Biochemistry from MobileReference

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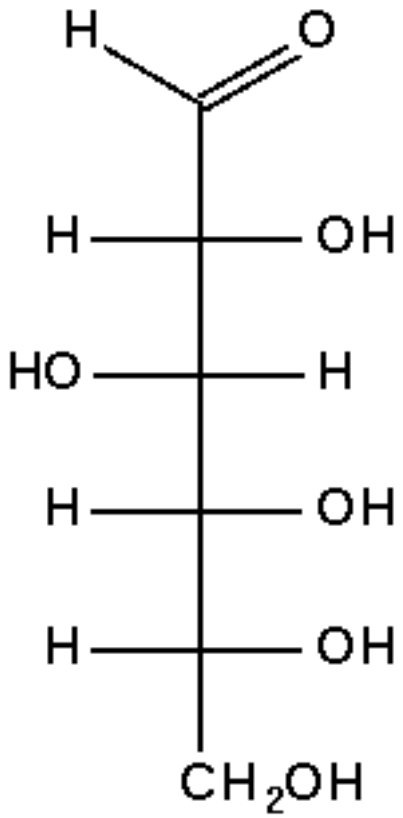
Carbohydrates

Carbohydrates are chemical compounds that contain oxygen, hydrogen, and carbon atoms. They consist of monosaccharide sugars of varying chain lengths and that have the general chemical formula $C_n(H_2O)_n$ or are derivatives of such.

Certain carbohydrates are an important storage and transport form of energy in most organisms, including plants and animals. Carbohydrates are classified by their number of sugar units: monosaccharides (such as glucose and fructose), disaccharides (such as sucrose and lactose), oligosaccharides, and polysaccharides (such as starch, glycogen, and cellulose).



Glucose as a straight-chain carbohydrate

Structure

Pure carbohydrates contain carbon, hydrogen, and oxygen atoms, in a 1:2:1 molar ratio, giving the general formula $C_n(H_2O)_n$. (This applies only to monosaccharides, see below, although all carbohydrates have the more general formula $C_n(H_2O)_m$.) However, many important "carbohydrates" deviate from this, such as deoxyribose and glycerol, although they are not, in the strict sense, carbohydrates. Sometimes compounds containing other elements are also counted as carbohydrates (e.g. chitin, which contains nitrogen).

The simplest carbohydrates are monosaccharides, which are small straight-chain aldehydes and ketones with many hydroxyl groups added, usually one on each carbon except the functional group. Other carbohydrates are composed of monosaccharide units and break down under hydrolysis. These may be classified as disaccharides, oligosaccharides, or polysaccharides, depending on whether they have two, several, or many monosaccharide units.

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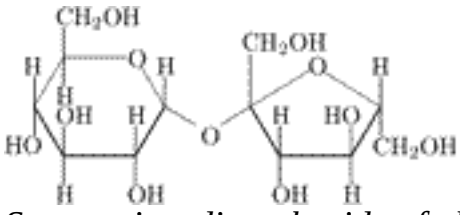
Disaccharide

A disaccharide is a sugar (a carbohydrate) composed of two monosaccharides.



Sucrose is a disaccharide of glucose (left) and fructose, important molecules in the body

Chemistry

The two monosaccharides are bonded via a condensation reaction. This bond can be between the 1-, 4-, or 6-carbon on each component monosaccharide. So, even if both component sugars are the same (e.g., glucose), different bond combinations result in disaccharides with different chemical and physical properties.

Like monosaccharides, they are crystalline, water-soluble, and sweet-tasting.

Common disaccharides

- **sucrose** (known as table sugar, cane sugar, saccharose, or beet sugar)
- **lactose** (milk sugar)
- **maltose** produced during the malting of barley
- **Trehalose** is present in fungi and insects, and has been successfully produced at an industial scale by enzymatic treatment of starch as a food ingredient.

Maltose and cellobiose are hydrolysis products of the polysaccharides, starch and cellulose, respectively.

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Gluconeogenesis

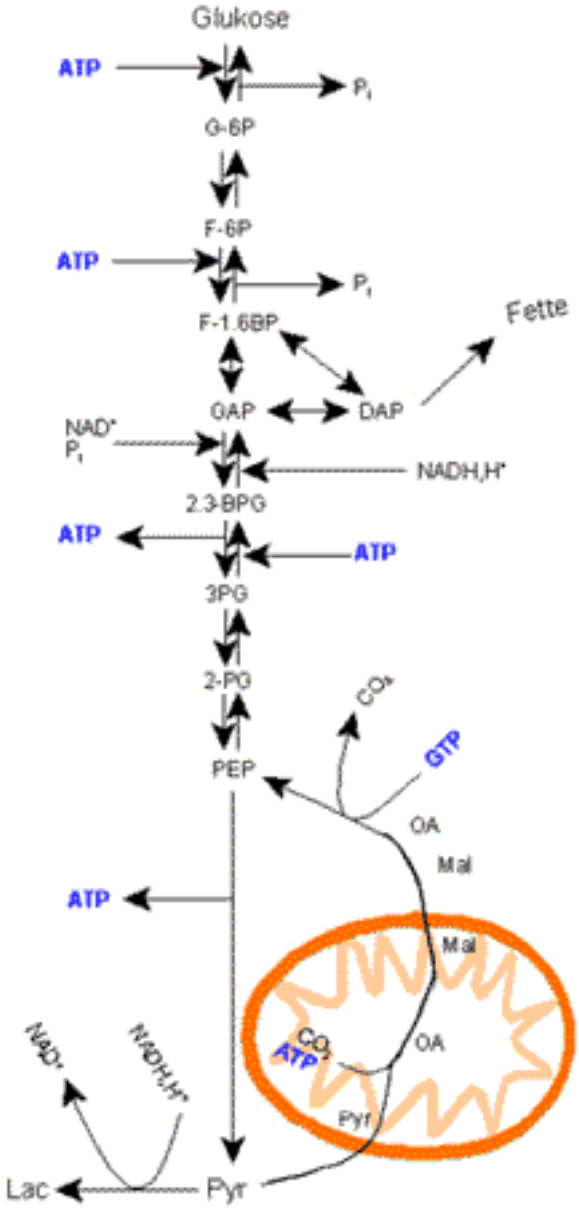

Diagram of Gluconeogenesis

Gluconeogenesis is the generation of glucose from other organic molecules like pyruvate, lactate, glycerol, and amino acids. Many 3- and 4-carbon substrates can enter the gluconeogenesis pathway. Lactate from anaerobic respiration in skeletal muscle is easily converted to pyruvate; this happens as part of the Cori cycle. However, the first designated substrate in the gluconeogenic pathway is pyruvate. The vast majority of gluconeogenesis takes place in the liver and, to a smaller extent, in the kidney. This process occurs during periods of starvation or intense exercise and is highly exergonic.

Gluconeogenesis cannot be considered to be a reverse process of glycolysis, as the three irreversible steps in glycolysis are bypassed in gluconeogenesis. This is done to ensure that glycolysis and gluconeogenesis do not operate at the same time in the cell, making it a futile cycle. The majority of the

enzymes responsible for gluconeogenesis are found in the cytoplasm; the exception is pyruvate carboxylase, which is located in the mitochondria. The rate of gluconeogenesis is ultimately controlled by the action of a key enzyme fructose-1,6-bisphosphatase. Most factors that regulate the activity of the gluconeogenesis pathway do so by inhibiting the activity of key enzymes. However, both acetyl CoA and citrate activate gluconeogenesis enzymes (pyruvate carboxylase and fructose-1,6-bisphosphatase, respectively).

Oxaloacetate (an intermediate in the citric acid cycle) can also be used for gluconeogenesis. Amino acids, after their amino group has been removed, feeds into parts of the citric acid cycle, and can thus generate glucose in this pathway.

Most fatty acids cannot be turned into glucose unless the glyoxylate cycle is used, the exception being odd-chain fatty acids, which can yield propionyl CoA, a precursor for succinyl CoA. Fatty acids are regularly broken down into the two-carbon acetyl CoA, which becomes degraded in the citric acid cycle. In contrast, glycerol, which is a part of all triacylglycerols, can be used in gluconeogenesis.

Gluconeogenesis begins with the formation of oxaloacetate through carboxylation of pyruvate at the expense of one molecule of ATP, but is inhibited in the presence of high levels of ADP. This reaction is catalyzed by pyruvate carboxylase. Oxaloacetate is then decarboxylated and simultaneously phosphorylated by phosphoenolpyruvate carboxykinase to produce phosphoenolpyruvate. One molecule of GTP is hydrolyzed to GDP in the course of this reaction. Both reactions take place in mitochondria. Oxaloacetate has to be transformed into malate in order to be transported out of the mitochondria.

Typically, the last step of gluconeogenesis is the formation of glucose-6-phosphate from fructose-6-phosphate by phosphoglucose isomerase. Free glucose is not generated automatically because glucose, unlike glucose-6-phosphate, tends to freely diffuse out of the cell. The reaction of actual glucose formation is carried out in the lumen of the endoplasmic reticulum. Here, glucose-6-phosphate is hydrolyzed by glucose-6-phosphatase, a regulated membrane-bound enzyme, to produce glucose. Glucose is then shuttled into cytosol by glucose transporters located in the membrane of the endoplasmic reticulum.

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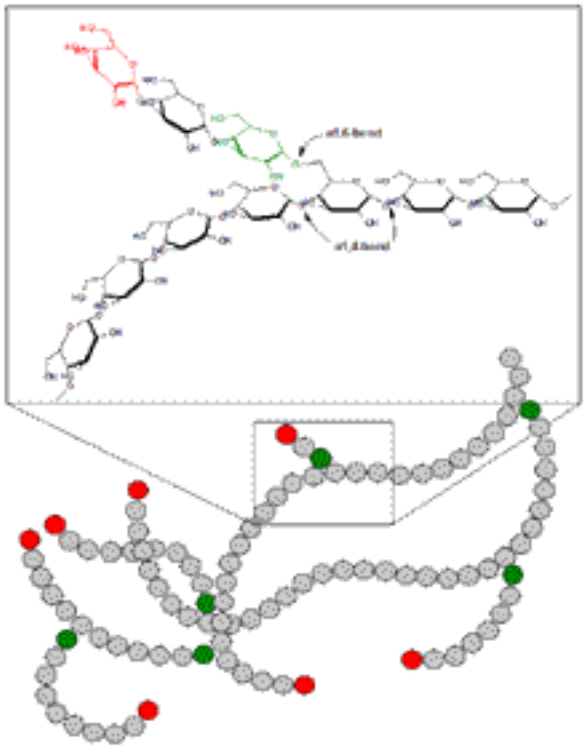
Glycogen

Structure and biochemistry | Function and regulation of liver glycogen | Glycogen in muscle and other cells | Glycogen and marathon running | Disorders of glycogen metabolism

Glycogen is a polysaccharide that is the principal storage form of glucose in animal cells. Glycogen is found in the form of granules in the cytosol in many cell types. Hepatocytes have the highest concentration of it - up to 8% of the fresh weight in well fed state, or 100–120 g in an adult - giving liver a distinctive, "starchy" taste. In the muscles, glycogen is found in a much lower concentration (1% of the muscle mass), but the total amount exceeds that in liver. Small amounts of glycogen are found in the kidneys, and even smaller amounts in certain glial cells in the brain and white blood cells.



Glycogen structure

Structure and biochemistry

Glycogen is a highly-branched polymer of 10,000 to 120,000 Glc residues and molecular weight between 106 and 107 daltons. Most of Glc units are linked by a α-1,4 glycosidic bonds, approximately 1 in 12 Glc residues also makes a α-1,6 glycosidic bond with a second Glc which results in creating of a branch. Glycogen has only one reducing end and a large number of nonreducing ends with a free hydroxy group at carbon 4. The glycogen granules contain both glycogen and the enzymes of glycogen synthesis (glycogenesis) and degradation (glycogenolysis). The enzymes are nested between the outer branches of the glycogen molecules and act on the nonreducing ends. Therefore, the many nonreducing end-branches of glycogen facilitate its rapid synthesis and breakdown.

Function and regulation of liver glycogen

As a carbohydrate meal is eaten and digested, blood glucose levels rise, and the pancreas secretes insulin. Glucose from the portal vein enters the liver cells (hepatocytes). Insulin acts on the hepatocytes to stimulate the action of several enzymes, including glycogen synthase. Glucose molecules are added to the chains of glycogen as long as both insulin and glucose remain plentiful. In this postprandial or "fed" state, the liver takes in more glucose from the blood than it releases.

After a meal has been digested and glucose levels begin to fall, insulin secretion is reduced, and glycogen synthesis stops. About four hours after a meal, glycogen begins to be broken down to be converted again to glucose. Glycogen phosphorylase is the primary enzyme of glycogen breakdown. For the next 8–12 hours, glucose derived from liver glycogen will be the primary source of blood glucose to be used by the rest of the body for fuel.

Glucagon is another hormone produced by the pancreas, which in many respects serves as a counter-signal to insulin. When the blood sugar begins to fall below normal, glucagon is secreted in increasing amounts. It stimulates glycogen breakdown into glucose even when insulin levels are abnormally high.

Glycogen in muscle and other cells

Muscle cell glycogen appears to function as an immediate reserve source of available glucose for muscle cells. Other cells that contain small amounts use it locally as well. Muscle cells lack the ability to pass glucose into the blood, so the glycogen they store internally is destined for internal use and is not shared with other cells, unlike liver cells.

Glycogen and marathon running

Due to the body's ability to hold around 2,000 kcal of glycogen, marathon runners commonly experience a phenomenon referred to as "hitting the wall" around the 20 mile (32 km) point of a marathon. (Approximately 100 kcal are utilized per mile, depending on the size of the runner and the race course.) When experiencing glycogen debt, runners many times undergo intense muscle cramping.

Disorders of glycogen metabolism

The most common disease in which glycogen metabolism becomes abnormal is diabetes, in which, because of abnormal amounts of insulin, liver glycogen can be abnormally accumulated or depleted. Restoration of normal glucose metabolism usually normalizes glycogen metabolism as well.

In hypoglycemia caused by excessive insulin, liver glycogen levels are high, but the high insulin level prevents the glycogenolysis necessary to maintain normal blood sugar levels. Glucagon is a common treatment for this type of hypoglycemia.

Various inborn errors of metabolism are caused by deficiencies of enzymes necessary for glycogen synthesis or breakdown. These are collectively referred to as glycogen storage diseases.

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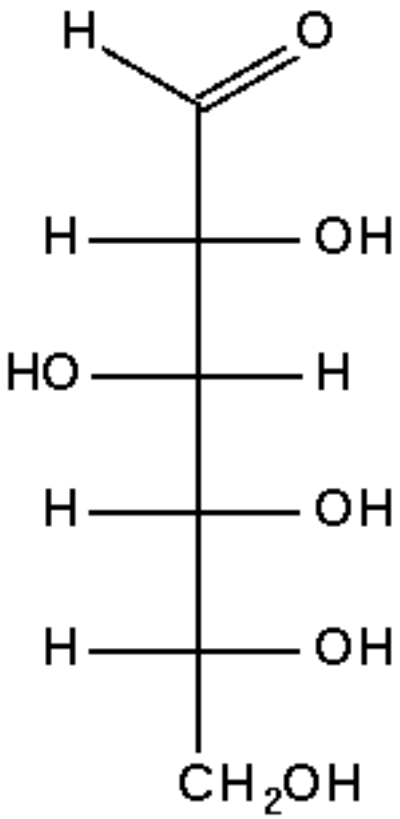
Monosaccharide

Monosaccharides are the simplest form of carbohydrates. They consist of one sugar and are usually colorless, water-soluble, crystalline solids. Some monosaccharides have a sweet taste. Examples of monosaccharides include glucose (dextrose), fructose, galactose, and ribose.

Monosaccharides are the building blocks of disaccharides like sucrose (common sugar) and polysaccharides (such as cellulose and starch). Further, each carbon atom that supports a hydroxyl group (except for the first and last) is chiral, giving rise to a number of isomeric forms all with the same chemical formula. For instance, galactose and glucose are both aldohexoses, but they have different chemical and physical properties.

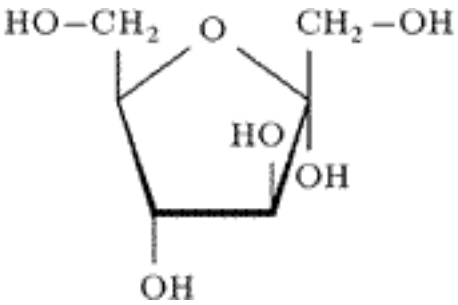


Glucose as a straight-chain carbohydrate

Structure

With few exceptions (e.g. deoxyribose), monosaccharides have the empirical chemical formula (CH2O)n and the chemical structure $H(CHOH)_nC=O(CHOH)_mH$. If n or m is zero, it is an aldose, otherwise it is a ketose. Monosaccharides contain either a ketone or aldehyde functional group, and hydroxyl groups on

most or all of the non-carbonyl carbon atoms.



Fructose, a monosaccharide

Cyclic structure

Most monosaccharides form cyclic structures, which predominate in aqueous solution, by forming hemiacetals or hemiketals (depending on whether they are aldoses or ketoses) with themselves. Glucose, for example, forms a hemiacetal linkage between its carbon-1 and the hydroxyl group of its carbon-5. Since such a reaction introduces an additional chiral center, two anomers are formed from each distinct straight-chain monosaccharide. The interconversion between these two forms is called mutarotation.

A common way of representing the cyclic structure of monosaccharides is the Haworth projection.

Isomerism

The total number of possible stereoisomers of one compound (n) is dependent on the number of chiral centers (c) in the molecule: $n = 2^c$.

Monosaccharide Nomenclature

Monosaccharides are classified by the number of carbon atoms they contain:
- **Monose**, 1 carbon atom
- **Diose**, 2 carbon atoms
- **Triose**, 3 carbon atoms
- **Tetrose**, 4 carbon atoms
- **Pentose**, 5 carbon atoms
- **Hexose**, 6 carbon atoms
- **Heptose**, 7 carbon atoms
- **Octose**, 8 carbon atoms
- **Nonose**, 9 carbon atoms

Monosaccharides are classified the type of keto group they contain:
- **Aldose**, -CHO (aldehyde)
- **Ketose**, C=O (ketone)

Monosaccharides are classified according to their molecular configuration at carbon 2:
- **D** or d, configuration like in D-glyceraldehyde
- **L** or l, configuration like in L-glyceraldehyde

All these classifications can be combined, resulting in names like D-aldohexose or ketotriose.

List of monosaccharides

This is a list of some common monosaccharides, not all are found in nature - some have been synthesised:
- **Monose**: formaldehyde
- **Diose**: glycolaldehyde
- **Trioses**: glyceraldehyde and dihydroxyacetone
- **Tetroses**: erythrose threose
- **Pentoses**:
> Aldo-pentoses: arabinose, lyxose, ribose, deoxyribose, xylose
> Keto-pentoses: ribulose, xylulose
- **Hexoses**:
>Aldo-hexoses: allose, altrose, galactose, glucose, gulose, idose, mannose, talose
>Keto-hexoses: fructose, psicose, sorbose, tagatose
- **Heptoses**:
> Keto-heptoses: mannoheptulose, sedoheptulose
- **Octoses**: octolose, 2-keto-3-deoxy-manno-octonate
- **Nonoses**: sialose

Reactions

- Formation of acetals.
- Formation of hemiacetals and hemiketals.
- Formation of ketals.

Oligosaccharide

An oligosaccharide is a saccharide polymer containing a small number (typically three to six) of component sugars, also known as simple sugars. They are generally found either O- or N-linked to compatible amino acid side chains in proteins or to lipid moieties.

Oligosaccharides are often found as a component of glycoproteins or glycolipids and as such are often used as chemical markers, often for cell recognition. An example is ABO blood type specificity. A and B blood types have two different oligosaccharide glycolipids embedded in the cell membranes of the red blood cells, AB-type blood has both, while O blood type has none.

Not all natural oligosaccharides occur as components of glycoproteins or glycolipids. Some, such as the raffinose series, occur as storage or transport carbohydrates in plants. Others, such as maltodextrins or cellodextrins, result from the microbial breakdown of larger polysaccharides such as starch or cellulose.

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Polysaccharide

Starches | Glycogen | Cellulose | Acidic polysaccharides | Bacterial Capsule Polysaccharides

Polysaccharides (sometimes called glycans) are relatively complex carbohydrates.

They are polymers made up of many monosaccharides joined together by glycosidic linkages. They are therefore very large, often branched, molecules. They tend to be amorphous, insoluble in water, and have no sweet taste.

When all the constituent monosaccharides are of the same type they are termed homopolysaccharides; when more than one type of monosaccharide is present they are termed heteropolysaccharides.

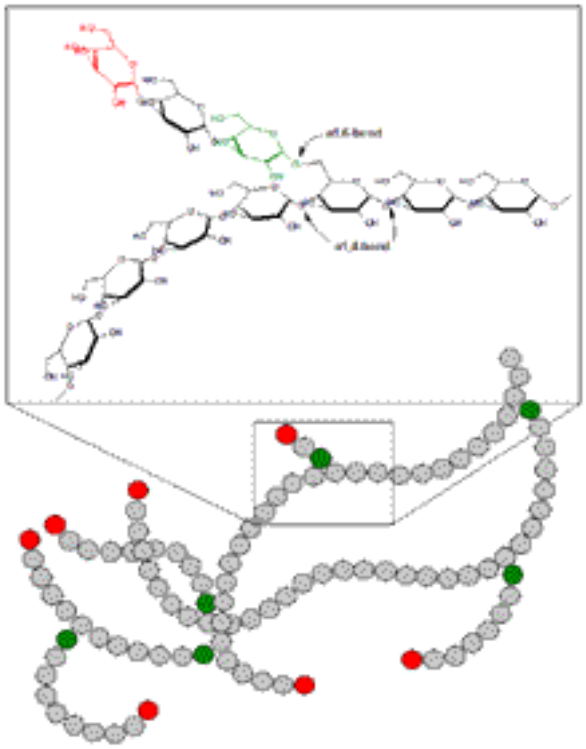
Examples include storage polysaccharides such as starch and glycogen and structural polysaccharides such as cellulose and chitin.

Polysaccharides have a general formula of $C_n(H_2O)_{n-1}$ where n is usually a large number between 200 and 500.

Starches

Starches are glucose polymers in which glucopyranose units are bonded by alpha-linkages. Amylose consists of a linear chain of several hundred glucose molecules. Amylopectin is a branched molecule made of several thousand of glucose units.
Starches are insoluble in water. They can be digested by hydrolysis catalyzed by enzymes called amylases, which can break the alpha-linkages. Humans and other animals have amylases, so they can digest starches. Potato, rice, wheat, and maize are major sources of starch in the human diet.

Glycogen



Glycogen structure

Glycogen is the storage form of glucose in animals. It is a branched polymer of glucose. Glycogen can be broken down to form substrates for respiration, through the process of glycogenolysis. This involves the breaking of most of the C-O-C bonds between the glucose molecules by the addition of a phosphate, rather than a water as in hydrolysis. This process yields phosphorylated glucose molecules, which can be metabolized with a saving of one ATP molecule.

Cellulose

The structural components of plants are formed primarily from cellulose. Wood is largely cellulose and lignin, while paper and cotton are nearly pure cellulose. Cellulose is a polymer made with repeated glucose units bonded together by beta-linkages. Humans and many other animals lack an enzyme to break the beta-linkages, so they do not digest cellulose. Certain animals can digest cellulose, because bacteria possessing the enzyme are present in their gut. The classic example is the termite.

Acidic polysaccharides

Acidic polysaccharides are polysaccharides that contain carboxyl groups, phosphate groups and/or sulfuric ester groups.

Bacterial Capsule Polysaccharides

Pathogenic bacteria commonly produce a thick, mucous-like, layer of polysaccharide. This "capsule" cloaks antigenic proteins on the bacterial surface that would otherwise provoke an immune response and

thereby lead to the destruction of the bacteria. Capsular polysaccharides are water soluble, commonly acidic, and have molecular weights on the order of 100-1000 kDa. They are linear and consist of regularly repeating subunits of one ~ six monosaccharides. There is enormous structural diversity; nearly two hundred different polysaccharides are produced by E. coli alone. Mixtures of capsular polysaccharides, either conjugated or native are used as vaccines.

Bacteria and many other microbes, including fungi and algae, often secrete polysaccharides as an evolutionary adaptation to help them adhere to surfaces and to prevent them from drying out. Humans have developed some of these polysaccharides into useful products, including xanthan gum, dextran, gellan gum, and pullulan.

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Starch

Starch is a complex carbohydrate which is insoluble in water. Starch (in particular cornstarch) is used in cooking for thickening sauces. In industry, it is used in the manufacture of adhesives, paper, and textiles. It is a white powder, and is tasteless and odorless.

Biochemically, starch is a combination of two polymeric carbohydrates (polysaccharides) called amylose and amylopectin. Amylose is constituted by glucose monomer units joined to one another head-to-tail forming alpha-1,4 linkages. Amylopectin differs from amylose in that branching occurs, with an alpha-1,6 linkage every 24-30 glucose monomer units. The overall structure of amylopectin is not that of a linear polysaccharide chain since two glucose units frequently form a branch point, so the result is the coiled molecule most suitable for storage in starch grains. Both amylopectin and amylose are polymers of glucose, and a typical starch polymer chain consists of around 2500 glucose molecules in their varied forms of polymerisation. In general, starches have the formula $(C_6H_{10}O_5)n$, where "n" denotes the total number of glucose monomer units.

Structurally, the starch forms clusters of linked linear polymers, where the alpha-1,4 linked chains form columns of glucose units which branch regularly at the alpha-1,6 links. The relative content of amylose and amylopectin varies between species, and between different cultivars of the same species. For example, high-amylose corn (maize) has starch consisting of about 85% amylose, which is the linear constituent of starch, while waxy corn starch is more than 99% amylopectin, or branched starch. The primary function of starch in plants, is to act as an energy storage molecule for the organism. In plants simple sugars are linked into starch molecules by specialized cellular organs called amyloplasts.

Starches are insoluble in water. They can be digested by hydrolysis, catalyzed by enzymes called amylases, which can break the glycosidic bonds between the 'alpha-glucose' components of the starch polysaccharide. Humans and other animals have amylases, so they can digest starch. Digestion of starches consists of the process of the cleavage of the starch molecules back into their constituent simple sugar units by the action of the amylases. The resulting sugars are then processed by further enzymes (such as maltase) in the body, in the same manner as other sugars in the diet.

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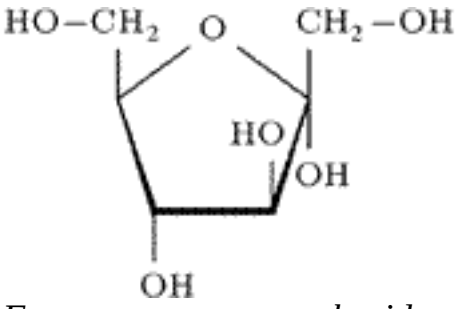
Sugar

In biochemistry, a sugar is the simplest molecule that can be identified as a carbohydrate. These include monosaccharides and disaccharides, trisaccharides and the oligosaccharides; these being sugars composed of 1, 2, 3 or more units. Sugars contain either aldehyde groups (-CHO) or ketone groups (C=O), where there are carbon-oxygen double bonds, making the sugars reactive. Most sugars conform to $(CH_2O)_n$ where n is between 3 and 7. A notable exception is deoxyribose, which as the name suggests is "missing" an oxygen. As well as being classified by their reactive group, sugars are also classified by the number of carbons they contain. Derivatives of trioses ($C_3H_6O_3$) are intermediates in glycolysis.

Pentoses (5 carbon sugars) include ribose and deoxyribose, which are present in nucleic acids. Ribose is also a component of several chemicals that are important to the metabolic process, including NADH and ATP. Hexoses (6 carbon sugars) include glucose which is a universal substrate for the production of energy in the form of ATP. Through photosynthesis plants produce glucose which is then converted for storage as an energy reserve in the form of other carbohydrates such as starch, or as in cane and beet as sucrose.



Fructose, a monosaccharide

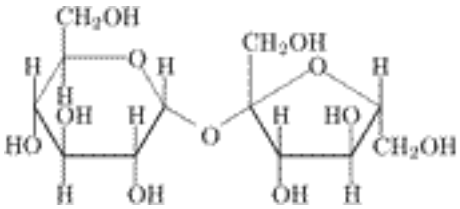
Many pentoses and hexoses are capable of forming ring structures. In these closed-chain forms the aldehyde or ketone group is not free, so many of the reactions typical of these groups cannot occur. Glucose in solution exists mostly in the ring form at equilibrium, with less than 0.1% of the molecules in the open-chain form.

Monosaccharides in a closed-chain form can form glycosidic bonds with other monosaccharides, creating disaccharides, such as sucrose, and polysaccharides such as starch. Glycosidic bonds must be hydrolysed or otherwise broken by enzymes before such compounds can be used in metabolism. After digestion and absorption the principal monosaccharides present in the blood and internal tissues are: glucose, fructose, and galactose.

The term "glyco-" indicates the presence of a sugar in an otherwise non-carbohydrate substance: for example, a glycoprotein is a protein to which one or more sugars are connected.

Simple sugars include sucrose, fructose, glucose, galactose, maltose, lactose and mannose. As far as disaccharides are concerned, the most common are sucrose (cane or beet sugar - made from one glucose

and one fructose), lactose (milk sugar - made from one glucose and one galactose) and maltose (made of two glucoses). The formula of these disaccharides is $C_{12}H_{22}O_{11}$.



Sucrose is a disaccharide of glucose (left) and fructose, important molecules in the body

Sucrose can be converted by hydrolysis into a syrup of fructose and glucose, producing what is called invert sugar. This resulting syrup is sweeter than the original sucrose, and is useful for making confections because it does not crystalize as easily and thus produces a smoother finished product.

