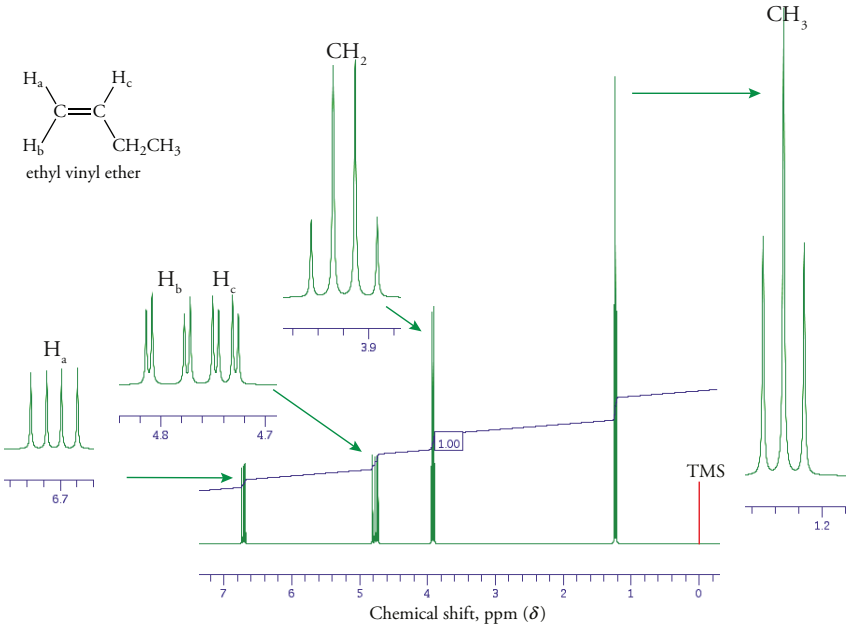


Answer: The intermediate alkoxide (CH_3CH_2—S—CH_2CH_2—O^-) that forms initially is not a strong enough base to remove a proton from the thiol and form the nucleophilic ethanethiolate.

Problem 16. 23

Deduce the structure of a compound with molecular formula $C_4H_{10}O$ having the following proton NMR spectrum.

Answer:

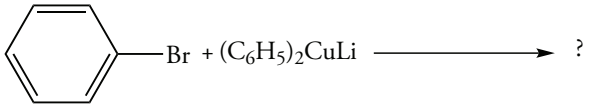


Solutions to In-Chapter Problems
Chapter 17

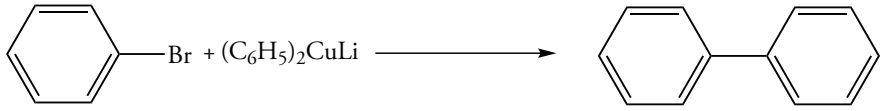
Gilman Reaction

Problem 17.2

What is the product of the following reaction?

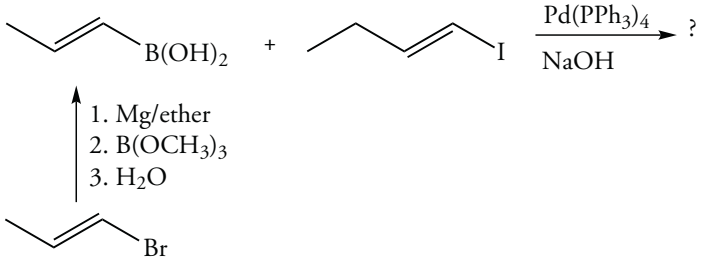


Answer:

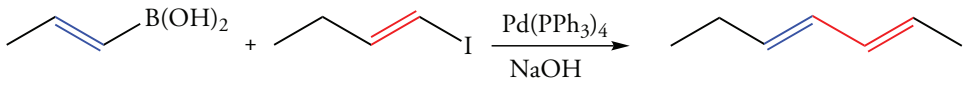


Problem 17.3

What is the product of the following reaction?



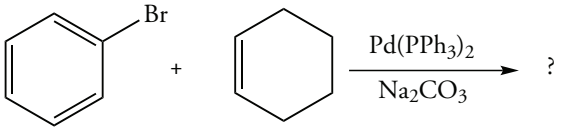
Answer:



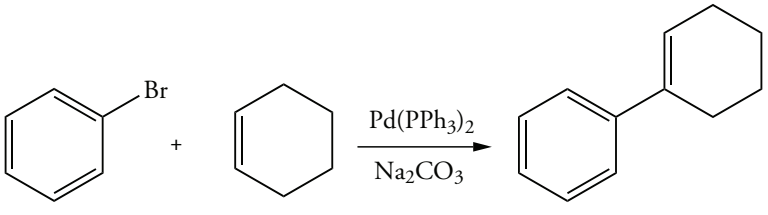
Heck Reaction

Problem 17.4

What is the product of the following reaction?

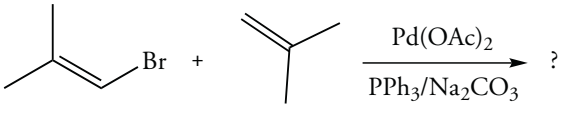


Answer:

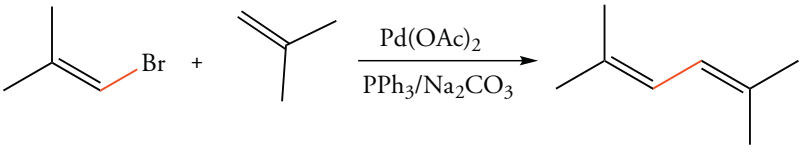


Problem 17.5

What is the product of the following reaction?



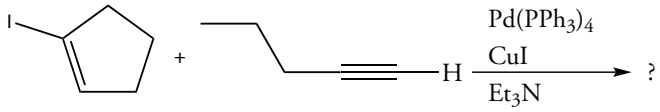
Answer:



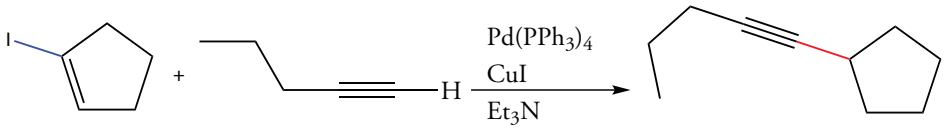
Sonogashira Reaction

Problem 17.6

What is the product of the following reaction?



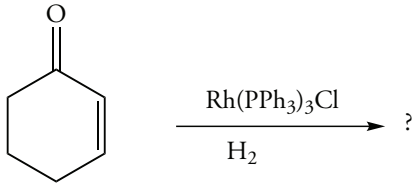
Answer:



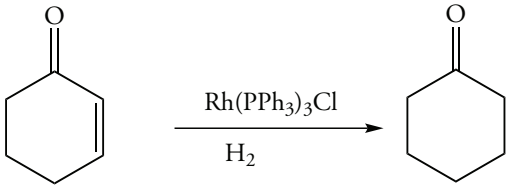
Wilkinson's Catalyst

Problem 17.7

What is the product of the following reaction?



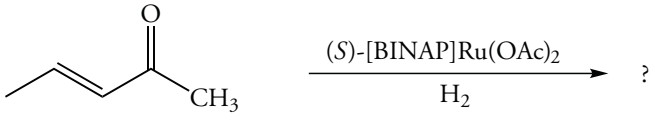
Answer:



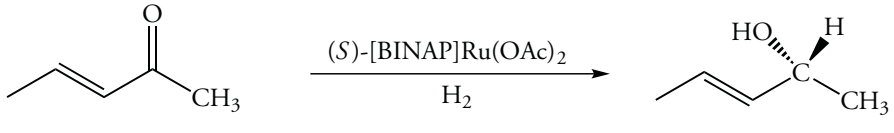
Asymmetric Hydrogenation:

Problem 17.9

What is the product of the following reaction?



Answer:

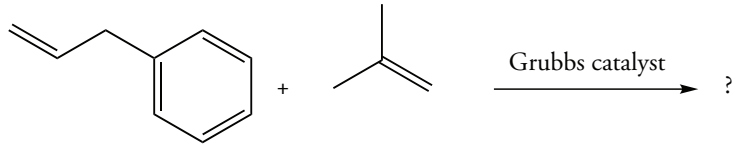


S isomer

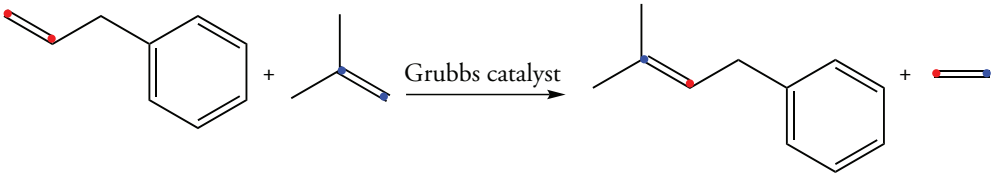
Grubbs Metathesis

Problem 17.10

What is the product of the following reaction?



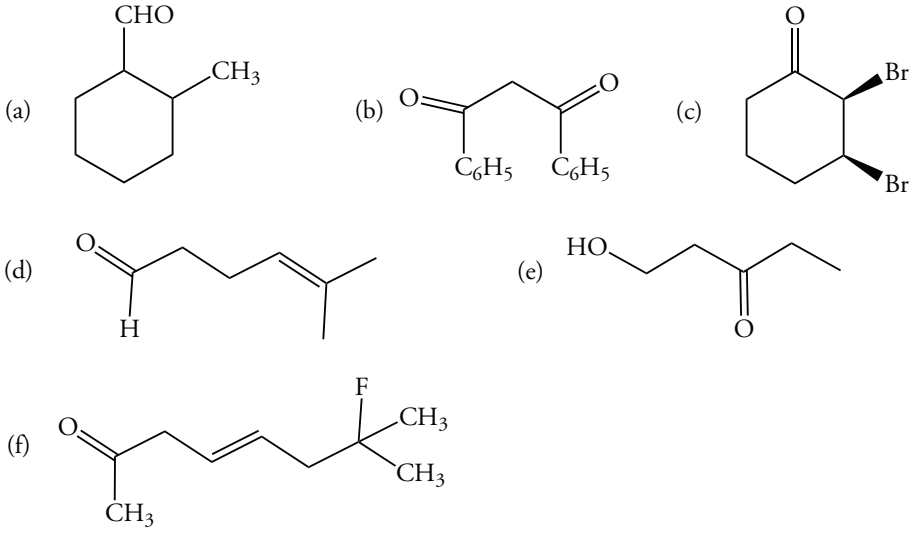
Answer:



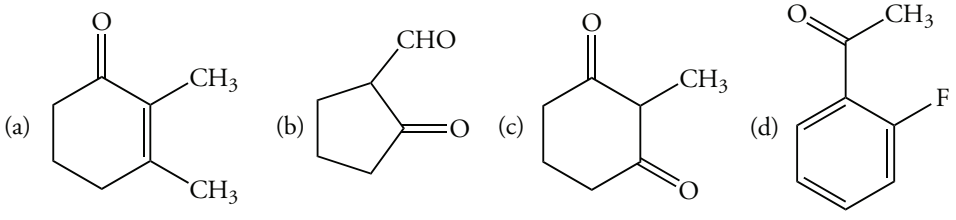
Solutions to In-Chapter Problems
Chapter 18

Problem 18. 3
Draw the structure of each of the following compounds.
(a) 2-methylcyclohexanecarbaldehyde (b) 1,3-dipheny1-1,3-propanedione
(c) *cis*-2,3-dibromocyclohexanone (d) 5-methyl-4-hexenal
(e) 1-hydroxy-3-pentanone (f) 7-fluoro-7-methyl-4-octen-2-one

Answers:



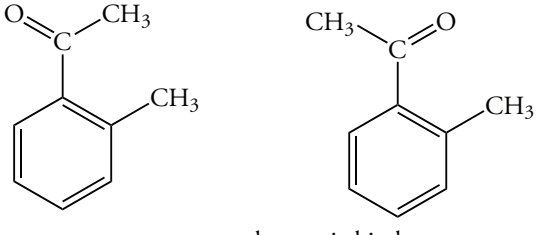
Problem 18. 4
Assign the IUPAC name to each of the following structures.



Answers:
(a) 2.3-dimethyl-2-cyclohexenone (b) 2-oxocyclopentanecarbaldehyde (c) 2-methyl-1,3-cyclohexanedione (d) 2-fluoroacetophenone

Problem 18. 6
Draw two conformations of 2-methylacetophenone that have the carbonyl group conjugated with the aromatic ring. Which is the more stable?

Answer:



less steric hindrance, more stable

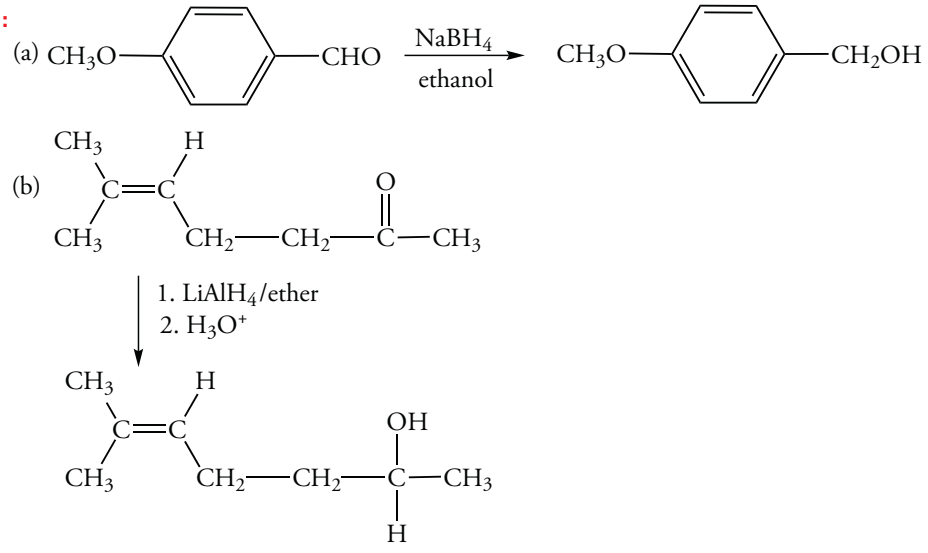
Problem 18. 7
Can the isomeric carbonyl-containing compounds of molecular formula C_4H_8O be distinguished by Tollens's reagent?

Answer:
Only 2-butanone can be, because it is not oxidized by Tollens reagent

Problem 18. 8

Draw the structure of the product of each of the following reactions.

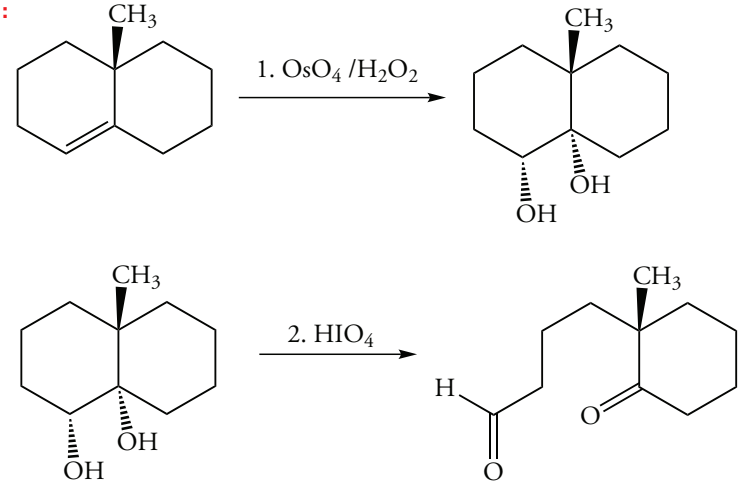
Answers:



Problem 18.10

Draw the structures of the compounds formed in each step of the following reaction sequence, showing the stereochemistry of each.

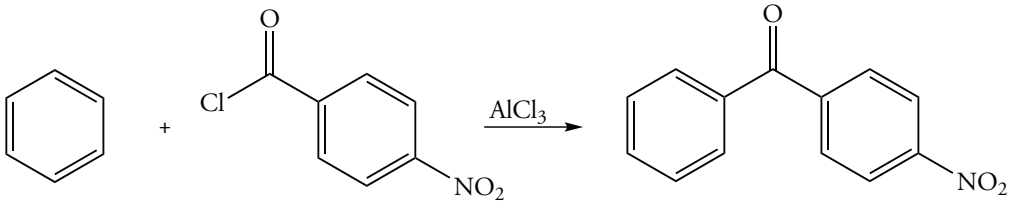
Answers:



Problem 18.11

Outline a synthesis of the following compound using starting materials that contain no more than seven carbon atoms.

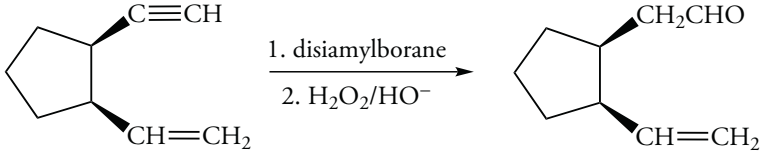
Answer:



Problem 18.12

Draw the structure of the product formed from reaction of the following compound with disiamylborane followed by oxidation with basic hydrogen peroxide.

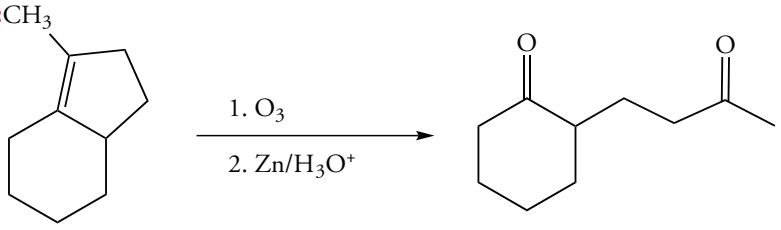
Answer:



Problem 18.13

A hydrocarbon with the molecular formula $C_{10}H_{16}$ reacts with ozone followed by a reductive workup to give the following compound. What is the structure of the hydrocarbon?