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Lipids

Types of lipids | Lipid functions | Structure

Lipids are a class of hydrocarbon-containing organic compounds essential for the structure and function of living cells. Lipids are characterized by being water-insoluble and soluble in nonpolar organic solvents such as ether. Usually they are aliphatic but they can have rings in their structure. Although the word lipid is commonly used as a synonym to fat, the latter is a subgroup of triglyceride lipids.

Types of lipids

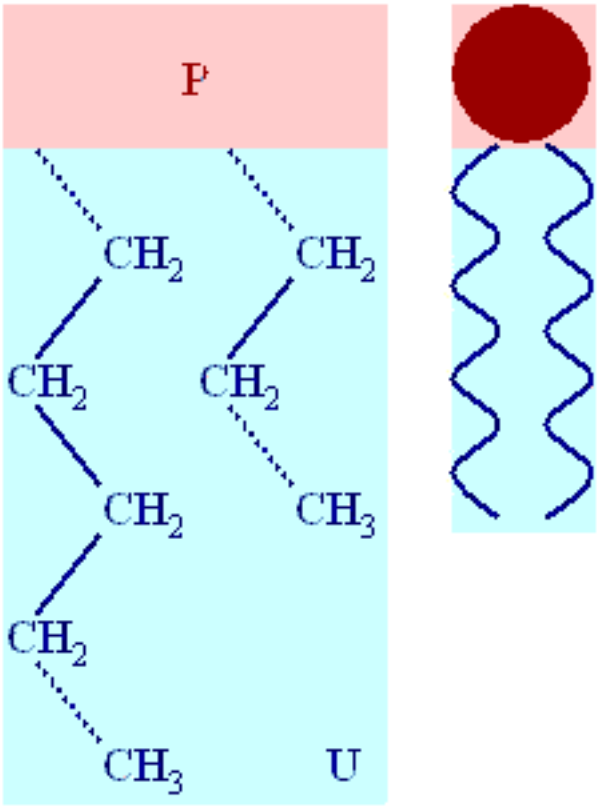

Figure 1: Structure of a Lipid. Many lipids consist of a polar head group (P) and a nonpolar tail (U for unpolar). The lipid shown is a phospholipid (two tails). The image on the left is a zoomed version of the more schematic image on the right, which will be used from now on to represent lipids with one, two, or three chains.

Lipids are usually classified by the kind and number of carbon chains, but they can also be categorized using other criteria. For instance, lipids containing a phosphate group are called phospholipids.
+ Fatty acids
-- Saturated
-- Unsaturated (eicosanoids)
+ Glycerides
-- Neutral

---- Monoglycerides
---- Diglycerides
---- Triglycerides (fats)
-- Phosphoglycerides
+ Nonglycerides
-- Sphingolipids
-- Steroids
-- Waxes
+ Complex lipids
-- Lipoproteins
-- Glycolipids

Lipid functions

+ Cell membrane structure
-- Constitutes a barrier for the cell
-- Controls the flow of material in and out of the cell
+ Energy storage (for instance fats stored in adipose tissue)
+ Lipid hormones - communication between cells
+ Interactions with vitamins - assist in the regulation of biological processes

Structure

Fatty acids

Chemically, fatty acids can be described as long chain monocarboxylic acids, and have a general structure of $CH_3(CH_2)_nCOOH$. The length of the chain usually ranges from 12 to 24, always with an even number of carbons. When the carbon chain contains no double bonds, it is called saturated. If it contains one or more such bonds, it is unsaturated. The presence of double bonds generally reduces the melting point of fatty acids. Furthermore, unsaturated fatty acids can occur either in cis or trans geometric isomers. In nature, almost all double bonds in fatty acids are found in the cis configuration.

Others

Some lipids are linear aliphatic molecules, while others have ring structures. Some are aromatic, while others are not. Some are flexible, while others are rigid.

Most lipids have some polar character in addition to being largely nonpolar. Generally, the bulk of their structure is nonpolar or hydrophobic ("water-fearing"), meaning that it does not interact well with polar solvents like water. Another part of their structure is polar or hydrophilic ("water-loving") and will tend to associate with polar solvents like water. This makes them amphiphilic molecules (having both

hydrophobic and hydrophilic portions). In the case of cholesterol, the polar group is a mere -OH (hydroxyl or alcohol). In the case of phospholipids, the polar groups are considerably larger and more polar, as described below.

Phospholipids or, more precisely, glycerophospholipids, are built on a glycerol core to which are linked two fatty acid-derived "tails" by ester linkages and one "head" group by a phosphate ester linkage. Fatty acids are unbranched hydrocarbon chains, connected by single bonds alone (**saturated** fatty acids) or by both single and double bonds (**unsaturated** fatty acids). The chains are usually 10–24 carbon groups long. The head groups of the phospholipids found in biological membranes are phosphatidylcholine (lecithin), phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol, whose head group can be modified by the addition of one to three more phosphate groups. While phospholipids are the major component of biological membranes, other lipid components like sphingolipids and sterols (such as cholesterol in animal cell membranes) are also found in biological membranes.

In an aqueous milieu, the heads of lipids tend to face the polar, aqueous environment, while the hydrophobic tails tend to minimize their contact with water. The nonpolar tails of lipids (U) tend to cluster together, forming a lipid bilayer (1) or a micelle (2). The polar heads (P) face the aqueous environment. Micelles form when single-tailed amphiphilic lipids are placed in a polar milieu, while lipid bilayers form when two-tailed phospholipids are placed in a polar environment (Fig. 2). Micelles are "monolayer" spheres and can only reach a certain size, whereas bilayers can be considerably larger. They can also form tubules. Bilayers that fold back upon themselves form a hollow sphere, enclosing a separate aqueous compartment, which is essentially the basis of cellular membranes.

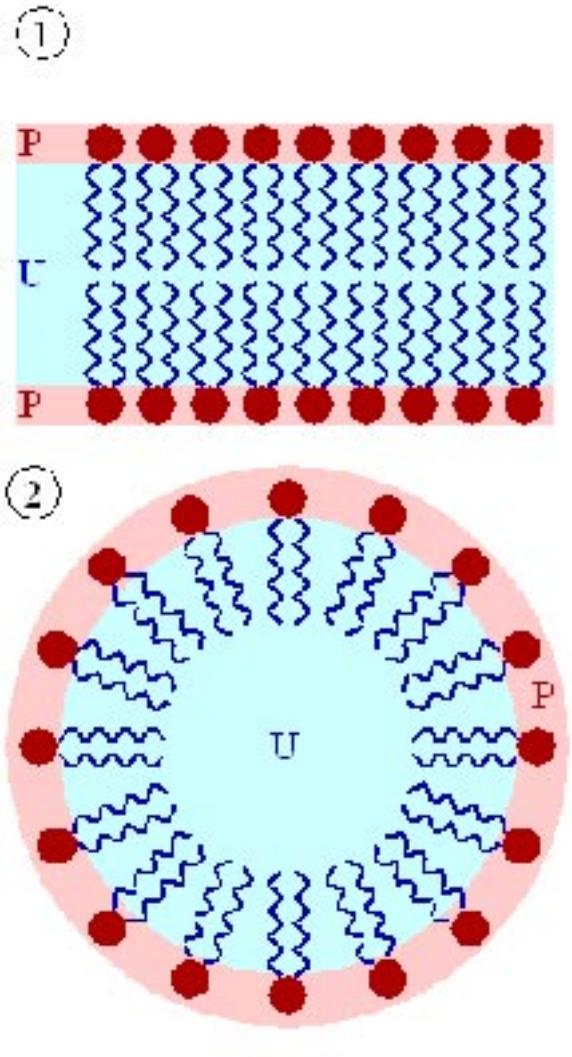

Figure 2: Self-organization of lipids. A lipid bilayer is shown on the top and a micelle on the bottom.

Micelles and bilayers separate out from the polar milieu by a process known as the "hydrophobic effect." When dissolving a nonpolar substance in a polar environment, the polar molecules (i.e. water in an aqueous solution) become more ordered around the dissolved nonpolar substance, since the polar molecules cannot form hydrogen bonds to the nonpolar molecule. Therefore, in an aqueous environment, the polar water molecules form an ordered "clathrate" cage around the dissolved nonpolar molecule. However, when the nonpolar molecules separate out from the polar liquid, the entropy (state of disorder) of the polar molecules in the liquid increases. This is essentially a form of phase separation, similar to the spontaneous separation of oil and water into two separate phases when one puts them together.

The self-organisation depends on the concentration of the lipid present in solution. Below the critical micelle concentration the lipids form a single layer on the liquid surface and are dispersed in solution. At the first critical micelle concentration (CMC-I), the lipids organise in spherical micelles, at the second critical micelle concentration (CMC-II) into elongated pipes, and at the lamellar point (LM or CMC-III) into stacked lamellae of pipes. The CMC depends on the chemical composition, mainly on the ratio of the head area and the tail length.

Lipid bilayers form the foundation of all biological membranes and of liposomes.

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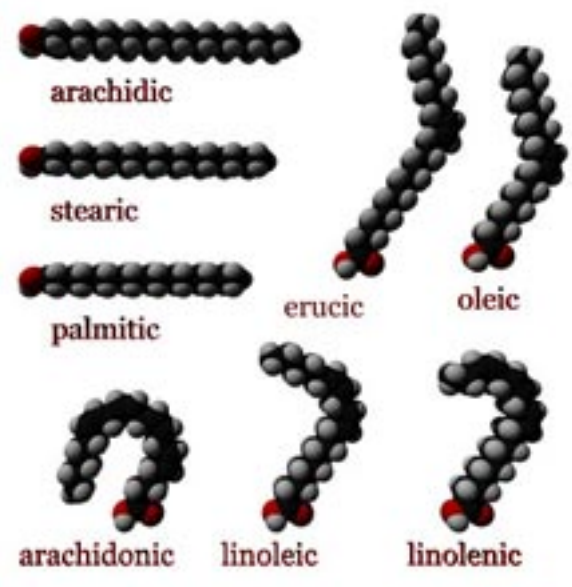
Fatty acid

In chemistry, especially biochemistry, a fatty acid is a carboxylic acid (or organic acid), often with a long aliphatic tail (long chains), either saturated or unsaturated. Depending on the context, fatty acids may be assumed to have at least 8 carbon atoms, e.g., caprylic acid (octanoic acid). Most of the natural fatty acids have an even number of carbon atoms, because their biosynthesis involves acetate which has two carbon atoms.

Industrially, fatty acids are produced by the hydrolysis of the ester linkages in a fat or biological oil (both of which are triglycerides), with the removal of glycerol.

Reduction of fatty acids yields fatty alcohols.

Types of fatty acids



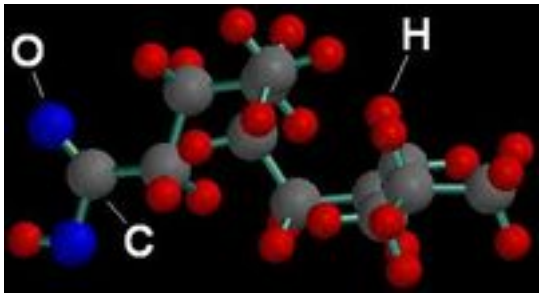
Several fatty acid molecules

Saturated fatty acids

Saturated fatty acids do not contain any double bonds or other functional groups along the chain. The term "saturated" refers to hydrogen, in that all carbons (apart from the carboxylic acid [-COOH] group) contain as many hydrogens as possible. In other words, the omega (ω) end contains 3 hydrogens (CH_3-) and each carbon within the chain contains 2 hydrogens (-CH_2-).

Saturated fatty acids form straight chains and, as a result, can be packed together very tightly, allowing living organisms to store chemical energy very densly. The fatty tissues of animals contain large amounts of long-chain saturated fatty acids. In IUPAC nomenclature, fatty acids have an -oic acid suffix. In common nomenclature, the suffix is usually -ic.

Some saturated fatty acids are:
- Acetic: CH_3COOH
- Butyric: $CH_3(CH_2)_2COOH$
- Lauric (dodecanoic acid): $CH_3(CH_2)_{10}COOH$
- Myristic (tetradecanoic acid): $CH_3(CH_2)_{12}COOH$
- Palmitic (hexadecanoic acid): $CH_3(CH_2)_{14}COOH$
- Stearic (octadecanoic acid): $CH_3(CH_2)_{16}COOH$
- Arachidic (eicosanoic acid): $CH_3(CH_2)_{18}COOH$



This is a computer generated image of Dodecanoic Acid, a fatty acid

Unsaturated fatty acids

Unsaturated fatty acids are of similar form, except that one or more alkene functional groups exist along the chain, with each alkene substituting a singly-bonded " $-CH_2-CH_2-$" part of the chain with a doubly-bonded "-CH=CH-" portion (that is, a carbon double bonded to another carbon).

The two hydrogen atoms (H) that are bound to the doubly-bonded carbon atoms (C) can occur in a *cis* or *trans* configuration.

cis: A cis configuration means that the two hydrogen atoms are on the same side of the chain. Because of the polarization of the hydrogen atoms, the hydrogen atoms repel each other and cause the chain to bend. The more double-bonds the chain has in the cis configuration, the more bent it is. When a chain has many cis bonds, it becomes quite curved. For example, oleic acid, with one double bond, has a "kink" in it, while linoleic acid, with two double bonds, has a more pronounced bend. Alpha-linolenic acid, with three double bonds, forms a hooked shape.

trans: A trans configuration, by contrast, means that the two hydrogen atoms occur on opposite sides of the chain. As a result, they don't cause the chain to bend much, and their shape is similar to the straight saturated fatty acids.

In most naturally occurring unsaturated fatty acids, each double bond has 3n carbon atoms after it, for some n, and all are cis bonds. Most fatty acids in the trans configuration (trans fats) are unnatural and the result of human processing.

The differences in geometry between these various types of unsaturated fatty acids, as well as between saturated and unsaturated fatty acids, plays an important role is biological processes, and in the construction of biological structures (such as cell membranes).

Nomenclature

There are two different ways to make clear where the double bonds are located in molecules. For example:
- *cis*/*trans*-Delta-*x* or *cis*/*trans*-Δ^x: The double bond is located on the *x*th carbon-carbon bond, counting from the carboxyl terminus. The *cis* or *trans* notation indicates whether the molecule is arranged in a *cis* or *trans* conformation. In the case of a molecule having more than one double bond, the notation is, for example, *cis*,*cis*-Δ^9,Δ^{12}.
- Omega-*x* or ω-*x* : A double bond is located on the *x*th carbon-carbon bond, counting from the ω (methyl carbon) end.

Example of unsaturated fatty acids:
- Alpha-linolenic acid: $CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)7COOH$
- Docosahexaenoic acid
- Eicosapentaenoic acid
- Linoleic acid: $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$
- Arachidonic acid $CH_3(CH_2)_4CH=CHCH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_3COOH$
- Oleic acid: $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$
- Erucic acid: $CH_3(CH_2)_7CH=CH(CH_2)_{11}COOH$

Alpha-linolenic, docosahexaenoic, and eicosapentaenoic acids are examples of omega-3 fatty acids. Linoleic acid and arachidonic acid are omega-6 fatty acids. Oleic and erucic acid are omega-9 fatty acids. Stearic and Oleic acid are both 18 C fatty acids. They differ only in that stearic acid is saturated with hydrogen, while oleic acid is an unsaturated fatty acid with two fewer hydrogens.

Essential fatty acids

Essential fatty acids are the polyunsaturated fatty acids, linoleic acid and alpha-linolenic acid, which are

the parent compounds of the omega-6 and omega-3 fatty acid series, respectively. They are essential in the human diet since they cannot be synthesized by the body. Humans can easily make saturated fatty acids or monounsaturated fatty acids with a double bond at the omega-9 position, but do not have the enzymes necessary to introduce a double bond at the omega-3 or omega-6 position. As a result, these fatty acids must be obtained from food sources; hence, they are "essential."

The essential fatty acids are very important to the human immune system and to help regulate blood pressure, since they are used to make compounds such as prostaglandins. The brain is also highly enriched in derivatives of linolenic and alpha-linoleic acids. Changes in the levels and balance of these fatty acids caused with a typical Western diet of processed food and high intensity agriculture has been associated with depression and behavioral change, including violence. Change to a more natural diet or consumption of supplements to compensate for dietary imbalance is associated with a reduction in violent behavior, and increases attention span. This finding has been replicated in studies within schools as well as a double blind study in a prison.

Trans fatty acids

A **trans fatty acid** (commonly shortened to **trans fat**) is an unsaturated fatty acid molecule that contains a *trans* double bond between carbon atoms, which makes the molecule less kinked compared to fatty acids with *cis* double bonds. Research suggests a correlation between diets high in trans fats and diseases like atherosclerosis and coronary heart disease.

Free fatty acids

Fatty acids can be bound or attached to other molecules, like triglycerides or phospholipids. When they are not attached to other molecules, they are known as "free" fatty acids.

The **uncombined fatty acids** or **free fatty acids** may come from the breakdown of a triglyceride into its components (fatty acids and glycerol).

Free fatty acids are an important source of fuel for many tissues since they can yield relatively large quantities of ATP. Many cell types can use either glucose or fatty acids for this purpose. However, heart and skeletal muscle prefer fatty acids. On the other hand, the brain cannot use fatty acids as a source of fuel, relying instead on glucose, or on ketone bodies produced by the liver from fatty acid metabolism during starvation, or periods of low carbohydrate intake.

pH

Formic acid and acetic acid are miscible with water and dissociate to form reasonably strong acids (pKa respectively 3.77 and 4.76). Longer chain fatty acids do not show a great change in pKa: nonanic acid, for example, has a pKa of 4.96. However, as the chain length increases the solubility of the fatty acids in water decreases very rapidly, so that the longer chain fatty acids have very little effect on the pH of a

solution. The significance of their pKa values therefore only has relevance to the types of reaction that they take part in.

Even those fatty acids that are insoluble in water will dissolve in warm ethanol, and can be titrated with sodium hydroxide solution using phenolphthalein as an indicator to a pale pink endpoint. This analysis is used to determine the free fatty acid content of fats, i.e. the proportion of the triglycerides that have been hydrolyzed.

Reaction of fatty acids

Fatty acids react just like any other carboxylic acid, which means they can undergo esterification, hydrolysis, and acid-base reactions. Unsaturated fatty acids can additionally undergo addition reactions, most commonly hydrogenation, which is used to convert vegatable oils into margarine. With partial hydrogenation, unsaturated fatty acids can be isomerized from *cis* to *trans* configuration.

Autoxidation and rancidity

Fatty acids at room temperature undergo a chemical change known as autoxidation. The fatty acid breaks down into hydrocarbons, ketones, aldehydes, and smaller amounts of epoxides and alcohols. Heavy metals present at low levels in fats and oils promote autoxidation. Fats and oils often are treated with chelating agents such as citric acid.

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Fatty Acid Degradation

Fatty acids are an important source of energy for many organisms. Triglycerides yield more than twice as much energy for the same mass as do carbohydrates or proteins. All cell membranes are built up of phospholipids, each of which contains two fatty acids. Fatty acids are also commonly used for protein modification, and all steroid hormones are ultimately derived from fatty acids. The metabolism of fatty acids, therefore, consists of catabolic processes which generate energy and primary metabolites from fatty acids, and anabolic processes which create biologically important molecules from fatty acids and other dietary carbon sources.

Fatty acids as an energy source

Fatty acids, stored as triglycerides in an organism, are an important source of energy because they are both reduced and anhydrous. The energy yield from a gram of fatty acids is approximately 9 kcal (39 kJ), compared to 4 kcal/g (17 kJ/g) for proteins and carbohydrates. Since fatty acids are non-polar molecules, they can be stored in a relatively anhydrous (water free) environment. Carbohydrates, on the other hand, are more highly hydrated. For example, 1 g of glycogen can bind approximately 2 g of water, which translates to 1.33 kcal/g (4 kcal/3 g). This means that fatty acids can hold more than six times the amount of energy. Put another way, if the human body relied on carbohydrates to store energy, then a person would need to carry 67.5 lb (31 kg) of glycogen to have the equivalent energy of 10 lb (5 kg) of fat.

Digestion

Fatty acids are usually ingested as triglycerides, which cannot be absorbed by the intestine. They are broken down into free fatty acids and monoglycerides by lipases with the help of bile salts. Once across the intestinal barrier, they are reformed into triglycerides and packaged into chylomicrons or liposomes, which are released in the lymph system and then into the blood. Eventually, they bind to the membranes of adipose cells or muscle, where they are either stored or oxidized for energy. The liver also acts as a major organ for fatty acid treatment, processing liposomes into the various lipoprotein forms, namely VLDL, LDL, IDL or HDL.

Degradation

Three major steps are involved in the degradation of fatty acids.

Release from adipose tissue

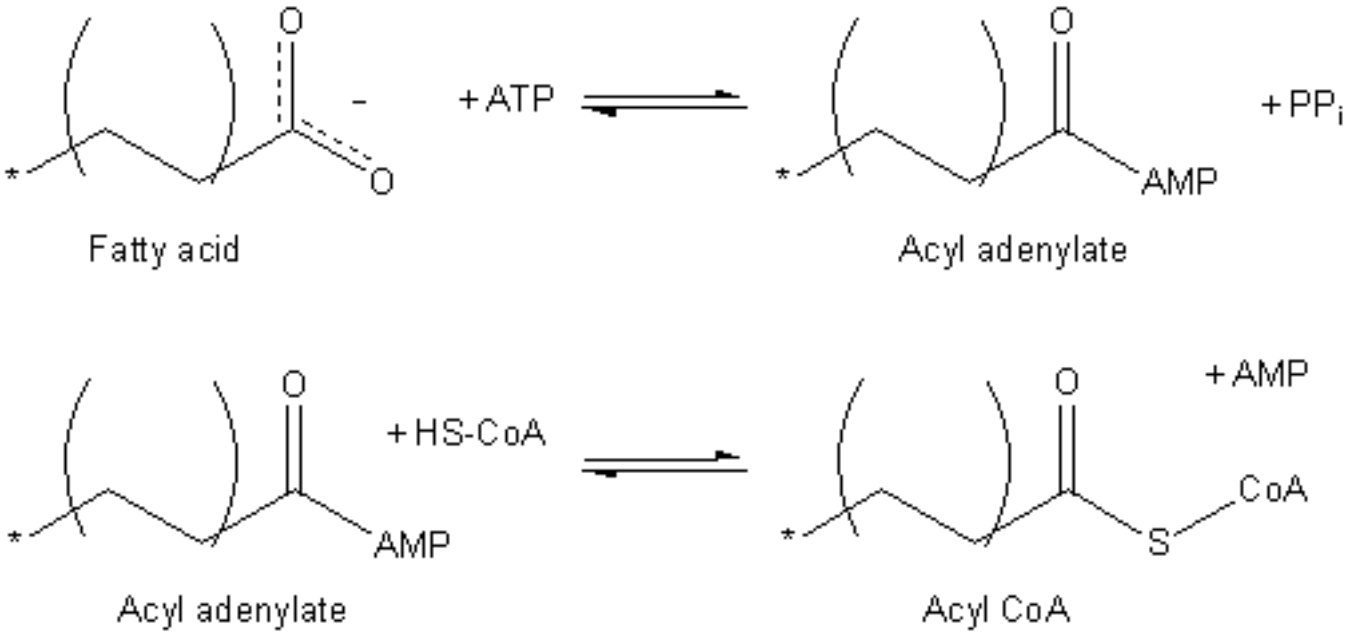
The breakdown of fat stored in fat cells is known as **lipolysis**. During this process, free fatty acids are released into the bloodstream and circulate throughout the body. Ketones are produced, leading to the process of ketosis in the case where insufficient carbohydrates are present in the diet. Lipolysis testing strips are available which can sometimes measure whether or not this process is taking place.

The following hormones induce lipolysis: epinephrine, norepinephrine, glucagon and adrenocorticotropic hormone. These trigger 7TM receptors, which activate adenylate cyclase. This results in increased production of cAMP, which activates protein kinase A, which subsequently activate lipases found in adipose tissue.

Triglycerides undergo lipolysis (hydrolysis by lipases) and are broken down into glycerol and fatty acids. Once released into the blood, the free fatty acids bind to serum albumin for transport to tissues that require energy. The glycerol backbone is absorbed by the liver and eventually converted into glyceraldehyde 3-phosphate (G3P), which is an intermediate in both glycolysis and gluconeogenesis.

Transport into mitochondria

Fatty acids must be activated before they can be carried into the mitochondria, where fatty acid oxidation occurs. This process occurs in two steps:



The formula for the above is:
$RCOO^- + CoA + ATP + H_2O \rightarrow RCO\text{-}CoA + AMP + P_i + 2H^+$

Once activated, the acyl CoA is transported into the mitochondrial matrix. This occurs via a series of similar steps:
1. Acyl CoA is conjugated to carnitine by *carnitine plamitoyltransferase I*

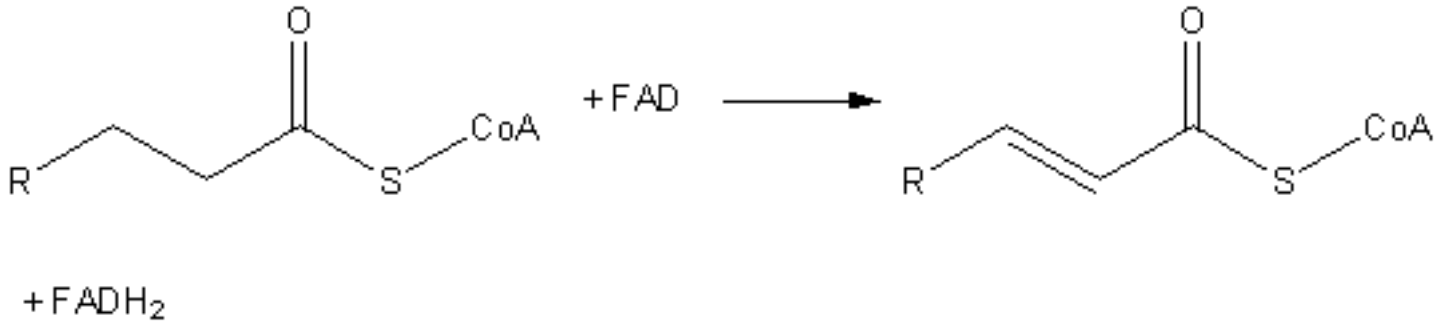
2. Acyl carnitine is shuttled inside by Carnitine acyltranslocase
3. Acyl carnitine is converted to acyl CoA by *carnitine palmitoyltransferase II*

β-Oxidation

Once inside the mitochondria, the β-oxidation of fatty acids occurs via four recurring steps:
1. Oxidation by FAD
2. Hydration
3. Oxidation by NAD^+
4. Thiolysis

Oxidation by FAD

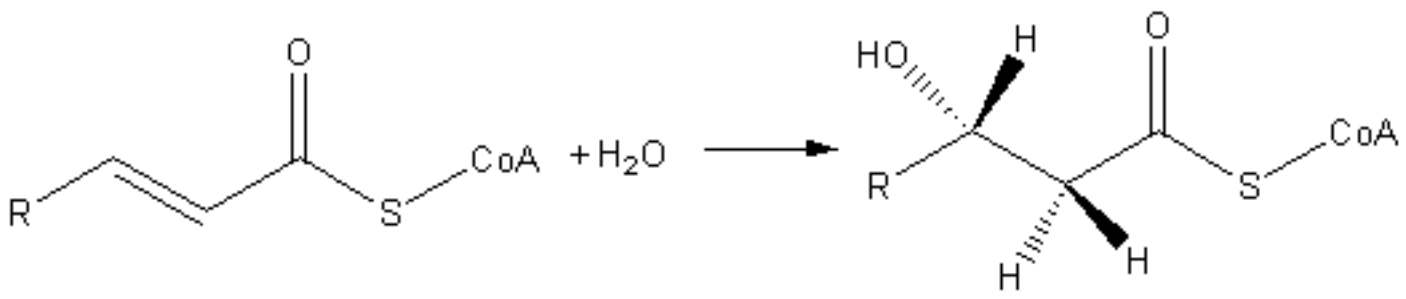
The first step is the oxidation of the fatty acid by FAD. The following reaction is catalyzed by *acyl CoA dehydrogenase*:



The enzyme catalyzes the formation of a double bond between the C-2 and C-3. The end product is **trans-Δ^2-enoyl-CoA**.

Hydration

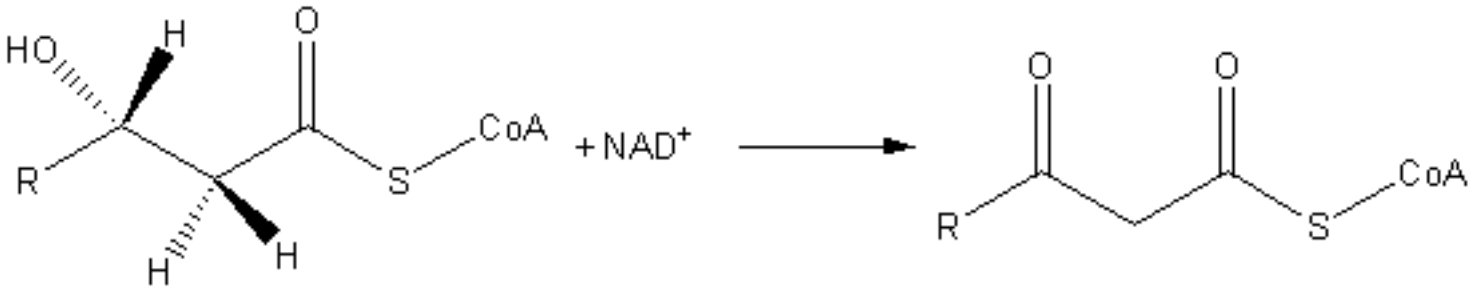
The next step is the hydration of the bond between C-2 and C-3. This reaction is catalyzed by *enoyl CoA hydratase*. The reaction is stereospecific, forming only the L isomer.



The end product is **L-3-hydroxyacyl CoA**.

Oxidation by NAD^+

The third step is the oxidation of L-3-hydroxyacyl CoA by NAD^+, catalyzed by *L-3-hydroxyacyl CoA dehydrogenase*. This converts the hydroxyl group into a keto group.

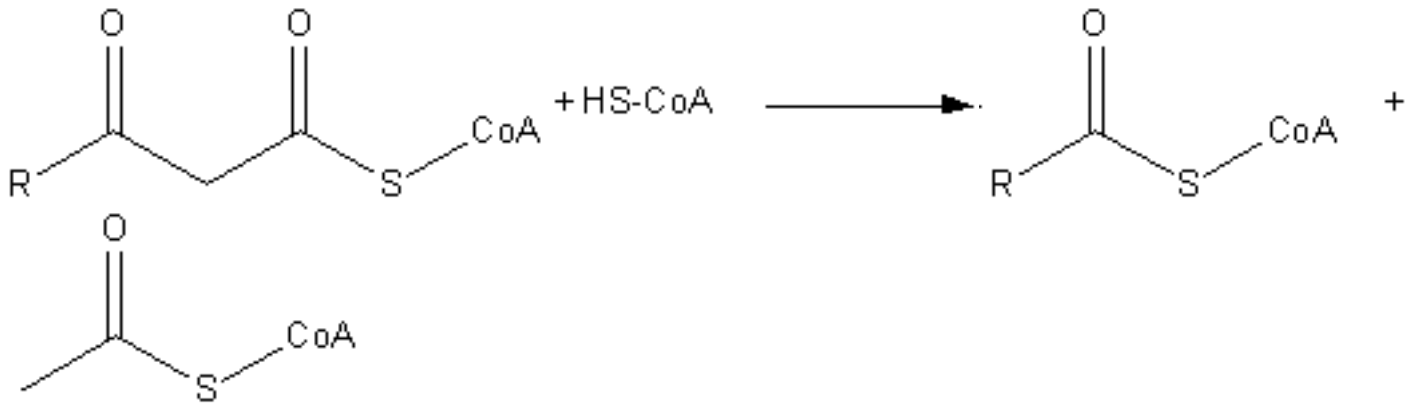


$+ NADH + H^+$

The end product is **3-ketoacyl CoA**.

Thiolysis

The final step is the cleavage of 3-ketoacyl CoA by the thiol group of another molecule of CoA. This reaction is catalyzed by *B-ketothiolase*. The thiol is inserted between C-2 and C-3, which yields an acetyl CoA molecule and an acyl CoA molecule, which is two carbons shorter.



This process continues until the entire chain is cleaved into acetyl CoA units. For every cycle, one molecule of $FADH_2$, NADH and acetyl CoA are formed.

β-oxidation of unsaturated fatty acids

β-oxidation of unsaturated fatty acids poses a problem since the location of a cis bond can prevent the formation of a trans-δ^2 bond. These situations are handled by an additional two enzymes: *cis-δ^3-Enoyl CoA isomerase* and *2,4 Dienoyl CoA reductase*. Whatever the conformation of the hydrocarbon chain, β-oxidation occurs normally until the acyl CoA (because of the presence of a double bond) is not an appropriate substrate for *acyl CoA dehydrogenase*, or *enoyl CoA hydratase*.

If the acyl CoA contains a cis-Δ^3 bond, then the isomerase will convert the bond to a trans-Δ^2 bond, which is a regular substrate.

If the acyl CoA contains a cis-Δ^4 double bond, then its dehydrogenation yields a 2,4-dienoyl intermediate, which is not a substrate for enoyl CoA hydratase. However, the enzyme 2,4-Dienoyl CoA reductase reduces the intermediate, using NADPH, into trans-Δ^3-enoyl CoA. As in the above case, this compound is converted into a suitable intermediate by cis-Δ3-Enoyl CoA isomerase.

To summarize, odd numbered double bonds are handled by the isomerase, and even numbered bonds by the reductase (which creates an odd numbered double bond) and the isomerase.

β-oxidation of odd-numbered chains

Chains with an odd-number of carbons are oxidized in the same manner as even-numbered chains, but the final products are propionyl CoA and acetyl CoA. Propionyl CoA is converted into succinyl CoA (which is an intermediate in the citric acid cycle) in a reaction that involves Vitamin B12. Succinyl CoA can then enter the citric acid cycle. Because it cannot be completely metabolized in the citric acid cycle, the products of its partial reaction must be removed in a process called cataplerosis. This allows regeneration of the citric acid cycle intermediates, possibly an important process in certain metabolic diseases.

Oxidation in peroxisomes

Fatty acid oxidation also occurs in peroxisomes. However, the oxidation ceases at octanyl CoA. One significant difference is that oxidation in peroxisomes is not coupled to ATP synthesis. Instead, the high-potential electrons are transferred to O_2, which yields H_2O_2. The enzyme catalase, found exclusively in peroxisomes, converts the hydrogen peroxide into water and oxygen.

Energy yield

The ATP yield for every oxidation cycle is 14 ATP, broken down as follows:
1 $FADH_2$ x 1.5 ATP = 1.5 ATP

1 NADH x 2.5 ATP = 2.5 ATP
1 acetyl CoA x 10 ATP = 10 ATP

For an even-numbered saturated fat (C_{2n}), n - 1 oxidations are necessary and the final process yields an additional acetyl CoA. In addition, two equivalents of ATP are lost during the activation of the fatty acid. Therefore, the total ATP yield can be stated as: (n - 1) * 14 + 10 - 2.

For instance, the ATP yield of palmitate (C_{16}, n = 8) is:

(8 - 1) * 14 + 10 - 2
106 ATP
or
7 $FADH_2$ x 1.5 ATP = 10.5 ATP

7 NADH x 2.5 ATP = 17.5 ATP
8 acetyl CoA x 10 ATP = 80 ATP
ATP equivalent used during activation = -2
Total: 106 ATP

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Fatty Acid Synthesis

Condensation | Reduction of acetoacetyl ACP | Dehydration | Reduction of crotonyl ACP

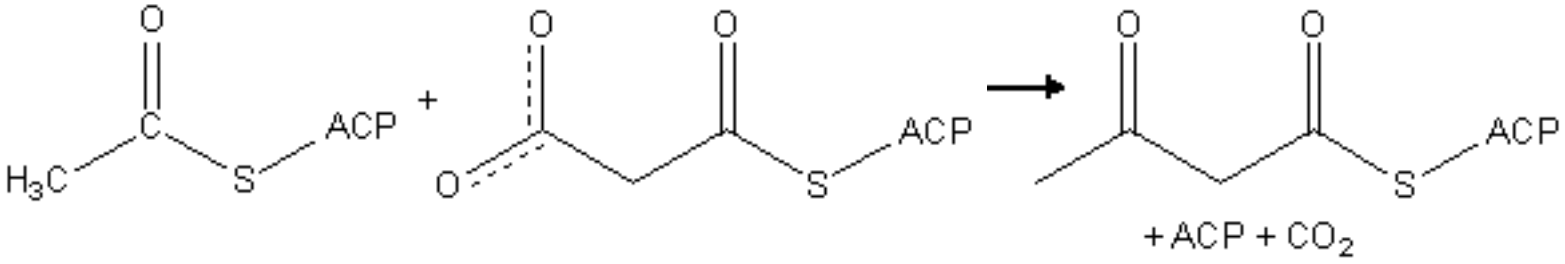
Elongation

Much like β-oxidation, elongation occurs via four recurring reactions:
1. Condensation
2. Reduction
3. Dehydration
4. Reduction

In the second step of elongation, butyryl ACP condenses with malonyl ACP to form an acyl ACP compound. This continues until a C_{16} acyl compound is formed, at which point it is hydrolyzed by a *thioesterase* into palmitate and ACP.

Condensation

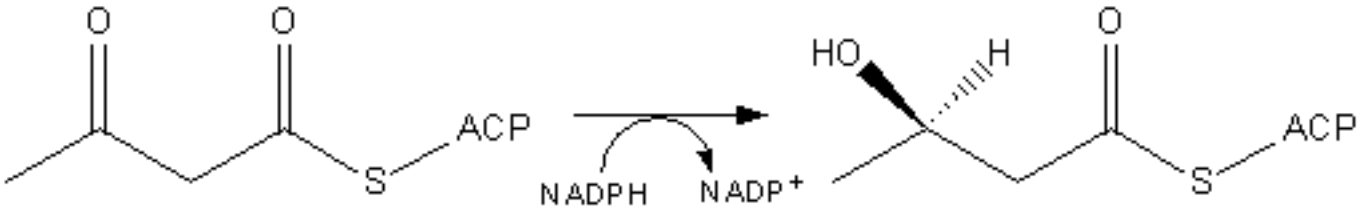
The first step is condensation of acetyl ACP and malonyl ACP, catalyzed by *acyl-malonyl ACP condensing enzyme*. This results in the formation of acetoacetyl ACP.



Although this reaction is thermodynamically unfavourable, the evolution of CO_2 drives the reaction forward.

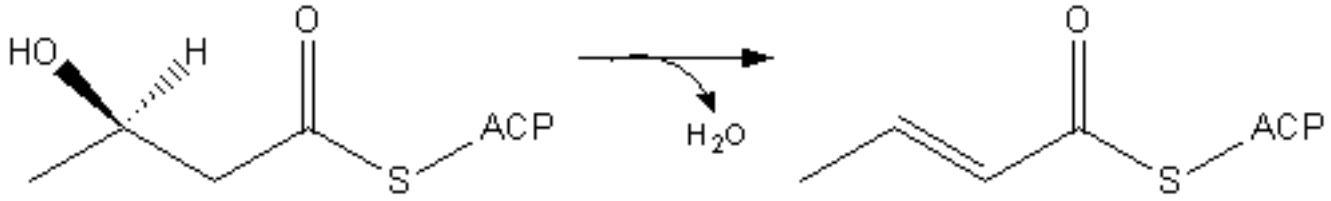
Reduction of acetoacetyl ACP

In this step, acetoacetyl ACP is reduced by NADPH into D-3-Hydroxybutyryl ACP. This reaction is catalyzed by *β-Ketoacyl ACP reductase*. The double bond is reduced to a hydroxyl group. Only the D isomer is formed.



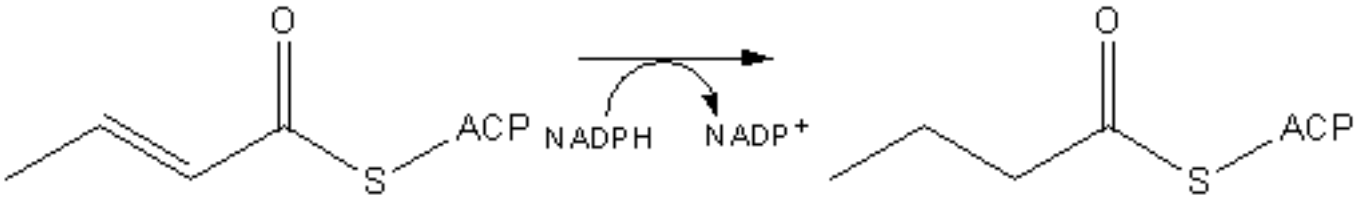
Dehydration

In this reaction, D-3-Hydroxybutyryl ACP is dehydrated to crotonyl ACP. This reaction is catalyzed by *3-Hydroxyacyl ACP dehydratase*.



Reduction of crotonyl ACP

During this final step, crotonyl ACP is reduced by NADPH into butyryl ACP. This reaction is catalyzed by *enoyl ACP reductase*.



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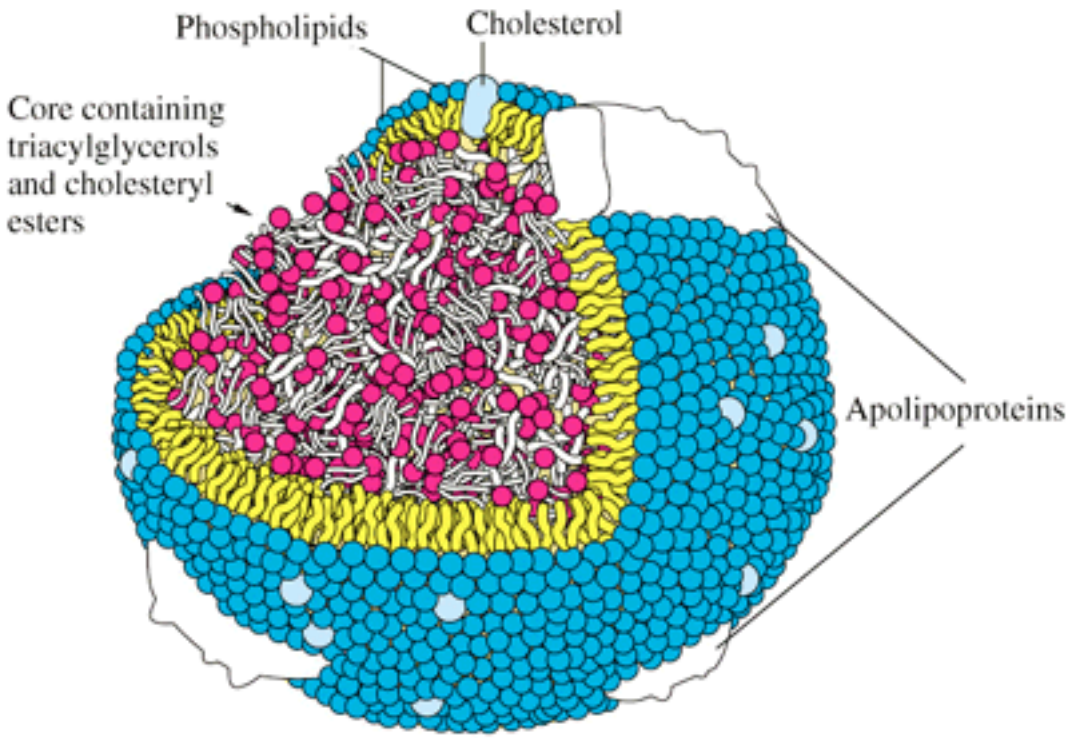
Lipoprotein

Function | Classification

A **lipoprotein** is a biochemical assembly that contains both proteins and lipids and may be structural or catalytic in function. Lipoproteins may be enzymes, proton pumps, ion pumps, or some combination of these functions. Examples include the high density and low density lipoproteins of the blood and the transmembrane proteins of the mitochondrion and the chloroplast.



Function

The lipids are often an essential part of the complex, even if they seem to have no catalytic activity themselves. To isolate transmembrane lipoproteins from their associated membranes, detergents are often needed.

All cells need fats and, for all animal cells, cholesterol to build the multiple membranes which cells use to both control water, and water soluble elements, and to organize their internal structure and protein enzymatic systems.

Lipoproteins in the blood carry fats around the body. The protein particles have charged groups aimed outward so as to attract water molecules; this makes them soluble in the salt water based blood pool. Triglyceride-fats and cholesterol are carried internally, shielded from the water.

The interaction of the proteins forming the surface of the particles with (a) enzymes in the blood, (b) with each other and (c) with specific proteins on the surfaces of cells determine whether triglycerides and cholesterol will be added to or removed from the lipoprotein transport particles.

Regarding atheroma development and progression vs. regression, the key issue has always been cholesterol transport patterns, not cholesterol concentration itself.

Classification

By density

General categories of lipoproteins, listed in order from larger and less dense (more fat than protein) to smaller and more dense (more protein, less fat):
* Chylomicrons - carry triacylglycerol (fat) from the intestines to the liver and to adipose tissue.
* Very low density lipoproteins - carry (newly synthesised) triacylglycerol from the liver to adipose tissue.
* Intermediate density lipoproteins - are intermediate between VLDL and LDL. They are not usually detectable in the blood.
* Low density lipoproteins - carry cholesterol from the liver to cells of the body. Sometimes referred to as the "bad cholesterol" lipoprotein.
* High density lipoproteins - collects cholesterol from the body's tissues, and brings it back to the liver. Sometimes referred to as the "good cholesterol" lipoprotein.

Alpha and beta

It is also possible to classify lipoproteins as "alpha" and "beta", akin to the classification of proteins in serum protein electrophoresis. This terminolgy is sometimes used in describing lipid disorders such as Abetalipoproteinemia.

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Waxes

Wax has traditionally referred to a substance that is secreted by bees (beeswax) and used by them in constructing their honeycombs.

In modern terms, **wax** is an imprecisely defined term generally understood to be a substance with properties similar to beeswax, namely
* plastic (malleable) at normal ambient temperatures
* a melting point above approximately 45 °C (which differentiates waxes from fats and oils)
* a relatively low viscosity when melted (unlike many plastics)
* insoluble in water
* hydrophobic

Waxes may be natural or artificial. In addition to beeswax, carnauba (a vegetable wax) and paraffin (a mineral wax) are commonly encountered waxes which occur naturally. *Ear wax* is an oily substance found in the human ear. Some artificial materials that exhibit similar properties are also described as wax or waxy.

Chemically, a wax may be an ester of ethylene glycol (ethan-1,2-diol) and two fatty acids, as opposed to a fat which is an ester of glycerin (propan-1,2,3-triol) and three fatty acids. It may also be an ester of a fatty acid with a fatty alcohol. It is a type of lipid.

Wax types

Animal and insect waxes:

* Beeswax - produced by honeybees
* Chinese wax - produced by scale insects *Coccus ceriferus*
* Shellac wax - from the lac insect *Coccus lacca*
* Spermaceti - from the head cavities and blubber of the Sperm Whale
* Lanolin (wool wax) - from the sebaceous glands of sheep

Vegetable waxes:

* Bayberry wax - from the surface of the berries of the bayberry shrub
* Candelilla wax - from the Mexican shrubs *Euphorbia cerifera* and *E. antisyphilitica*
* Carnauba wax - from the leaves of the Carnauba Palm
* Castor wax - catalytically hydrogenated castor oil
* Esparto wax - a byproduct of making paper from esparto grass
* Japan wax - a vegetable tallow (not a true wax), from the berries of *Rhus* and *Toxicodendron* species

* Jojoba oil - pressed from the seeds of the jojoba tree, a replacement for spermaceti
* Ouricury wax - from the Brazilian Feather Palm
* Rice bran wax - obtained from rice bran

Mineral waxes

* Ceresin waxes
* Montan wax - extracted from lignite and brown coal
* Ozocerite - found in lignite beds
* Peat waxes

Petroleum waxes

* Paraffin wax - made of long-chain alkane hydrocarbons
* Microcrystalline wax - with very fine crystalline structure

Synthetic waxes

* Polyethylene waxes - based on polyethylene
* Fischer-Tropsch waxes
* Chemically modified waxes - usually esterified or saponified
* substituted amide waxes
* polymerized α-olefins

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Nucleic Acids

A **nucleic acid** is a complex, high-molecular-weight biochemical macromolecule composed of nucleotide chains that convey genetic information. The most common nucleic acids are **deoxyribonucleic acid** (DNA) and **ribonucleic acid** (RNA). Nucleic acids are found in all living cells and viruses.

Chemical Structure

The term "nucleic acid", termed because of its prevalence in cellular nuclei, is the generic name of a family of biopolymers. The monomers themselves are called nucleotides. Each monomer consists of three components: a nitrogenous heterocyclic base, either a purine or a pyrimidine, a pentose sugar, and a phosphate group. Different nucleic acid types differ in the specific sugar found in their chain. For example, DNA contains 2-deoxyriboses. Likewise, the nitrogenous bases possible in the two nucleic acids are different: adenine, cytosine, and guanine are possible in both RNA and DNA, while thymine is possible only in DNA and uracil is possible only in RNA.

Nucleic acids may be single-stranded or double-stranded. A double-stranded nucleic acid consists of two single-stranded nucleic acids hydrogen-bonded together. RNA is usually single-stranded, but any given strand is likely to fold back upon itself to form double-helical regions. DNA is usually double-stranded, though some viruses have single-stranded DNA as their genome. The sugars and phosphates in nucleic acids are connected to each other in an alternating chain, linked by shared oxygens, forming a phosphodiester functional group. In conventional nomenclature, the carbons to which the phosphate groups are attached are the 3' and the 5' carbons. The bases extend from a glycosidic linkage to the 1' carbon of the pentose ring.

Hydrophobic interaction of nucleic acids is poorly understood. For example, nucleic acids are insoluble in ethanol, TCA, cold and hot water, and diluted hydrochloric acid; but they are soluble in diluted NaOH, alcohol and HCl.

Nucleic acids are primarily biology's means of storing and transmitting genetic information, though RNA is also capable of acting as an enzyme.

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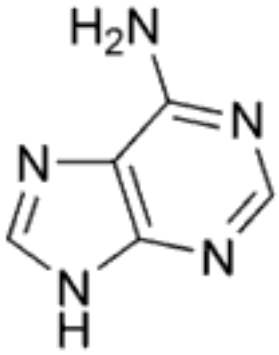
Adenin



Chemical name 9H-Purin-6-amine
Alternate name 6-aminopurine
Chemical formula C5H5N5
Molecular mass 135.1267 g/mol
Melting point 360 - 365 °C
CAS number 73-24-5
SMILES NC1=NC=NC2=C1N=CN2

Adenine is one of the two purine nucleobases used in forming nucleotides of the nucleic acids DNA and RNA. In DNA, adenine binds to thymine via two hydrogen bonds to assist in stabilizing the nucleic acid structures. In RNA, adenine binds to uracil, which is used in the cytoplasm for protein synthesis.

It forms several tautomers, compounds that can be rapidly interconverted and are often considered equivalent. Guanine, a related compounds (also a purine derivative), forms tautomers in the same way, and has more detailed information too.

Adenine forms adenosine, a nucleoside, when attached to ribose, and deoxyadenosine when attached to deoxyribose; it forms adenosine triphosphate (ATP), a nucleotide, when three phosphate groups are added to adenosine. Adenosine triphosphate is used in cellular metabolism as one of the basic methods of transferring chemical energy between chemical reactions.

In older literature, adenine was sometimes called Vitamin B4. However it is no longer considered a true vitamin or part of Vitamin B.

Some think that, at the origin of life on Earth, the first adenine was formed by the polymerizing of five hydrogen cyanide (HCN) molecules.

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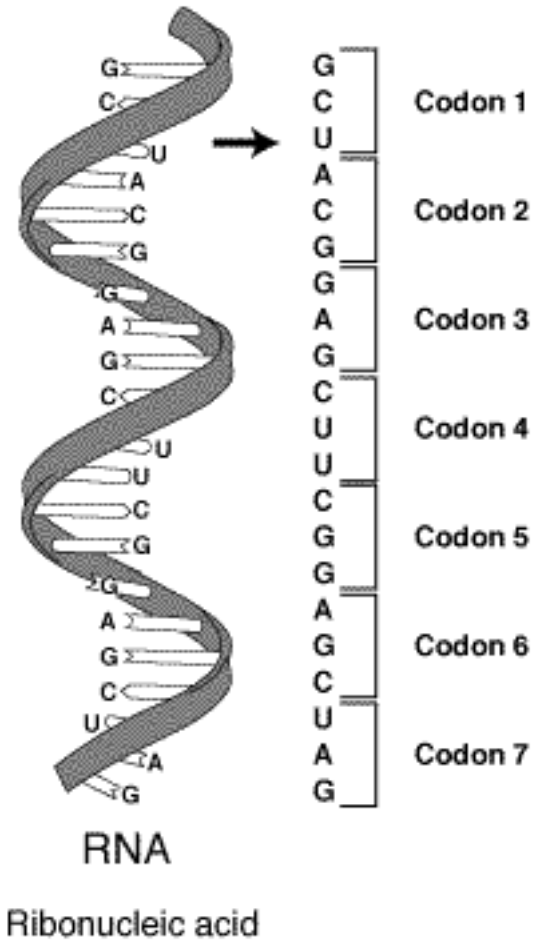
Genetic code

The **genetic code** is a set of rules that maps DNA sequences to proteins in the living cell, and is employed in the process of protein synthesis. Nearly all living things use the same genetic code, called the **standard genetic code**, although a few organisms use minor variations of the standard code.



RNA codons

Genome expression

The genetic information carried by an organism - its genome - is inscribed in one or more DNA molecules. Each functional portion of a DNA molecule is referred to as a gene. Each gene is transcribed into a short template molecule of the related polymer RNA, which is better suited for protein synthesis. This in turn is translated by mediation of a machinery consisting of ribosomes and a set of transfer RNAs and associated enzymes into an amino acid chain (polypeptide), which will then be folded into a protein.

The gene sequence inscribed in DNA, and in RNA, is composed of tri-nucleotide units called **codons**, each coding for a single amino acid. Each nucleotide sub-unit consists of a phosphate, deoxyribose sugar and one of the 4 nitrogenous nucleotide bases grouped into 2 categories, purine and pyrimidine. The purine bases adenine (**A**) and guanine (**G**) are larger and consist of two aromatic rings. The pyrimidine bases cytosine (**C**) and thymine (**T**) are smaller and consist of only one aromatic ring. In RNA, however, thymine (**T**) is substituted by uracil (**U**), and the deoxyribose is substituted by ribose.

Overall, there are $4^3 = 64$ different codon combinations. For example, the RNA sequence UUUAAACCC contains the codons UUU, AAA and CCC, each of which specifies one amino acid. So, this RNA sequence represents a protein sequence, three amino acids long. (DNA is also a sequence of nucleotide bases, but there thymine takes the place of uracil.)

The standard genetic code is shown in the following tables. Table 1 shows what amino acid each of the 64 codons specifies. Table 2 shows what codons specify each of the 20 standard amino acids involved in translation. These are called forward and reverse codon tables, respectively. For example, the codon AAU represents the amino acid asparagine (Asn), and cysteine (Cys) is represented by UGU and by UGC.

RNA codon table

UUU (Phe/F)Phenylalanine UU
UUC (Phe/F)Phenylalanine
UUA (Leu/L)Leucine
UUG (Leu/L)Leucine, *Start*

UCU (Ser/S)Serine UC
UCC (Ser/S)Serine
UCA (Ser/S)Serine
UCG (Ser/S)Serine

UAU (Tyr/Y)Tyrosine UA
UAC (Tyr/Y)Tyrosine
UAA Ochre (*Stop*)
UAG Amber (*Stop*)

UGU (Cys/C)Cysteine UG
UGC (Cys/C)Cysteine
UGA Opal (*Stop*)
UGG (Trp/W)Tryptophan

CUU (Leu/L)Leucine CU

CUC (Leu/L)Leucine
CUA (Leu/L)Leucine
CUG (Leu/L)Leucine, *Start*

CCU (Pro/P)Proline CC
CCC (Pro/P)Proline
CCA (Pro/P)Proline
CCG (Pro/P)Proline

CAU (His/H)Histidine CA
CAC (His/H)Histidine
CAA (Gln/Q)Glutamine
CAG (Gln/Q)Glutamine

CGU (Arg/R)Arginine CG
CGC (Arg/R)Arginine
CGA (Arg/R)Arginine
CGG (Arg/R)Arginine

AUU (Ile/I)Isoleucine, *Start*[2] AU
AUC (Ile/I)Isoleucine
AUA (Ile/I)Isoleucine
AUG (Met/M)Methionine, *Start*[1]

ACU (Thr/T)Threonine AC
ACC (Thr/T)Threonine
ACA (Thr/T)Threonine
ACG (Thr/T)Threonine

AAU (Asn/N)Asparagine AA
AAC (Asn/N)Asparagine
AAA (Lys/K)Lysine
AAG (Lys/K)Lysine

AGU (Ser/S)Serine AG
AGC (Ser/S)Serine
AGA (Arg/R)Arginine
AGG (Arg/R)Arginine

GUU (Val/V)Valine GU
GUC (Val/V)Valine
GUA (Val/V)Valine

GUG (Val/V)Valine, *Start*[2]

GCU (Ala/A)Alanine GC
GCC (Ala/A)Alanine
GCA (Ala/A)Alanine
GCG (Ala/A)Alanine

GAU (Asp/D)Aspartic acid GA
GAC (Asp/D)Aspartic acid
GAA (Glu/E)Glutamic acid
GAG (Glu/E)Glutamic acid

GGU (Gly/G)Glycine GG
GGC (Gly/G)Glycine
GGA (Gly/G)Glycine
GGG (Gly/G)Glycine

[1]The codon AUG both codes for methionine and serves as an initiation site: the first AUG in an mRNA's coding region is where translation into protein begins.
[2]This is a start codon for prokaryotes only

Reverse codon table

Ala - A - GCU, GCC, GCA, GCG
Arg - R - CGU, CGC, CGA, CGG, AGA, AGG
Asn - N - AAU, AAC
Asp - D - GAU, GAC
Cys - C - UGU, UGC
Gln - Q - CAA, CAG
Glu - E - GAA, GAG
His - H - CAU, CAC
Ile - I - AUU, AUC, AUA
Start **---** AUG, CUG, UUG, GUG, AUU

Leu - L **-** UUA, UUG, CUU, CUC, CUA, CUG
Lys - K **-** AAA, AAG
Met - M **- AUG**
Phe - F**-** UUU, UUC
Pro - P CCU, CCC, CCA, CCG
Ser - S - UCU, UCC, UCA, UCG, AGU,AGC
Thr - T - ACU, ACC, ACA, ACG
Trp - W - UGG

Tyr - Y - UAU, UAC
Val - V - GUU, GUC, GUA, GUG
***Stop* ---- UAG, UGA, UA**

Marshall W. Nirenberg and Heinrich J. Matthaei at the National Institutes of Health performed the experiments that first elucidated the correspondence between the codons and the amino acids that they code. Har Gobind Khorana expanded on Nirenberg's work and found the codes for the amino acids that Nirenberg's methods could not find. Khorana and Nirenberg won a share of the 1968 Nobel Prize in Physiology or Medicine for this work.