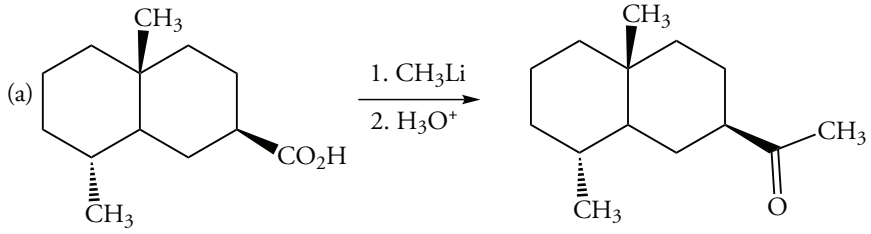
Answer:

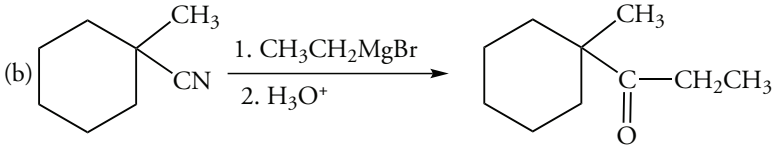


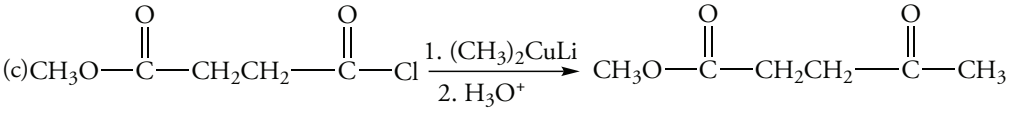
Problem 18. 14

Draw the structure of the product of each of the following reactions.

Answers:



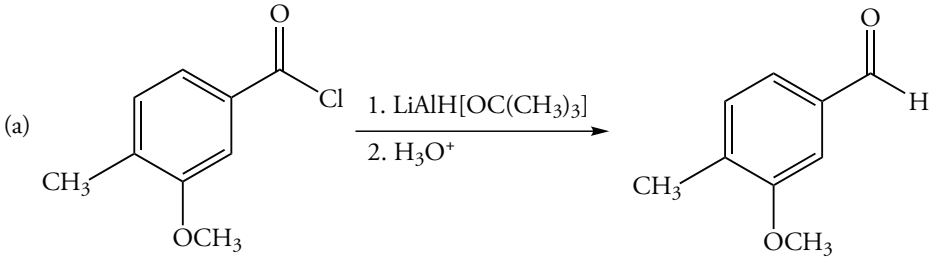


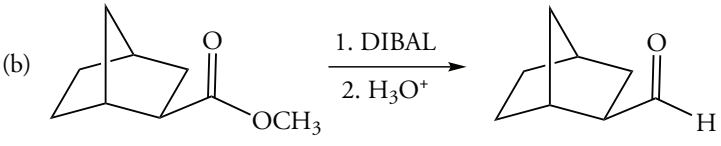


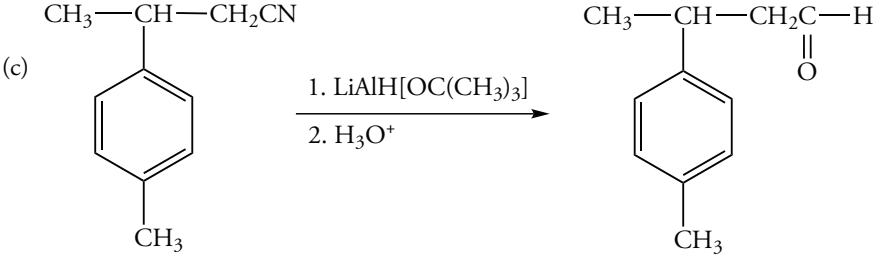
Problem 18. 15

Draw the structure of the product of each of the following reactions.

Answers:







Problem 18. 16

How could IR spectroscopy be used to distinguish between the isomers of each of the following pairs?

(a) 2-methylcyclopentanone and 2-ethylcyclobutanone
(b) 3-cyclohexenone and 2-cyclohexenone
(c) 4-methylbenzaldehyde and 4-methoxybenzaldehyde
(d) 2-methylcyclohexanone and cyclohexanecarbaldehyde

Answers:

(a) 2-Ethylcyclobutanone has a carbonyl stretching vibration at 1780 cm^{-1}, compared to 1745 cm^{-1} for 2-methylcyclopentanone.
(b) The conjugated 2-cyclohexenone has a carbonyl stretching vibration at 1670 cm^{-1}, whereas the unconjugated ketone has a carbonyl stretching vibration at 1715 cm^{-1}.
(c) 4-Methoxybenzaldehyde has a carbonyl stretching vibration at lower wavenumber.
(d) 2-Methylcyclohexanone has a carbonyl stretching vibration at somewhat lower wavenumber.

Problem 18. 17

Suggest a reason for the observation that the IR absorption of the carbonyl group of a ketone is at lower wavenumber than that of the carbonyl group of an aldehyde.

Answer: The alkyl group is inductively electron donating and stabilizes the dipolar resonance form.

Problem 18. 18

Deduce the structure of isomeric compounds having the molecular formula C_4H_8O based on the following C-13 NMR data.

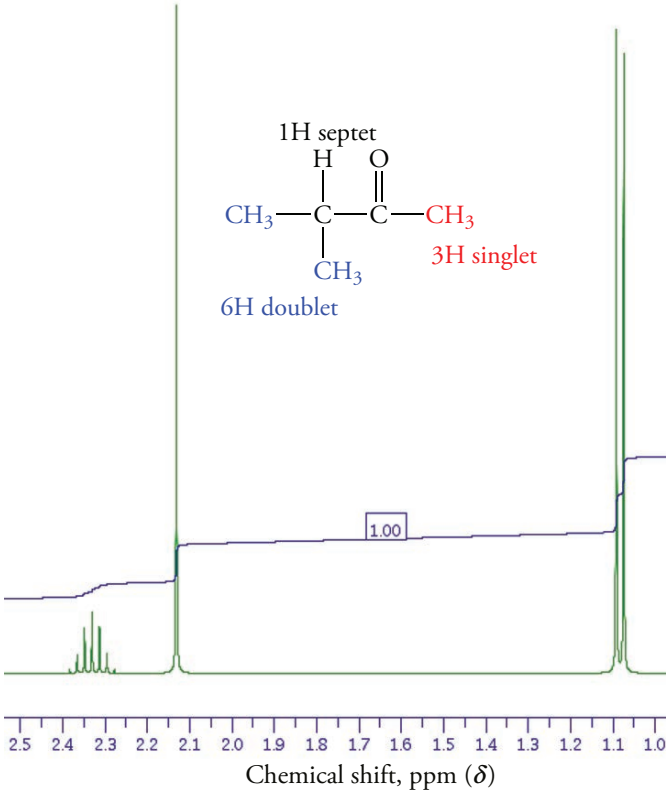
(a) 7.6 ppm, 28.8 ppm, 36.4 ppm, 206.3 ppm
(b) 13.3 ppm, 15.7 ppm, 45.7 ppm, 201.6 ppm

Answers:

(a) Compound (a) is 2-butanone
(b) Compound (b) is butanal.

Problem 18. 20

Deduce the structure of a compound with the molecular formula $C_5H_{10}O$ based on the following proton NMR spectrum.



Solutions to In-Chapter Problems
Chapter 19

Problem 19. 1
The equilibrium constants for the formation of cyanohydrins of benzaldehyde and *p*-methoxyacetophenone are approximately 210 and 30, respectively. Does this difference reflect a steric effect, a resonance effect, or an inductive effect?

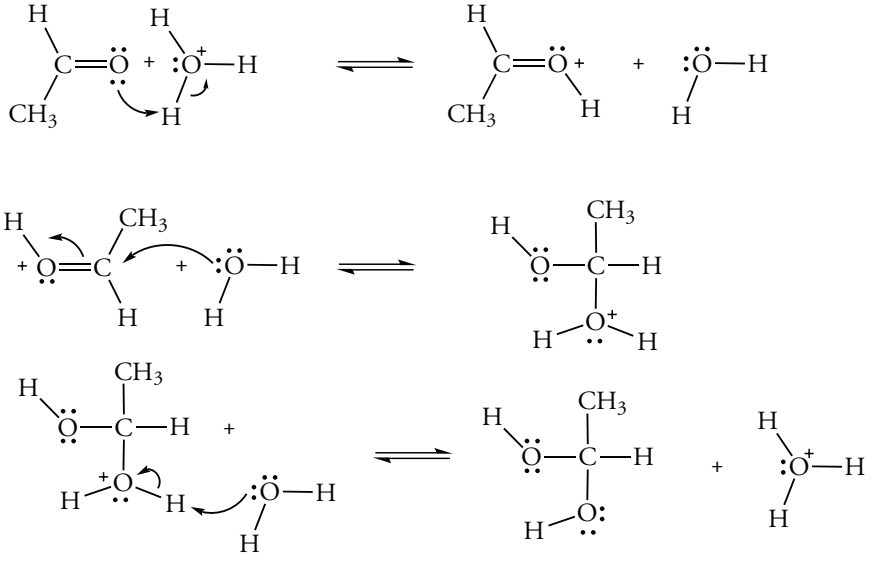
Answer:
Resonance stabilization of carbonyl group by *p*-methoxy group disfavors the addition reaction.

Problem 19. 4
The equilibrium constants for the formation of cyanohydrins of acetaldehyde and acetone are 1×10^4 and 30, respectively. What structural features of the reactants account for the difference between the equilibrium constants?

Answer:
The steric effect of the methyl groups of the ketone destabilizes the addition product.

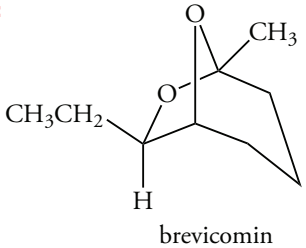
Problem 19. 5
Write the steps for the acid-catalyzed hydration of CH_3CHO in aqueous solution.

Answer:



Problem 19. 6
Identify the functional group of brevicomin, the sex attractant of a species of pine beetle.

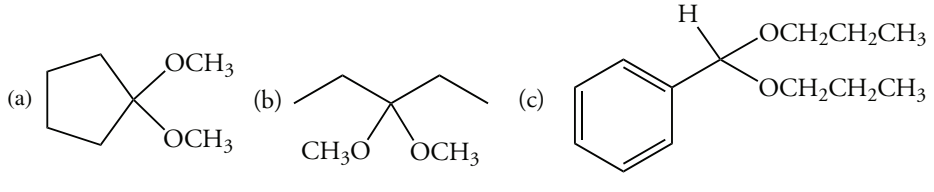
Answer:
ketal



brevicomin

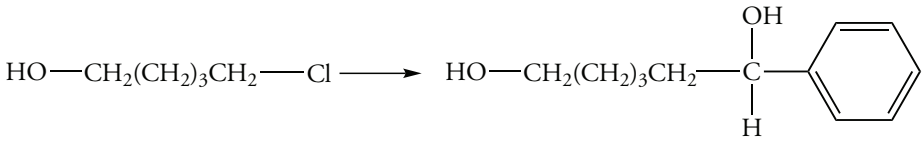
Problem 19. 7
Write the structures of the acetal or ketal formed in each of the following pairs of compounds.
(a) cyclopentanone and methanol (b) 3-pentanone and ethanol (c) benzaldehyde and 1-propanol

Answers:



Problem 19.9

The following reaction cannot be accomplished by preparing a Grignard reagent and reacting it with benzaldehyde. Explain why not and outline a method to obtain the product using appropriate protecting groups.



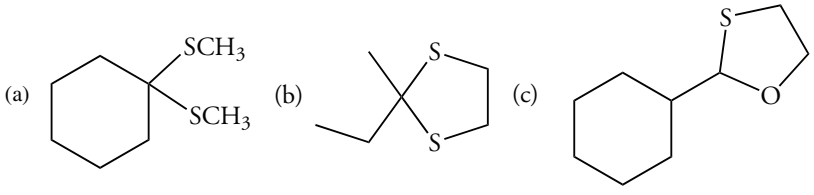
Answer:

The acidic hydrogen of the hydroxyl group would destroy the Grignard reagent as it forms. Prepare the THP derivative of the alcohol and then prepare the Grignard reagent to react with the alcohol.

Problem 19.10

Draw the structures of the products of each of the following combination of reagents.
(a) cyclohexanone and methanethiol (b) 2-butanone and 1,2-ethanedithiol (c) cyclohexanecarbaldehyde and 2-thioethanol

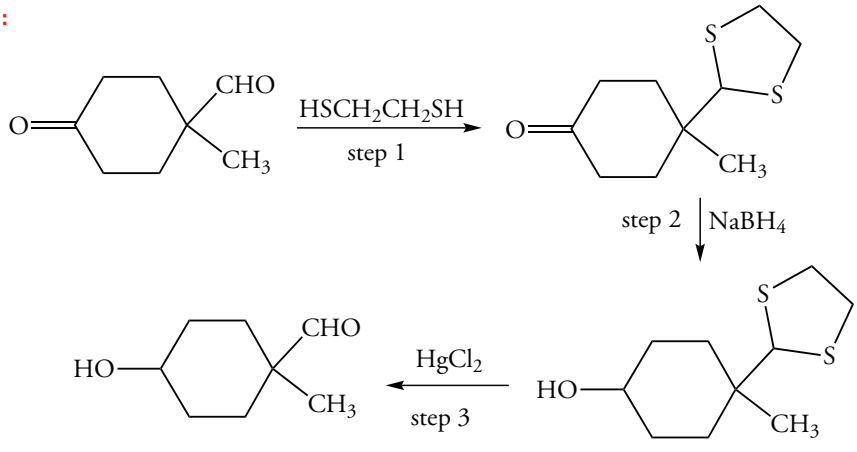
Answers:



Problem 19.11

Outline the steps required to accomplish the following synthesis using a thioacetal derivative in one of the steps.

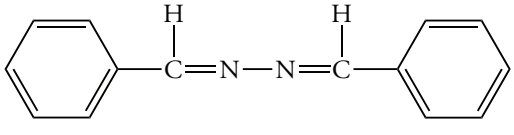
Answer:



Problem 19.12

Two equivalents of benzaldehyde react with hydrazine to give a compound with molecular formula $C_{14}H_{12}N2_2$. Draw the structure of the compound.

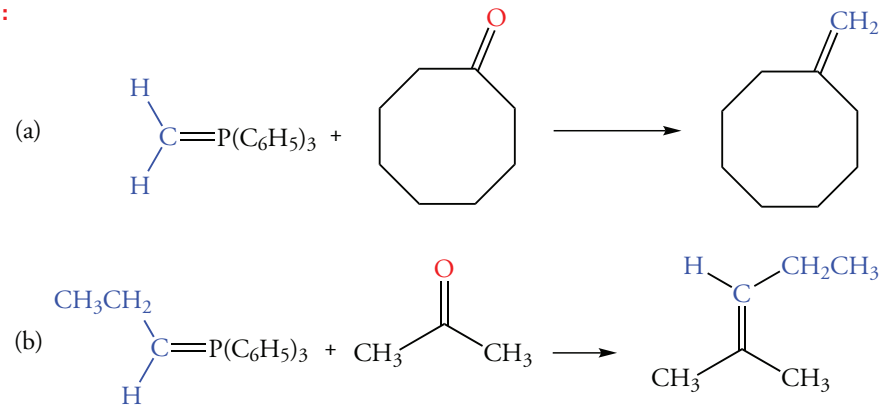
Answer:



Problem 19.14

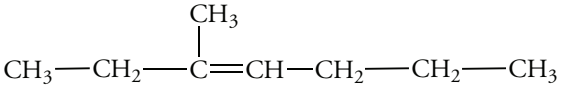
What combination of phosphorus ylide and a carbonyl compound could be used to prepare each of the following alkenes?
(a) methylenecyclooctane (b) 2-methyl-2-pentene

Answers:



Problem 19. 15

Outline two possible syntheses of the following compound. Would you predict any difficulties in obtaining a pure product?



Answer:

Either 2-methylpropanal and the ylide from 1-bromobutane, or butanal and the ylide from 2-methyl-1-bromopropane will give a mixture of (*E*) and (*Z*) isomers

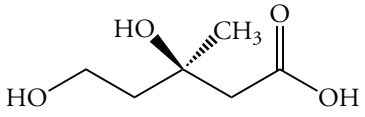
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Solutions to In-Chapter Problems
Chapter 20

Problem 20. 1
Propose two reasons why the C—O single bond of carboxylic acids (136 pm) is shorter than that of an alcohol (142 pm). Which of the two factors is the more important?

Answer:
The sp^2-hybridized carbon atom makes the C—O bond shorter. There is an additional small shortening as a result of resonance donation of lone pair electrons to the carbonyl carbon atom to give a double bond.

Problem 20. 3
Mevalonic acid is required to form isopentenyl pyrophosphate, an intermediate in terpene synthesis. It has the following structure. What is its IUPAC name?



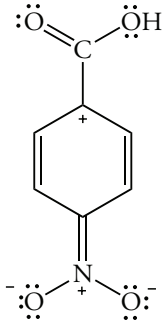
Answer:
The parent contains five carbons, so it is a pentanoic acid. There are hydroxyl groups at C-3 and C-5; C-3 is chiral, with configuration (*R*). The name is (*R*)-3,5-dihydroxy-3-methylpentanoic acid

Problem 20. 4
(a) Rank toluene, benzyl alcohol, benzaldehyde, and benzoic acid in the order of increasing boiling point. (b) Rank them in increasing order of solubility in water.

Answer:
The polarity of these three aromatic compound changes in the order toluene < benzaldehyde < benzyl alcohol < benzoic acid. Their boiling points and solubility in water are in the same order.

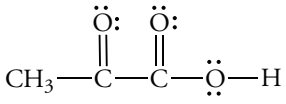
Problem 20.6
Explain why *p*-nitrobenzoic acid is a stronger acid than *m*-nitrobenzoic acid.

Answer:
The nitro group can withdraw electron density from the carboxyl group by an inductive effect at both the *meta* and *para* positions. However, a *para*-nitro group also withdraws electron density from the carboxyl from the ring by a resonance effect. Therefore, the *para* isomer is more acidic.



Problem 20.7

Explain why pyruvic acid (pK_a 4.7) is about 100 times more acidic than propanoic acid (pK_a 2.5). Pyruvic acid is a key metabolic intermediate in oxidative processes that provide energy for the growth and maintenance of cells.



pyruvic acid

Answer:

The carbon atom of the carbonyl group withdraws electron density from the carboxyl carbon by an inductive effect, increasing the acidity of the carboxyl group.

Problem 20.8

Ibuprofen, the active ingredient in Motrin, Advil, and Nuprin, is a carboxylic acid with pK_a = 5.2. Determine the ratio of the conjugate base to acid in stomach acid at (a) pH 2 and (b) blood at pH 7.4.

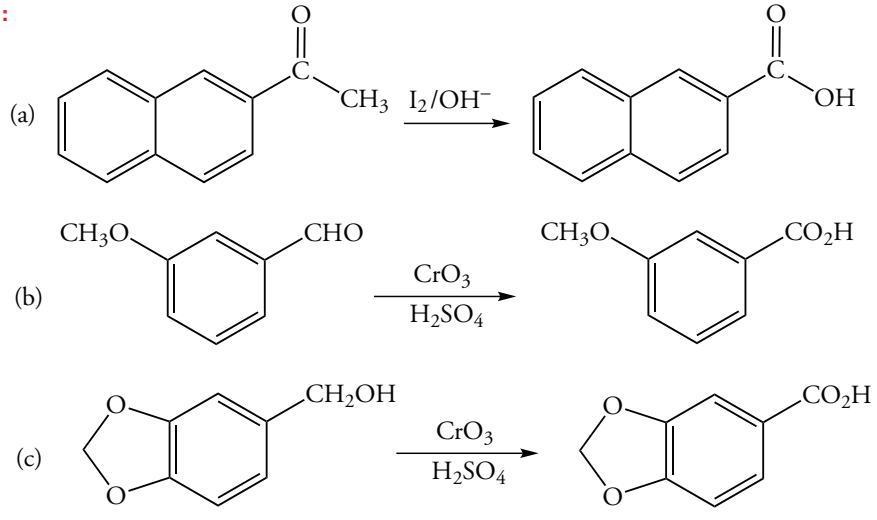
Answer:

At pH 2, the ratio of the acid to the conjugate base is $10^{3.2}$. Therefore the ratio is 1.6×10^3. At pH 7, the situation is reversed, and the base predominates. The ratio of the conjugate base to the acid is $10^{-2.2}$, or 6.3×10^{-4}.

Problem 20.10

Suggest synthetic sequences for the following transformations.

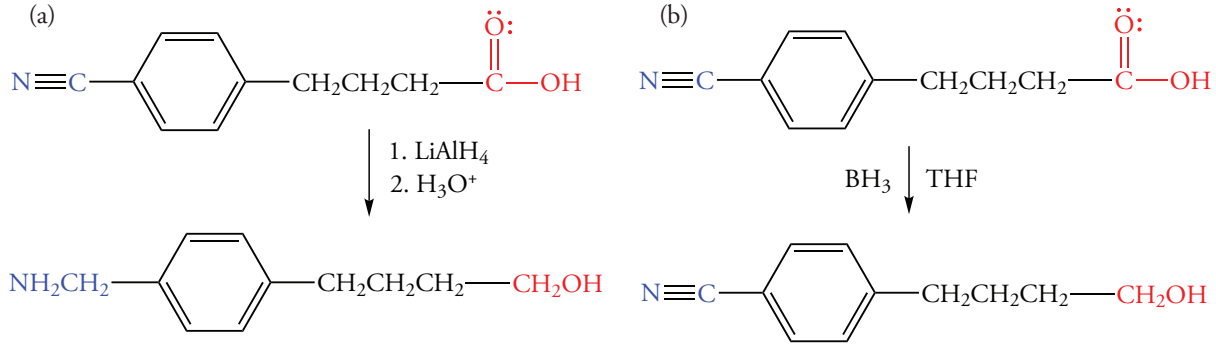
Answers:



Problem 20.11

What is the product of the reaction of 3-(*p*-cyanophenyl)propanoic acid with $LiAlH_4$? What is the product using B_2H_6?

Answers:

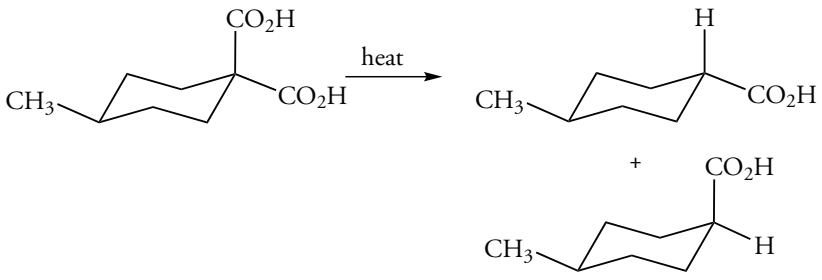


Problem 20.12

Heating 4-methyl-1,1-cyclohexanedicarboxylic acid yields a mixture of two isomers. (a) Draw their structures and (b) explain their origin.

Answer:

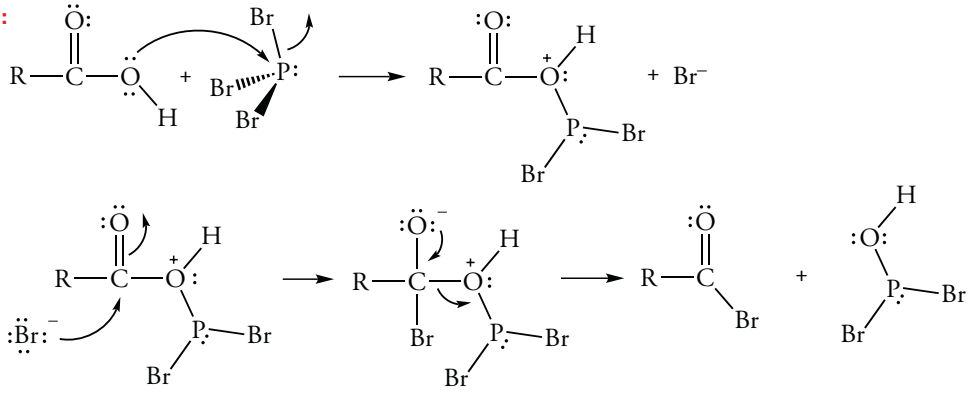
Decarboxylation can occur by loss of either an axial or an equatorial carboxyl group. The products are a mixture of *cis*- and *trans*-4-methylcyclohexanecarboxylic acids.



Problem 20. 13

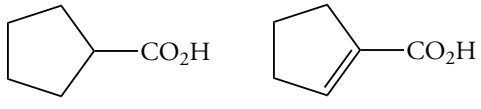
Carboxylic acids can be converted into acyl bromides by reaction with PBr_3. Write a mechanism for the reaction of this reagent with carboxylic acids.

Answer:



Problem 20. 14

How can the following two carboxylic acid isomers be distinguished by infrared spectroscopy?



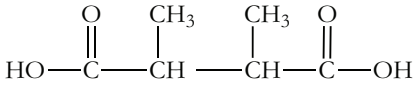
I II

Answer:

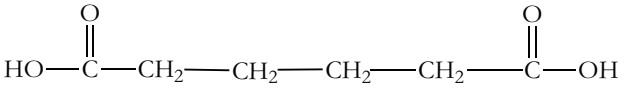
The carbonyl stretching vibration of I occurs at lower wavenumber than 1710 cm^{-1} because the double bond in II is conjugated with the carboxyl group.

Problem 20. 15

How could the following two isomers be distinguished using proton NMR spectroscopy?



2,3-dimethylbutanedioic acid
(α,β-dimethylsuccinic acid)



hexanedioic acid
(adipic acid)

Answer:

In proton NMR, hexanedioic acid has two triplets at high field, whereas the isomer has a quartet and a doublet.

Problem 20. 16

Deduce the structure of a compound with molecular formula $C_8H_8O_2$ based on the following C-13 NMR data.
C-13 chemical shifts: 21.2 ppm, 128. 1 ppm , 129.1 ppm , 129.4 ppm, 143.0 ppm, 167.4 ppm

Answer:

The compound must be a benzoic acid since there are far too few hydrogens for a saturated carboxylic acid. Since there are has eight carbon atoms, but only six C-13 resonances, the ring must be *para*-substituted. Therefore, it is *p*-methylbenzoic acid.

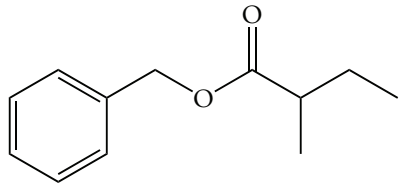
Solutions to In-Chapter Problems
Chapter 21

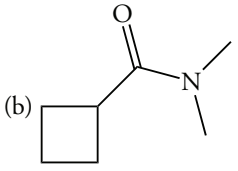
Problem 21. 2

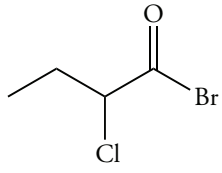
Write the structure of each of the following compounds.

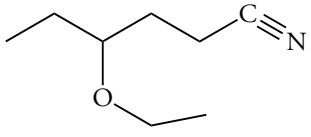
(a) benzyl 2-methylbutanoate
(b) *N*,*N*-dimethylcyclobutanecarboxamide
(c) 2-chlorobutanoyl bromide
(d) 4-ethoxyhexanenitrile
(e) 3,3,3-trifluoropropanoic anhydride
(f) 6-aminohexanoic acid lactam

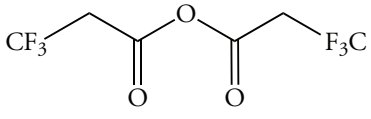
Answers:

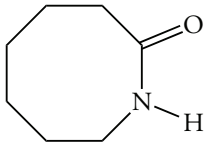
(a) 

(b) 

(c) 

(d) 

(e) 

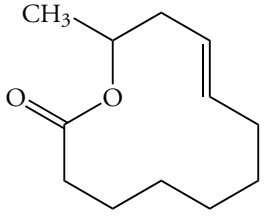
(f) 

Problem 21. 3

What is the name of the following large-ring lactone, which has been isolated from a species of fungus?

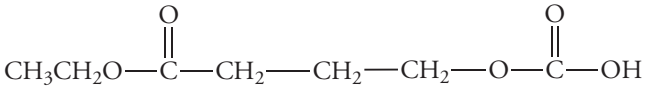
Answer:

11-Hydroxy-8-dodecenoic acid lactone

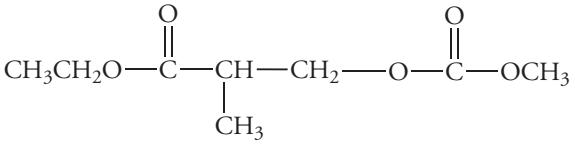


Problem 21. 4

Explain why one of the following compounds is more soluble in water.



I



II

Answer:

Compound is more soluble because it has a carboxylic acid group capable of making hydrogen bonds to water both as a hydrogen bond donor and as a hydrogen bond acceptor.

Problem 21. 5

Explain why the dipole moment of methyl acetate (1.7 D) is smaller than the dipole moment of acetone (2.9 D).

Answer:

Donation of lone pair electrons of the ester to the carbonyl carbon atom decreases the polarity of the carbonyl group.

Problem 21.6

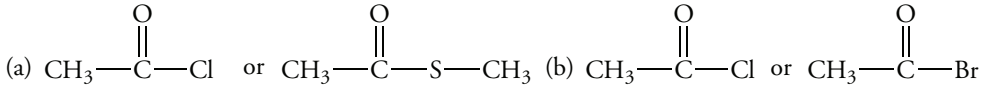
The pK_a of the conjugate acid of propanone is –7.1. Why is this species a stronger acid than the conjugate acid of ethanoic acid (pK_a = –6)?

Answer:

Propanone is not resonance stabilized. Two equivalent resonance forms can be written for the conjugate acid of ethanoic acid.

Problem 21.7

Which member of each of the following pairs of compounds reacts faster with water?

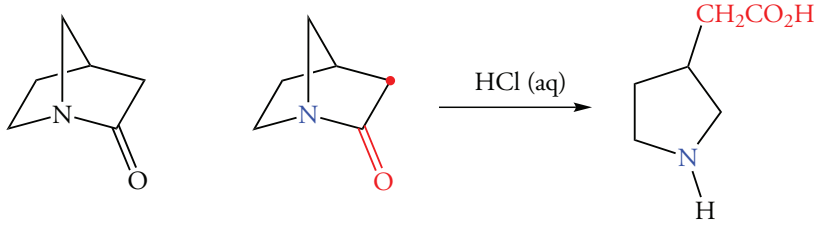


Answer:

(a) The acyl chloride reacts faster than the thioester because the thioester has greater resonance stabilization. (b) The acyl bromide reacts faster than the acyl chloride because the acid chloride is more resonance stabilized than the acid bromide. The C—Br bond is longer and weaker than the C—Cl bond. Orbital overlap between bromine and the sp²-hybridized carbonyl carbon is even less than in the acyl chloride. In general, the stabilities of the tetrahedral intermediates in nucleophilic addition elimination reactions are nearly the same for all of the acyl derivatives. The relative reactivity therefore depends upon differences in the stabilities of the reactants. Bromide is also a better leaving group than chloride, but this has no effect on the rate because cleavage of the C—X bond does not occur in the rate-determining step of the reaction.

Problem 21.10

Give two reasons why the following bicyclic amide is easily hydrolyzed.

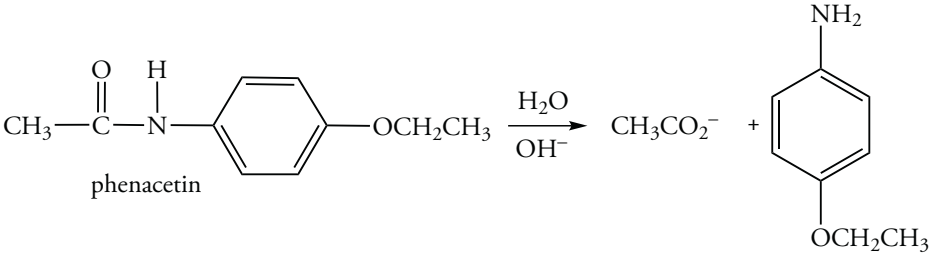


Answer:

(a) The amide group cannot be stabilized by resonance donation of electrons of the nitrogen atom because the double bond at a bridgehead atom in this resonance form is too strained. (b) Hydrolysis relieves ring strain.

Problem 21.11

What are the products of the hydrolysis of phenacetin by a base? Phenacetin was once used in APC analgesic tablets consisting of aspirin, phenacetin, and caffeine.



Answer:

The products are acetate and *p*-ethoxyaniline.

Problem 21.12

The principal component of the wax of the sperm whale is an unbranched ester that hydrolyzes to give $C_{16}H_{34}O$ and $C_{16}H_{32}O_2$. Write the structure of the ester.

Answer:

The ester is made from a 16-carbon carboxylic acid and a 16-carbon alcohol. It is $CH_3(CH_2)_{14}CO_2(CH_2)_{15}CH_3$.

Problem 21.14

Why are the esters of tertiary alcohols prepared by reaction with acid chlorides rather than by the Fischer esterification method?

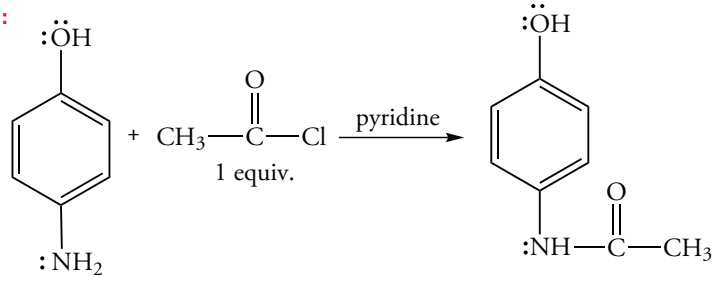
Answer:

Tertiary alcohols would dehydrate under acid conditions.

Problem 21.16

Draw the structure of the product of the following reaction.

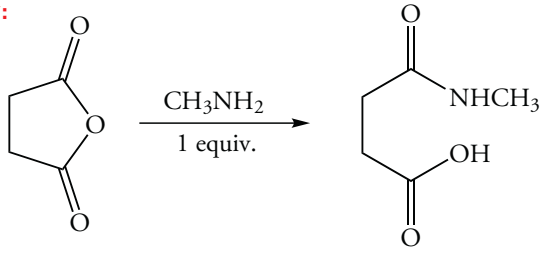
Answer:



Problem 21.17

Draw the structure of the product of the reaction of maleic anhydride with methylamine (CH_3NH_2).