Technical details

Start/stop codons

In classical genetics, the stop codons were given names: UAG was *amber*, UGA was *opal* (sometimes also called *umber*), and UAA was *ochre*. These names were originally the names of the specific genes in which mutation of each of these stop codons was first detected.

Translation starts with a chain initiation codon (start codon). Unlike stop codons, the codon alone is not sufficient to begin the process; nearby initiation sequences are also required to induce transcription into mRNA and binding by ribosomes. The most notable start codon is AUG, which also codes for methionine. CUG and UUG, and in prokaryotes GUG and AUU, also function as start codons, but occur much less frequently.

Stop codons are also called terminators.

Degeneracy of the genetic code

Many codons are **redundant**, meaning that two or more codons can code for the same amino acid. Degenerate codons may differ in their third positions; e.g., both GAA and GAG code for the amino acid glutamic acid. A codon is said to be **four-fold degenerate** if any nucleotide at its third position specifies the same amino acid; it is said to be **two-fold degenerate** if only two of four possible nucleotides at its third position specify the same amino acid. In two-fold degenerate codons, the equivalent third position nucleotides are always either two purines (A/G) or two pyrimidines (C/T). The degeneracy of the genetic code is what accounts for the existence of silent mutations.

Degeneracy is mandatory in order to produce enough different codons to code for 20 amino acids and a stop and start codon. Because there are four bases, triplet codons are required to produce at least 22 different codes. For example, if there were two bases per codon, then only 16 amino acids could be coded for (4^2=16). Because at least 22 codes are required, then 4^3 gives 64, which is the number of possible codons.

These properties of the genetic code make it more fault-tolerant for point mutations. For example, four-fold degenerate codons can tolerate any point mutation at the third position; two-fold degenerate codons can tolerate one out of the three possible point mutations at the third position. Since transition mutations (purine to purine or pyrimidine to pyrimidine mutations) are more likely than transversion (purine to pyrimidine or vice-versa) mutations, the equivalence of purines or that of pyrimidines at two-fold degenerate sites adds a further fault-tolerance.

A practical consequence of redundancy is that some errors in the genetic code only cause a silent mutation or an error that would not affect the amino acid's hydrophilic/hydrophobic property; e.g., a codon of NUN (where N = any nucleotide) tends to code for hydrophobic amino acids. Even so, it is a single point mutation that causes a modified hemoglobin molecule in sickle-cell disease. The hydrophilic glutamate (Glu) is substituted by the hydrophobic valine (Val), which reduces the solubility of β-globin. This causes hemoglobin to form linear polymers linked by the hydrophobic interaction between the valine groups causing sickle-cell deformation of erythrocytes. Sickle-cell disease is generally not caused by a *de novo* mutation. Rather it is selected for in malarial regions (in a similar way to thalassemia), as heterozygous people have some resistance to the malarial *Plasmodium* parasite (heterozygote advantage).

In general, these properties are widely interpreted to form part of the reason for the origin of the standard genetic code.

These variable codes for amino acids are possible because of modified bases in the first base of the anticodon, and the basepair formed is called a wobble base pair. The modified bases include inosine and the U-G basepair.

Only two amino acids are specified by a single codon; one of these is the amino-acid methionine, specified by the codon AUG, which also specifies the start of transcription; the other is tryptophan, specified by the codon UGG.

Phase or reading frame of a sequence

Note that a "codon" is entirely defined by your starting position. For example, the string GGGAAACCC, if read from the first position, contains the codons GGG, AAA and CCC. If read from the second position, it contains the codons GGA and AAC (partial codons being ignored). If read starting from the third position, GAA and ACC. Every DNA sequence can thus be read in three **reading frames**, each of which will produce a radically different amino acid sequence (in our example, Gly-Lys-Pro, Gly-Asp, and Glu-Thr, respectively). The actual frame a protein sequence is translated in is defined by a **start codon**, usually the first occurrence of AUG in the RNA sequence. Mutations that disrupt the reading frame (i.e. insertions or deletions of one or two nucleotide bases) severely impair the function of a protein and are thus exceedingly rare in *in vivo* protein-coding sequences, since they often lead to death before an organism is viable.

Variations

Numerous variations of the standard genetic code are found in mitochondria, which are energy-producing organelles. Mycoplasma translate the codon UGA as tryptophan. Ciliate protozoa also have some variation in the genetic code: UAG and often UAA code for Glutamine (a variant also found in some green algae), or UGA codes for Cysteine. Another variant is found in some species of the yeast candida, where CUG codes for Serine.

In certain proteins, non-standard amino acids are substituted for standard stop codons, depending upon associated signal sequences in the messenger RNA: UGA can code for selenocysteine and UAG can code for pyrrolysine. There may be other non-standard interpretations that are not yet known.

A detailed description of variations in the genetic code can be found at the NCBI web site.

Origin of the genetic code

Despite the variations that exist, the genetic codes used by all known forms of life on Earth are very similar. Since there are many possible genetic codes that are thought to have similar utility to the one used by Earth life, the theory of evolution suggests that the genetic code was established very early in the history of life.

One can ask the question: is the genetic code completely random, just one set of codon-amino acid correspondences that happened to establish itself and be "frozen in" early in evolution, although *functionally* any other of the near-infinite set of possible transcription tables would have done just as well? Already a cursory look at the table shows patterns that suggest that this is not the case.

There are three themes running through the many theories that seek to explain the evolution of the genetic code (and hence the origin of these patterns). One is illustrated by recent aptamer experiments which show that some amino acids have a selective chemical affinity for the base triplets that code for them. This suggests that the current, complex transcription mechanism involving tRNA and associated enzymes may be a later development, and that originally, protein sequences were directly templated on base sequences. Another is that the standard genetic code that we see today grew from a simpler, earlier code through a process of "biosynthetic expansion". Here the idea is that primordial life 'invented' new amino acids (e.g. as by-products of metabolism) and later back-incorporated some of these into the machinery of genetic coding. Although much circumstantial evidence has been found to indicate that originally the number of different amino acids used may have been considerably smaller than today, precise and detailed hypotheses about exactly which amino acids entered the code in exactly what order has proved far more controversial. A third is that natural selection organized the codon assignments of the genetic code to minimize the effects of genetic errors (mutations).

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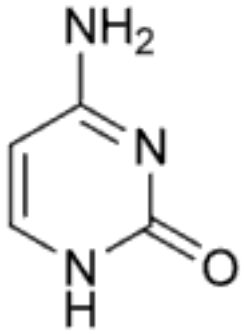
Cytosine



Chemical name: 4-Aminopyrimidin-2(1H)-one
Chemical formula: $C_4H_5N_3O$

Molecular mass: 111.10 g/mol
Melting point: 320 - 325°C (decomp)
CAS number: 71-30-7
SMILES: NC1=NC(NC=C1)=O

Cytosine is one of the 5 main nucleobases used in storing and transporting genetic information within a cell in the nucleic acids DNA and RNA. It is a pyrimidine derivative, with a heterocyclic aromatic ring and two substituents attached (an amine group at position 4 and a keto group at position 2). The nucleoside of cytosine is cytidine. In Watson-Crick base pairing, it forms three hydrogen bonds with guanine.

Cytosine was first discovered in 1894 when it was isolated from calf thymus tissues. A structure was proposed in 1903, and was synthesized (and thus confirmed) in the laboratory in the same year.

Cytosine recently found use in quantum computation. The first time any quantum mechanical properties were harnessed to process information took place on August 1st in 1998 when researchers at Oxford implemented David Deutsch's algorithm on a two qubit NMRQC (Nuclear Magnetic Resonance Quantum Computer) based on the cytosine molecule.

Cytosine can be found as part of DNA, RNA, or as a part of a nucleotide. As cytosine triphosphate (CTP), it can act as a co-factor to enzymes, and can transfer a phosphate to convert adenosine diphosphate (ADP) to adenosine triphosphate (ATP).

In DNA and RNA, cytosine is paired with guanine. However, it is inherently unstable, and can change into uracil (spontaneous deamination). This can lead to a point mutation if not repaired by the DNA repair enzymes.

Cytosine can also be methylated into 5-methylcytosine by an enzyme called DNA methyltransferase.

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DNA

Deoxyribonucleic acid (**DNA**) is a nucleic acid — usually in the form of a double helix — that contains the genetic instructions specifying the biological development of all cellular forms of life, and most viruses. DNA is a long polymer of nucleotides and encodes the sequence of the amino acid residues in proteins using the genetic code, a triplet code of nucleotides.

In complex eukaryotic cells such as those from plants, animals, fungi and protists, most of the DNA is located in the cell nucleus. By contrast, in simpler cells called prokaryotes, including the eubacteria and archaea, DNA is not separated from the cytoplasm by a nuclear envelope. The cellular organelles known as chloroplasts and mitochondria also carry DNA.

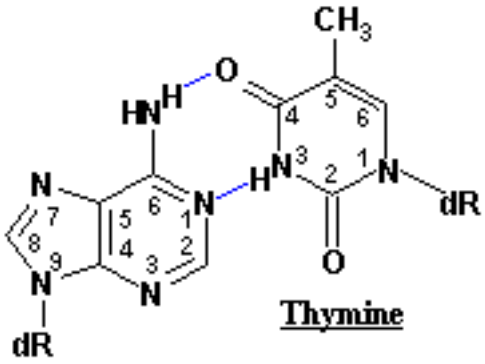
DNA is often referred to as the molecule of heredity as it is responsible for the genetic propagation of most inherited traits. In humans, these traits can range from hair colour to disease susceptibility. During cell division, DNA is replicated and can be transmitted to offspring during reproduction. Lineage studies can be done based on the facts that the mitochondrial DNA only comes from the mother, and the male Y chromosome only comes from the father.

Every person's DNA, their genome, is inherited from both parents. The mother's mitochondrial DNA together with twenty-three chromosomes from each parent combine to form the genome of a zygote, the fertilized egg. As a result, with certain exceptions such as red blood cells, most human cells contain 23 pairs of chromosomes, together with mitochondrial DNA inherited from the mother.

Overview

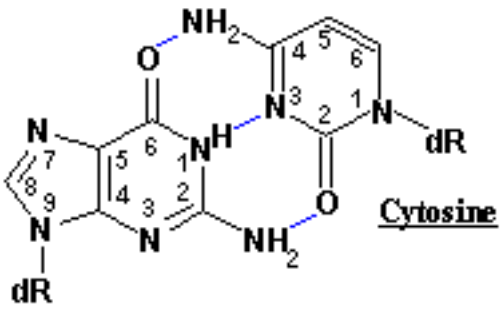
Contrary to a common misconception, the DNA is not a single molecule, but rather a pair of molecules joined by hydrogen bonds: it is organized as two complementary strands, head-to-toe, with the hydrogen bonds between them. Each strand of DNA is a chain of chemical "building blocks", called nucleotides, of which there are four types: adenine (abbreviated A), cytosine (C), guanine (G) and thymine (T). In some organisms, most notably the PBS1 phage, Uracil (U) replaces T in the organism's DNA. These allowable base components of nucleic acids can be polymerized in any order giving the molecules a high degree of uniqueness.

CORRECT PAIRINGS



Thymine

Adenine



Cytosine

Guanine

Between the two strands, each base can only "pair up" with one single predetermined other base: A+T, T +A, C+G and G+C are the only possible combinations; that is, an "A" on one strand of double-stranded DNA will "mate" properly only with a "T" on the other, complementary strand; therefore, naming the bases on the conventionally chosen side of the strand is enough to describe the entire double-strand sequence. Two nucleotides paired together are called a base pair. On rare occasions, wrong pairing can happen, when thymine goes into its enol form or cytosine goes into its imino form. The double-stranded structure of DNA provides a simple mechanism for DNA replication: the DNA double strand is first "unzipped" down the middle, and the "other half" of each new single strand is recreated by exposing each half to a mixture of the four bases. An enzyme makes a new strand by finding the correct base in the mixture and pairing it with the original strand. In this way, the base on the old strand dictates which base will be on the new strand, and the cell ends up with an extra copy of its DNA.

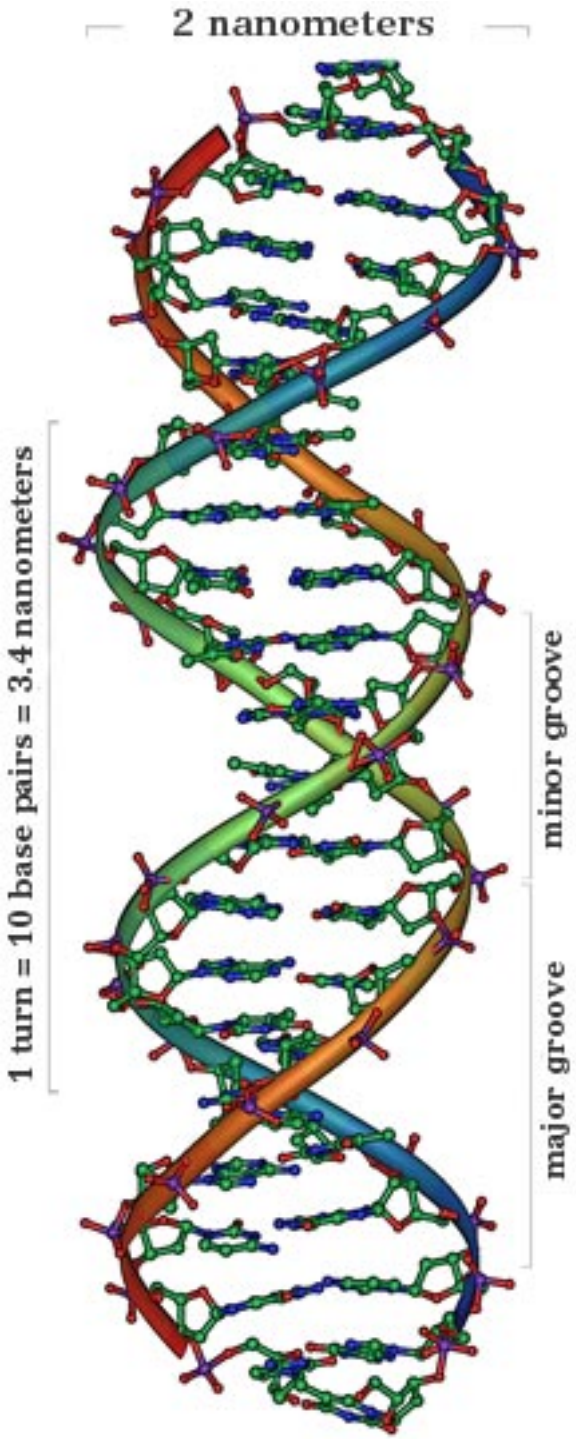
DNA contains the genetic information that is inherited by the offspring of an organism; this information is determined by the sequence of base pairs along its length. A strand of DNA contains genes, areas that regulate genes, and areas that either have no function, or a function yet unknown. Genes can be loosely viewed as the organism's "cookbook" or "blueprint".

Other interesting points:
* DNA is an acid because of the phosphate groups between each deoxyribose. This the primary reason why DNA has a negative charge.
* The "polarity" of each pair is important: A+T is not the same as T+A, just as C+G is not the same as G

+C (note that "polarity" as such is never used in this context -- it's just a suggestive way to get the idea across)
* Mutations are chemical imperfections in this process, where a base is accidentally skipped, inserted, or incorrectly copied, or the chain is trimmed, or added to; many basic mutations can be described as combinations of these accidental "operations". Mutations can also occur through chemical damage (through mutagens), light (UV damage), or through other more complicated gene swapping events.
* DNA molecules that act as enzymes are known in laboratories, but none have been known to be found in life so far.
* In addition to the traditionally viewed duplex form of DNA, DNA can also acquire triplex and quadruplex forms. Here instead of the Watson Crick base pairing, Hoogsten base pairing comes into picture.
* DNA differs from ribonucleic acid (RNA) by having a sugar 2-deoxyribose instead of ribose in its backbone. This is the basic chemical distinction between RNA and DNA. In addition, in RNA, the nucleotides T are replaced by U.

Molecular Structure

Although sometimes called "the molecule of heredity", DNA macromolecules as people typically think of them are not single molecules. Rather, they are pairs of molecules, which entwine like vines to form a double helix.



The general structure of a section of DNA

Each vine-like molecule is a strand of DNA: a chemically linked chain of nucleotides, each of which consists of a sugar (deoxyribose), a phosphate and one of five kinds of nucleobases ("bases"). Because DNA strands are composed of these nucleotide subunits, they are polymers.

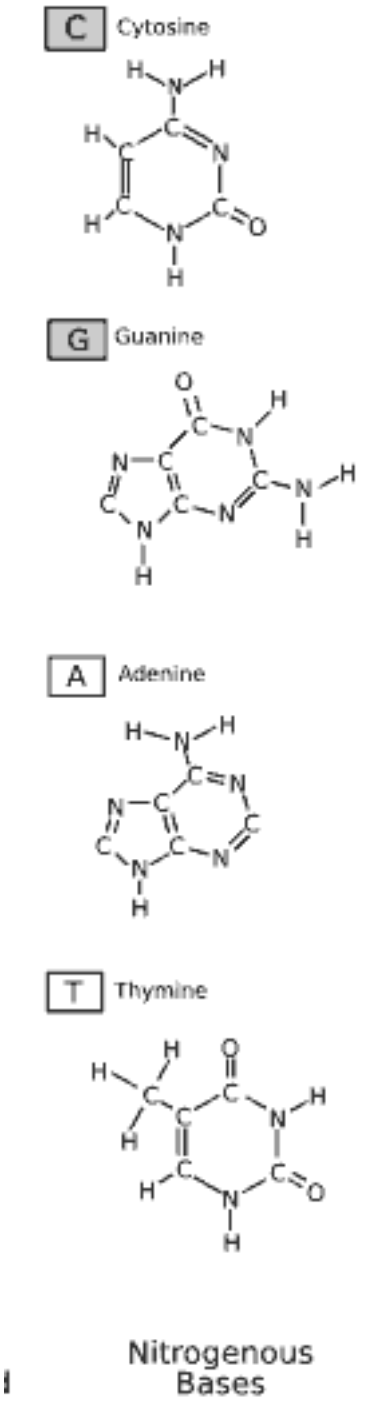
The diversity of the bases means that there are five kinds of nucleotides, which are commonly referred to by the identity of their bases. These are adenine (A), thymine (T), uracil (U), cytosine (C), and guanine (G). U is rarely found in DNA except as a result of chemical degradation of C, but in some viruses, notably PBS1 phage DNA, U completely replaces the usual T in its DNA. Similarly, RNA

usually contains U in place of T, but in certain RNAs such as transfer RNA, T is always found in some positions. Thus, the only true difference between DNA and RNA is the sugar, 2-deoxyribose in DNA and ribose in RNA.

In a DNA double helix, two polynucleotide strands can associate through the hydrophobic effect and pi stacking. Specificity of which strands stay associated is determined by complementary pairing. Each base forms hydrogen bonds readily to only one other - A to T and C to G - so that the identity of the base on one strand dictates the strength of the association; the more complementary bases exist, the stronger and longer-lasting the association.

The cell's machinery is capable of melting or disassociating a DNA double helix, and using each DNA strand as a template for synthesizing a new strand which is nearly identical to the previous strand. Errors that occur in the synthesis are known as mutations. The process known as PCR (polymerase chain reaction) mimics this process in vitro in a nonliving system.

Because pairing causes the nucleotide bases to face the helical axis, the sugar and phosphate groups of the nucleotides run along the outside; the two chains they form are sometimes called the "backbones" of the helix. In fact, it is chemical bonds between the phosphates and the sugars that link one nucleotide to the next in the DNA strand.



Strand Direction

The asymmetric shape and linkage of nucleotides means that a DNA strand always has a discernible orientation or directionality. Because of this directionality, close inspection of a double helix reveals that nucleotides are heading one way along one strand (the "*ascending strand*"), and the other way along the other strand (the "*descending strand*"). This arrangement of the strands is called antiparallel.

Chemical nomenclature (5' and 3')

For reasons of chemical nomenclature, people who work with DNA refer to the asymmetric ends of

("five prime" and "three prime"). Within a cell, the enzymes that perform replication and transcription read DNA in the "**3' to 5' direction**", while the enzymes that perform translation read in the opposite directions (on RNA). However, because chemically produced DNA is synthesized and manipulated in the opposite or in non-directional manners, the orientation should not be assumed. In a vertically oriented double helix, the 3' strand is said to be ascending while the 5' strand is said to be descending.

Sense and antisense

As a result of their antiparallel arrangement and the sequence-reading preferences of enzymes, even if both strands carried identical instead of complementary sequences, cells could properly translate only one of them. The other strand a cell can only read backwards. Molecular biologists call a sequence "**sense**" if it is translated or translatable, and they call its complement "**antisense**". It follows then, somewhat paradoxically, that the template for transcription is the antisense strand. The resulting transcript is an RNA replica of the sense strand and is itself sense.

Distinction between sense and antisense strands

A small proportion of genes in prokaryotes, and more in plasmids and viruses, blur the distinction made above between sense and antisense strands. Certain sequences of their genomes do double duty, encoding one protein when read 5' to 3' along one strand, and a second protein when read in the opposite direction (still 5' to 3') along the other strand. As a result, the genomes of these viruses are unusually compact for the number of genes they contain, which biologists view as an adaptation. This merely confirms that there is no biological distinction between the two strands of the double helix. Typically each strand of a DNA double helix will act as sense and antisense in different regions.

As viewed by topologists

Topologists like to note that the juxtaposition of the 3' end of one DNA strand beside the 5' end of the other at both ends of a double-helical segment makes the arrangement a "crab canon".

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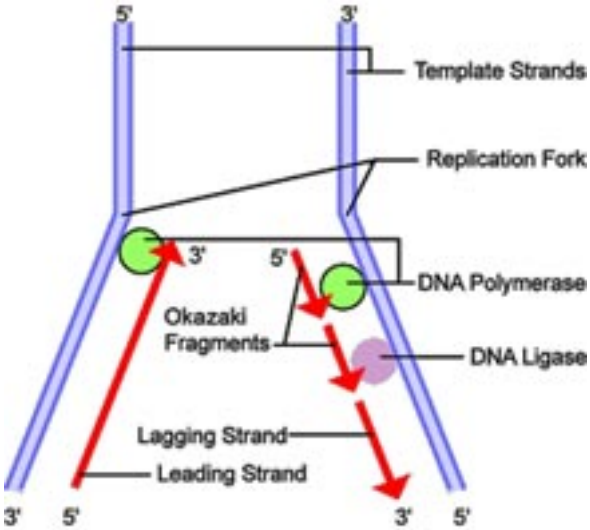
DNA Replication

DNA replication or **DNA synthesis** is the process of copying a double-stranded DNA strand in a cell, prior to cell division. In eukaryotes, this is during the S phase of the cell cycle, preceding mitosis and meiosis. The two resulting double strands are identical (if the replication went well), and each of them consists of one original and one newly synthesized strand. This is called *semiconservative replication*. The process of replication consists of three steps, *initiation*, *replication* and *termination*. *Artificial* DNA replication is carried out through polymerase chain reaction.



DNA replication. In the first step, the double helix shown above in blue is unwound by a helicase. Next, a molecule of DNA polymerase shown in green binds to one strand of the DNA. It moves along the strand, using it as a template for assembling a leading strand shown above in red of nucleotides and reforming a double helix. A second DNA polymerase molecule (also green) is used to bind to the other template strand as the double helix opens. This molecule must synthesize discontinuous segments of polynucleotides (called Okazaki fragments). Another enzyme, DNA ligase shown in violet, then stitches these together into the lagging strand.

Steps

Initiation

In the initiation step, several key factors are recruited to an origin of replication. This origin of replication is unwound, and the partially unwound strands form a "replication bubble", with one replication fork on either end. Each group of enzymes at the replication fork moves away from the origin, unwinding and replicating the original DNA strands as they proceed. Primers mark the individual sequences and their start and end points, to be replicated.

The factors involved are collectively called the pre-replication complex. It consists of the following:
* A **topoisomerase**, which introduces negative supercoils into the DNA in order to minimize tortional strain induced by the unwinding of the DNA by helicase. This prevents the DNA from knotting up.
* A **helicase**, which unwinds and splits the DNA ahead of the fork. Thereafter, single-strand binding proteins (SSB) swiftly bind to the separated DNA, thus preventing the strands from reuniting.
* A **primase**, which generates an RNA primer to be used in DNA replication.
* A **DNA holoenzyme**, which in reality is a complex of enzymes that together perform the actual replication.

Elongation

After the helicase unwinds the DNA, RNA primase is bound to the starting DNA site.

At the beginning of replication, an enzyme called DNA polymerase binds to the RNA primase, which indicates the starting point for the replication. DNA polymerase can only synthesize new DNA from the 5’ to 3’ (of the new DNA). Because of this, the DNA polymerase can only travel on one side of the original strand without any interruption. This original strand, which goes from 3’ to 5’, is called the leading strand. The complement of the leading strand, from 5’ to 3’, is the lagging strand.

Each time the helicase unwinds additional DNA, new DNA polymerase needs to be added to ensure there remains enough. As a result, the DNA of the lagging strand is replicated in a piecemeal fashion. Another enzyme, DNA ligase, is used to connect the so-called Okazaki fragments.

In prokaryotes, coupled leading strand and lagging strand synthesis is achieved by the action of the DNA polymerase III holoenzyme.

In eukaryotes, there are a number of DNA polymerases with exonuclease and proof-reading abilities to carry out replication.

Termination

Termination occurs when DNA replication forks meet one another or run to the end of a linear DNA molecule. Also, termination may occur when a replication fork is deliberately stopped by a special protein, called a replication terminator protein, that binds to specific sites on a DNA molecule.

When the polymerase reaches the end of a length of DNA, there is a potential problem due to the antiparallel structure of DNA. Because an RNA primer must be regularly laid down on the lagging strand, the last section of the lagging-strand DNA cannot be replicated because there is no DNA template for the primer to be synthesized on. To solve this problem, the ends of most chromosomes consist of noncoding DNA that contains repeat sequences. The end of a linear chromosome is called the telomere.

The repeat DNA in the telomere is not essential for survival, because it does not contain genes, so cells can endure the shortening of the chromosome at the telomere. Many cells use an enzyme called telomerase that adds the repeat units to the end of the chromosome so the ends do not become too short after multiple rounds of DNA replication. Many simple, single-celled organisms overcome the whole problem by having circular chromosomes.

Before the DNA replication is finally complete, enzymes are used to proofread the sequences to make sure the nucleotides are paired up correctly in a process called DNA repair. If mistake or damage occurs, enzymes such as a nuclease will remove the incorrect DNA. DNA polymerase will then fill in the gap.

Equation

A chemical equation can be written that represents the process:
$(DNA)_n + dNTP <--> (DNA)_{n+1} + PP_i$

Organization of multiple replication sites

The human genome contains 6 billion nucleotide pairs (arrayed in 46 linear chromosomes) that are copied at about 50 base pairs per second by each replication fork. Yet, in a typical cell the entire replication process takes only about 8 hours. This is because there are many replication origin sites on a eukaryotic chromosome. Therefore, replication can begin at some origins earlier than at others. As replication nears completion, "bubbles" of newly replicated DNA meet and fuse, forming two new molecules.

There must be some form of regulation and organisation of these multiple replication sites to prevent conflict. To date, two replication control mechanisms have been identified: one positive and one negative. For DNA to be replicated, each replication origin site must be bound by a set of proteins called the *origin recognition complex*. These remain attached to the DNA throughout the replication process. Specific accessory proteins, called licensing factors, must also be present for initiation of replication. Destruction of these proteins after initiation of replication prevents further replication cycles from occurring. This is because licensing factors are only produced when the nuclear membrane of a cell breaks down the during mitosis.

Measurement with conditional mutants

Measurement of DNA replication can be done using conditional mutants. Mutants that grow at 30°C but not at 42°C are collected. At this temperature these mutants should incorporate nucleotides into DNA. Protein synthesis should not be affected.

There are two outcomes for a graph of incorporation of labelled nucleotides into DNA vs time:

1. Quick stop indicates the mutation is in a DNA synthesis factor.
2. Slow stop indicates the mutation is possibly in an initiation factor such as dnaA.

The assay can measure the incorporation of deoxyribonucleotides into acid or ethanol insoluble forms. Gel filtration chromatography or ion exchange chromatography is used to get all protein fractions and is followed by assay for DNA polymerase.

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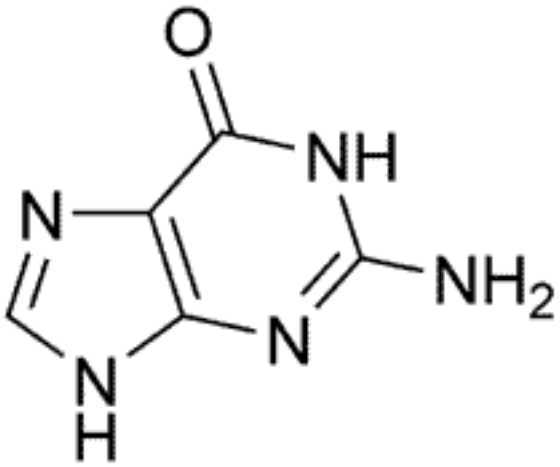
Guanine



Systematic name: 2-amino-1H-purin-6(9H)-one
Other names: 2-amino-6-oxo-purine,
2-aminohypoxanthine, Guanine
Molecular formula: $C_5H_5N_5O$

SMILES NC: (NC1=O)=NC2=C1N=CN2
Molar mass: 151.13 g/mol
Appearance: White amorphous solid.

Guanine is one of the five main nucleobases found in nucleic acids (*e.g.*, DNA and RNA). Guanine is a purine derivative, and in Watson-Crick base pairing forms three hydrogen bonds with cytosine. Guanine "stacks" vertically with the other nucleobases via aromatic interactions. Guanine is a tautomer. The guanine nucleoside is called guanosine.