Answer:

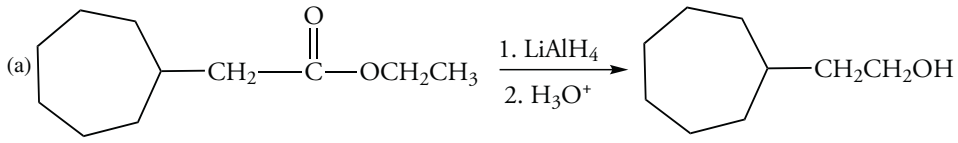


Problem 21.18

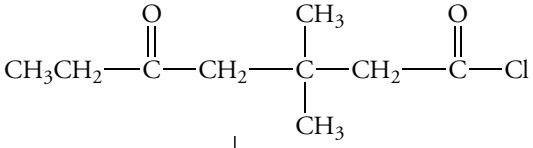
Draw the structure of the product of each of the following the reactions.

Answers:

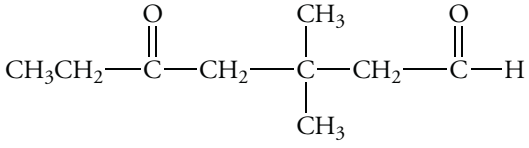
(a)



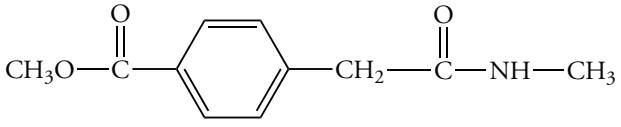
(b)



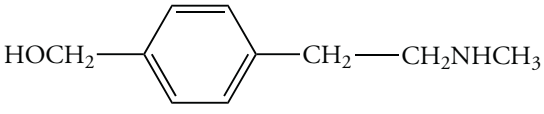
1. $LiAlH(OtBu)_3$ 2. H_3O^+



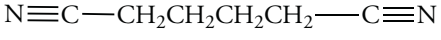
(c)



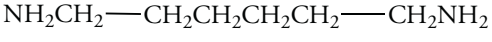
1. $LiAlH_4$ 2. H_3O^+



(d)

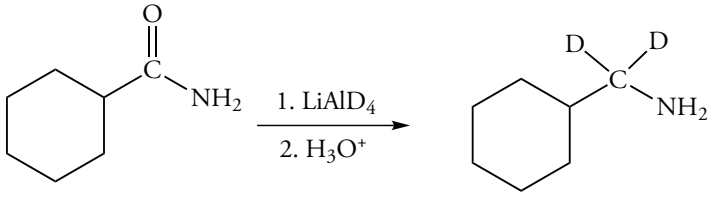


1. $LiAlH_4$ 2. H_3O^+



Problem 21. 19

Reduction of cyclohexanecarboxamide with $LiAlD_4$, followed by aqueous workup gives $C_7H_{13}D_2N$. What is the structure of the product?



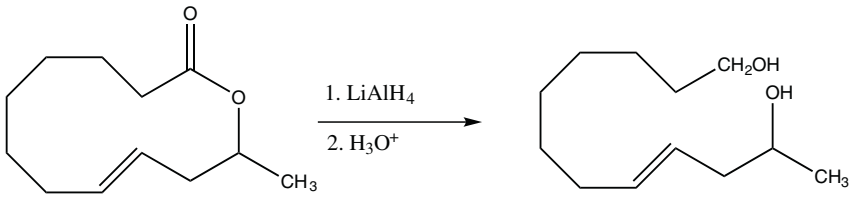
Answer:

The deuteride reagent, $LiAlD_4$, supplies deuteride ions to the carbonyl carbon atom. The hydrogen atoms eventually bonded to the nitrogen atom are supplied by the water in workup.

Problem 21. 20

Reduction by $LiAlH_4$, of a substance with molecular formula $C_{12}H_{20}O_2$ obtained from a fungus, gives (*E*)-4-dodecene-2,12-diol. Write the structure of the compound.

Answer:



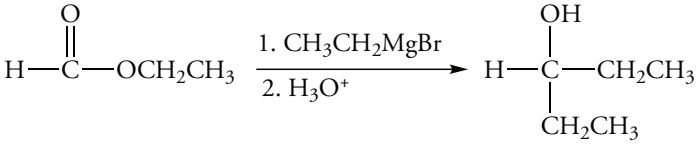
(*E*)-4-dodecene-2,12-diol

Problem 21. 22

Explain how symmetrical secondary alcohols of the type R_2CHOH can be prepared by adding a Grignard reagent to an ester.

Answer:

Add two moles of a Grignard reagent to an ester of methanoic acid such as ethyl methanoate.

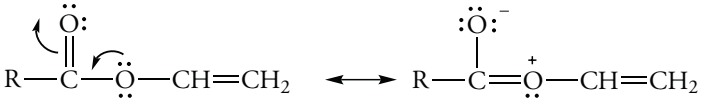


Problem 21. 23

Although esters of unsaturated acids have carbonyl stretching absorptions at 1720 cm^{-1}, a lower value than the esters of saturated acids, the carbonyl stretching absorption of unsaturated esters of the following type is at 1760 cm^{-1}. Explain why.

Answer:

The vinyl group withdraws electrons from the oxygen atom. Thus, the oxygen atom cannot as readily supply electrons to stabilize the dipolar resonance form.

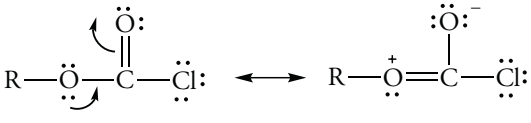


Problem 21. 24

Explain why chlorocarbonates have carbonyl stretching absorptions at 1780 cm^{-1}, a lower wavenumber value than shown by acyl chlorides.

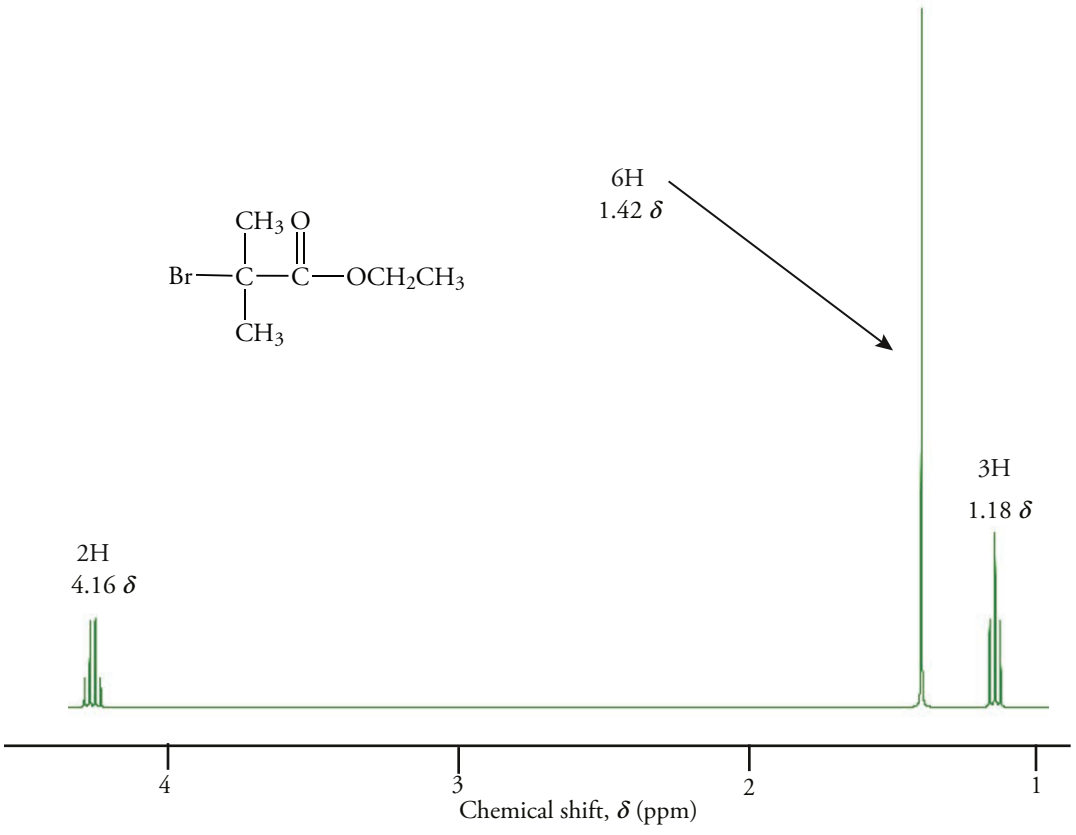
Answer:

The lone pair electrons of the oxygen atom can be supplied to the carbonyl carbon atom, and thus stabilize the dipolar resonance form.



Problem 21. 25

Deduce the structure of a compound with molecular formula $C_6H_{11}BrO_2$ with a carbonyl stretching absorption at 1730 cm^{-1}, and having the following hydrogen NMR spectrum.



Answer:

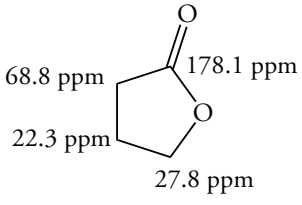
The carbonyl stretching frequency indicates that the compound is an ester. The 3H and 2H resonances correspond to an ethyl ester. The 6H singlet corresponds to two methyl groups on a carbon with no hydrogens. This carbon is bonded to a bromine atom and carbonyl carbon. The compound is ethyl 2-bromo-2-methylpropanoate.

Problem 21. 26

Deduce the structure of a compound with molecular formula $C_4H_6O_2$ that has a carbonyl stretching absorption, and whose carbon-13 NMR spectrum has resonances at 178.1, 22.3, 27.8, and 68.8 ppm.

Answer:

The formula and the carbonyl stretching frequency of the compound indicate that the compound is an ester. The formula also indicates that the compound is a cyclic ester, 4-hydroxybutanoic acid lactone. The resonance at 178.1 ppm corresponds to the carbonyl carbon; the resonance at 68.8 ppm corresponds to the α carbon, and the resonances at 22.3 and 27.8 ppm correspond to the β and γ carbons, respectively.



Solutions to In-Chapter Problems

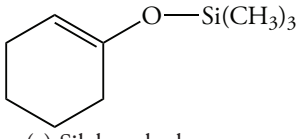
Chapter 22

Problem 22. 2

Chlorotrimethylsilane, $(CH_3)_3SiCl$, reacts with enolates to give the enol product with silicon bonded to oxygen. (a) Draw the product of the reaction with the enolate of cyclohexanone. (b) Explain why this product forms rather than the keto product.

Answers:

(b) The high bond energy of the Si—O makes the enol ether more stable than the keto form.



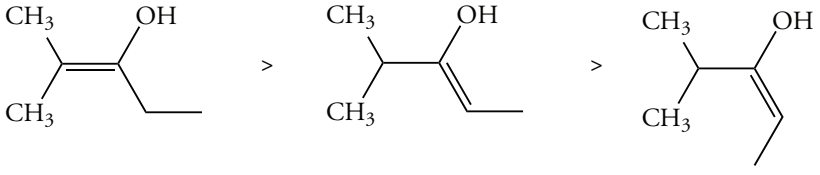
(a) Silyl enol ether.

Problem 22. 4

(a) Draw three possible enols for 2-methyl-3-pentanone and (b) describe their relative stabilities.

Answer:

The most stable enol is the most substituted one, and *trans* is more stable than *cis*.

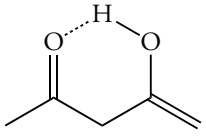


Problem 22. 5

An enol of 2,4-pentanedione can form an intramolecular hydrogen bond. (a) Draw its structure and (b) explain why it occurs in substantially smaller concentrations than 4-hydroxy-3-penten-2-one.

Answer:

The most stable enol is the most substituted one.



Problem 22. 6

Determine whether each of the following chiral compounds may enolize to produce a racemic mixture.

(a) (*R*)-2-ethyl-2-methylcyclopentanone
(b) (*S*)-3-ethylcyclohexanone
(c) (*S*)-3-phenyl-2-butanone

Answer:

Both (b) and (c) may enolize. Only (c) produces a racemic mixture.

Problem 22. 7

How can 2-methylcyclohexanone and 3-methylcyclohexanone be distinguished by acid-catalyzed enolization in D_2O?

Answer:

2-Methylcyclohexanone can incorporate three deuterium atoms; 3-methylcyclohexanone can incorporate four.

Problem 22.8

Which of the following compounds will give a positive iodoform test?

(a) 3-pentanone (b) 2-pentanone (c) 2-methyl-3-pentanone (d) 2-methylcyclohexanone

Answer:

Only (b), 2-pentanone, is a methyl ketone; therefore only (b) gives a positive iodoform test.

Problem 22.10

Based on the structural factors that affect the stability of an enol, predict the product of the reaction of 3-methyl-2-butanone with bromine under acidic conditions.

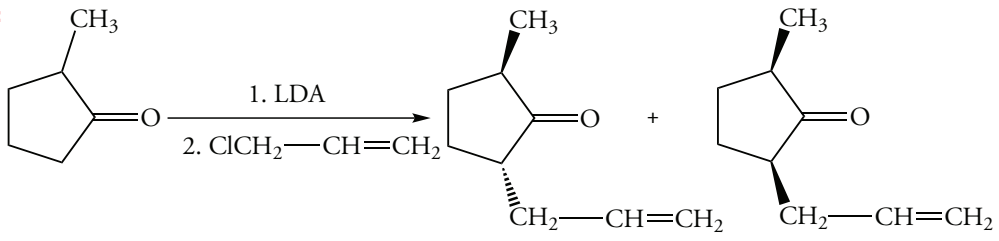
Answer:

Only (b), 2-pentanone, is a methyl ketone; therefore only (b) gives a positive iodoform test.

Problem 22.12

Draw the products of the reaction of 2-methylcylopentanone with LDA by reaction with allyl chloride.

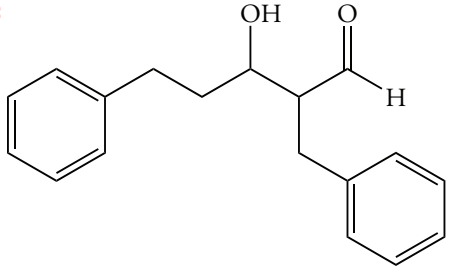
Answer:



Problem 22.13

Draw the product of the aldol condensation of 3-phenylpropanal.

Answer:



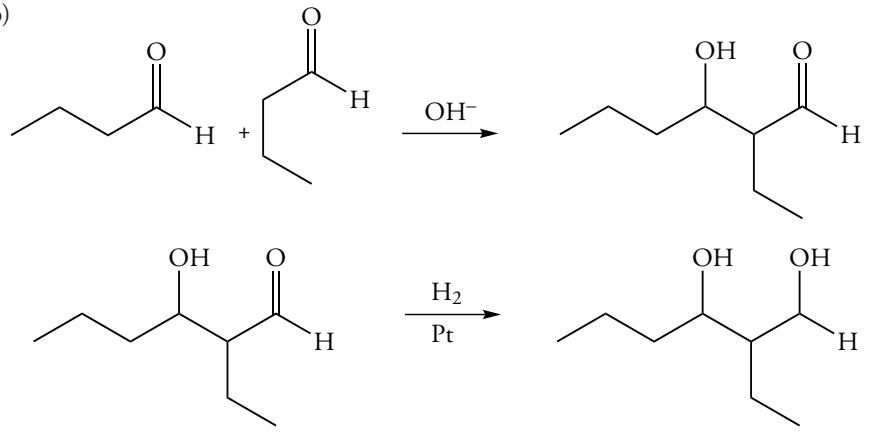
Problem 22.15

A commercial process to produce the insect repellent 2-ethyl-1,3-hexanediol starts with an aldol condensation. (a) What starting material is used? (b) Write equations for the reactions required to form the diol.

Answer:

(a)The starting material is butanal. The aldol product of butanal is reduced to form the diol.

(b)

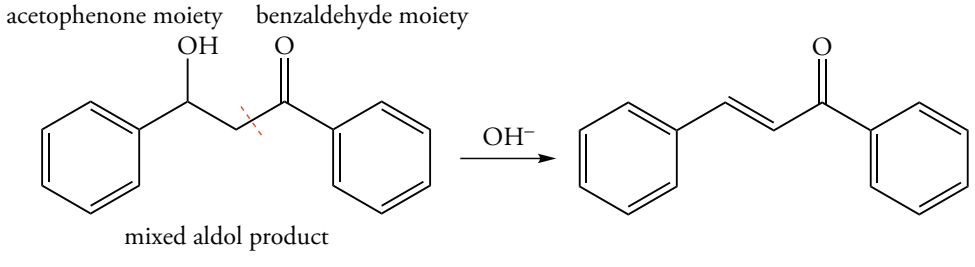


Problem 22.16

Acetophenone undergoes a condensation reaction with benzaldehyde to give a product with the molecular formula $C_{15}H_{12}O$. (a) Draw its structure and (b) explain why it forms.

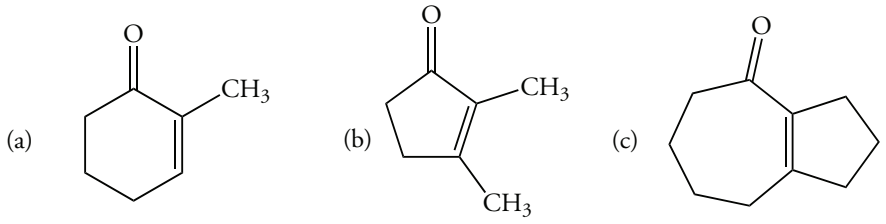
Answer:

The product forms by a mixed aldol condensation, which is followed by dehydration, which occurs because a conjugated system results.

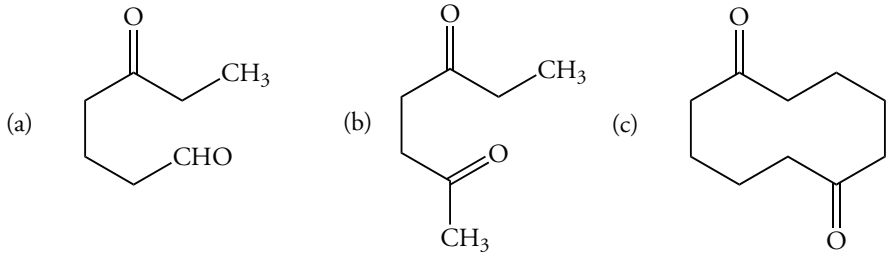


Problem 22.18

Draw the structure of the dicarbonyl compound required for synthesis of each of the following products by an aldol condensation.



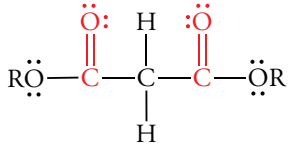
Answers:



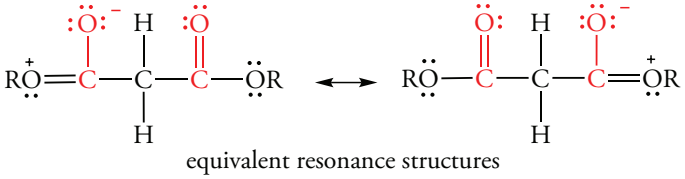
Problem 22. 19

Rank the three resonance forms of the malonate ester in order of their stability. Are any two of the resonance forms equivalent?

Answer:



most stable form



equivalent resonance structures

Problem 22. 21

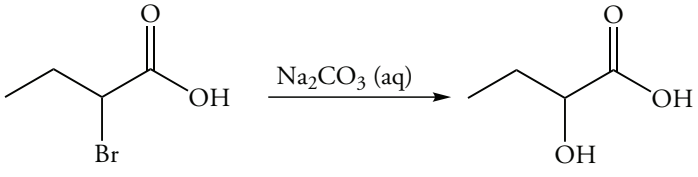
Calculate the equilibrium constant for the reaction of ethoxide ion with diethyl malonate.

Answer:

The pK_a of diethyl malonate is 13. The pK_a of ethanol is 16. The pK_a difference is 3; $K_{eq} = 10^3$.

Problem 22. 22

Predict the product of the reaction of 2-bromobutanoic acid with an aqueous sodium carbonate solution.



Problem 22. 24

Suggest two methods to prepare 2-isopropylpentanenitrile using an alkylation reaction. Which would give the better yield?

Answer:

Pentanenitrile and LDA followed by addition of 2-bromopropane will largely give elimination product. 3-Methylbutanenitrile and LDA followed by addition of 1-bromopropane will give a better yield.

Problem 22. 25

Which of the following esters cannot undergo a Claisen condensation?

(a) $CH_3CH_2CH_2CO_2CH_3$ (b) $CH_3CH_2CH_2CO_2CH_3$

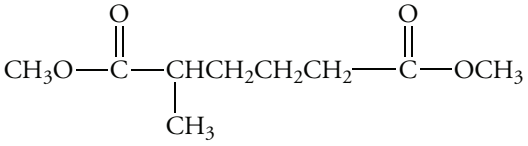
(c) $(CH_3)_2CHCO_2CH_2CH_3$ (d) $C_6H_5CO_2CH_3$

Answers:

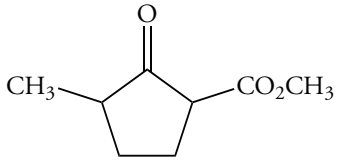
(a) and (b) can undergo a Claisen condensation, but (c) and (d) cannot because neither has two α hydrogen atoms.

Problem 22. 28

The dimethyl ester of 2-methyladipic acid is not symmetrical. However, a good yield of a single Dieckmann condensation product is possible. (a) Explain why. (b) Write the structure of the product.



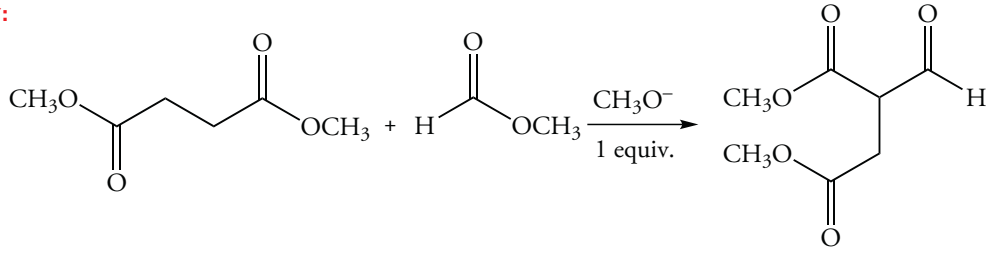
Answer: The α carbon atom on the left does not have two hydrogen atoms, so the condensation reaction using this site to attack the carbon on carbonyl carbon atom on the right is reversible. Only the carbanion derived from the α carbon atom on the right can attack the carbonyl carbon atom on the left to give the product shown below.



Problem 22. 29

Draw the structure of the major product formed in the reaction of methyl formate and dimethyl succinate using a molar equivalent of sodium methoxide.

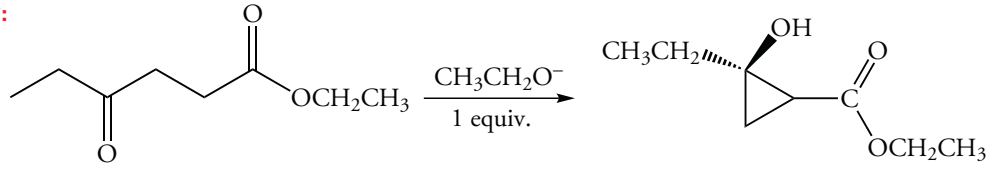
Answer:



Problem 22. 30

Ethyl 4-oxohexanoate forms a cyclic product when treated with a molar equivalent of sodium ethoxide. Draw the structure of the product.

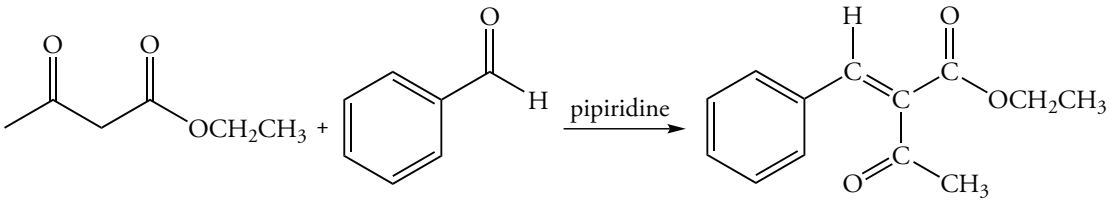
Answer:



Problem 22. 31

Draw the structure of the product formed in the reaction of ethyl acetoacetate and benzaldehyde catalyzed by piperidine.

Answer:

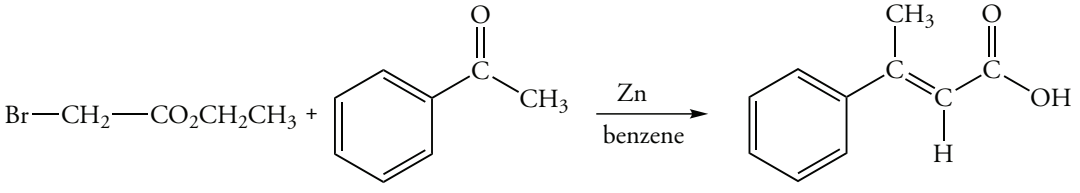


Problem 22. 33

(a) Outline a synthesis of 3-phenyl-2-butenoic acid using the Reformatskii reaction as one of the steps in the reaction sequence. (b) Will a single product result from this reaction?

Answer:

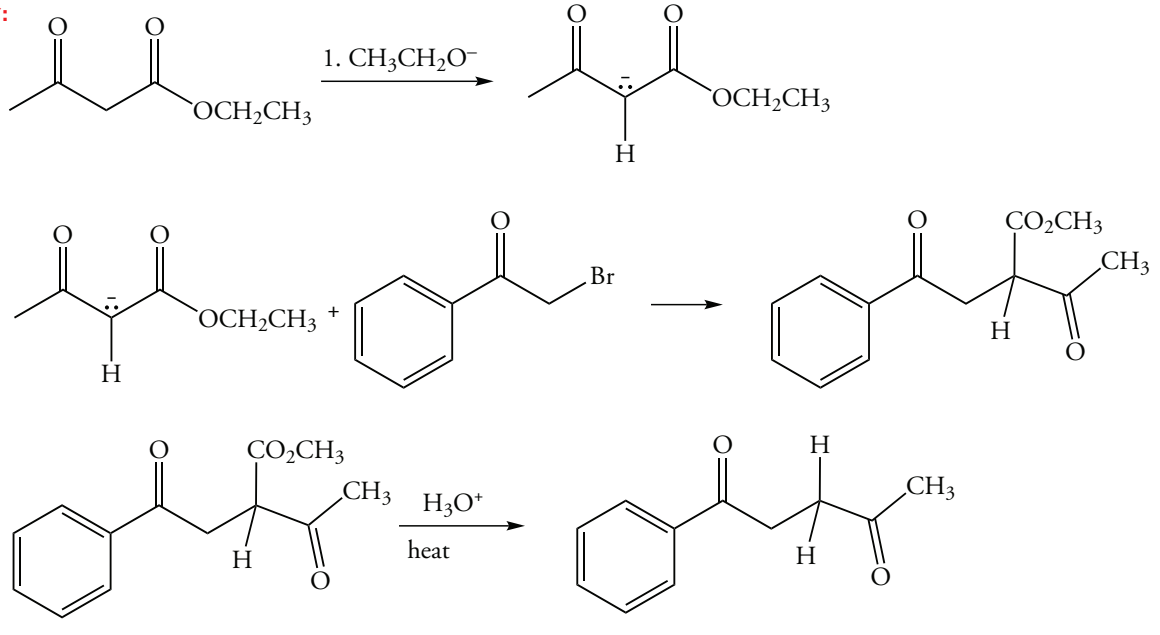
(a) React ethyl 2-bromoacetate with acetophenone and then heat with aqueous acid. (b) A mixture of *cis–trans* isomers forms.



Problem 22. 35

What alkylating agent is required to prepare 1-phenyl-1,4-pentanedione using ethyl acetoacetate as the other reactant?

Answer:



Problem 22. 36

Ethyl acetoacetate can be doubly alkylated. Outline a multistep synthetic sequence to produce 3-propyl-5-hexen-2-one from ethyl acetoacetate as one of the starting materials.

Answer:

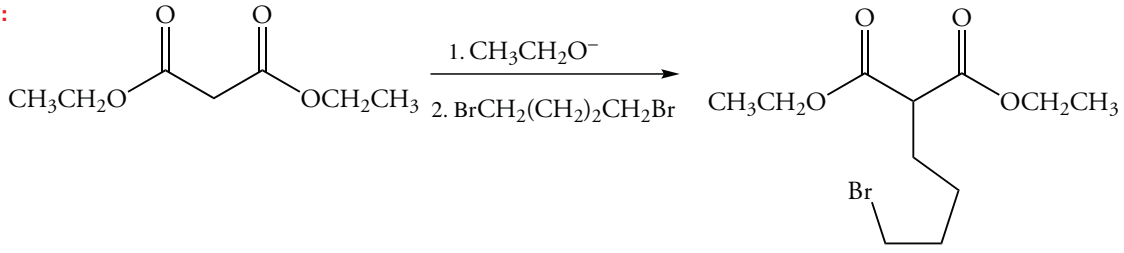
1. Alkylate ethyl acetoacetate with 1-bromopropane. 2. Alkylate the product with 3-bromo-1-propene. 3. Hydrolyze the dialkylated product. 4. Decarboxylate the dicarboxylic acid.

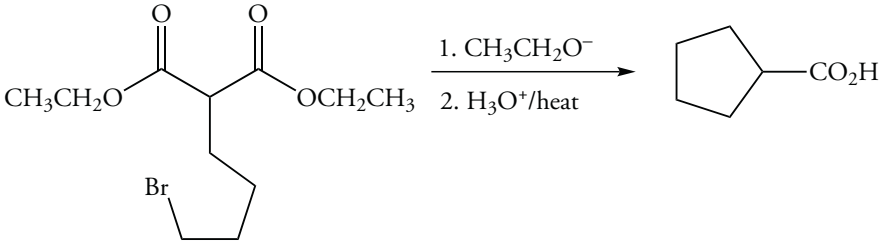
Problem 22. 38
Explain why 3,3-dimethylpentanoic acid cannot be prepared by the malonate ester synthesis.

Answer:
The required alkyl halide, 2-bromo-2-methylbutane, is tertiary and therefore cannot undergo S_N2 displacement.

Problem 22. 39
The reaction of diethyl malonate and 1,4-dibromobutane in the presence of two moles of sodium ethoxide followed by acidification and heat gives a compound $C_6H_{10}O_2$. What is the structure of the product?

Answer:

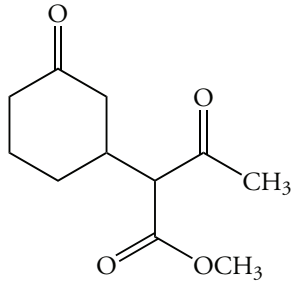




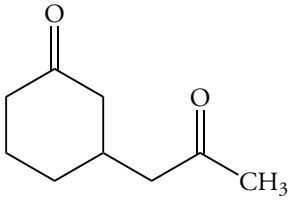
Problem 22. 40
(a) Draw the product of the Michael addition of methyl acetoacetate to 2-cyclohexenone. (b) Draw the product obtained by hydrolyzing the adduct followed by heating to decarboxylate the intermediate acid.

Answer:

(a)

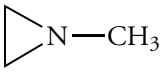


(b)



Solutions to In-Chapter Problems
Chapter 22

Problem 23. 1
Explain why the inversion barrier for N-methylaziridine (80 kJ mole^{-1}) is larger than the inversion barrier for trimethylamine (25 kJ mole^{-1}).



N-methylaziridine

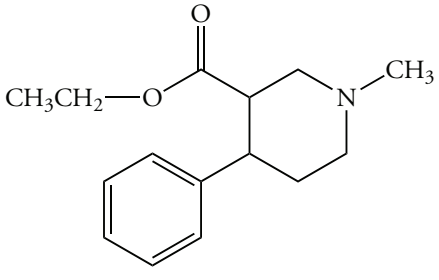
Answer:
The C—N—C bond angle is highly compressed, so it is difficult to achieve the ideal transition state bond angle of 120°.

Problem 23. 2
(a) Explain why the N—H bond of ammonia is shorter than the C—H bond in methane. (b) The C—N bond length of aniline is 140 pm. Give two reasons why this bond length is shorter than the 147 pm C—N bond length of alkylamines.

Answers:
(a) Nitrogen has a smaller atomic radius (77 pm) than carbon (70 pm). Therefore, the C—N bond in ammonia is shorter than the C—H bond in methane. Viewed slightly differently, the C—N bond of ammonia is more polar than the C—H bond of methane. Therefore, it is shorter.
(b) The carbon atoms of the benzene ring are sp² hybridized. Thus, the sp²–sp³ C—N bond in aniline is shorter than the sp³–sp³ C—N bond in an alkyl amine.

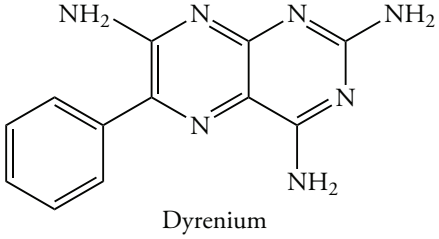
Problem 23. 4
Classify Demerol, a synthetic narcotic analgesic, as an amine.

Answer:
The nitrogen atom is bound to three carbon atoms. It is a tertiary amine.

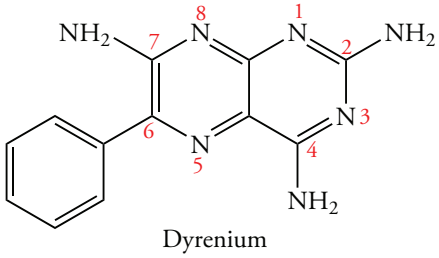


Demerol

Problem 23. 5
The systematic name for Dyrenium, a diuretic, is 2,4,7-triamino-6-phenylpteridine. (a) Number the heterocyclic pteridine ring. (b) Explain this choice of numbers.



Dyrenium



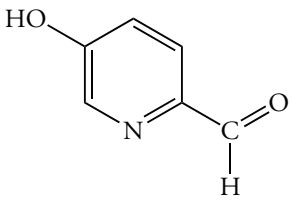
Dyrenium

Answer:
The two nitrogen atoms in a 1,3 relationship in the ring on the right give the lowest numbers for the name

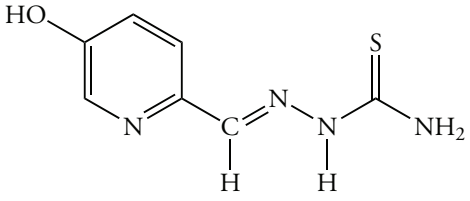
Problem 23. 6

The thiosemicarbazide of 5-hydroxypyridine-2-carbaldehyde has some antitumor activity. Write the structure of the aldehyde and the thiosemicarbazide.

Answers:



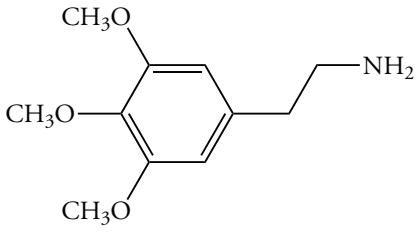
5-hydroxypyridine-2-carbaldehyde



Problem 23. 7

2-(3,4,5-Trimethoxyphenyl)ethanamine is the systematic name of mescaline, a hallucinogen. Write its structure.