Guanine is also the name of a white amorphous substance found in the scales of certain fishes, the guano of sea-birds, and the liver and pancreas of mammals. In fact, the name of the nucleobase is derived from the term 'guano', because it was first isolated from bird manure.

In cosmetic industry, crystallic guanine is used as an additive to various products (eg. shampoos), where it provides the pearly iridescent effect. It provides shimmering lustre to eye shadow and nail polish.It may irritate eyes. Its alternatives are synthetic pearl, and aluminium and bronze particles.

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Mitochondrial DNA

Origin of mitochondrial DNA | Genetic illness | Mitochondrial inheritance

Mitochondrial DNA (**mtDNA**, or less popularly, **mDNA**) is DNA that is located in mitochondria. This is in contrast to most DNA of eukaryotic organisms, which is found in the nucleus. Mitochondria are the parts of the cell that generate energy in the form of adenosine triphosphate (ATP).

Unlike most of the cell, the function of which is defined by nuclear DNA, mitochondria have their own DNA and are assumed to have evolved separately. Human mitochondrial DNA consists of 5-10 rings of DNA and appears to carry 16,568 base pairs with 37 genes (13 proteins, 22 tRNAs and two rRNAs) which are concerned with the production of proteins involved in cellular respiration. However many proteins found in the mitochondria are encoded by nuclear DNA: some, if not most, are thought to have been originally part of the mitochondrial DNA but have since been transferred to the nucleus during evolution.

mtDNA is typically passed on only from the mother during sexual reproduction (mitochondrial genetics), meaning that the mitochondria are clones. This means that there is little change in the mtDNA from generation to generation, unlike nuclear DNA which changes by 50% each generation. Since the mutation rate is easily measured, mtDNA is a powerful tool for tracking matrilineage, and has been used in this role for tracking many species back hundreds of generations.

Origin of mitochondrial DNA

The existence of mitochondrial DNA also supports the endosymbiotic theory, which suggests that eukaryotic cells first appeared when a prokaryotic cell was absorbed into another cell without being digested. These two cells are thought to have then entered into a symbiotic relationship, forming the first organelle. The existence of separate mitochondrial DNA suggests that, at one point, mitochondria were separate entities from their current host cells.

Genetic illness

Mutations of mitochondrial DNA can lead to a number of illnesses including exercise intolerance and Kearns-Sayre syndrome (KSS), which causes a person to lose full function of their heart, eye, and muscle movements.

Mitochondrial inheritance

Mitochondria in mammalian sperm are usually destroyed by the egg cell after fertilization. In 1999 it was reported that paternal sperm mitochondria (containing mtDNA) are marked with ubiquitin to select

them for later destruction inside the embryo. Some *in vitro* fertilization techniques, particularly injecting a sperm into an oocyte, may interfere with this. Occasionally this process goes wrong, for example in inter-species hybrids. It has also been reported that mitochondria can occasionally be inherited from the father, e.g. in bananas. However, it has also been proven that about 1-2% of a person's mitochondrias can be inherited from the father.

The fact that mitochondrial DNA is maternally inherited enables researchers to trace uterine lineage far back in time. (Y chromosomal DNA, paternally inherited, is used in an analogous way to trace the agnate lineage.) This is accomplished in humans by sequencing one or more of the hypervariable control regions (HVR1 or HVR2) of the mitochondrial DNA. HVR1 consists of about 440 base pairs. These 440 base pairs are then compared to the control regions of other individuals (either specific people or subjects in a database) to determine maternal lineage. Most often, the comparison is made to the revised. Vilà et al have published studies tracing the matrilineal descent of domestic dogs to 4 individuals. The concept of the Mitochondrial Eve is based on the same type of analysis, attempting to discover the origin of humanity by tracking the lineage back in time.

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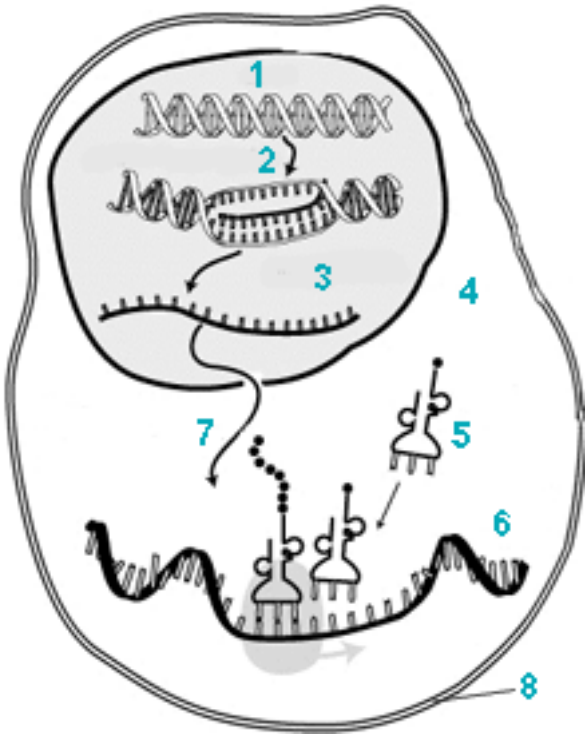
Messenger RNA

Messenger RNA (**mRNA**) is RNA that encodes and carries information from DNA during transcription to sites of protein synthesis to undergo translation in order to yield a gene product.

mRNA "life cycle"

The brief life of an mRNA molecule begins with transcription and ultimately ends in degradation. During its life, an mRNA molecule may also be processed, edited, and transported prior to translation. Eukaryotic mRNA molecules often require extensive processing and transport, while prokaryotic molecules do not.

The "life cycle" of an **mRNA** in a eukaryotic cell. RNA is transcribed in the nucleus; once completely processed, it is transported to the cytoplasm and translated by the ribosome. At the end of its life, the mRNA is degraded:



1. DNA
2. mRNA Transcription
3. Mature mRNA
4. Nucleus
5. tRNA
6. mRNA
7. Transport to cytoplasm for protein synthesis (translation)
8. Cell membrane

Transcription

During transcription, RNA polymerase makes a copy of a gene from the DNA to mRNA as needed. This process is similar in eukaryotes and prokaryotes. One notable difference, however, is that eukaryotic RNA polymerase associates with mRNA processing enzymes during transcription so that processing can proceed quickly after the start of transcription. The short-lived, unprocessed or partially processed, product is termed *pre-mRNA*; once completely processed, it is termed *mature mRNA*.

Eukaryotic pre-mRNA processing

Processing of mRNA differs greatly between eukaryotes and prokaryotes. Prokaryotic mRNA is essentially mature upon transcription and requires no processing, except in rare cases. Eukaryotic pre-mRNA, however, requires extensive processing.

Splicing

Splicing is the process by which pre-mRNA is modified to remove certain stretches of non-coding sequences called introns; the stretches that remain include protein-coding sequences and are called exons. Sometimes pre-mRNA messages may be spliced in several different ways, allowing a single gene to encode multiple proteins. This process is called alternative splicing. Splicing is usually performed by an RNA-protein complex called the spliceosome, but some RNA molecules are also capable of catalyzing their own splicing.

5' cap addition

The 5' cap is modified guanine nucleotide is added to the "front" (5' end) of the pre-mRNA. This modification is critical for recognition and proper attachment of mRNA to the ribosome. It may also be important for other essential processes, such as splicing and transport.

Polyadenylation

Polyadenylation is the covalent linkage of a polyadenylyl moiety to a messenger RNA molecule. In eukaryotic organisms, polyadenylation is the mechanism by which most messenger RNA (mRNA) molecules are terminated at their 3' ends. The poly(A) tail aids in mRNA stability by protecting it from exonucleases. Polyadenylation is also important for transcription termination, export of the mRNA from the nucleus, and translation. Some prokaryotic mRNAs also are polyadenylated, although the poly(A) tail's function is different from that in eukaryotes.

Polyadenylation occurs during and immediately after transcription of DNA into RNA. After transcription has been terminated, the mRNA chain is cleaved through the action of an endonuclease complex associated with RNA polymerase. The cleavage site is characterized by the presence of the base sequence AAUAAA near the cleavage site. After the mRNA has been cleaved, 80 to 250 adenosine

residues are added to the free 3' end at the cleavage site. This reaction is catalyzed by polyadenylate polymerase.

Editing

In some instances, an mRNA will be edited, changing the nucleotide composition of that mRNA. An example in humans is the apolipoprotein B mRNA, which is edited in some tissues, but not others. The editing creates an early stop codon, which upon translation, produces a shorter protein.

Transport

Another difference between eukaryotes and prokaryotes is mRNA transport. Because eukaryotic transcription and translation is compartmentally separated, eukaryotic mRNAs must be exported from the nucleus to the cytoplasm. Mature mRNAs are recognized by their processed modifications and then exported through the nuclear pore.

Translation

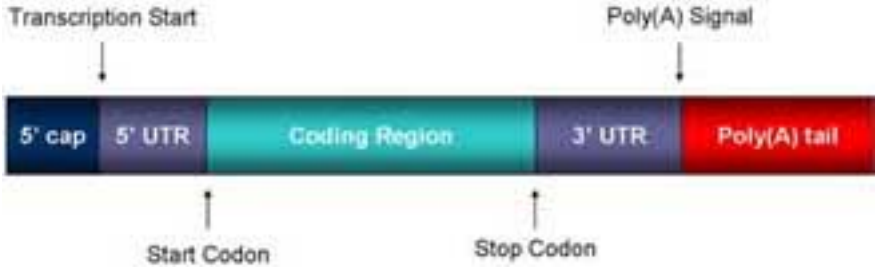
Because prokaryotic mRNA does not need to be processed or transported, translation by the ribosome can begin immediately after the start of transcription. Therefore, it can be said that prokaryotic translation is *coupled* to transcription and occurs *co-transcriptionally*.

Eukaryotic mRNA that has been processed and transported to the cytoplasm (i.e. mature mRNA) can then be translated by the ribosome. Translation may occur at ribosomes free-floating in the cytoplasm, or directed to the endoplasmic reticulum by the signal recognition particle. Therefore, unlike prokaryotes, eukaryotic translation is not directly coupled to transcription.

Degradation

After a certain amount of time the message degrades into its component nucleotides, usually with the assistance of RNases. Due to mRNA processing, eukaryotic mRNAs are generally more stable than prokaryotic mRNAs.

mRNA Structure



The structure of a mature eukaryotic mRNA. A fully processed mRNA includes a 5' cap, 5' UTR, coding

region, 3' UTR, and poly(A) tail

5' cap

A 5' cap, also termed an RNA cap, an RNA 7-methylguanosine cap or an RNA m^7G cap, is a modified guanine nucleotide that has been added to the "front" or 5' end of the messenger RNA shortly after the start of transcription. The 5' cap consists of a terminal 7-methylguanosine residue which is linked through a 5'-5'-triphosphate bond to the first transcribed nucleotide. Its presence is critical for recognition by the ribosome and protection from RNases.

Cap addition is coupled to transcription, and occurs co-transcriptionally, such that each influences the other. Shortly after the start of transcription, the 5' end of the mRNA being synthesized is bound by a cap-synthesizing complex associated with RNA polymerase. This enzymatic complex catalyzes the chemical reactions that are required for mRNA capping. Synthesis proceeds as a multi-step biochemical reaction.

First, the triphosphate at the 5' end of the newly synthesized RNA is cleaved. The enzyme phosphohydrolase cleaves the gamma phosphodiester bonds while leaving the α and beta phosphates. Second, the enzyme guanylyltransferase transfers a guanine and its alpha phosphate onto the beta phosphate of the 5' end of the mRNA producing a 5'-5'-triphosphate linkage. Third, the nitrogen-7 (N-7) position of the newly added guanine is methylated (guaninemethylation) by the enzyme guanine-7-methyltransferase. Finally, 2'-O-methyltransferase methylates the 2' position of the ribose sugar. This methyl group provides extra stability to the RNA due to the protection from phosphoester cleavage by nucleophilic attack of the neighbor hydrogen. After the 5' end has been capped, it is released from the cap-synthesizing complex and is subsequently bound by a cap-binding complex associated with RNA polymerase.

Coding regions

Coding regions are composed of codons, which are decoded and translated into protein by the ribosome. Coding regions begin with the start codon and end with the one of three possible stop codons. In addition to protein-coding, portions of coding regions may also serve as regulatory sequences as exonic splicing enhancers or exonic splicing silencers.

Untranslated regions

Untranslated regions (UTRs) are sections of the RNA before the start codon and after the stop codon that are not translated, termed the five prime untranslated region (5' UTR) and three prime untranslated region (3' UTR), respectively. These regions are transcribed as part of the same transcript as the coding region. Several roles in gene expression have been attributed to the untranslated regions, including mRNA stability, mRNA localization, and translational efficiency. The ability of a UTR to perform these functions depends on the sequence of the UTR and can differ between mRNAs.

Stability of mRNAs may be mediated by the 5' UTR and 3' UTR due to varying affinity for certain RNA degrading enzymes called ribonucleases, which can promote or inhibit the relative stability of the RNA molecule. The greater the stability of an mRNA, the more protein that may be produced from that transcript.

Cytoplasmic localization of mRNA is thought to be a function of the 3' UTR. Proteins that are needed in a particular region of the cell can actually be translated there; in such a case, the 3' UTR may contain sequences that allow the transcript to be localized to this region for translation.

Translational efficiency, and even inhibition of translation altogether, can be mediated by UTRs. Proteins that bind to either the 3' or 5' UTR may affect translation by interfering with the ribosome's ability to bind to the mRNA.

Some of the elements contained in untranslated regions form a characteristic secondary structure when transcribed into RNA. These structural mRNA elements are involved in regulating the mRNA. Some, such as the SECIS element, are targets for proteins to bind. One class of mRNA element, the riboswitches, directly bind small molecules, changing their fold to modify levels of transcription or translation. In these cases, the mRNA regulates itself.

3' poly(A) tail

The 3' poly(A) tail is a long sequence (often several hundred) of adenine nucleotides added to the "tail" or 3' end of the pre-mRNA through the action of an enzyme, polyadenylate polymerase. The poly(A) tail is added on to the transcripts that contain a specific sequence, the AAUAAA signal. The importance of the AAUAAA signal is demonstrated by a mutation in the human alpha 2-globin gene which mutates the original sequence AATAAA into AATAAG, which can lead to hemoglobin deficiencies.

Anti-sense mRNA

During transcription, double stranded DNA produces mRNA from the *sense* strand; the other, complementary, strand of DNA is termed *anti-sense*. Anti-sense mRNA is an RNA complementary in sequence to one or more mRNAs. In some organisms, the presence of an anti-sense mRNA can inhibit gene expression by base-pairing with the specific mRNAs. In biochemical research, this effect has been used to study gene function, by simply shutting down the studied gene by adding its anti-sense mRNA transcript. Such studies have been done on the worm Caenorhabditis elegans and the bacteria Escherichia coli. This plays a part in RNA interference.

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Non-coding RNA

Types (families) of non-coding RNAs | Transfer RNA | Ribosomal RNA | Untranslated regions of mRNAs | Small nuclear RNA | Small nucleolar RNA | microRNA | gRNAs | efference RNA | Signal recognition particle RNA | pRNA | tmRNA

A **non-coding RNA** (**ncRNA**) is any RNA molecule that functions without being translated into a protein. A commonly used synonym is **small RNA** (**sRNA**). Less-frequently used synonyms are non-messenger RNA (nmRNA), small non-messenger RNA (snmRNA), or functional RNA (fRNA). The DNA sequence from which a non-coding RNA is transcribed as the end product is often called an **RNA** gene or non-coding RNA gene.

The most prominent examples of non-coding RNAs are **transfer RNA** (**tRNA**) and **ribosomal RNA** (**rRNA**), both of which are involved in the process of translation and gene expression. However, since the late 1990s, many new non-coding RNAs have been found, and thus non-coding RNAs may play a much more significant role than previously thought.

Human mitochondrial genome contains 24 RNA genes: 2 for 23S and 16S rRNR subunits of mitochondrial ribosomes. Nuclear genome contains c.a. 3000 RNA genes (less than 10% of total gene number). To identify RNA genes in sequenced DNA is very difficult. In addition to the RNA genes there are many related pseudogene/gene fragments.

Types (families) of non-coding RNAs

Transfer RNA

Transfer RNA (tRNA) is RNA that transfers a specific amino acid to a growing polypeptide chain at the ribosomal site of protein biosynthesis during translation.

Ribosomal RNA

Ribosomal RNA (rRNA) is the primary constituent of ribosomes. Ribosomes are the protein-manufacturing organelles of cells and exist in the cytoplasm. rRNA is transcribed from DNA, like all RNA. Ribosomal proteins are transported into the nucleus and assembled together with rRNA before being transported through the nuclear membrane. This type of RNA makes up the vast majority of RNA found in a typical cell. While proteins are also present in the ribosomes, solely rRNA is able to form peptides. Therefore ribosome often is referred to as ribozyme.

There are 2 mitochondrial (23S and 16S) rRNA moleculesand 4 types of cytoplasmic rRNA (28S, 5.8S, 5S (large ribosome subunit) and 18S (small subunit)). 28S, 5.8S and 18S rRNAs are encoded by a *single*

transcription unit organized into 5 clusters (each has 30-40 repeats) on the 13,14,15, 21 and 22 chromosomes. 5S occurs in tandem arrays (~200-300 true 5S genes and many dispersed pseudogenes), the largest one on the chromosome 1q41-42.

Cytoplasmic rRNA genes are highly repetitive because of huge demand of ribosomes for protein synthesis ('gene dosage') in the cell.

Untranslated regions of mRNAs

Many non-coding RNAs are structural elements in the untranslated regions (see 5'UTR, 3'UTR) of mRNAs (i.e. cis-regulatory RNAs), for example riboswitches and the SECIS element .

Small nuclear RNA

Small nuclear RNA (snRNA) is a class of small RNA molecules that are found within the nucleus of eukaryotic cells. They are transcribed by RNA polymerase II or RNA polymerase III. They are involved in a variety of important processes such as RNA splicing (removal of introns from hnRNA), regulation of transcription factors (7SK RNA) or RNA polymerase II (B2 RNA), and maintaining the telomeres. They are always associated with specific proteins, and the complexes are referred to as small nuclear ribonucleoproteins (snRNP) or sometimes as snurps.

Small nucleolar RNA

Small nucleolar RNAs (snoRNAs) are a class of small RNA molecules that guide chemical modifications (methylation or pseudouridylation) of ribosomal RNAs (rRNAs) and other RNA genes. These modifications are thought to subtly enhance the function of the mature RNA. They are frequently encoded in the introns of ribosomal proteins and are synthesized by RNA polymerase II, but can also be transcribed as independant (sometimem polycistronic) transcriptional units. snoRNAs are a component in the small nucleolar ribonucleoprotein (snoRNP), which contains snoRNA and proteins. The snoRNA guides the snoRNP complex to the modification site of the target RNA gene via sequences (base pairing) in the snoRNA that hybridize to the target site. The proteins then catalyze modification of the RNA gene.

1. snoRNA lines up the RNA-modifying enzyme at the correct position by complementary base pairing
2. 2'-O-methylated ribose causes an invrease in the 3'-endo conformation
3. Pseudouridine (psi) adds another option for H-bonding.
4. Heavily methylated RNA is protected from hydrolysis. rRNA acts as a ribozyme by catalyzing its own hydrolysis and splicing.

microRNA

microRNA (also miRNA) are RNA genes that are the reverse complement of another gene's mRNA transcript and inhibit the expression of the target gene.

gRNAs

gRNAs (for guide RNA) are RNA genes that function in RNA editing. Thus far, RNA editing has been found only in the mitochondria of kinetoplastids, in which mRNAs are edited by inserting or deleting stretches of uridylates (Us). The gRNA forms part of the **editosome** and contains sequences that hybridize to matching sequences in the mRNA, to guide the mRNA modifications.

The term "guide RNA" is also sometimes used generically to mean any RNA gene that guides an RNA/protein complex via hybridization of matching sequences.

efference RNA

Efference RNA (eRNA) is derived from intron sequences of genes or from non-coding DNA. The function is assumed to be regulation of translational activity by interference with the transcription apparatus or target proteins of the translated peptide in question, or by providing a concentration-based measure of protein expression, basically introducing a fine-tuned analog element in gene regulation as opposed to the digital on-or-off regulation by promoters. Research into the role of eRNAs is in its infancy.

Signal recognition particle RNA

The signal recognition particle (SRP) is an RNA-protein complex present in the cytoplasm of cells that binds to the mRNA of proteins that are destined for secretion from the cell. The RNA component of the SRP in eukaryotes is called 4.5S RNA.

pRNA

At least one species of DNA-containing phages, phi-29, uses a complex of six identical short RNA sequences as mechanical components (utilizing ATP for energy) of its DNA packaging machinery. How common this phenomenon is has yet to be determined.

tmRNA

tmRNA has a complex structure with tRNA-like and mRNA-like regions. It has currently only been found in bacteria, but is ubiquitous in all bacteria. tmRNA recognizes ribosomes that have trouble translating or reading an mRNA and stall, leaving an unfinished protein that may be detrimental to the cell. tmRNA acts like a tRNA first, and then an mRNA that encodes a peptide tag. The ribosome translates this mRNA region of tmRNA and attaches the encoded peptide tag to the C-terminus of the unfinished protein. This attached tag targets the protein for destruction or proteolysis.

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Oligonucleotide

Oligonucleotides are short sequences of nucleotides (RNA or DNA), typically with twenty or fewer bases. Automated synthesizers allow the synthesis of oligonucleotides up to 160 to 200 bases. Oligonucleotides are often used as probes for detecting complementary DNA or RNA because they bind readily to their complements. Examples of procedures that use oligonucleotides are DNA microarrays, Southern blots, and fluorescent in situ hybridization (FISH). Oligonucleotides can also be used for the synthesis a artificial genes.

Oligonucleotides composed of DNA (deoxyoligonucleotides) are often used in the polymerase chain reaction (PCR), a procedure that can be employed to amplify almost any piece of DNA. In this instance, the oligonucleotide is often referred to as a primer, or a short piece of DNA that binds to its complementary target sequence. This generates a place for a polymerase to bind and extend the primer by the addition of nucleotides to make a copy of the target sequence.

Oligonucleotides are often referred to as oligos, in "science slang".

Antisense oligonucleotides

Antisense oligonucleotides are single strands of DNA or RNA that are complementary to a chosen sequence. In the case of antisense RNA they prevent translation of complementary RNA strands by binding to it. Antisense DNA can be used to target a specific, complementary (coding or non-coding) RNA. If binding takes places this DNA/RNA hybrid can be degraded by the enzyme RNase H. Antisense oligonucleotides are being created to use on RNA that eventually produces telomerase, which is active in cancer cells.

DNA MicroArray

One subtype of DNA MicroArrays can be described as substrates (nylon, glass etc.) to which oligonucleotides have been bound at high density. Currently there exist three applications of DNA MicroArrays: polymorphism studies, gene expression studies, and tracking down certain diseases.

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RNA

Ribonucleic acid (**RNA**) is a nucleic acid polymer consisting of covalently bound nucleotides. RNA nucleotides contain ribose rings and uracil unlike deoxyribonucleic acid (DNA), which contains deoxyribose and thymine. It is transcribed from DNA by enzymes called RNA polymerases and further processed by other enzymes. RNA serves as the template for translation of genes into proteins, transferring amino acids to the ribosome to form proteins, and also translating the transcript into proteins.

History

Nucleic acids were discovered in 1869 by Johann Friedrich Miescher (1844-1895), who called the material 'nuclein' since it was found in the nucleus. It was later discovered that prokaryotic cells, which do not have a nucleus, also contain nucleic acids.

The role of RNA in protein synthesis had been suspected since 1939, based on experiments carried out by Torbjörn Caspersson, Jean Brachet and Jack Schultz.

The sequence of the 77 nucleotides of a yeast tRNA was found by Robert W. Holley in 1964, winning Holley the 1968 Nobel Prize for Medicine.

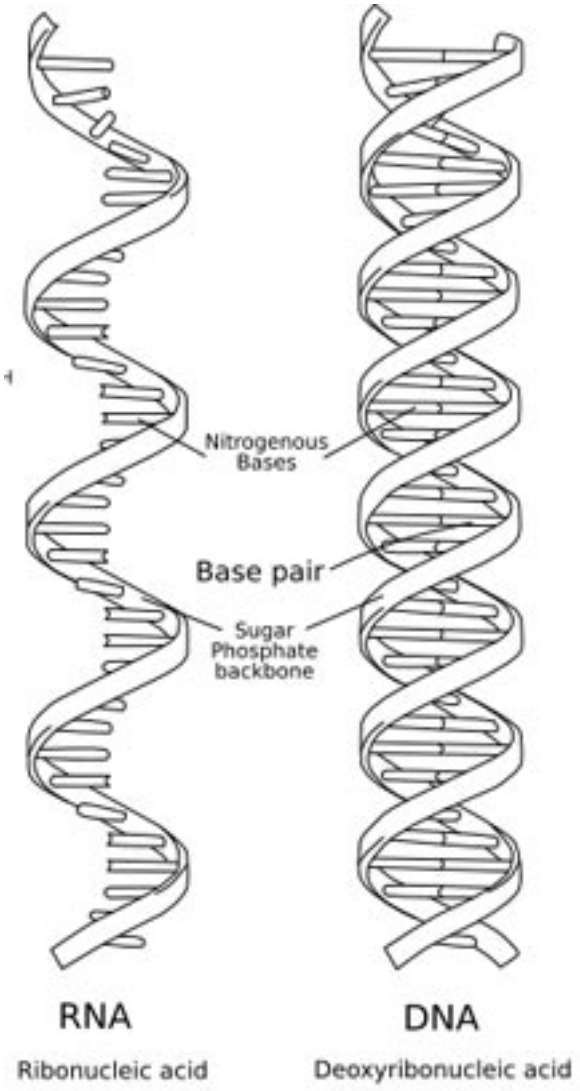
Chemical structure

RNA with its nitrogenous bases to the left and DNA to the right.RNA is primarily made up of four different bases: adenine, guanine, cytosine, and uracil. The first three are the same as those found in DNA, but uracil replaces thymine as the base complementary to adenine. This base is also a pyrimidine and is very similar to thymine. Uracil is energetically less expensive to produce than thymine, which may account for its use in RNA. In DNA, however, uracil is readily produced by chemical degradation of cytosine, so having thymine as the normal base makes detection and repair of such incipient mutations more efficient. Thus, uracil is appropriate for RNA, where quantity is important but lifespan is not, whereas thymine is appropriate for DNA where maintaining sequence with high fidelity is more critical.

There are also numerous modified bases found in RNA that serve many different roles. Pseudouridine (Ψ) and the DNA base thymidine are found in various places (most notably in the TΨC loop of every tRNA). There are nearly 100 other naturally occurring modified bases, many of which are not fully understood.

Comparison with DNA

Unlike DNA, RNA is almost always a single-stranded molecule and has a much shorter chain of nucleotides. RNA contains ribose, rather than the deoxyribose found in DNA (there is a hydroxyl group attached to the pentose ring in the 2' position whereas DNA has a hydrogen atom rather than a hydroxyl group). This hydroxyl group makes RNA less stable than DNA because it is more prone to hydrolysis. Several types of RNA (tRNA, rRNA) contain a great deal of secondary structure, which help promote stability.



RNA with its nitrogenous bases to the left and DNA to the right

Synthesis

Synthesis of RNA is usually catalyzed by an enzyme, RNA polymerase, using DNA as a template. Initiation of synthesis begins with the binding of the enzyme to a promoter sequence in the DNA (usually found "upstream" of a gene). The DNA double helix is unwound by the helicase activity of the enzyme. The enzyme then progresses along the template strand in the 3' -> 5' direction, synthesizing a

complementary RNA molecule with elongation occurring in the 5' -> 3' direction. The DNA sequence also dictates where termination of RNA synthesis will occur.

Biological roles

Messenger RNA (mRNA)

Messenger RNA is RNA that carries information from DNA to the ribosome sites of protein synthesis in the cell. Once mRNA has been transcribed from DNA, it is exported from the nucleus into the cytoplasm (in eukaryotes mRNA is "processed" before being exported), where it is bound to ribosomes and translated into protein. After a certain amount of time the message degrades into its component nucleotides, usually with the assistance of RNases.

Transfer RNA (tRNA)

Transfer RNA is a small RNA chain of about 74-93 nucleotides that transfers a specific amino acid to a growing polypeptide chain at the ribosomal site of protein synthesis during translation. It has sites for amino-acid attachment and an anticodon region for codon recognition that binds to a specific sequence on the messenger RNA chain through hydrogen bonding. It is a type of non-coding RNA.

Ribosomal RNA (rRNA)

Ribosomal RNA (rRNA) is a component of the ribosomes, the protein synthetic factories in the cell. Eukaryotic ribosomes contain four different rRNA molecules: 18S, 5.8S, 28S, and 5S rRNA. Three of the rRNA molecules are synthesized in the nucleolus, and one is synthesized elsewhere. rRNA molecules are extremely abundant. They make up at least 80% of the RNA molecules found in a typical eukaryotic cell.

Non-coding RNA or "RNA genes"

RNA genes (sometimes referred to as non-coding RNA or small RNA) are genes that encode RNA that is not translated into a protein. The most prominent examples of RNA genes are transfer RNA (tRNA) and ribosomal RNA (rRNA), both of which are involved in the process of translation. However, since the late 1990s, many new RNA genes have been found, and thus RNA genes may play a much more significant role than previously thought.

In the late 1990s and early 2000, there has been persistent evidence of more complex transcription occurring in mammalian cells (and possibly others). This could point towards a more widespread use of RNA in biology, particularly in gene regulation. A particular class of non-coding RNA, micro RNA, has been found in many metazoans (from *Caenorhabditis elegans* to *Homo sapiens*) and clearly plays an important role in regulating other genes.