Answer:

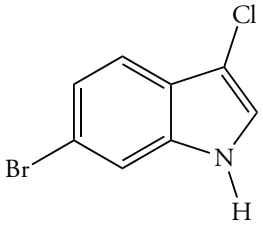


mescaline

Problem 23. 8

Name the following compound, which is produced by the marine acorn worm *Enteropneusta*, 6-bromo-3-chloroindole.

Answer: 6-bromo-3-chloroindole

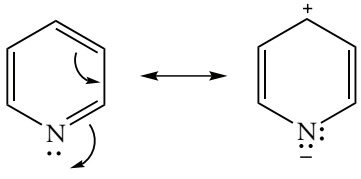


Problem 23.10

The dipole moments of pyridine (2.26 D) and piperidine (1.17 D) are both directed toward nitrogen. Explain why pyridine has a larger dipole moment than piperidine.

Answer:

The π electrons in the pyridine ring are delocalized onto the nitrogen atom of pyridine, placing a negative charge on nitrogen and decreasing the electron density of the carbon atoms of the pyridine ring. Two contributing structures of the resonance hybrid are shown below.



Problem 23.11

The pK_a of the conjugate acid of diazepam (Valium) is 3.3. (a) What is its K_a? (b) Calculate the K_b and pK_b of diazepam.

Answers:

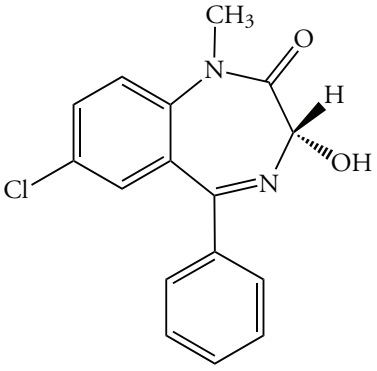
(a) Since $pK_a = -\log K_a$

$K_a\ 1 \times 10^{-3.3} = 5 \times 10^{-4}$.

(b) Since $pK_b + pK_a = 14$,

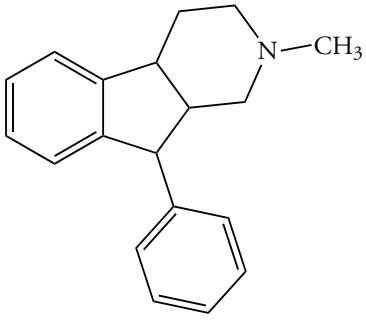
$pK_b = 14 - 3.3 = 10.7$.

And, $pK_b = 2 \times 10^{-11}$.



Problem 23.12

Based on the data in Table 23.2, estimate the pK_a of phenindamine, an antihistamine.

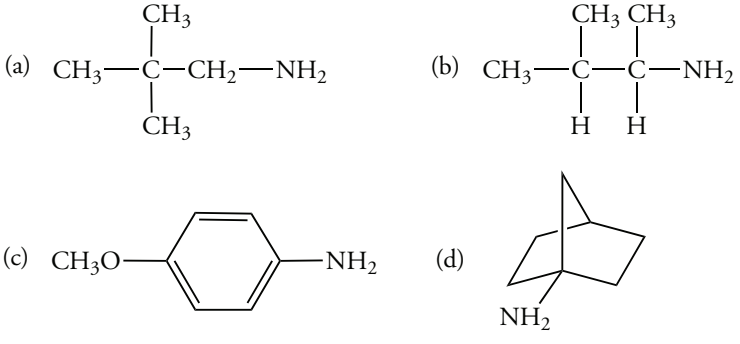


Answer:

Since phenindamine is a tertiary amine, its pK_a should be approximately 3—4.

Problem 23.13

Consider the possible synthesis of each of the following amines using the Gabriel synthesis. What limitations are there in each case?



Answers:

(a) The amino group is bonded to a neopentyl alkyl group and is highly sterically hindered.

(b) Elimination reactions at a secondary site are far more favorable than S_N2 reactions.

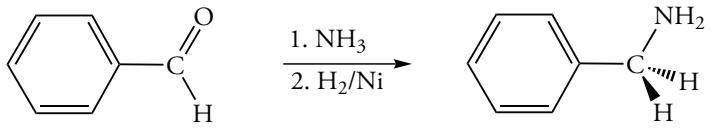
(c) Aromatic rings do not undergo S_N2 reactions.

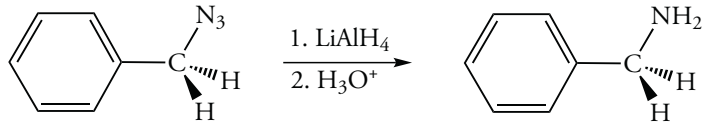
(d) Back-side attack at the bridgehead nitrogen in an S_N2 reaction is impossible.

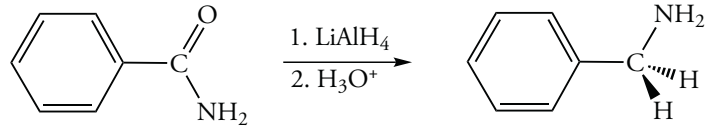
Problem 23.15

Outline three synthetic methods to prepare 2-phenylethylamine using a reductive step.

Answers:

(a) 

(b) 

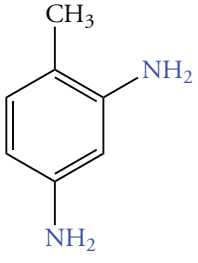
(c) 

Problem 23.16

Outline a synthesis of the following diamine starting from toluene.

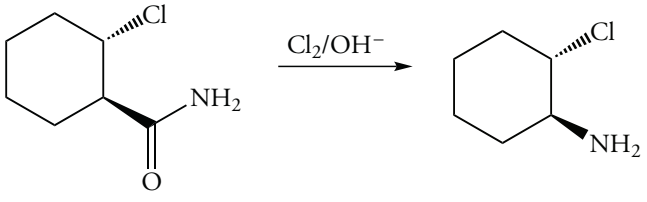
Answer:

1. Convert toluene to 2,4-dinitrotoluene by electrophilic aromatic substitution with nitric acid in sulfuric acid.
2. Reduce 2,4-dinitrotoluene to the diamine with Sn/HCl.



Problem 23.18

Draw the product of the following reaction.

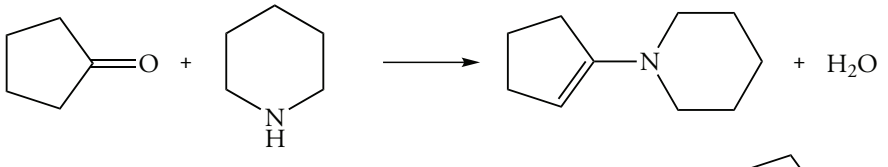


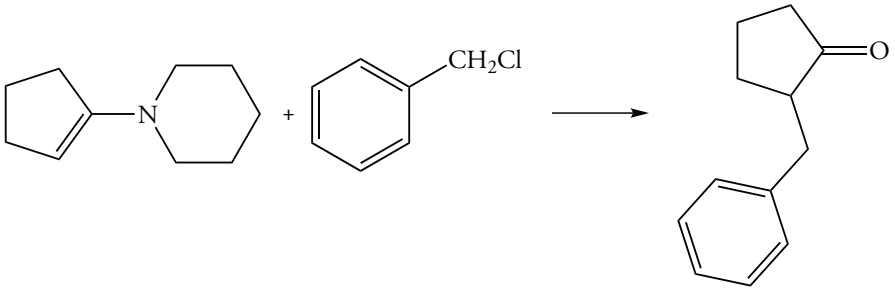
Answer: This is a Hoffman elimination.

Problem 23.19

(a) Draw the structure of the enamine formed from cyclopentanone and piperidine. (b) Draw the structure of the product of reaction between this enamine and benzyl chloride.

Answers:

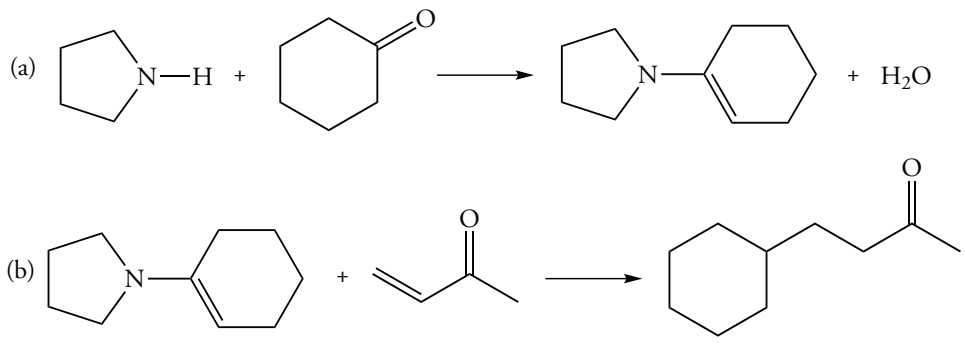
(a) 

(b) 

Problem 23.20

Enamines act as Michael donors in conjugate addition reactions (Section 21.12). Draw the structure of the product formed by reaction of the enamine of cyclohexanone and pyrrolidine with methyl vinyl ketone.

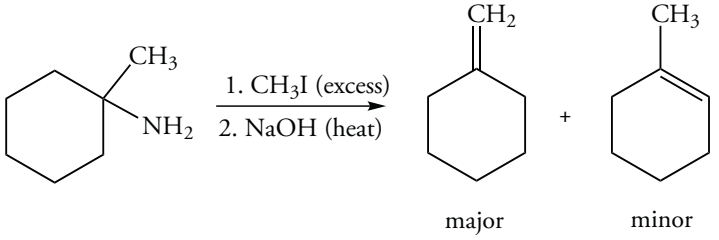
Answers:



Problem 23. 21

Two isomeric alkenes form in a 10:1 ratio when the quaternary ammonium hydroxide derived from 1-methylcyclohexylamine and methyl iodide is heated. (a) Draw the structures of the isomers. (b) Which one forms in the larger amount?

Answers:



Problem 23. 22

Explain why benzylic and allylic C—H bonds are more easily eliminated in the Hofmann reaction than other alkyl C—H bonds.

Answer:

They are more acidic as a result of resonance stabilization of the negative charge that develops as the C—H bond breaks in the transition state of the reaction.

Problem 23. 23

Explain why iodoethane cannot be used in place of iodomethane in the exhaustive alkylation of amines for the Hofmann elimination reaction.

Answer:

Elimination would occur preferentially at the β carbon of the ethyl group to give ethene.

Problem 23. 24

Write the structures of all compounds with molecular formula $C_5H_{13}N$ that have no absorption in the 3200–3400 cm^{-1} region.

Answer:

The absence of an absorption in the 3200–3400 cm^{-1} region means that the compounds do not have an N—H bond. They are all tertiary amines: diethylmethylamine, dimethylpropylamine, and dimethylisopropylamine.

Problem 23. 25

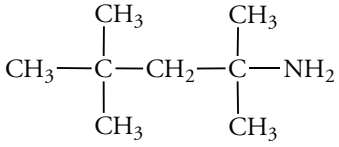
Deduce the structure of a compound with molecular formula $C_8H_{19}N$ that has the following absorptions in its hydrogen NMR spectrum, all of which are singlets. The N—H resonance at 1.34 δ is eliminated by exchange with D_2O. The number of hydrogen atoms is indicated within parentheses. The ^{13}C NMR has four resonances.

1.02 δ (9H), 1.17 δ (6H), 1.44 δ (2H), 1.34 δ (2H, exchanges)

Answer:

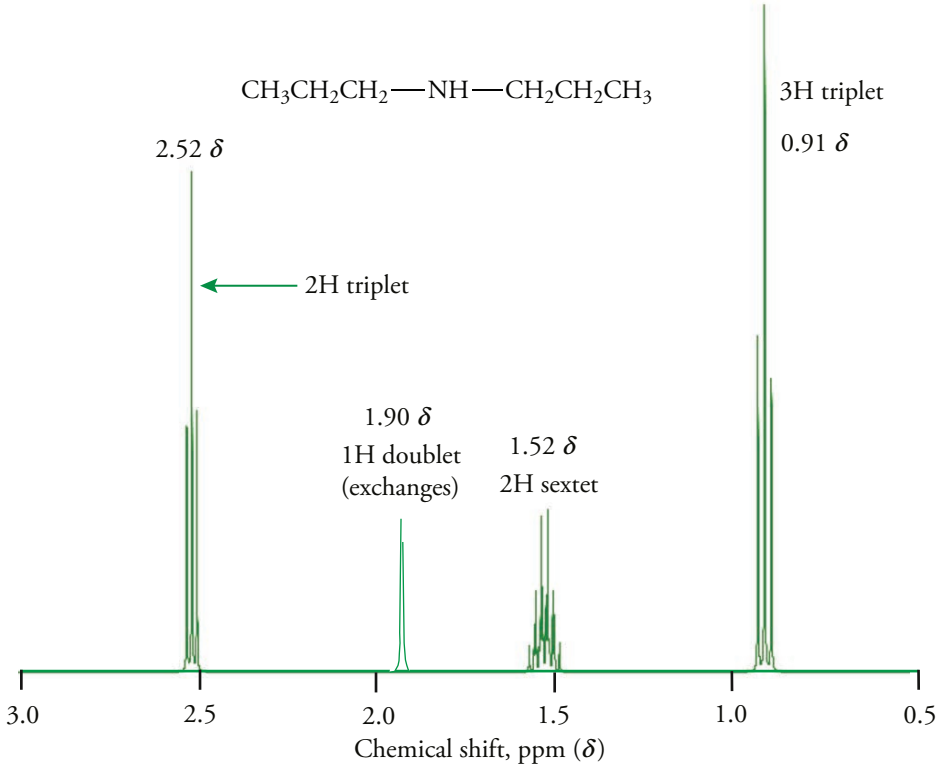
Since all the absorbances are singlets, there are no neighboring hydrogen atoms. The 2H absorbance at 1.34 δ that exchanges in D_2O corresponds to an NH_2 group, the other absorbances correspond to a methylene group at 1.44 δ, two equivalent methyl groups at 1.17 δ, and three equivalent methyl groups at 1.02 δ. Since the ^{13}C NMR has four resonances, there are four nonequivalent carbon atoms. The compound is 1,1,3,3-tetramethylbutylamine.

Answer:



Problem 23. 26

Deduce the structure of a compound with molecular formula $C_6H_{15}N$ that has the following proton NMR spectrum.



Answer:

The 3H triplet at 0.91 δ corresponds to a methyl group bonded to a CH_2 group. The 2H triplet at 2.52 δ corresponds to a methyl group bonded to a CH_2 group. The sextet at 1.52 δ corresponds to CH_2 group with five neighbors. The 1H doublet at 1.90 δ that exchanges corresponds to an NH group. The compound is dipropylamine.

Solutions to In-Chapter Problems

Chapter 24

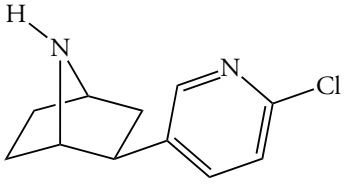
24.1 The dipole moment of toluene is 0.4 D. Predict the direction of this dipole. The dipole moment of *p*-fluorotoluene is 2.0 D. Predict the direction of dipole moment of fluorobenzene.

Answer: The negative end is pointed toward aromatic ring. The net dipole moment is 1.6 D

24.1 The dipole moment of toluene is 0.4 D. Predict the direction of this dipole. The dipole moment of *p*-fluorotoluene is 2.0 D. Predict the direction of dipole moment of fluorobenzene.

Answer: The negative end is pointed toward aromatic ring. The net dipole moment is 1.6 D.

24.3 Estimate the pK_a values for each basic site in the following compound, which is a poison secreted by an Ecuadoran frog.

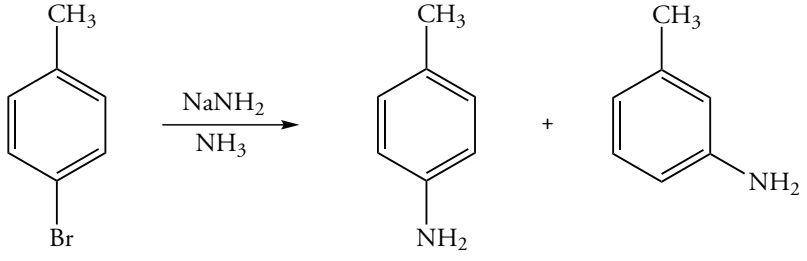


Answer: See Section 24.5. The pK_a for a secondary amine is approximately 4. The pK_a for the substituted pyridine is greater than 8.75 because chlorine is an electron-withdrawing group, which decreases basicity.

24.4 The pK_a values of pyridine and aniline are similar, but the pK_a of 4-aminopyridine is much smaller. Which of the two nitrogen atoms of 4-aminopyridine is more basic? Why is it more basic than the corresponding site in one of the reference compounds?

Answer: The nitrogen atom of pyridine ring is more basic. The pyridine ring decreases the basicity of the amino group as a result of electron withdrawal. The nitrogen atom of the amino-substituted pyridine ring has a larger electron density than in pyridine itself because of electron donation by the amino group.

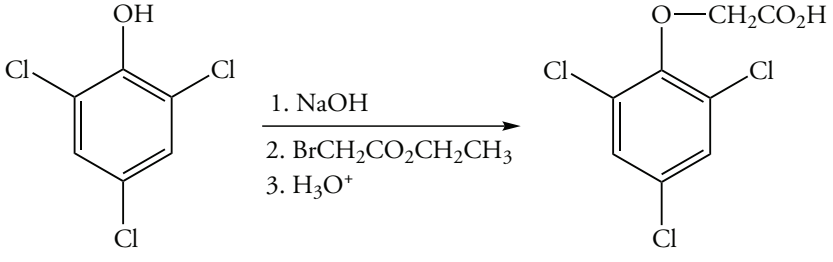
24.6 *p*-Bromotoluene reacts with sodium amide in liquid ammonia to give a mixture of two aniline derivatives. Draw their structures and explain the origin of the two products. Estimate the relative amounts of the two products formed.