Double-stranded RNA

Double-stranded RNA (or dsRNA) is RNA with two complementary strands, similar to the DNA found in all "higher" cells. dsRNA forms the genetic material of some viruses. In eukaryotes, it acts as a trigger to initiate the process of RNA interference and is present as an intermediate step in the formation of siRNAs (small interfering RNAs). siRNAs are often confused with miRNAs; siRNAs are double-stranded, whereas miRNAs are single-stranded.

RNA world hypothesis

The RNA world hypothesis proposes that the earliest forms of life relied on RNA both to carry genetic information (like DNA does now) and to catalyze biochemical reactions like an enzyme. According to this hypothesis, descendants of these early lifeforms gradually integrated DNA and proteins.

RNA secondary structures

The functional form of single stranded RNA molecules (like proteins) frequently requires a specific tertiary structure. The scaffold for this structure is provided by secondary structural elements which are hydrogen bonds within the molecule. This leads to several recognizable "domains" of secondary structure like hairpin loops, bulges and internal loops. The secondary structure of RNA molecules can be predicted computationally by calculating the minimum free energies (MFE) structure for all different combinations of hydrogen bondings and domains.

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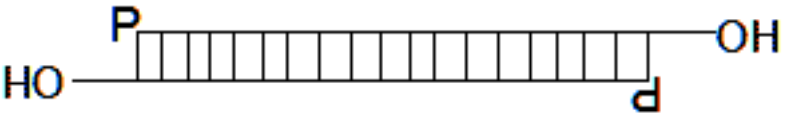
Small interfering RNA

Small interfering RNA (**siRNA**), sometimes known as **short interfering RNA** or **silencing RNA**, are a class of 20-25 nucleotide-long RNA molecules that play a variety of roles in biology. Most notably, this is the RNA interference pathway (RNAi) where the siRNA interferes with the expression of a specific gene. While this article largely deals with siRNAs in the RNAi pathway, it should be noted that siRNAs play additional roles in RNAi-related pathways, e.g. as an antiviral mechanism or in shaping the chromatin structure of a genome; the complexity of these pathways is only now being elucidated. SiRNAs were first discovered by David Baulcombe's group in Norwich, England, as part of post-transcriptional gene silencing (PTGS) in plants. Shortly thereafter, in 2001, synthetic siRNAs were then shown to able to induce RNAi in mammalian cells by Thomas Tuschl and colleagues. This discovery led to a surge in interest in harnessing RNAi for biomedical research and drug development.

Structure

SiRNAs have a well defined structure: a short (usually 21-nt) double-strand of RNA (dsRNA) with 2-nt 3' overhangs on either end:



Schematic representation of a siRNA molecule: a ~19-21bacepair RNA core duplex that is followed by a 2 nucleotide 3' overhang on each strand. OH: 3' hydroxyl; P: 5' phosphate.

Each strand has a 5' phosphate group and a 3' hydroxyl (-OH) group. This structure is the result of processing by Dicer, an enzyme that converts either long dsRNAs or hairpin RNAs into siRNAs. SiRNAs can also be exogenously (artificially) introduced into cells by various transfection methods to bring about the specific knockdown of a gene of interest. Essentially any gene of which the sequence is known can thus be targeted based on sequence complementarity with an appropriately tailored siRNA. This has made siRNAs an important tool for gene function and drug target validation studies in the post-genomic era.

RNAi induction using siRNAs or their biosynthetic precursors

Transfection of an exogenous siRNA can be problematic, since the gene knockdown effect is only transient, particularly in rapidly dividing cells. One way of overcoming this challenge is to modify the siRNA in such a way as to allow it to be expressed by an appropriate vector, e.g. a plasmid. This is done by the introduction of a loop between the two strands, thus producing a single transcript, which can be

processed into a functional siRNA. Such transcription cassettes typically use an RNA polymerase III promoter (e.g. U6 or H1), which usually direct the transcription of small nuclear RNAs (snRNAs) (U6 is involved in gene splicing; H1 is the RNase component of human RNase P). It is assumed (although not known for certain) that the resulting siRNA transcript is then processed by Dicer.

Challenges: Avoiding non-specific effects

RNAi intersects with a number of other pathways, so it is not surprising that on occasion non-specific effects are triggered by the experimental introduction of an siRNA. When a mammalian cell encounters a double-stranded RNA such as an siRNA, it may mistake it as a viral by-product and mount an immune response. Furthermore, since structurally related microRNAs modulate gene expression largely via incomplete complementarity with a target mRNA, unintended off-targeting may be effected by the introduction of an siRNA.

Innate Immunity

Introduction of too much siRNA can result in non-specific events due to activation of innate immune responses. Most papers suggest that this is probably due to activation of the dsRNA sensor PKR, although retinoic acid inducible Gene I (RIG-I) may also be involved. One promising method of reducing the non-specific effects is to convert the siRNA into a microRNA. MicroRNAs occur naturally, and by harnessing this endogenous pathway it should be possible to achieve similar gene knockdown at comparatively low concentrations of resulting siRNAs. This should minimise non-specific effects.

Off-targeting

Off-targeting is another challenge facing siRNAs as a gene knockdown tool. Here, genes with incomplete complementarity are inadvertantly downregulated by the siRNA (effectively, the siRNA acts as an miRNA), leading to problems in data interpretation and potentially toxicity. This however can be partly addressed by designing appropriate control experiments, and siRNA design algorithms are currently being developed to produce siRNAs free from off-targeting. Genome-wide expression analysis, e.g. by microarray technology, can then be used to verify this and further refine the algorithms. A 2006 paper from the laboratory of Dr Khvorova implicates 6 or 7 basepairs long stretches from position 2 onwards in the siRNA matching with 3'UTR regions in off-targeting genes.

The Future

(Opinion 1) Given the ability to knockdown essentially any gene of interest, RNAi via siRNAs has generated a great deal of interest in both basic and applied biology. There is an increasing number of large-scale RNAi screens that are designed to identify the important genes in various biological pathways. As disease processes also depend on the activity of multiple genes, it is expected that by turning off their activity with siRNAs or their biosynthetic precursors, therapeutic benefit can be derived directly via RNAi. Indeed, phase I results of the first two therapeutic RNAi trials (indicated for age-

related macular degeneration, aka AMD) reported at the end of 2005, demonstrate that siRNAs are well tolerated and have suitable pharmacokinetic properties. SiRNAs and related RNAi induction methods therefore stand to become an important new class of drugs in the foreseeable future.

(Opinion 2) Using siRNA's/shRNA's to knockdown specific genes is certainly a valuable tool in the laboratory. However, there are a great deal of challenges when it comes to taking a laboratory technique and applying it to living animals, especially humans. Firstly, siRNA's show different effectiveness in different cell types, apparently indiscriminately - some cells respond well to siRNA's and show a robust knockdown, others show no such knockdown (even despite efficient transfection). Secondly, and most importantly, the non-specific responses of si/shRNA's are still relatively poorly understood. Until these responses can be understood and overcome, the chances of using si/shRNA's outside of the lab, e.g. as an effective new class of drug, remain slim. (As such, Ian McEwan's novel "Saturday" suggests false promise in the hope of an siRNA-based treatment for Huntington's Disease).

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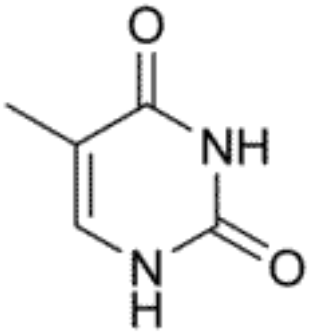
Thymine



Chemical name: 5-Methylpyrimidine-2,4(1H,3H)-dione
Chemical formula: $C_5H_6N_2O_2$

Molecular mass: 126.11 g/mol
Melting point 316 - 317 °C
CAS number 65-71-4
SMILES CC1=CNC(NC1=O)=O

Thymine, also known as **5-methyluracil**, is a pyrimidine nucleobase. It is found in the nucleic acid DNA. In RNA thymine is replaced with uracil in most cases. In DNA, thymine(T) binds to adenine (A) via two hydrogen bonds to assist in stabilizing the nucleic acid structures.

Thymine combined with deoxyribose creates the nucleoside deoxythymidine, which is synonymous with the term thymidine. Thymidine can be phosphorylated with one, two or three phosphoric acid groups, creating respectively TMP, TDP or TTP (thymidine mono- di- or triphosphate).

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Transfer RNA

Transfer RNA (abbreviated **tRNA**) is a small RNA chain (74-93 nucleotides) that transfers a specific amino acid to a growing polypeptide chain at the ribosomal site of protein synthesis during translation. It has sites for amino-acid attachment and codon (a particular sequence of 3 bases) recognition. The codon recognition is different for each tRNA and is determined by the anticodon region, which contains the complementary bases to the ones encountered on the mRNA. Each tRNA molecule binds only one type of amino acid, but because the genetic code is degenerate, more than one codon exists for each amino acid.

Transfer RNA is the "adaptor" molecule hypothesized by Francis Crick, which mediates recognition of the codon sequence in mRNA and allows its translation into the appropriate amino acid.

Structure of tRNA

tRNA has primary structure (the order of nucleotides from 5' to 3'), secondary structure (usually visualized as the *cloverleaf structure*), and tertiary structure (all tRNAs have a similar L-shaped 3D structure that allows them to fit into the P and A sites of the ribosome). The primary structure was reported in 1969 by Robert W. Holley. The secondary and tertiary structures were derived from X-ray crystallographic studies reported independently in 1974 by American and British research groups headed, respectively, by Alexander Rich and Aaron Klug.

Structure of tRNA

Features

1. The 5'-terminal phosphate.
2. The acceptor stem (also called the amino acid stem) is a 7-bp stem that incudes the 5'-terminal nucleotide and the 3'-terminal nucleotide with the 3'-terminal OH group (which can bind the amino acid). The acceptor stem may contain non-Watson-Crick base pairs.
3. The CCA tail is a CCA sequence added to the 3' end of the tRNA molecule. This sequence is important for the recognition of tRNA by enzymes critical in translation.
4. The D arm is a 4 bp stem ending in a loop that often contains dihydrouridine.
5. The anticodon arm is a 5-bp stem containing the anticodon.
6. The T arm is a 5 bp stem containing the sequence TΨC.
7. Modified bases are bases contained in tRNA that are not "canonical" bases, i.e. modified forms of the standard adenine, guanine, cytosine, and uracil bases.

Anticodon

An **anticodon** is a unit made up of three nucleotides which play an important role in various DNA cycles, including RNA translation. Each tRNA contains a specific anticodon triplet sequence that can base-pair to one or more codons for an amino acid. For example, one codon for lysine is AAA; the anticodon of a lysine tRNA might be UUU (some anticodons can pair with more than one codon due to a phenomenon known as degeneracy or *wobble*). Frequently, the third nucleotide of the anticodon is one of two not found on mRNA: inosine and pseudouridine. Consequently, the link between an anticodon and an mRNA codon is less strict than those links in DNA and RNA-DNA hybrids.

Aminoacylation

Aminoacylation is the process of adding an aminoacyl group to a compound.

Each tRNA is aminoacylated (or charged) with a specific amino acid by an aminoacyl tRNA synthetase. There is often just one aminoacyl tRNA synthetase for each amino acid, despite the fact that there can be more than one tRNA, and more than one anticodon, for an amino acid. Recognition of the appropriate tRNA by the synthetases in not mediated solely by the anticodon, and the acceptor stem often plays a prominent role.

Reaction:
1. amino acid + ATP --> aminoacyl-AMP + PPi
2. aminoacyl-AMP + tRNA --> aminoacyl-tRNA + AMP

tRNA genes

There are 497 nuclear human genes encoding cytoplasmic tRNA molecules + 22 mitochondrial tRNA genes. 324 tRNA-derived putative pseudogenes are revealed.

Cytoplasmic tRNA genes can be grouped into 49 families according to their anticodon features. These

genes are found on all chromosomes, except 22 and Y chromosome. High clustering on 6p is observed (140 tRNA genes), as well on 1 chromosome.

tRNA molecules are transcribed (in eukaryotic cells) by RNA polymerase III, unlike messenger RNA which is transcribed by RNA polymerase II.

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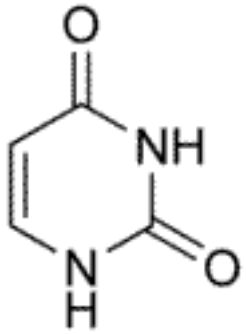
Uracil



Chemical name: Pyrimidine-2,4(1H,3H)-dione
Chemical formula: $C_4H_4N_2O_2$

Molecular mass: 112.09 g/mol
Melting point: 335 °C
CAS number: 66-22-8
SMILES: O=C(N1)NC=CC1=O

Uracil is one of the four major RNA nucleobases, and replaces the DNA base thymine. Similar to thymine, uracil can form a base pair with adenine via two hydrogen bonds, but it lacks the methyl group present in thymine. Uracil is not normally incorporated into DNA and is only very rarely observed in DNA. Incorporation of uracil by polymerase chain reactions (PCR) coupled with the enzyme, uracil DNA glycosylase (UDG), is used as a method of cross-over contamination prevention, which is important in clinical diagnostic assays.

Replacement of thymine

Uracil is thought to replace thymine in RNA for a number of reasons. First, it requires less energy to produce. RNA is present in large quantities and only exists transiently in cells. Thymine contains a methyl group that is not present in uracil and can provide more stability. DNA needs to last longer than RNA and uses thymine; the stability outweighs the increased energy required to produce thymine.

Uracil can be produced by the deamination of cytosine, so if it were present in DNA, the genetic code could be corrupted undetectably. Methylating uracil to producing thymine makes it possible to distinguish between thymine and a cytosine to uracil mutation. UDG, an enzyme that follows DNA polymerase during DNA repair can check DNA for uracil and allow base excision repair to take place.

Uracil is also more likely to form non Watson-Crick bases pairs than thymine, which can be highly desirable in RNA due to its high degree of secondary structure. However, this can be

detrimental in DNA, which requires great precision in basepairing to reduce the chances for mutations.

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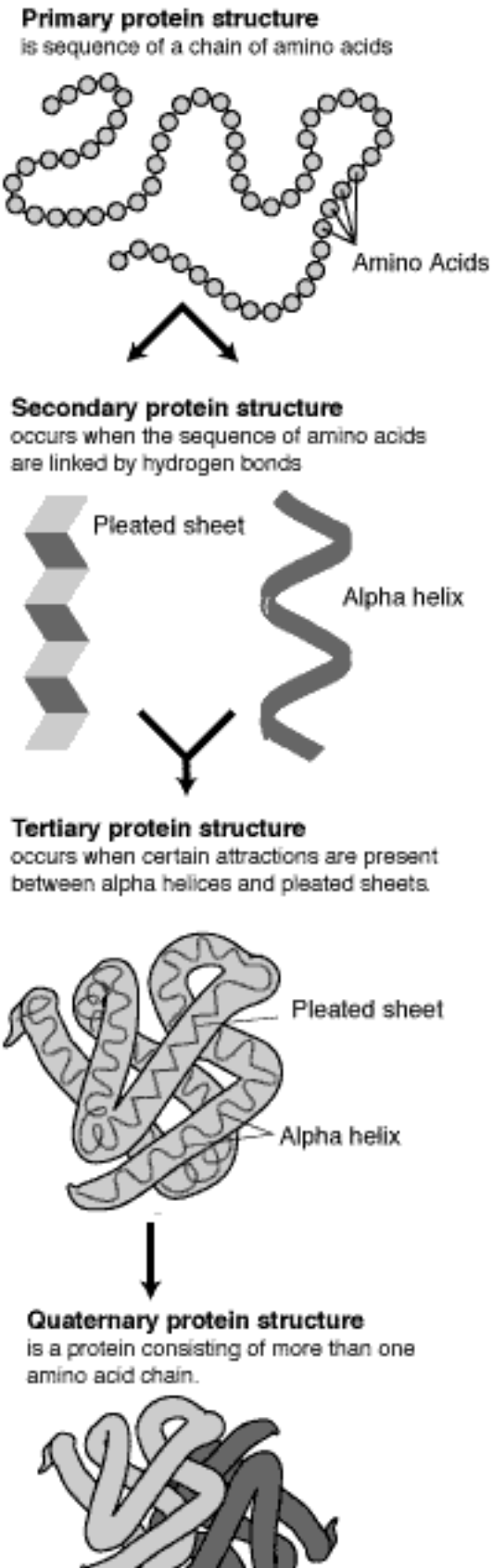
Protein



Protein

A **protein** (from the Greek *protas* meaning "*of primary importance*") is a complex, high-molecular-mass, organic compound that consists of amino acids joined by peptide bonds. Proteins are essential to the structure and function of all living cells and viruses.

Different proteins perform a wide variety of biological functions. Some proteins are enzymes, which catalyze chemical reactions. Other proteins play structural or mechanical roles, such as those that form the struts and joints of the cytoskeleton, which is like a system of scaffolding within a cell. Still more functions filled by proteins include immune response and the storage and transport of various ligands.

Proteins are a class of bio-macromolecules, alongside polysaccharides, lipids, and nucleic acids, that make up the primary constituents of biological organisms. Proteins are essentially polymers made up of a specific sequence of amino acids. The details of this sequence are stored in the code of a gene. Through the processes of transcription and translation, a cell reads the genetic information and uses it to construct the protein. In many cases, the resulting protein is then chemically altered (post-translational modification), before becoming functional. It is very common for proteins to work together to achieve a particular function, and often physically associate with one another to form a complex.

In nutrition, proteins are broken down through digestion back into free amino acids for the organism, including those the organism may not be able to synthesize itself.

Proteins are among the most actively-studied molecules in biochemistry, and were discovered by Jons Jakob Berzelius in 1838.

Properties of protein

Components and synthesis

Proteins are polymers built from 20 different L-alpha-amino acids. Proteins are assembled from amino acids using information present in genes. Genes are transcribed into RNA, RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA that undergoes translation into a protein. mRNA is translated by ribosomes that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. The enzyme aminoacyl tRNA synthetase catalyzes the addition of the correct amino acid to their tRNAs.

The two ends of the amino acid chain are referred to as the carboxy terminus (C-terminus) and the amino terminus (N-terminus) based on the nature of the free group on each extremity.

Structure

Proteins fold into unique 3-dimensional structures. The shape into which a protein naturally folds is known as its native state, which is determined by its sequence of amino acids. Thus, proteins are their own polymers, with amino acids being the monomers. Biochemists refer to four distinct aspects of a protein's structure:

- *Primary structure*: the amino acid sequence
- *Secondary structure*: highly patterned sub-structures - alpha helix and beta sheet - or segments of chain that assume no stable shape and are formed by hydrogen bonding. Secondary structures are defined, meaning that there can be many different secondary motifs present in one single protein molecule.
- *Tertiary structure*: the overall shape of a single protein molecule; the spatial relationship of the secondary structural motifs to one another; primarily formed by hydrophobic interactions, but hydrogen bonds, ionic interactions, and disulfide bonds are usually involved too.
- *Quaternary structure*: the shape or structure that results from the union of more than one protein molecule, usually called *protein subunits* in this context, which function as part of the larger assembly or protein complex.

In addition to these levels of structure, proteins may shift between several similar structures in performing their biological function. In the structures are usually referred to as "conformations," and transitions between them are called **conformational changes.**

The process by which the higher structures are formed is called protein folding and is a consequence of the primary structure. The mechanism of protein folding is not entirely understood. Although any unique polypeptide may have more than one stable folded conformation, each conformation has its own biological activity and only one conformation is considered to be the active one.

Protein regulation

Various molecules and ions are able to bind to specific sites on proteins. These sites are called binding sites. They exhibit chemical specificity. The particle that binds is called a ligand. The strength of ligand-protein binding is a property of the binding site known as affinity.

Since proteins are involved in practically every function performed by a cell, the mechanisms for controlling these functions therefore depend on controlling protein activity. Regulation can involve a protein's shape or concentration. Some forms of regulation include:

- *Allosteric modulation*: When the binding of a ligand at one site on a protein affects the binding of ligand at another site.
- *Covalent modulation*: When the covalent modification of a protein affects the binding of a ligand or some other aspect of the protein's function.

Diversity

Proteins are generally large molecules, having molecular masses of up to 3,000,000 (the muscle protein titin has a single amino acid chain 27,000 subunits long) however protein masses are generally measured in kiloDaltons (kDa). Such long chains of amino acids are almost universally referred to as proteins, but shorter strings of amino acids are referred to as "polypeptides," "peptides" or rarely, "oligopeptides". The dividing line is undefined, though "polypeptide" usually refers to an amino acid chain lacking tertiary structure which may be more likely to act as a hormone (like insulin), rather than as an enzyme (which depends on its defined tertiary structure for functionality).

Proteins are generally classified as soluble, filamentous or membrane-associated. Nearly all the biological catalysts known as enzymes are soluble proteins. Antibodies, the basis of the adaptive immune system, are another example of soluble proteins. Membrane-associated proteins include exchangers and ion channels, which move their substrates from place to place but do not change them; receptors, which do not modify their substrates but may simply shift shape upon binding them. Filamentous proteins make up the cytoskeleton of cells and some of the structure of animals: examples include tubulin, actin, collagen and keratin, all of which are important components of skin, hair, and cartilage. Another special class of proteins consists of motor proteins such as myosin, kinesin, and dynein. These proteins are "molecular motors," generating physical force which can move organelles, cells, and entire muscles.

Role of protein

Functions

Proteins are involved in practically every function performed by a cell, including regulation of cellular functions such as signal transduction and metabolism. Life, chemically speaking, is nothing but the function of proteins, although the information to make a unique protein resides, passively, in the DNA. The protein involved in functions control almost all the molecular processes of the body. Proteins are the actors, that *do* everything that happens within us. Although proteins do almost everything in an organism, several particularly important functional classes may be recognized:

- enzymes, that catalyze all of the reactions of metabolism;
- structural proteins, such as tubulin, or collagen;
- regulatory proteins, such as transcription factors or cyclins that regulate the cell cycle;
- signalling molecules or their receptors such as some hormones and their receptors;
- defensive proteins, which can include everything from antibodies of the immune system, to toxins (e. g., dendrotoxins of snakes), to proteins that include unusual amino acids like canavanine.

Nutrition

In nutrition, proteins are broken down through digestion, which begins in the stomach. There proteins are broken down into proteases and polypeptides to provide amino acids for the organism, including those the organism may not be able to synthesize itself. Pepsinogen is converted into the enzyme pepsin

when it comes into contact with hydrochloric acid. Pepsin is the only proteolytic enzyme that digests collagen, the major protein of connective tissue. Most protein digestion takes place in the duodenum with the overall contribution from the stomach being small. Almost all protein is absorbed when it reaches the jejunum with only 1% of ingested protein left in the feces. Some amino acids remain in the epithelial cells and are used for synthesis of new proteins, including some intestinal proteins, constantly being digested, recycled and absorbed from the small intestine.

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Amino acid

In chemistry, an **amino acid** is any molecule that contains both amino and carboxylic acid functional groups. In biochemistry, this shorter and more general term is frequently used to refer to alpha amino acids: those amino acids in which the amino and carboxylate functionalities are attached to the same carbon, the so-called α–carbon.

An **amino acid residue** is what is left of an amino acid once a molecule of water has been lost (an H^+ from the nitrogenous side and an OH^- from the carboxylic side) in the formation of a peptide bond.

Overview

Amino acids are the basic structural building units of proteins. They form short polymer chains called peptides or polypeptides which in turn form structures called proteins. The process of such formation from an mRNA template is known as translation, which is part of protein synthesis.

Twenty amino acids are encoded by the standard genetic code and are called proteinogenic or **standard amino acids**. At least two others are also coded by DNA in a non-standard manner as follows:
• Selenocysteine is incorporated into some proteins at a UGA codon, which is normally a stop codon.
• Pyrrolysine is used by some methanogens in enzymes that they use to produce methane. It is coded for similarly to selenocysteine but with the codon UAG instead.

Other amino acids contained in proteins are usually formed by post-translational modification, which is modification after translation in protein synthesis. These modifications are often essential for the function of the protein.

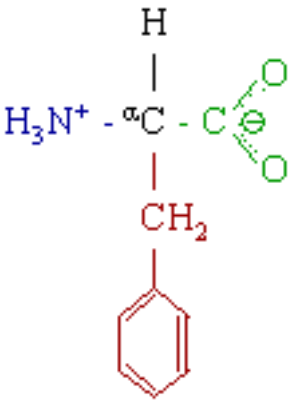
Proline is the only proteinogenic amino acid whose side group is cyclic and links to the α-amino group, forming a secondary amino group. Formerly, proline was misleadingly called an imino acid.

Over one hundred amino acids have been found in nature. Some of these have been detected in meteorites, especially in a type known as carbonaceous chondrites. Microorganisms and plants can produce uncommon amino acids, which can be found in peptidic antibiotics (e.g., nisin or alamethicin). Lanthionine is a sulfide-bridged alanine dimer which is found together with unsaturated amino acids in lantibiotics (antibiotic peptides of microbial origin). 1-Aminocyclopropane-1-carboxylic acid (ACC) is a small disubstituted cyclic amino acid and a key intermediate in the production of the plant hormone ethylene.

In addition to protein synthesis, amino acids have other biologically-important roles. Glycine and glutamate are neurotransmitters as well as standard amino acids in proteins. Many amino acids are used to synthesize other molecules, for example:

• tryptophan is a precursor of the neurotransmitter serotonin
• glycine is one of the reactants in the synthesis of porphyrins such as heme.

Numerous non-standard amino acids are also biologically-important: Gamma-aminobutyric acid is another neurotransmitter, carnitine is used in lipid transport within a cell, ornithine, citrulline, homocysteine, hydroxyproline, hydroxylysine, and sarcosine.



Phenylalanine
(Phe / F)

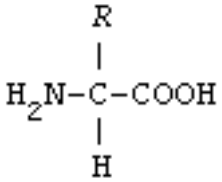
Phenylalanine is one of the standard amino acids.

Some of the 20 standard amino acids are called essential amino acids because they cannot be synthesized by the body from other compounds through chemical reactions, but instead must be taken in with food. In humans, the essential amino acids are lysine, leucine, isoleucine, methionine, phenylalanine, threonine, tryptophan, valine. Histidine and arginine are generally considered essential only in children, because of their inability to synthesise them given their undeveloped metabolisms.

The phrase "branched-chain amino acids" is sometimes used to refer to the aliphatic amino acids: leucine, isoleucine and valine.

General structure

The general structure of proteinogenic alpha amino acids is:



Where *R* represents a *side chain* specific to each amino acid. Amino acids are usually classified by the properties of the side chain into four groups. The side chain can make them behave like a weak acid, a weak base, a hydrophile, if they are polar, and hydrophobe if they are nonpolar.

Isomerism

Most amino acids occur in two possible optical isomers, called D and L. Using the newer Cahn Ingold Prelog priority rules for designating the configuration of optical isomers, the L isomer is assigned the letter S and the D isomer is assigned the letter R. The L amino acids represent the vast majority of amino acids found in proteins. D amino acids are found in some proteins produced by exotic sea-dwelling organisms, such as cone snails. They are also abundant components of the proteoglycan cell walls of bacteria.

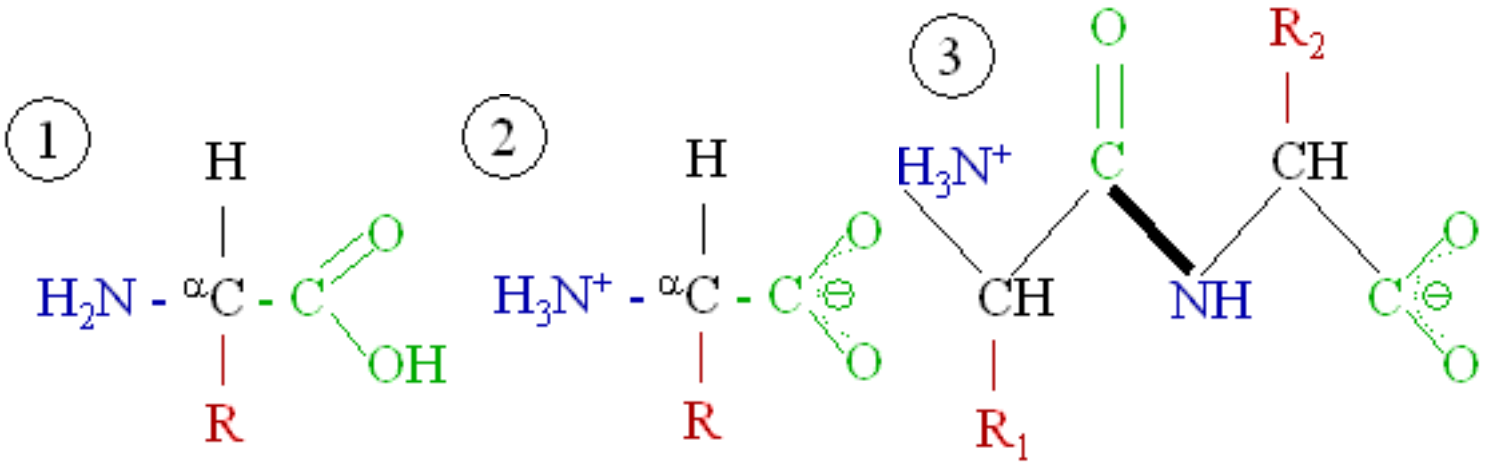
The L and D conventions for amino acid do not refer to their own optical activity, but rather to the optical activity of glyceraldehyde as an analogue of the amino acids. S-glyceraldehyde is levorotary, and R-glyceraldehyde is dexterorotary, and so S- amino acids are called "L-" even if they are not levorotary, and R- amino acids are likewise called "D-" even if they are not dexterorotary.

Exceptions

Two exceptions exist:
• In glycine, where R = H, and there is no isomerism, because two groups on the central carbon atom are identical
• In cysteine, the L-S and D-R assignment is reversed to L-R and D-S. Cysteine is structured similarly (with respect to glyceraldehyde) to the other amino acids but the sulfur atom alters the interpretation of the Cahn Ingold Prelog rules.

Reactions

Proteins are created by polymerization of amino acids by peptide bonds in a process called translation. This condensation reaction yields the newly formed peptide bond and a molecule of water.



Peptide bond formation
1. Amino acid; 2, zwitterion structure; 3, two amino acids forming a peptide bond.

List of standard amino acids

L-Alanine (Ala / A)
L-Arginine (Arg / R)
L-Asparagine (Asn / N)
L-Aspartic acid (Asp / D)
L-Cysteine (Cys / C)
L-Glutamic Acid (Glu / E)
L-Glutamine (Gln / Q)
L-Glycine (Gly / G)
L-Histidine (His / H)
L-Isoleucine (Ile / I)
L-Leucine (Leu / L)
L-Lysine (Lys / K)
L-Methionine (Met / M)
L-Phenylalanine (Phe / F)
L-Proline (Pro / P)
L-Serine (Ser / S)
L-Threonine (Thr / T)
L-Tryptophan (Trp / W)
L-Tyrosine (Tyr / Y)
L-Valine (Val / V)

Hydrophilic and hydrophobic amino acids

Depending on how polar the side chain, aminoacids can be hydrophilic or hydrophobic to various degree. This influences their interaction with other structures, both within the protein itself and within other proteins. The distribution of hydrophilic and hydrophobic aminoacids determines the tertiary structure of the protein, and their physical location on the outside structure of the proteins influences their quaternary structure. For example, soluble proteins have surfaces rich with polar aminoacids like serine and threonine, while integral membrane proteins tend to have outer ring of hydrophobic aminoacids that anchors them to the lipid bilayer, and proteins anchored to the membrane have a hydrophobic end that locks into the membrane. Similarly, proteins that have to bind to positive-charged molecules have surfaces rich with negatively charged aminoacids like glutamate and aspartate, while proteins binding to negative-charged molecules have surfaces rich with positively charged chains like lysine and arginine.

Hydrophilic and hydrophobic interactions of the proteins do not have to rely only on aminoacids themselves. By various posttranslational modifications other chains can be attached to the proteins, forming hydrophobic lipoproteins or hydrophilic glycoproteins.

Nonstandard amino acids

Aside from the twenty standard amino acids and the two special amino acids, selenocysteine and pyrrolysine, already mentioned above, there are a vast number of "nonstandard amino acids" which are not incorporated into protein. Examples of nonstandard amino acids include the sulfur-containing taurine and the neurotransmitters GABA and dopamine. Other examples are lanthionine, 2-Aminoisobutyric acid, and dehydroalanine. Nonstandard amino acids often occur in the metabolic pathways for standard amino acids - for example ornithine and citrulline occur in the urea cycle, part of amino acid breakdown.

Nonstandard amino acids are usually formed through modifications to standard amino acids. For example, taurine can be formed by the decarboxylation of cysteine, while dopamine is synthesized from tyrosine and hydroxyproline is made by a posttranslational modification of proline (common in collagen).

Uses of substances derived from amino acids

• **Aspartame** (aspartyl-phenylalanine-1-methyl ester) is an artificial sweetener.
• **5-HTP** (5-hydroxytryptophan) has been used to treat neurological problems associated with PKU (phenylketonuria), as well as depression (as an alternative to L-Tryptophan).
• **L-DOPA** (L-dihydroxyphenylalanine) is a drug used to treat Parkinsonism.
• **Monosodium glutamate** is a food additive to enhance flavor.

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Protein folding

Protein folding is the process by which a protein structure assumes its functional shape or conformation. All protein molecules are heterogeneous unbranched chains of amino acids. By coiling and folding into a specific three-dimensional shape they are able to perform their biological function.

The reverse of this process is protein denaturation, whereby a native protein is caused to lose its functional conformation, and become an amorphous, and non-functional amino acid chain. Denatured proteins may lose their solubility, and precipitate, becoming insoluble solids. In some cases, denaturation is reversible, and proteins may refold. In many other cases, however, denaturation is irreversible.

Known facts about the process

The relationship between folding and amino acid sequence

The particular amino-acid sequence (or "primary structure") of a protein predisposes it to fold into its native conformation. Many proteins do so spontaneously during or after their synthesis inside cells. While these macromolecules may be seen as "folding themselves," in fact their folding depends a great deal on the characteristics of their surrounding solution, including the identity of the primary solvent (either water or lipid inside cells), the concentration of salts, the temperature, and molecular chaperones.

For the most part, scientists have been able to study many identical molecules folding together en masse. It appears that in transitioning to the native state, a given amino acid sequence always takes roughly the same route and proceeds through roughly the same number of fundamental intermediates. At the coarsest level, folding involves first the establishment of secondary structure, particularly alpha helices and beta sheets, and only afterwards tertiary structure (formation of quaternary structure appears to involve the "assembly" or "coassembly" of subunits that have already folded). Unlike primary or secondary structures, tertiary (and sometimes quaternary) structure may involve covalent bonding in the form of disulfide bridges formed between two cysteine residues. This is unusual since the electrostatic interactions (hydrogen bonding, Van der Waals interactions) between amino acid R groups usually mediate folding. Shortly before settling into their more stable native conformation, molecules appear to pass through an additional "molten globule" state.

The essential fact of folding, however, remains that the amino acid sequence of each protein contains the information that specifies both the native structure and the pathway to attain that state: Folding is a spontaneous process. The passage of the folded state is mainly guided by Van der Waals forces and entropic contributions to the Gibbs free energy: an increase in entropy is achieved by moving the hydrophobic parts of the protein inwards, and the hydrophilic ones outwards. This endows surrounding water molecules with more degrees of freedom. During the folding process, the number of hydrogen bonds does not change appreciably, because for every internal hydrogen bond in the protein, a hydrogen

bond of the unfolded protein with the aqueous medium has to be broken.

Preconditions for correct folding

In certain solutions and under some conditions proteins will not fold at all. Temperatures above or below the range that cells tend to live in will cause proteins to unfold or "denature" (this is why boiling makes the white of an egg opaque). High concentrations of solutes and extremes of pH can do the same. A fully denatured protein lacks both tertiary and secondary structure, and exists as a so-called random coil. Cells sometimes protect their proteins against the denaturing influence of heat with enzymes known as chaperones or heat shock proteins, which assist other proteins both in folding and in remaining folded. Some proteins never fold in cells at all except with the assistance of chaperone molecules, that isolate individual proteins so that their folding is not interrupted by interactions with other proteins. DNA conformation is maintained by another set of enzymes: the topoisomerases.

Incorrect protein folding and neurodegenerative disease

Incorrectly folded proteins are responsible for prion related illness such as Creutzfeldt-Jakob disease and Bovine spongiform encephalopathy (mad cow disease), and amyloid related illnesses such as Alzheimer's Disease. These diseases are associated with the aggregation of misfolded proteins into insoluble plaques; it is not known whether the plaques are the cause or merely a symptom of illness.

Time scales of protein folding

The entire duration of the folding process varies dramatically depending on the protein of interest. The slowest folding proteins require many minutes or hours to fold, primarily due to steric hindrances. However, small proteins, with lengths of a hundred or so amino acids, typically fold on time scales of milliseconds. The very fastest known protein folding reactions are complete within a few microseconds.

Folding and unfolding rates also depend on environment conditions like temperature, solvent viscosity, pH and more. The folding process can also be slowed down (and the unfolding sped up) by applying mechanical forces, as revealed by single-molecule experiments.

Techniques for studying protein folding

Modern studies of folding with high time resolution

The study of protein folding has been greatly advanced in recent years by the development of fast, time-resolved techniques. These are experimental methods for rapidly triggering the folding of a sample of unfolded protein, and then observing the resulting dynamics. Fast techniques in widespread use include ultrafast mixing of solutions, photochemical methods, and laser temperature jump spectroscopy. Among the many scientists who have contributed to the development of these techniques are Heinrich Roder, Martin Gruebele, Brian Dyer, William Eaton, Sir Alan R. Fersht and Bengt Nölting.

Predicting energy landscapes: A theoretical approach

Since the late 1980s, a theoretical approach to understanding protein folding has been the calculation of protein energy landscapes. The energy landscape of a protein is the variation of its free energy as a function of its conformation, owing to the interactions between the amino acid residues. It has been proposed that natural proteins have evolved such that this complicated energy surface has a funnelled shape which leads towards the native state, which is the lowest-energy conformation available to the protein. This "folding funnel" landscape allows the protein to fold to the native state through any of a large number of pathways and intermediates, rather than being restricted to a single mechanism. The theory is supported by computational simulations of model proteins and has been used to improve methods for protein structure prediction and design.

Computational prediction of protein tertiary structure

De novo or *ab initio* techniques for computational protein structure prediction employ simulations of protein folding to determine the protein's final folded shape.

Imaging techniques for determination of protein structure

The determination of the folded structure of a protein is a lengthy and complicated process, involving methods like X-ray crystallography and NMR. In bioinformatics, one of the major areas of interest is the prediction of native structure from amino-acid sequences alone.

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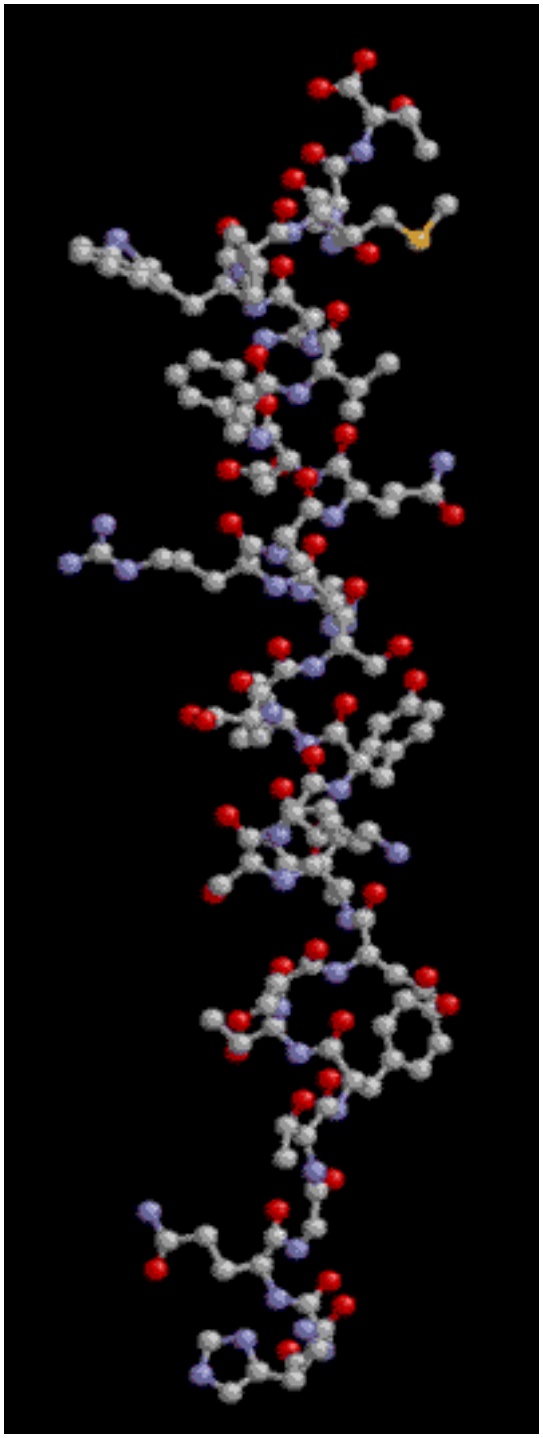
Peptide

Peptides (from the Greek "digestible"), are the family of short molecules formed from the linking, in a defined order, of various α-amino acids. The link between one amino acid residue and the next is an amide bond, and is sometimes referred to as a peptide bond.



Glucagon *is a 29-amino acid polypeptide acting as an important hormone in carbohydrate metabolism. The polypeptide has a molecular weight of 3485 daltons and was discovered in 1923 by Kimball and Murlin*

Like proteins, peptides are **polypeptide** molecules. The distinction is that peptides are short and proteins are long. There are several different conventions to determine these, all of which have flaws.

One convention is that those peptide chains that are short enough to be made synthetically from the constituent amino acids are called peptides rather than proteins. However with the advent of better synthetic techniques, peptides as long as hundreds of amino acids can be made, including full proteins like ubiquitin. Native chemical ligation has given access to even longer proteins, and so this convention seems to be outdated.

Another convention places an informal dividing line is at approximately 50 amino acids in length (some people claim shorter lengths). However, this definition is somewhat arbitrary — some peptides such as alzheimer's beta peptide come close and some proteins (such as insulin) are close to the lower limit for proteins. Because of the arbitrary nature of this definition, there is considerable movement within the scientific community to ascribe the more-specific definition that "a peptide is an amino acid molecule without secondary structure; on gaining defined structure, it is a protein." Thus the same molecule can be either a peptide or a protein depending on its environment, though there are peptides that cannot be proteins.

There are three large classes of peptides, according to how they are produced:

Ribosomal peptides

Are synthesized by translation of mRNA. They are often subjected to proteolysis to generate the mature form. These function, typically in higher organisms, as hormones and signaling molecules. Some lower organisms produce peptides as antibiotics, such as microcin J25. Since they are translated, the amino acid residues involved are restricted to the 20 amino acids (plus selenomethionine and pyrrolysine), and posttranslational modifications thereof, such as phosphorylation, hydroxylation, sulfonation, disulfide formation, etc. In general, they are linear, although lariat structures are not uncommon.

Nonribosomal peptides

Are synthesized using a modular enzyme complex (which functions much like a conveyor belt on a factory). Nonribosomal peptides and are confined primarily to unicellular organisms, plants, and fungi. There is a common core structure to all of these complexes, and they can contain many different modules to perform chemical manipulations on the evolving product. In general, these peptides are cyclic (often with highly-complex cyclic structures), although linear nonribosomal peptides are common. Since the system is modular and closely related to the machinery for building fatty acids and polyketides, hybrid compounds are often found. Oxazoles, thiazoles, and their reduced counterparts often indicate that the compound was synthesized in this fashion.

Digested peptides

Are the result of nonspecific proteolysis as part of the digestive cycle. It has also been documented that, when certain food proteins such as gluten, casein, egg protein and spinach protein are broken down, opioid peptides are formed. These peptides mimic the effects of morphine, and those individuals that are unable to break them down will experience mental illness. These peptides are quite short and are given names such as casomorphine, gluten exorphine and dermorphine. Ultimately digested peptides are ribosomal peptides, although they aren't made on the ribosome of the organism that contains them.

The Grand Peptide Families

These peptides are ribosomal peptides, usually with hormonal activity. All of these peptides are synthesized by cells as longer "propeptides" or "proproteins" and truncated prior to exiting the cell. They are released into the bloodstream where they perform their signalling functions.

Vasopressin and oxytocin

- Vasopressin
- Oxytocin

The Tachykinin peptides

- Substance P
- Kassinin
- Neurokinin A
- Eledoisin
- Neurokinin B

Vasoactive intestinal peptides

- VIP *Vasoactive intestinal peptide*
- PACAP *Pituitary adenylate cyclase activating peptide*
- PHI 27
- PHM 27
- GHRH 1-24 *Growth hormone releasing hormone 1-24*
- Glucagon
- Secretin

Pancreatic polypeptide-related peptides

- NPY
- PYY *Peptide YY*
- APP *Avian pancreatic polypeptide*
- HPP *Human pancreatic polypeptide*

Opioid peptides

• Proopiomelanocortin (POMC) Peptides
• The Enkephalin pentapeptides
• The Prodynorphin peptides

Calcitonin peptides

• Calcitonin
• Amylin

Notes on terminology

• A polypeptide is a single linear chain of amino acids.
• A *protein* is one or more polypeptides more than about 50 amino acids long.
• An *oligopeptide* or (simply) a peptide is a polypeptide less than 30-50 amino acids long.
• A *tripeptide* has three amino acids.
• A *dipeptide* has two amino acids.
• A *neuropeptide* is a peptide that is active in association with neural tissue
• A *peptide hormone* is a peptide that acts as a hormone.

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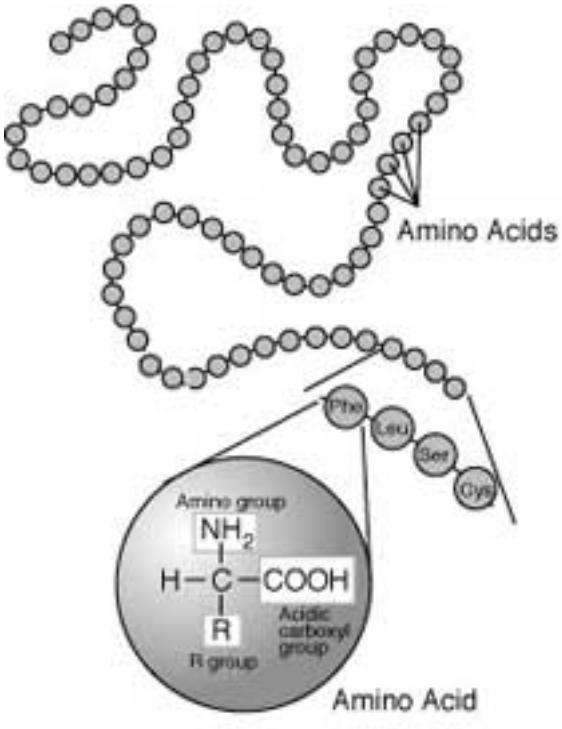
Primary structure

In biochemistry, the **primary structure** of an unbranched biopolymer, such as a molecule of DNA, RNA or protein, is the specific nucleotide or peptide sequence from the beginning to the end of the molecule. The primary structure, in other words, identifies a biopolymer's exact chemical composition and the sequence of its monomeric subunits.



A protein primary structure is a chain of amino acids.

The primary structure of a biological polymer to a large extent determines the three-dimensional shape known as the tertiary structure, but nucleic acid and protein folding are so complex that knowing the primary structure often doesn't help either to deduce the shape or to predict localized secondary structure, such as the formation of loops or helices. However, knowing the structure of a similar homologous sequence (for example a member of the same protein family) can unambiguously identify the tertiary structure of the given sequence. Sequence families are often determined by sequence clustering, and structural genomics projects aim to produce a set of representative structures to cover the sequence space of possible non-redundant sequences.

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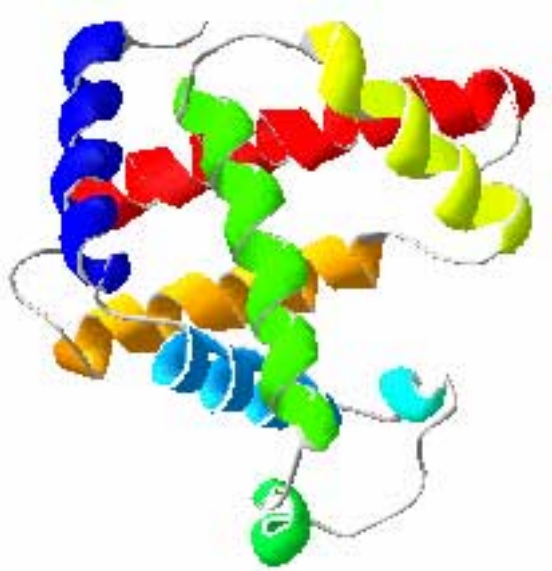
Secondary structure

Secondary structure in biochemistry and structural biology describes the general three-dimensional form of local regions or overall shape of biopolymers. It does not, however, refer to specific positions in three-dimensional space, which are considered to be tertiary structure. The secondary structure of a protein may include regions of alpha helices, beta sheets, turns, and random coil, or a few less common structures. Secondary structures can often be identified by circular dichroism spectroscopy. Nucleic acids also have secondary structure, most notably single-stranded RNA molecules.



3D structure of the Myoglobin protein: alpha helices are shown in colour, and random coil in white, there are no beta sheets in shown. This protein was the first to have its structure solved by X-ray crystallography by Max Perutz and Sir John Cowdery Kendrew in 1958, which led to them receiving a Nobel Prize in Chemistry in 1962.

Proteins

The DSSP Code

The DSSP code is frequently used to describe the protein secondary structures with a single letter code. DSSP is an acronym for "Dictionary of Protein Secondary Structure", which was the title of the original article actually listing the secondary structure of the proteins with known 3D structure. The secondary structure is assigned based on hydrogen bonding patterns as those initially proposed by Pauling et al. in 1951 (before any protein structure had ever been experimentally determined).

- G = 3-turn helix (3_10 helix). Min length 3 residues.
- H = 4-turn helix (alpha helix). Min length 4 residues.
- I = 5-turn helix (pi helix). Min length 5 residues.
- T = hydrogen bonded turn (3, 4 or 5 turn)

• E = beta sheet in parallel and/or anti-parallel sheet conformation (extended strand). Min length 2 residues.
• B = residue in isolated beta-bridge (single pair beta-sheet hydrogen bond formation)
• S = bend (the only non-hydrogen-bond based assignment)

In DSSP residues which are not in any of the above conformations is designated as ' ' (space), which sometimes gets designated with C (coil) or L (loop). The helices (G,H and I) and sheet conformations are all required to have a reasonable length. This means that 2 adjacent residues in the primary structure must form the same hydrogen bonding pattern. If the helix or sheet hydrogen bonding pattern is too short they are designated as T or B, respectively. Other protein secondary structure assignment categories exist (sharp turns, Omega loops etc.), but they are less frequently used.

RNA

RNA secondary structure is generally divided into helices (contiguous base pairs), and various kinds of loops (unpaired nucleotides surrounded by helices). Another reasonable definition of secondary structure of RNA is that it defines which nucleotides bind each other, and, for example, nucleotide pairs that are bound form helices. RNA secondary structure can also include pseudoknots and base triples.

For many RNA molecules, the secondary structure is highly important to the correct function of the RNA — often more so than the actual sequence. This fact aids in the analysis of non-coding RNA sometimes termed "RNA genes". RNA secondary structure can be predicted with some accuracy by computer, and many bioinformatics applications use some notion of secondary structure in analysis of RNA.

Alignment

Both protein and RNA secondary structures can be used to analyze sequences by alignment. These alignments can be made more accurate by the inclusion of secondary structure information, in addition to the usual use of sequence.

Distant relationships between proteins whose primary structures are unalignable can sometimes be found by secondary structure.

Prediction

Algorithms to predict RNA secondary structure typically use dynamic programming, and many algorithms are based on Stochastic context-free grammars.

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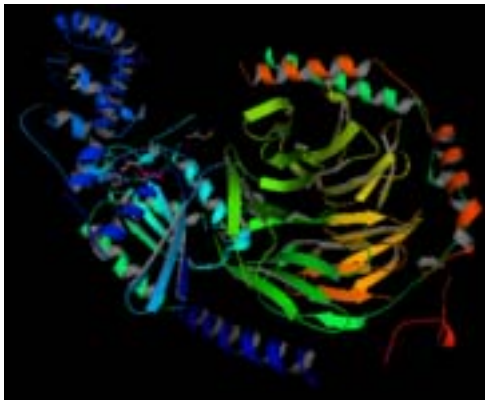
Tertiary structure

In biochemistry, the **tertiary structure** of a protein is its overall shape, also known as its fold. Protein molecules are linear chains of amino acids that typically assume a specific three-dimensional structure in which they perform their biological function. The study of protein tertiary structure is known as structural biology.



G-Protein

Relationship to Primary Sequence

Tertiary structure is considered to be largely determined by the protein's primary sequence, or the sequence of amino acids it is composed of. Efforts to predict tertiary structure from the primary sequence are known generally as protein structure prediction. However, the environment in which a protein is synthesized and allowed to fold are significant determinants of its final shape and are usually not directly taken into account by current prediction methods. (Most such methods do rely on comparisons between the sequence to be predicted and sequences of known structure in the Protein Data Bank and thus account for environment indirectly, assuming the target and template sequences share similar cellular contexts.) A large-scale experiment known as CASP directly compares the performance of state-of-the-art prediction methods and is run once every two years.

Determinants of Tertiary Structure

In globular proteins, tertiary interactions are frequently stabilized by the sequestration of hydrophobic amino acid residues in the protein core, from which water is excluded, and by the consequent enrichment of charged or hydrophilic residues on the protein's water-exposed surface. In secreted proteins that do not spend time in the cytoplasm, disulfide bonds between cysteine residues help to maintain the protein's tertiary structure. A variety of common and stable tertiary structures appear in a large number of proteins that are unrelated in both function and evolution - for example, many proteins are shaped like a TIM barrel, named for the enzyme triosephosphateisomerase. Another common structure is a highly stable dimeric coiled-coil structure composed of four alpha helices. Proteins are classified by the folds they represent in databases like SCOP and CATH.

Not every polypeptide chain has a well-defined tertiary structure. Some proteins, especially short proteins, are natively disordered and exist in as random coils under standard physiological conditions. Disordered regions can also occur in otherwise well-structured proteins, especially at the termini and in loop or linker regions connecting domains whose relative orientation can change depending on the environment.

Stability of Native States

The most typical conformation of a protein in its cellular environment is generally referred to as the native state or native conformation. It is commonly assumed that this most-populated state is also the most thermodynamically stable conformation attainable for a given primary sequence; this is a reasonable first approximation but the claim assumes that the reaction is not under kinetic control - that is, that the time required for the protein to attain its native conformation after being translated is small.

In the cell, a variety of protein chaperones assist a newly synthesized polypeptide in attaining its native conformation. Some such proteins are highly specific in their function, such as protein disulfide isomerase; others are very general and can be of assistance to most globular proteins - the prokaryotic GroEL/GroES system and the homologous eukaryotic Hsp60/Hsp10 system fall into this category.

Some proteins explicitly take advantage of the fact that they can become kinetically trapped in a relatively high-energy conformation due to folding kinetics. Influenza hemagglutinin, for example, is synthesized as a single polypeptide chain that acts as a kinetic trap. The "mature" activated protein is proteolytically cleaved to form two polypeptide chains that are trapped in a high-energy conformation. Upon encountering a drop in pH, the protein undergoes an energetically favorable conformational rearrangement that enables it to penetrate a host cell membrane.

Experimental Determination

The majority of protein structures known to date have been solved with the experimental technique of X-ray crystallography, which typically provides data of high resolution but provides no time-dependent information on the protein's conformational flexibility. A second common way of solving protein structures uses NMR, which provides somewhat lower-resolution data in general and is limited to relatively small proteins, but can provide time-dependent information about the motion of a protein in solution. More is known about the tertiary structural features of soluble globular proteins thatn about membrane proteins because the latter class is extremely difficult to study using these methods.

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Common Atoms

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Chemical symbols

Specific chemical elements

Before chemistry became a science, alchemists had designed arcane symbols for both metals and common compounds. These were however used as abbreviations in diagrams or procedures; there was no concept of one atoms combining to form molecules. With his advances in the atomic theory of matter, John Dalton devised his own simpler symbols, based on circles, which were to be used to depict molecules.

The current system of chemical notation was invented by Berzelius. In this typographical system chemical symbols are not used as mere abbreviations - though each consists of letters of the Latin alphabet - they are symbols intended to be used by peoples of all languages and alphabets. The first of these symbols were intended to be fully universal; since Latin was the common language of science at that time, they were abbreviations based on the Latin names of metals - Fe comes from Ferrum, Ag from Argentum. The symbols were not followed by a period (full stop) as abbreviations were. Later chemical elements were also assigned unique chemical symbols, based on the name of the element, but not necessarily in English. For example, sodium has the chemical symbol 'Na' after the Latin *natrium*. The same applies to "W" (wolfram) for tungsten, "Hg" (hydrargyrum) for mercury, "K" (kalium) for potassium, and "Sb" (stibium) for antimony.

Chemical symbols are understood internationally when element names might need to be translated. There are sometimes differences; for example, the Germans have used "J" instead of "I" for iodine, so the character would not be confused with a roman numeral.

The first letter of a chemical symbol is always capitalized, as in the preceding examples, and the subsequent letters, if any, are always lower case (small letters).

General chemical symbols

There are also symbols for series of chemical elements, for comparative formulas. These are one capital letter in length, and the letters are reserved so they are not permitted to be given for the names of specific elements. For example, an "X" is used to indicate a variable group amongst a class of compounds (though usually a halogen), while "R" is used for a radical, meaning a compound structure such as a hydrocarbon chain. The letter "Q" is reserved for "heat" in a chemical reaction. "Y" is also often used as a general chemical symbol, although it is also the symbol of Yttrium. "Z" is also frequently used as a general variable group. "L" is used to represent a general ligand in inorganic and organometallic chemistry. "M" is also often used in place of a general metal.

Isotope symbols

Although not officially used, in nuclear physics the three main isotopes of the element hydrogen are often written as H for protium, D for deuterium and T for tritium. This is in order to make it easier to use them in chemical equations, as it replaces the need to write out the AMU for each isotope. It is written like this: D_2O (heavy water), instead of writing it like this: ^2H_2O

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Naming of elements

The naming of elements precedes the atomic theory of matter, although at the time it was not known which chemicals were elements and which compounds. When it was learned, existing names (*e.g.*, gold, mercury, iron) were kept in most countries, and national differences emerged over the names of elements either for convenience, linguistic niceties, or nationalism. For example, the Germans use "Wasserstoff" for "hydrogen" and "Sauerstoff" for "oxygen," while English and some romance languages use "sodium" for "natrium" and "potassium" for "kalium," and the French prefer the term "azote" for "nitrogen." This is also used by the Greeks.