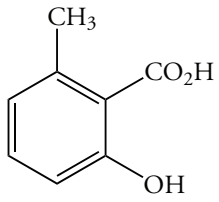
Answer: 3-Methylaniline and 4-methylaniline form in approximately equal amounts as a result of adding ammonia to either carbon atom of the triple bond in the benzyne intermediate.

24.7 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) is a herbicide. Propose a synthesis of 2,4,5-T using the Williamson ether synthesis.

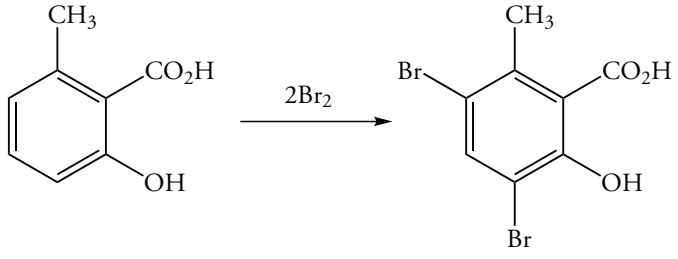
Answer: Step 1. Form the phenoxide of 2,4,5-trichlorophenol by adding sodium hydroxide to it. Step 2. React the phenoxide with ethyl ester of bromoacetic acid. Step 3. Hydrolyze the resulting ethyl ester.



24.8 The structure of 6-methylsalicylic acid is shown below. (a) What ring carbon atom is selected as C-1 to give this name? What is the structure of the dibrominated product of 6-methyl-salicylic acid?

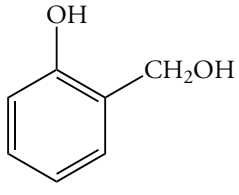


Answer: (a) The ring atom bearing carboxyl group is C-1. (b) Bromination occurs *ortho* and *para* to hydroxyl group

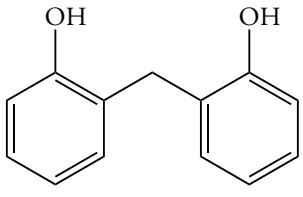


24.9 Draw the structure of the addition product of formaldehyde with phenol at the *ortho* position. Draw the structure of the Michael product of this compound with phenol at the *ortho* position.

Answers:



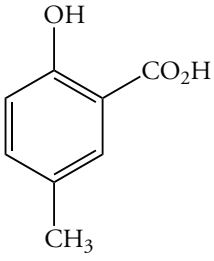
addition product



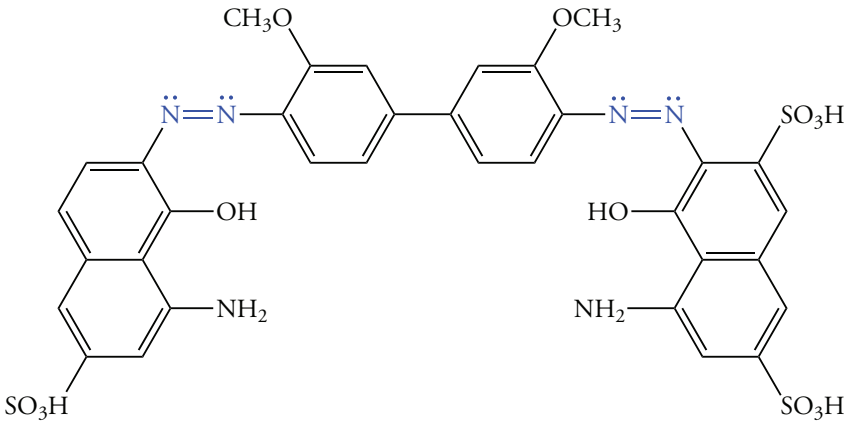
Michael addition product

24.10 Draw the structure of the product obtained by the Kolbe reaction of *p*-methylphenol (*p*-cresol).

Answer:

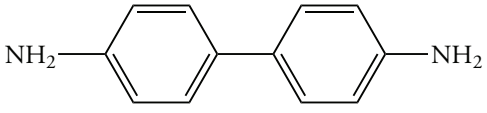


24.11 Draw the structure of the amine needed to form the diazonium ion required to synthesize Direct Blue 2B.



Direct Blue 2B

Answer:



Solutions to In-Chapter Problems

Chapter 25

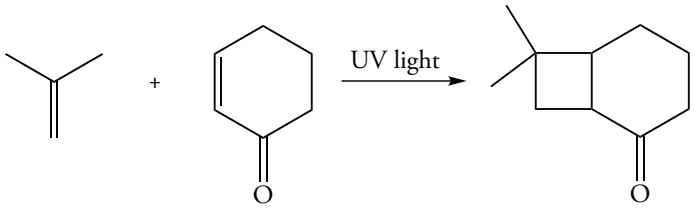
Problem 25. 1

Classify each of the following pericyclic reactions as an electrocyclic reaction, a cycloaddition, or a sigmatropic shift.

Answers:

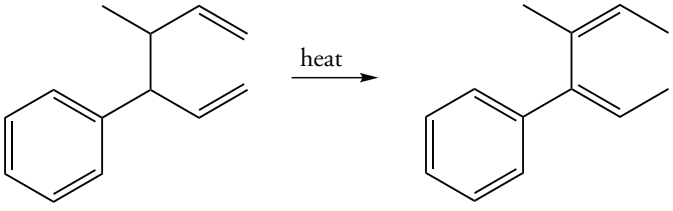
(a) Cycloaddition

(a)



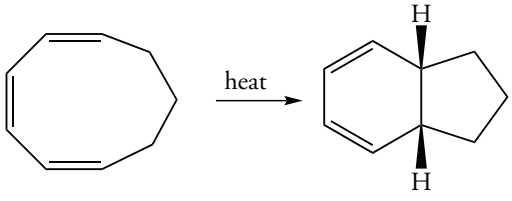
(b) Electrocyclic reaction

(b)



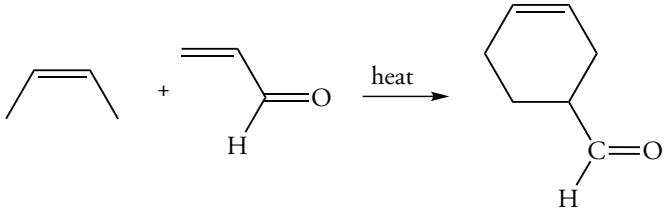
(c) Sigmatropic rearrangement

(c)



(d) Cycloaddition

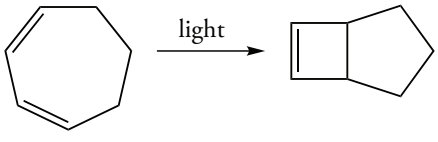
(d)



Problem 25.3

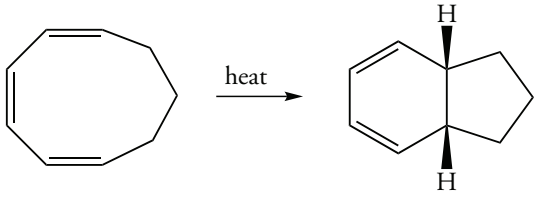
Draw the product of the photochemical cyclization of 1,3-cycloheptadiene.

Answer:



Problem 25.4

Is the following thermal cyclization reaction of 1,3,5-cyclononatriene symmetry allowed or forbidden?



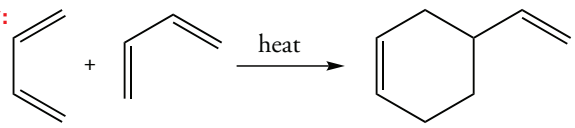
1,3,5-cyclononatriene

Answer: The reaction is symmetry forbidden because the product is the result of conrotatory motion.

Problem 25.6

Two molecules of 1,3-butadiene react in a thermal [4 + 2] cycloaddition reaction. Draw the structure of the product.

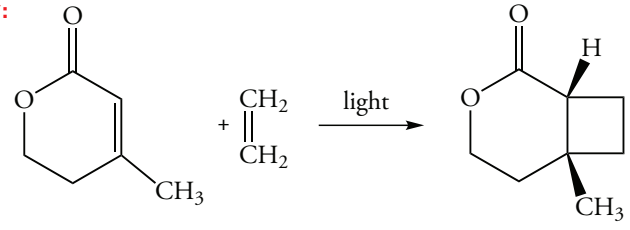
Answer:



Problem 25.7

What type of reaction and reactants are required to synthesize the following compound using a cycloaddition reaction?

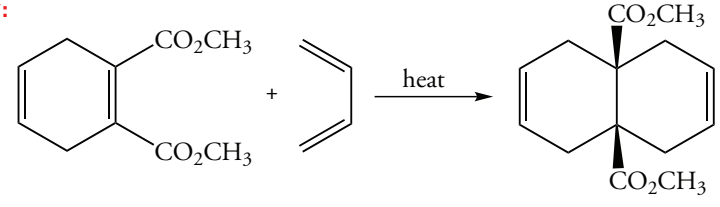
Answer:



Problem 25.8

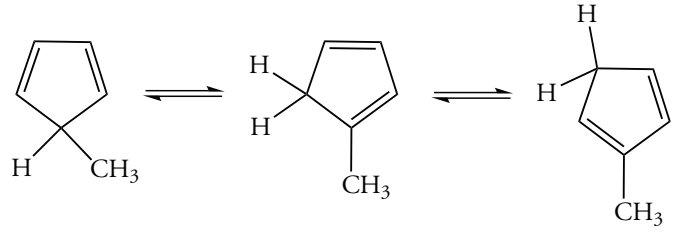
What type of reaction and reactants are required to synthesize the following compound using a cycloaddition reaction?

Answer:



Problem 25.10

5-Methyl-1,3-cyclopentadiene rapidly rearranges to give a mixture of that compound and its 1-methyl and 3-methyl isomers. Explain how this isomerization occurs.



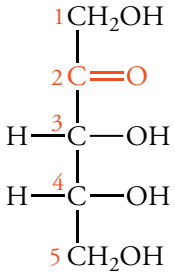
Answer: A series of [1,5] sigmatropic shifts occur that result in the transfer of a hydrogen atom to an adjacent carbon atom.

Solutions to In-Chapter Problems

Chapter 26

Problem 26.1

D-Ribulose, which has the following structure, is an intermediate in the pentose phosphate pathway that produces ribose, a precursor for nucleic acid biosynthesis. Classify D-ribulose by chain length and its carbonyl group.



D-ribulose

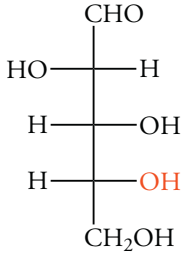
Answer: D-Ribulose is a 2-D-ketopentose

Problem 26.2

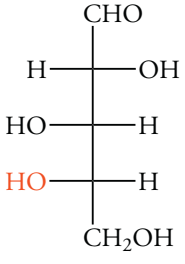
Draw the structure of each of the following monosaccharides.
(a) L-arabinose, the enantiomer of D-arabinose
(b) a 3-ketose structurally related to D-glucose
(c) 6-deoxymannos

Answers:

(a)

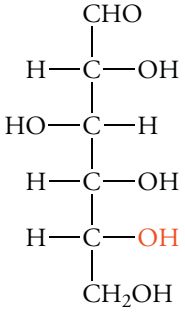


D-arabinose

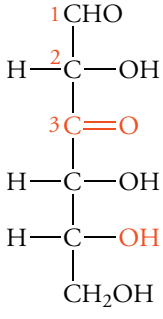


L-arabinose

(b)

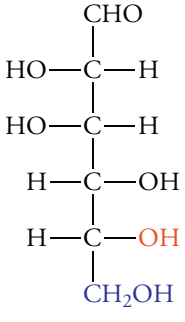


D-glucose

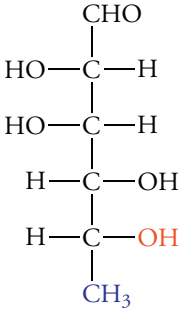


a 3-ketohexose related to D-glucose

(c)



D-mannose

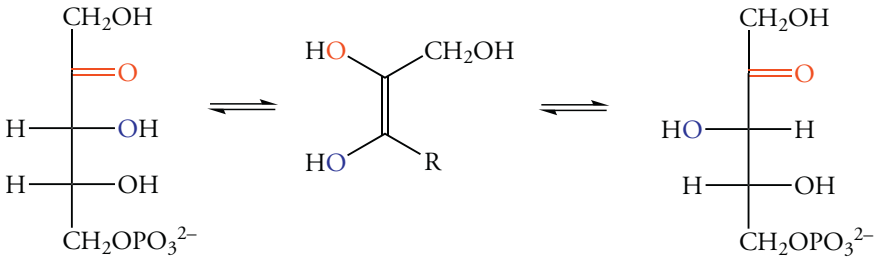


6-deoxy-D-mannose

Problem 26.4

Ribulose 5-phosphate is converted to xylulose 5-phosphate in one of the steps of the pentose phosphate pathway. Suggest a mechanism for this reaction?

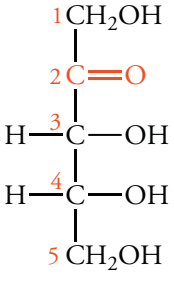
Answer: Formation of an enediol with a double bond between C-2 and C-3 leads to a mixture of ribulose and xylulose mixture.



D-ribulose-5-phosphate enediol D-xylulose-5-phosphate

Problem 26.8

Is ribulose a reducing sugar?



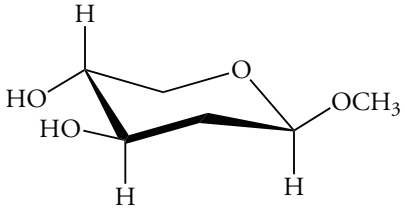
D-ribulose

Answer: Yes, formation of an enediol intermediate with a double bond between C-1 and C-2 leads to a mixture of ribulose and ribose, and the aldose is a reducing sugar.

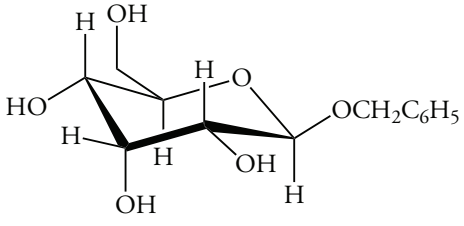
Problem 26.9

What cyclic precursors are required to form each of the following acetals?

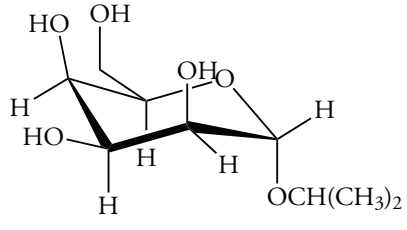
(a)



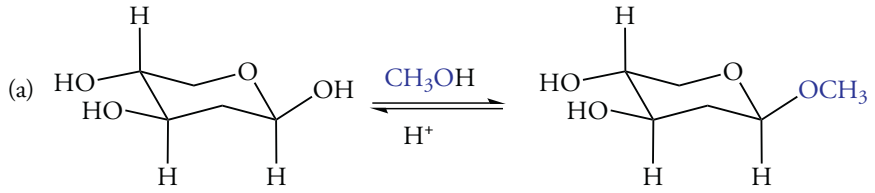
(b)



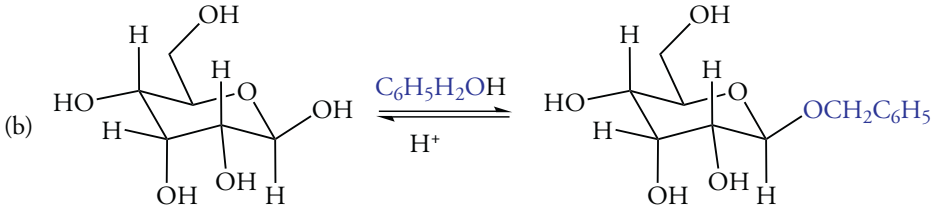
(c)



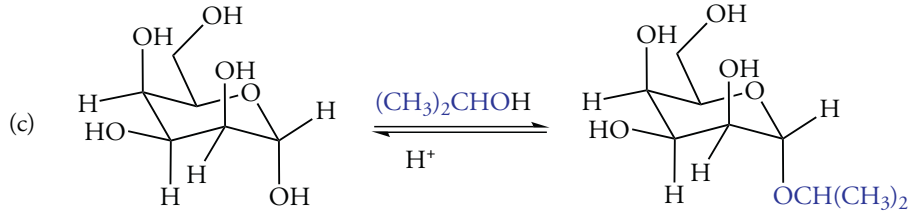
Answers: (a) 2-deoxy-β-D-ribopyranose and methanol (b) β-D-allopyranose and benzyl alcohol (c) α-D-talopyranose and isopropyl alcohol



2-deoxy-β-D-ribopyranose methyl 2-deoxy-β-D-ribopyranoside



β-D-allopyranose benzyl β-D-allopyranoside

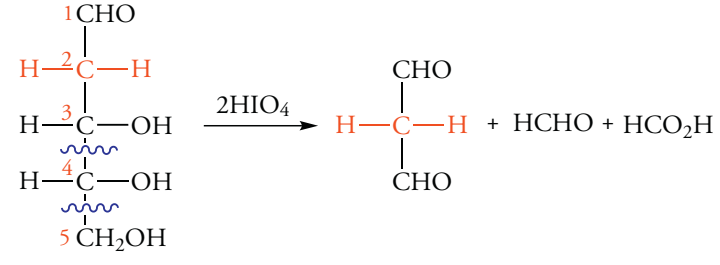


α-D-talopyranose isopropyl α-D-talopyranoside

Problem 26.11

(a) What are the products of the periodate oxidation of 2-deoxyribose? (b) How many moles of periodate are required for complete oxidation?

Answers: (a) Formaldehyde, formic acid, and 1,3-propanedial; (b) two moles of periodate

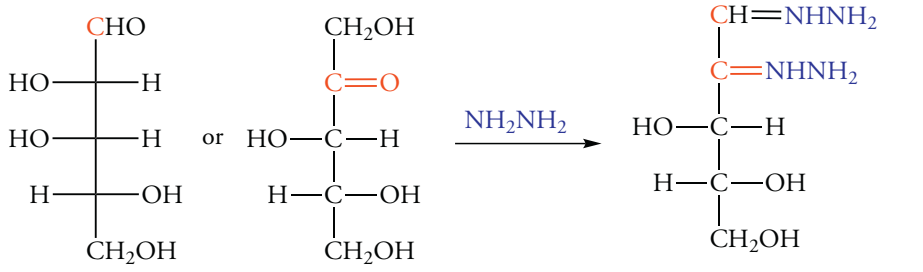


2-deoxy-D-ribose 1,3-propanedial

Problem 26.12

Draw the structures of an aldose and a ketose that give the same osazone as xylose.

Answer: Lyxose and xylulose give the same osazone.

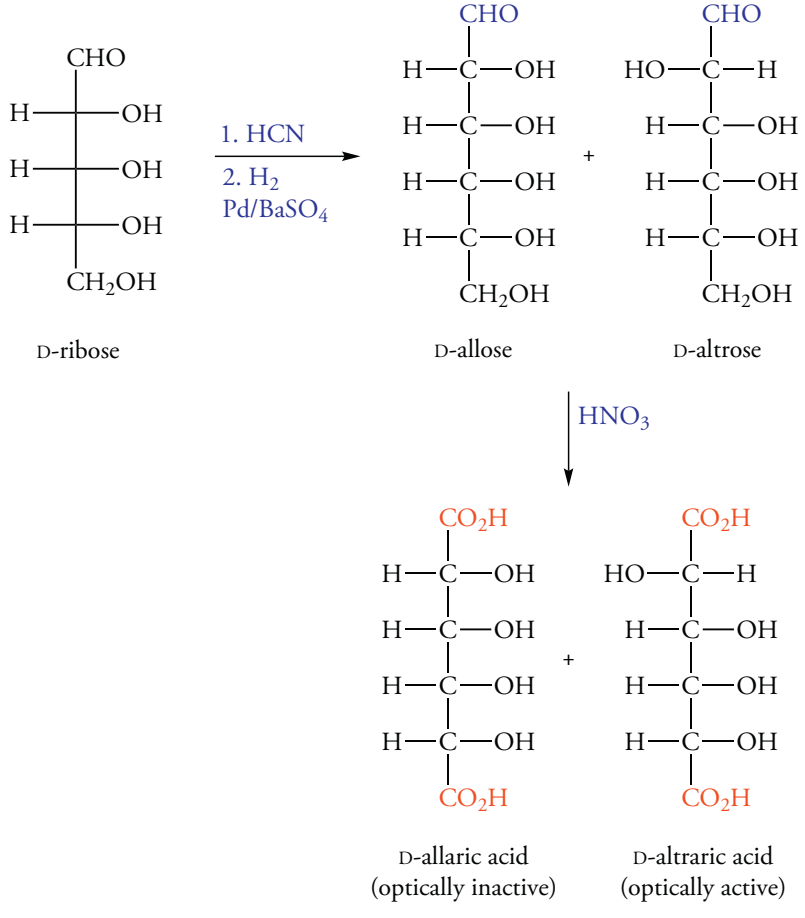


D-lyxose D-xlyulose osazone of lyxose and xylulose

Problem 26.13

(a) What are the products of the Kiliani–Fischer chain extension of D-ribose? (b) Which products, if any, would give an optically inactive aldaric acid when oxidized by nitric acid?

Answer: Beginning with D-ribose, a Kiliani–Fischer synthesis gives allose and altrose. Oxidation D-allose with nitric acid gives the optically inactive product aldaric acid. Oxidation of D-altrose with nitric acid gives optically active altraric acid.



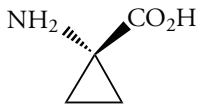
D-ribose D-allose D-altrose

D-allaric acid (optically inactive) D-altraric acid (optically active)

Solutions to In-Chapter Problems
Chapter 27

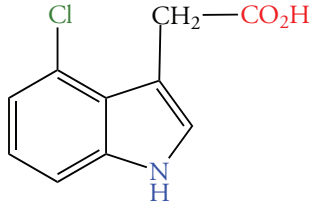
27.2 Draw the structure of 1-aminocyclopropanecarboxylic acid. This compound undergoes an enzymatic decarboxylation to produce the plant hormone ethene, which is responsible for the initiation of fruit ripening.

Answer:



1-aminocyclopropane carboxylic acid

27.3 The following carboxylic acid and its methyl ester are found in green peas and many other plants. It is a plant hormone in the auxin family. Which amino acid is a likely (and in fact actual) precursor?

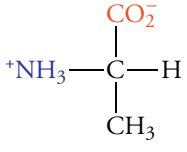


4-chloroindole-3-acetic acid

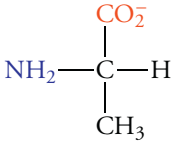
Answer: The precursor of auxin is tryptophan.

27.4 What are the structures of the dipolar ion and conjugate base of alanine?

Answer:



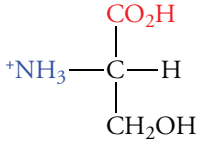
structure of alanine dipolar ion



conjugate base of alanine

27.5 In what form does serine exist in 0.1 M HCl?

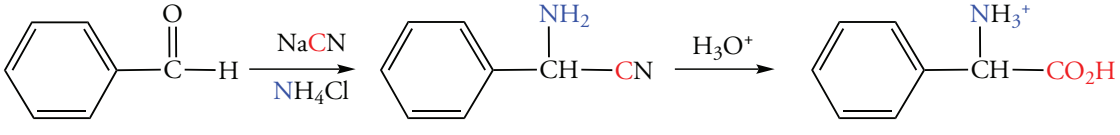
Answer: In 0.1 M HCl serine exists as its conjugate acid.



conjugate acid of serine

27.7 What reagents are required for the Strecker synthesis of phenylalanine?

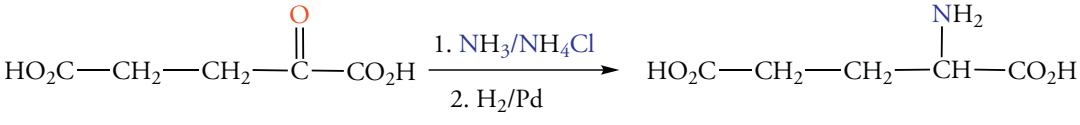
Answer:



(an α-amino nitrile)

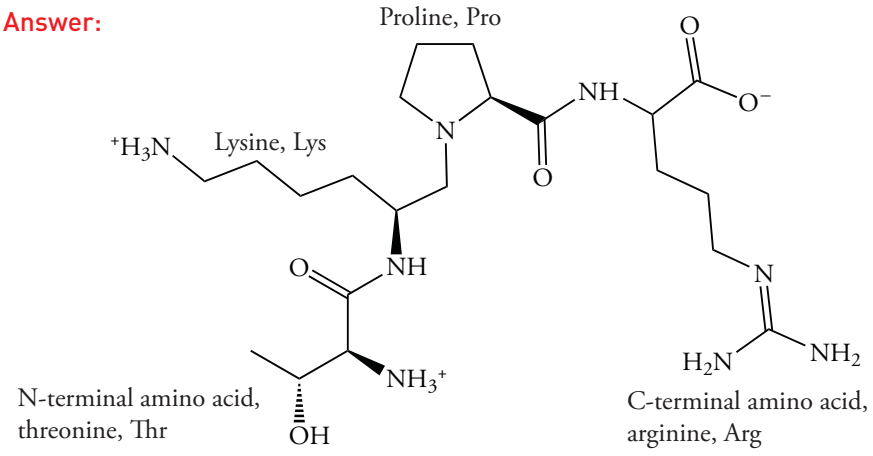
27.8 What keto acid is required to produce glutamic acid by reductive amination?

Answer:



27.10 (a) Identify each of the amino acids of tuftsin. (b) Write the name of tuftsin as three-letter abbreviations. (c) Write the name of tuftsin without abbreviations.

Answer:



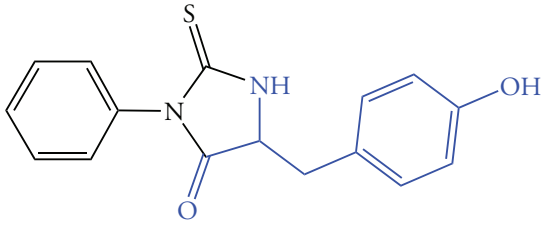
tuftsin
threonyllysylprolylarginine

27.11 (a) How many isomeric peptides exist that contain one alanine and two glycine residues? (c) Write their names as three-letter abbreviations.

Answer: Three peptides are possible: Ala-Gly-Gly, Gly-Ala-Gly, Gly-Gly-Ala

27.12 Treating β-endorphin with phenyl isothiocyanate followed by hydrolysis with anhydrous trifluoroacetic acid, and then with water, releases the following phenylthiohydantoin. What is the N-terminal amino acid of the peptide?

Answer: The N-terminal amino acid is tyrosine.



Solutions to In-Chapter Problems

Chapter 28

Problem 28.1

How would the properties of an addition polymer formed from 3-methyl-1-pentene differ from those of a polymer formed from propene?

Answer: Propene does not have any branches, and therefore its polymer chains would pack more tightly than polymers made from 3-methyl-1-propene. Thus, a propene polymer would have a greater density and a higher melting point.

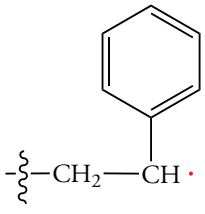
Problem 28.3

(a) What type of plastic is best suited to make the handles for cooking utensils for the home? (a)What type of plastic is most likely to be used for the frames of eyeglasses?

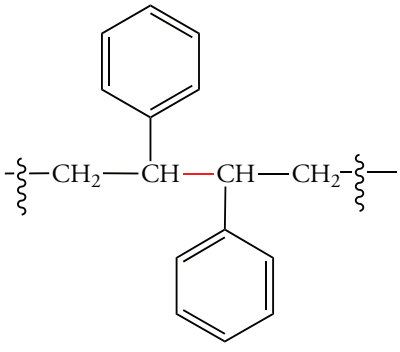
Answer: (a) Objects such as handles have to be rigid. Therefore, thermosetting plastics are best for handles. (b) Objects such as the frame of eyeglasses need to be molded or shaped to fit; thermoplastics for applications of that type.

Problem 28.5

(a) Draw a structure of the reacting end of a polystyrene. (b) What structural feature should exist in a chain terminated by a dimerization reaction?



(a) benzylic radical



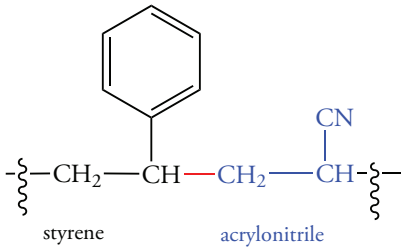
(b) polystyrene

Answer: (a) The reacting end of polystyrene is a benzylic radical. (b) The chain termination step links the benzyl radicals shown in (a).

Problem 28.6

Styrene and acrylonitrile (CH_2=CH—CN) form an alternating copolymer that is used in the lenses of automobile headlights. Draw the structure of two units of the copolymer.

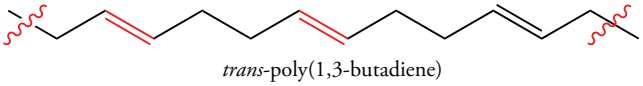
Answer:



Problem 28.8

Draw the structure of the product of ozonolysis of *trans*-poly(l,3-butadiene) under oxidation workup conditions.

Answer: We recall that ozonolysis followed by oxidative workup gives a dicarboxylic acid if there are no substituents on the double bond; in this case it is succinic acid.



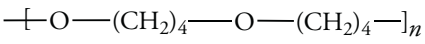
trans-poly(1,3-butadiene)

1. O_3
2. H_2O_2

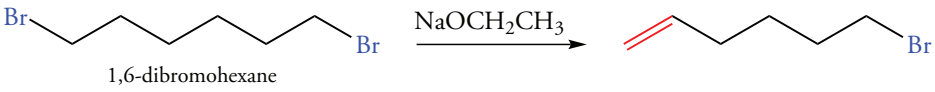
$HO_2C—CH_2—CH_2—CO_2H$

Problem 28.9

Can the disodium salt of 1,4-butanediol be used with 1,6-dibromohexane to yield a polyether represented by the following formula?



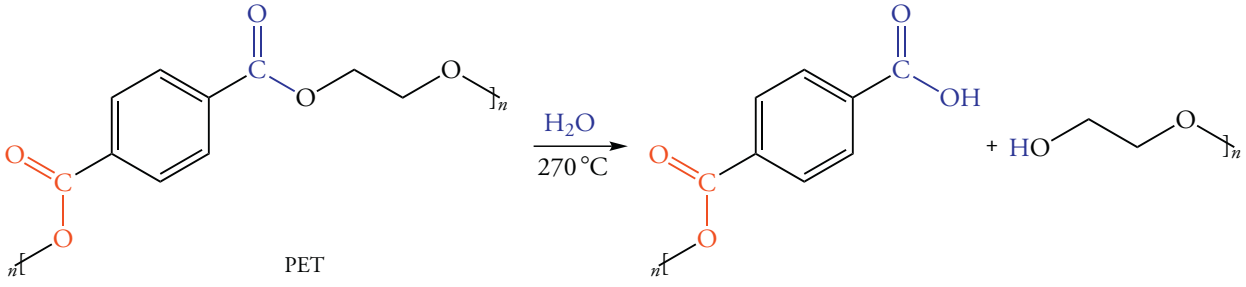
Answer: The reaction requires alkoxide as a base, and there would be some competing dehydrobromination reaction of the bromo compound by the alkoxide in an E2 reaction.



1,6-dibromohexane

Problem 28.10

Poly(ethylene terephthalate) is melted and spun into fibers at 270 °C. Explain why the surrounding air must be "dry" while the polymer is hot.

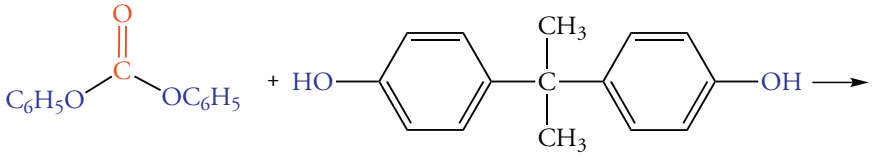


PET

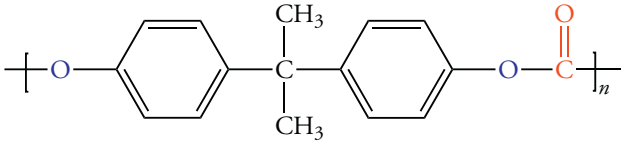
Answer: At the high temperature at which this process is carried out a hydrolysis reaction of the ester can occur.

Problem 28.11

Lexan can be prepared by using diphenyl carbonate rather than diethyl carbonate. Which reaction is thermodynamically more favorable?



bisphenol A



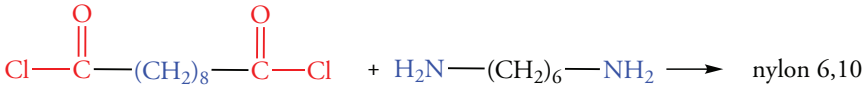
Lexan

Answer: Reaction with diphenyl carbonate would be more favorable because alkyl esters are more stable than phenyl esters.

Problem 28.12

Nylon 6,10 is prepared by reaction of a diamine and a diacid chloride. Draw the structures of the reactants.

Answer:



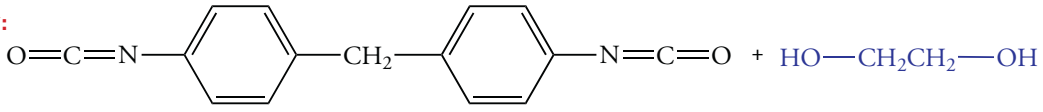
Problem 28.13 Explain why phenol and acetone do not react to give a condensation polymer.

Answer: We recall that ketones do not undergo addition reactions as favorably as do aldehydes (Section 19.1). The nucleophilic addition reactions with formaldehyde are especially favorable.

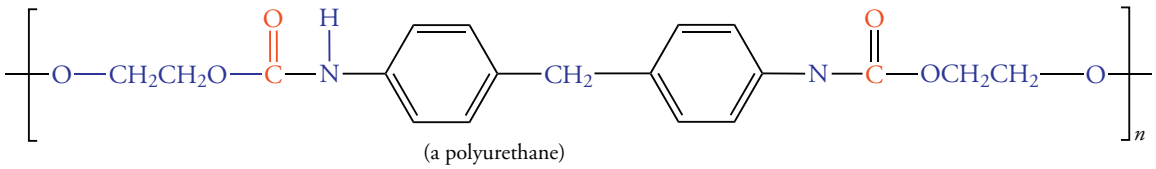
Problem 28.14

Methanediphenyl diisocyanate (MDI) is used to prepare a polyurethane. Draw the structure of a polyurethane prepared from MDI and ethylene glycol.

Answer:



MDI



(a polyurethane)

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