But for international trade, the official names of the chemical elements both ancient and recent are decided by the International Union of Pure and Applied Chemistry, which has decided on a sort of international English language. That organization has recently prescribed that "aluminium" and "caesium" take the place of the US spellings "aluminum" and "cesium," while the US "sulfur" takes the place of the British "sulphur." But chemicals which are practicable to be sold in bulk within many countries, however, still have national names, and those which do not use the Latin alphabet cannot be expected to use the IUPAC name. According to IUPAC, the full name of an element is not capitalized, even if it is derived from a proper noun (unless it would be capitalized by some other rule, for instance if it begins a sentence).

In the second half of the twentieth century physics laboratories became able to produce nuclei of chemical elements that have a half life too short for them to remain in any appreciable amounts. These are also named by IUPAC, which generally adopts the name chosen by the discoverer. This can lead to the controversial question of which research group actually discovered an element, a question which delayed the naming of elements with atomic number of 104 and higher for a considerable time.

Precursors of such controversies involved the nationalistic namings of elements in the late nineteenth century. For example, *lutetium* was named in reference to Paris, France. The Germans were reluctant to relinquish naming rights to the French, often calling it *cassiopeium*. The British discoverer of *niobium* originally named it *columbium*, in reference to the New World. It was used extensively as such by American publications prior to international standardization.

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IUPAC nomenclature of inorganic chemistry

The **IUPAC nomenclature of inorganic chemistry** is a systematic way of naming inorganic chemical compounds as recommended by the International Union of Pure and Applied Chemistry (IUPAC). Ideally, every inorganic compound should have a name from which an unambiguous formula can be determined. There is also a IUPAC nomenclature of organic chemistry.

The names "caffeine" and "3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione" both describe the same chemical. The systematic name encodes the structure and composition of the caffeine molecule in some detail, and provides an unambiguous reference to this compound, whereas the name "caffeine" just names it. These advantages make the systematic name far superior to the common name when absolute clarity and precision is required. However, even professional chemists will use the non-systematic name almost all of the time, because caffeine is a well-known common chemical with a unique structure. Similarly, the chemical water is always known as such, never as "dihydrogen monoxide."

1. Single atom anions are named with an *-ide* suffix: for example, H^- is hydride.
2. Compounds with a positive ion (cation), the name of the compound is simply the cation's name (usually the same as the element's), followed by the anion. For example, NaCl is *sodium chloride*, and CaF_2 is *calcium fluoride*.
3. Cations able to take on more than one positive charge are labeled with Roman numerals in parentheses. For example, Cu^+ is copper(I), Cu^{2+} is copper(II). An older, deprecated notation is to append *-ous* or *-ic* to the root of the Latin name to name ions with a lesser or greater charge. Under this naming convention, Cu^+ is cuprous and Cu^{2+} is cupric. For naming metal complexes see the page on complex (chemistry).
4. Oxyanions (polyatomic anions containing oxygen) are named with *-ite* or *-ate*, for a lesser or greater quantity of oxygen. For example, NO_2^- is nitrite, while NO_3^- is nitrate. If four oxyanions are possible, the prefixes *hypo-* and *per-* are used: Hypochlorite is ClO^-, Perchlorate is ClO_4^-,
5. The prefix *bi-* is a deprecated way of indicating the presence of a single hydrogen ion, as in "sodium bicarbonate" ($NaHCO_3$). The modern method specifically names the hydrogen atom. Thus, $NaHCO_3$ would be pronounced "sodium hydrogen carbonate".

Positively charged ions are called cations and negatively charged ions are called anions. The cation is **always** named first. Ions can be metals or polyatomic ions. Therefore the name of the metal or positive polyatomic ion is followed by the name of the non-metal or negative polyatomic ion. The positive ion retains its element name whereas for a single non-metal anion the ending is changed to -ide.

Example: sodium chloride, potassium oxide, or calcium carbonate.

When the metal has more than one possible ionic charge or oxidation number the name becomes

ambiguous. In these cases the oxidation number of the metal ion is represented by a Roman numeral in parentheses immediately following the metal ion name. For example in uranium(VI) fluoride the oxidation number of uranium is 6. Another example is the iron oxides. FeO is iron(II) oxide and Fe_2O_3 is iron(III) oxide.

An older system used prefixes and suffixes to indicate the oxidation number, according to the following scheme (oxidation state lowest on the left to highest on the right:):
Cations and acids: hypo- -ous | -ous | -ic | per- -ic
Anions: hypo- -ite | -ite | -ate | per- -ate

Thus the four oxyacids of chlorine are called hypochlorous acid (HOCl), chlorous acid (HOClO), chloric acid ($HOClO_2$) and perchloric acid ($HOClO_3$), and their respective conjugate bases are the hypochlorite, chlorite, chlorate and perchlorate ions. This system has partially fallen out of use, but survives in the common names of many chemical compounds: the modern literature contains few references to "ferric chloride" (instead calling it "iron(III) chloride"), but names like "potassium permanganate" (instead of "potassium manganate(VII)") and "sulfuric acid" abound.

Traditional Naming

Naming simple ionic compounds

An ionic compound is named by its cation followed by its anion. See polyatomic ions for a list of possible ions.

For cations that take on multiple charges, the charge is written using Roman numerals in parentheses immediately following the element name) For example, $Cu(NO_3)_2$ is *copper(II) nitrate*, because the charge of two nitrate ions is 2 x -1 = -2, and since the net charge of the ionic compound must be zero, the Cu ion has a 2+ charge. This compound is therefore copper(II) nitrate.

The Roman numerals in fact show the oxidation number, but in simple ionic compounds (i.e., not metal complexes) this will always equal the ionic charge on the metal.

List of common ion names

Monatomic anions:

Cl^- chloride
S^{2-} sulfide
P^{3-} phosphide

Polyatomic ions:

NH_4^+ ammonium

H_3O^+ hydronium

NO_3^- nitrate

NO_2^- nitrite

ClO^- hypochlorite
ClO_2^- chlorite

ClO_3^- chlorate

ClO_4^- perchlorate

SO_3^{2-} sulfite

SO_4^{2-} sulfate

HSO_3^- hydrogen sulfite (or bisulfite)

HCO_3^- hydrogen carbonate (or bicarbonate)

CO_3^{2-} carbonate

PO_4^{3-} phosphate

HPO_4^{2-} hydrogen phosphate

$H_2PO_4^-$ dihydrogen phosphate

CrO_4^{2-} chromate

$Cr_2O_7^{2-}$ dichromate

BO_3^{3-} orthoborate

AsO_4^{3-} arsenate

$C_2O_4^{2-}$ oxalate

CN^- cyanide
SCN^- thiocyanate
MnO_4^- permanganate

Naming hydrates

Hydrates are ionic compounds that have absorbed water. They are named as the ionic compound followed by a numerical prefix and -*hydrate*. The numerical prefixes used are listed below:

1. mono-
2. di-
3. tri-
4. tetra-
5. penta-
6. hexa-
7. hepta-
8. octa-
9. nona-
10. deca-

For example, $CuSO_4 \cdot 5H_2O$ is "copper(II) sulfate pentahydrate".

Naming molecular compounds

Inorganic molecular compounds are named with a prefix (see list above) before each element. The more electronegative element is written last and with an *-ide* suffix. For example, CO_2 is *carbon dioxide*, and CCl_4 is *carbon tetrachloride*. There are some exceptions to the rule, however. The prefix **mono-** is not used with the first element; for example, CO_2 is *carbon dioxide*, not "monocarbon dioxide". Sometimes prefixes are shortened when the ending vowel of the prefix "conflicts" with a starting vowel in the compound. This makes the compound easier to speak; for example, CO is "carbon monoxide" (as opposed to "monooxide").

Naming acids

Acids are named by the anion they form when dissolved in water. If an acid forms an anion named ___*ide*, it is named *hydro*___*ic acid*. For example, *hydro*chlor*ic acid* forms a chlor*ide* anion. Secondly, anions with an *-ate* suffix are formed when acids with an *-ic* suffix are dissolved, e.g. chlor*ic* acid; anions with an *-ite* suffix are formed when acids with an *-ous* suffix are dissolved in water, e.g. chlor*ous acid* disassociates into chlor*ite* anions.

2005 Revision of IUPAC's Nomenclature for Inorganic Compounds

With the last revision of the nomenclature, many things changed. Most important is, that there is no absolute right name for one compound anymore. As long as the name describes the compound sufficiently and unambiguously, the name is correct. Old names such as *water*, *carbonyl* or *cyano* are still tolerated. - The "old names" may still have to be understood, but the systematic IUPAC nomenclature is easier to learn (because it is systematic) and always right to use.

There are basically two different ways to describe a compound: compositional and substituive

nomenclature.

Compositional nomenclature

This ansatz tries to describe how a molecule is constructed from some kind of core, one might say complex like. The core(s) of the molecule is the sort of atom with the lowest electronegativity EN (e.g. in CO, C is the core with EN=2.5 whereas O has EN=3.5). This element defines the stem name of the compound. If the compound is negatively charged, the name is complimented by a suffix: *-ide* if there is no other element is present and *-ate* in any other case.

Then the surrounding atoms and groups are described in a ligand manner. The ligand names are determined similarly to the core name. A *-o* suffix marks them as a ligand group. Identical groups are taken together with a multiplication prefix (i.e. *tri-*, *tetra-* or *bis-*).

After the actual naming, designators for charge, radical function, water of crystallization, bridging or multi co-ordinating ligands are indicated. Brackets are set to eliminate ambiguities. Last but not least, the ligand names (if there are different) are brought separately into alphabetical order: multiplication prefices (only!) are ignored.

Cations and anions are treated separately (in this order).

Exemplification:

compound: H_2O; **core:** dihydrogen; **ligand(s):** oxido; **functional markers:** μ; **name:** μ-oxido dihydrogen

compound: ClO_3^-; **core:** chlorate; **ligand(s):** oxido; **functional markers:** (1-); **name:** trioxido chlorate (1-)

compound: ClO_2^-; **core:** chlorate; **ligand(s):** oxido; **functional markers:** (1-); **name:** dioxido chlorate (1-)

compound: $NO^{\bullet}$; **core:** nitrogen; **ligand(s):** oxido; **functional markers:** (•); **name:** oxido nitrogen(•)

compound: $ONOO^-$; **core:** nitrate; **ligand(s):** dioxido / oxido; **functional markers:** (1-); **name:** (dioxido)oxido nitrate(1-)

compound: $K_4[Fe(CN)_6]$; **core:** potassium / ferrate; **ligand(s):** hexacyanido; **functional markers:** (4-); **name:** potassium hexacyanidoferrate(4-)

compound: K[AuS(S_2)]; **core:** potassium / aurate; **ligand(s):** disulfido / sulfido; **functional markers:** (1-); **name:** potassium (disulfido)sulfido aurate(1-)

compound: [Ni($CO)_4$]; **core:** niccol; **ligand(s):** oxidocarbon; **functional markers:** -; **name:** tetra (oxidocarbon) niccol

compound: $CuSO_4$•$5H_2O$; **core:** copper / sulfate; **ligand(s):** oxido; **functional markers:** water(1/5); **name:** copper tetraoxidosulfate-water(1/5)

Substitutive nomenclature

This ansatz generalises the organic nomenclature and follows basically the same rules. All elements are given -*ane* base names and the unsaturated bonds are filled up with hydrogen atoms. E.g. *oxidane* is a single oxygen atom, the loose ends of which are connected to hydrogen atoms, we also call it water H_2O. *Dioxidane* is a molecule with a chain of two oxygen atoms, with hydrogen atoms at every loose bond, this makes H_2O_2 or hydrogen peroxide.

BH3 borane | CH4 methane | NH3 azane | H2O oxidane | HF fluorane
AlH3 alumane | SiH4 silane | PH3 phosphane | H2S sulfane | HCl chlorane
GaH3 gallane | GeH4 germane | AsH3 arsane | H2Se selane | HBr bromane
InH3 indigane | SnH4 stannane | SbH3 stibane | H2Te tellane | HI iodane
TlH3 thallane | PbH4 plumbane | BiH3 bismuthane | H2Po polane | HAt astatane

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Boron

Boron is a chemical element with atomic number 5 and the chemical symbol **B**. A trivalent metalloid element, boron occurs abundantly in the ore borax. Boron is never found free in nature.

Several allotropes of boron exist; amorphous boron is a brown powder, though metallic (crystalline) boron is black, hard (9.3 on Mohs' scale), and a weak conductor at room temperature.

Elemental boron is used as a dopant in the semiconductor industry, while boron compounds play important roles as light structural materals, nontoxic insecticides and preservatives, and reagents for chemical synthesis.

Boron is an essential plant nutrient, and as an ultratrace mineral is necessary for the optimal health of animals, though its physiological role in animals is poorly understood.

Group, Period, Block: 13, 2, p
Atomic mass: 10.811(7) g/mol
Electron configuration: $1s^2\ 2s^2\ 2p^1$
Electrons per shell: 2, 3

Notable physical and chemical characteristics of the element and boron nitride

Brown amorphous boron is a product of certain chemical reactions. It contains boron atoms randomly bonded to each other without long range order.

Crystalline boron, a very hard material with a high melting point, exists in many polymorphs. Two rhombohedral forms, α-boron and β-boron containing 12 and 106.7 atoms in the rhombohedral unit cell respectively, and 50-atom tetragonal boron are the three most characterised crystalline forms. These forms are somewhat analogous to carbon crystals (diamond), with the exception that boron has many different possible structures because the 3-bond structure of boron atoms forces them to be asymmetrically bonded in 3-dimensional space.

Optical characteristics of crystalline/metallic boron include the transmittance of infrared light. At standard temperatures, metallic boron is a poor electrical conductor, but is a good electrical conductor at high temperatures.

Chemically boron is electron-deficient, possessing a vacant p-orbital. It is an electrophile. Compounds of boron often behave as Lewis acids, readily bonding with electron-rich substances to compensate for boron's electron deficiency. The reactions of boron are dominated by such requirement for electrons. Also, boron is the least electronegative non-metal, meaning that it is usually oxidized (loses electrons) in

reactions.

Boron nitride is a material in which the extra electron of nitrogen (with respect to carbon) in some ways compensates for boron's deficiency of an electron. Boron nitride can be used to make crystals that are extremely hard, second in hardness only to diamond, and the similarity of this compound to diamond extends to other applications. Like diamond, boron nitride acts as an electrical insulator but is an excellent conductor of heat.

Like carbon, boron nitride exists in a second form that has structural and lubricating qualities similar to graphite. This form of boron nitride is composed of layers of fused hexagonal sheets (analogous to graphite). These sheets (unlike those in graphite) are **in registry**. This means that layers are placed directly upon one another such that a viewer looking down onto the structure would view only the top layer. The polar B-N bonds interfere with electron transfer so that boron nitride in this form is not an electrical conductor (in contrast to graphite which is a semimetal that conducts electricity through a network of pi bonds in the plane of its hexagonal sheets).

Boron nitride nanotubes can be constructed analogously to carbon nanotubes.

Boron is also similar to carbon with its capability to form stable covalently bonded molecular networks.

Occurrence

The United States and Turkey are the world's largest producers of boron. Boron does not appear in nature in elemental form but is found combined in borax, boric acid, colemanite, kernite, ulexite and borates. Boric acid is sometimes found in volcanic spring waters. Ulexite is a borate mineral that naturally has properties of fiber optics.

Economically important sources are from the ore rasorite (kernite) and tincal (borax ore) which are both found in the Mojave Desert of California, with borax being the most important source there. Turkey is another place where extensive borax deposits are found.

Even a boron-containing natural antibiotic, boromycin, isolated from streptomyces, is known.

Pure elemental boron is not easy to prepare. The earliest methods used involve reduction of boric oxide with metals such as magnesium or aluminium. However the product is almost always contaminated with metal borides. (The reaction is quite spectacular though). Pure boron can be prepared by reducing volatile boron halogenides with hydrogen at high temperatures. The highly pure boron, for the use in semiconductor industry, is produced by the decomposition of diborane at high temperatures and than further purified with the Czochralski process.

Food

Boron occurs in all foods produced by plants. Since 1989 its nutritional value has been argued. The U.S. Department of agriculture conducted an experiment in which postmenopausal women took 3 mg of boron a day. The results showed that boron can drop excretion of calcium by 44%, and activate estrogen and vitamin D.

Analytical quantification

For determination of boron content in food or materials the colorimetric curcumin method is used. Boron has to be transferred to boric acid or borates and on reaction with curcumin in acidic solution a red colored boron-chelate complex - rosocyanine - is formed.

Isotopes

Boron has two naturally-occurring and stable isotopes, ^{11}B (80.1%) and ^{10}B (19.9%). The mass difference results in a wide range of $\delta^{11}B$ values in natural waters, ranging from -16 to +59. There are 13 known isotopes of boron, the shortest-lived isotope is ^{7}B which decays through proton emission and alpha decay. It has a half-life of 3.26500×10^{-22} s. Isotopic fractionation of boron is controlled by the exchange reactions of the boron species $B(OH)_3$ and $B(OH)_4$. Boron isotopes are also fractionated during mineral crystallization, during H_2O phase changes in hydrothermal systems, and during hydrothermal alteration of rock. The latter effect species preferential removal of the $^{10}B(OH)_4$ ion onto clays results in solutions enriched in $^{11}B(OH)_3$ may be responsible for the large ^{11}B enrichment in seawater relative to both oceanic crust and continental crust; this difference may act as an isotopic signature.

The exotic ^{17}B exhibits a Nuclear halo.

Depleted boron

The ^{10}B isotope is good at capturing thermal neutrons from cosmic radiation. It then undergoes fission - producing a gamma ray, an alpha particle, and a lithium ion. When this happens inside of an integrated circuit, the fission products may then dump charge into nearby chip structures, causing data loss (bit flipping, or single event upset). In critical semiconductor designs, **depleted boron** -- consisting almost entirely of ^{11}B -- is used to avoid this effect, as one of radiation hardening measures. ^{11}B is a by-product of the nuclear industry.

B-10 enriched boron

The ^{10}B isotope is good at capturing thermal neutrons, and this quality has been used in both radiation shielding and in neutron capture medical therapy where a tumor is treated with a compound containing

^{10}B is attached to a tissue, and the patient treated with a relatively low dose of thermal neutrons which go on to cause energetic and short range alpha radiation in the tissue treated with the boron isotope.

In nuclear reactors, ^{10}B is used for reactivity control and in emergency shutdown systems. It can serve either function in the form of borosilicate rods or as boric acid. In pressurized water reactors, boric acid is added to the reactor coolant when the plant is shut down for refueling. It is then slowly filtered out over many months as fissile material is used up and the fuel becomes less reactive.

In future manned interplanetary spacecraft, ^{10}B has a theoretical role as structural material (as boron fibers or BN nanotube material) which also would serve a special role in the radiation shield. One of the difficulties in dealing with cosmic rays which are mostly high energy protons, is that some secondary radiation from interaction of cosmic rays and spacecraft structural materials, is high energy spallation neutrons. Such neutrons can be moderated by materials high in light elements such as structural polyethylene, but the moderated neutrons continue to be a radiation hazard unless actively absorbed in a way which dumps the absorption energy in the shielding, far away from biological systems. Among light elements that absorb thermal neutrons, ^{6}Li and ^{10}B appear as potential spacecraft structural materials able to do double duty in this regard.

History

Compounds of boron (Arabic *Buraq* from Persian *Burah* from Turkish *Bor) have been known of for thousands of years. In early Egypt, mummification depended upon an ore known as natron, which contained borates as well as some other common salts. Borax glazes were used in China from 300 AD, and boron compounds were used in glassmaking in ancient Rome.*

The element was not isolated until 1808 by Sir Humphry Davy, Joseph Louis Gay-Lussac, and Louis Jacques Thénard, to about 50 percent purity, by the reduction of boric acid with sodium or magnesium. These men did not recognize the substance as an element. It was Jöns Jakob Berzelius in 1824 that identified boron as an element. The first pure boron was produced by the American chemist W. Weintraub in 1909, which is doubted by some researchers.

Boron was not believed to be useful to the human body until 1989 research suggested its signficance

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Carbon

Carbon has the symbol **C** and atomic number 6. An abundant nonmetallic, tetravalent element, carbon has several allotropic forms.

Group, Period, Block: 14, 2, p
Atomic mass: 12.0107(8) g/mol
Electron configuration: $1s^2\ 2s^2\ 2p^2$
Electrons per shell: 2, 4

Carbon occurs in all organic life and is the basis of organic chemistry. This nonmetal also has the interesting chemical property of being able to bond with itself and a wide variety of other elements, forming nearly ten million known compounds. When united with oxygen it forms carbon dioxide, which is vital to plant growth. When united with hydrogen, it forms various compounds called hydrocarbons which are essential to industry in the form of fossil fuels. When combined with both oxygen and hydrogen it can form many groups of compounds including fatty acids, which are essential to life, and esters, which give flavor to many fruits. The isotope carbon-14 is commonly used in radioactive dating.

Notable characteristics

Carbon is a remarkable element for many reasons. Its different forms include the hardest naturally occurring substance (diamond) and one of the softest substances (graphite) known. Moreover, it has a great affinity for bonding with other small atoms, including other carbon atoms, and its small size makes it capable of forming multiple bonds. Because of these properties, carbon is known to form nearly ten million different compounds, the large majority of all chemical compounds. Carbon compounds form the basis of all life on Earth and the carbon-nitrogen cycle provides some of the energy produced by the Sun and other stars. Moreover, carbon has the highest melting/sublimation point of all elements. At atmospheric pressure it has no actual melting point as its triple point is at 10 MPa (100 bar) so it sublimates above 4000 K. Thus it remains solid at higher temperatures than the highest melting point metals like tungsten or rhenium, regardless of its allotropic form.

Carbon was not created during the Big Bang due to the fact that it needs a triple collision of alpha particles (helium nuclei) to be produced. The universe initially expanded and cooled too fast for that to be possible. It is produced, however, in the interior of stars in the horizontal branch, where stars transform a helium core into carbon by means of the triple-alpha process. It was also created in a multi-atomic state.

Organic compounds

The most prominent oxide of carbon is carbon dioxide, CO_2. This is a minor component of the Earth's

atmosphere, produced and used by living things, and a common volatile elsewhere. In water it forms trace amounts of carbonic acid, H_2CO_3, but as most compounds with multiple single-bonded oxygens on a single carbon it is unstable. Through this intermediate, though, resonance-stabilized carbonate ions are produced. Some important minerals are carbonates, notably calcite. Carbon disulfide, CS_2, is similar.

The other oxides are carbon monoxide, CO, the uncommon carbon suboxide, C_3O_2 and even carbon trioxide, CO_3. Carbon monoxide is formed by incomplete combustion, and is a colorless, odorless gas. The molecules each contain a triple bond and are fairly polar, resulting in a tendency to bind permanently to hemoglobin molecules, so that the gas is highly poisonous. Cyanide, CN^-, has a similar structure and behaves a lot like a halide ion; the nitride cyanogen, $(CN)_2$, is related.

With reactive metals, such as tungsten, carbon forms either carbides, C^-, or acetylides, C_2^{2-} to form alloys with very high melting points. These anions are also associated with methane and acetylene, both very weak acids. All in all, with an electronegativity of 2.5, carbon prefers to form covalent bonds. A few carbides are covalent lattices, like carborundum, SiC, which resembles diamond.

Carbon chains

Carbon has the ability to form long chains with interconnecting C-C bonds. This property is called catenation. Carbon-carbon bonds are fairly strong, and abnormally stable. This property is important as it allows carbon to form a huge number of compounds; in fact, there are more known carbon-containing compounds than all the compounds of the other chemical elements combined.

The simplest form of an organic molecule is the hydrocarbon - a large family of organic molecules that, by definition, are composed of hydrogen atoms bonded to a chain of carbon atoms. Chain length, side chains and functional groups all affect the properties of organic molecules.

Allotropes

The allotropes of carbon are the different molecular configurations that pure carbon can take.

The three relatively well-known allotropes of carbon are amorphous carbon, graphite, and diamond. Several exotic allotropes have also been synthesized or discovered, including fullerenes, carbon nanotubes, lonsdaleite and aggregated diamond nanorods.

In its amorphous form, carbon is essentially graphite but not held in a crystalline macrostructure. It is, rather, present as a powder which is the main constituent of substances such as charcoal, lampblack (soot) and activated carbon.

At normal pressures carbon takes the form of graphite, in which each atom is bonded to three others in a plane composed of fused hexagonal rings, just like those in aromatic hydrocarbons. The two known forms of graphite, alpha (hexagonal) and beta (rhombohedral), both have identical physical properties, except for their crystal structure. Graphites that naturally occur have been found to contain up to 30% of the beta form, when synthetically-produced graphite only contains the alpha form. The alpha form can be converted to the beta form through mechanical treatment and the beta form reverts back to the alpha form when it is heated above 1000 °C.

Because of the delocalization of the pi-cloud, graphite conducts electricity. The material is soft and the sheets, frequently separated by other atoms, are held together only by Van der Waals forces, so easily slip past one another.

At very high pressures carbon forms an allotrope called diamond, in which each atom is bonded to four others. Diamond has the same cubic structure as silicon and germanium and, thanks to the strength of the carbon-carbon bonds, is together with the isoelectronic boron nitride (BN) the hardest substance in terms of resistance to scratching. The transition to graphite at room temperature is so slow as to be unnoticeable. Under some conditions, carbon crystallizes as Lonsdaleite, a form similar to diamond but hexagonal.

Fullerenes have a graphite-like structure, but instead of purely hexagonal packing, also contain pentagons (or possibly heptagons) of carbon atoms, which bend the sheet into spheres, ellipses or cylinders. The properties of fullerenes (also called "buckyballs" and "buckytubes") have not yet been fully analyzed. All the names of fullerenes are after Buckminster Fuller, developer of the geodesic dome, which mimics the structure of "buckyballs".

A nanofoam allotrope has been discovered which is ferromagnetic.

Carbon allotropes include:

- Diamond: Hardest known natural mineral. Structure: each atom is bonded tetrahedrally to four others, making a 3-dimensional network of puckered six-membered rings of atoms.
- Graphite: One of the softest substances. Structure: each atom is bonded trigonally to three other atoms, making a 2-dimensional network of flat six-membered rings; the flat sheets are loosely bonded.
- Fullerenes: Structure: comparatively large molecules formed completely of carbon bonded trigonally, forming spheroids (of which the best-known and simplest is the buckminsterfullerene or buckyball, because of its soccerball-shaped structure).
- Chaoite: A mineral believed to be formed in meteorite impacts.
- Lonsdaleite: A corruption of diamond. Structure: similar to diamond, but forming a hexagonal crystal lattice.
- Amorphous carbon: A glassy substance. Structure: an assortment of carbon molecules in a non-crystalline, irregular, glassy state.
- Carbon nanofoam (discovered in 1997): An extremely light magnetic web. Structure: a low-density

web of graphite-like clusters, in which the atoms are bonded trigonally in six- and seven-membered rings.
- Carbon nanotubes: Tiny tubes. Structure: each atom is bonded trigonally in a curved sheet that forms a hollow cylinder.
- Aggregated diamond nanorods (synthesised in 2005): The most recently discovered allotrope and the hardest substance known to man.
- Lampblack: Consists of small graphitic areas. These areas are randomly distributed, so the whole structure is isotropic.
- 'Glassy carbon': An isotropic substance that contains a high proportion of closed porosity. Unlike normal graphite, the graphitic layers are not stacked like pages in a book, but have a more random arrangement.

Carbon fibers are similar to glassy carbon. Under special treatment (stretching of organic fibers and carbonization) it is possible to arrange the carbon planes in direction of the fiber. Perpendicular to the fiber axis there is no orientation of the carbon planes. The result are fibers with a higher specific strength than steel.

The system of carbon allotropes spans a range of extremes.

Between diamond and graphite:

- Graphite is soft and is used in pencils
- Diamond is the hardest mineral known to man (although aggregated diamond nanorods are now believed to be even harder), but graphite is one of the softest.
- Diamond is the ultimate abrasive, but graphite is a very good lubricant.
- Diamond is an excellent electrical insulator, but graphite is a conductor of electricity.
- Diamond is usually transparent, but graphite is opaque.
- Diamond crystallizes in the cubic system but graphite crystallizes in the hexagonal system.

Between amorphous carbon and nanotubes:

- Amorphous carbon is among the easiest materials to synthesize, but carbon nanotubes are extremely expensive to make.
- Amorphous carbon is completely isotropic, but carbon nanotubes are among the most anisotropic materials ever produced.

History and Etymology

Carbon was discovered in prehistory and was known to the ancients, who manufactured it by burning organic material in insufficient oxygen (making charcoal). Diamonds have long been considered rare and beautiful. One of the last-known allotropes of carbon, fullerenes, were discovered as byproducts of molecular beam experiments in the 1980s.

The name comes from French *charbone*, which in turn came from Latin *carbo*, meaning charcoal. In German and Dutch, the names for carbon are *Kohlenstoff* and *koolstof* respectively, both literally meaning "coal-stuff".

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Halogen

The **halogens** are a chemical series. They are the elements in Group 17 (old-style: VII or VIIA) of the periodic table: fluorine (**F**), chlorine (**Cl**), bromine (**Br**), iodine (**I**), astatine (**At**) and the as yet undiscovered ununseptium (**Uus**). The term halogen was coined to mean elements which produce salt in union with a metal. It comes from 18th century scientific French nomenclature based on erring adaptations of Greek roots.

These elements are diatomic molecules in their natural form. They require one more electron to fill their outer electron shells, and so have a tendency to form a singly-charged negative ion. This negative ion is referred to as a *halide* ion; salts containing these ions are known as halides.

Fluorine (from L. fluere, meaning "to flow") has the symbol F and atomic number 9. Atomic fluorine is univalent and is the most chemically reactive and electronegative of all the elements.
Group, Period, Block: 17, 2, p
Atomic mass: 18.9984032(5) g/mol
Electron configuration: $1s^2\ 2s^2\ 2p^5$
Electrons per shell: 2, 7

Chlorine (from the Greek chloros, meaning "pale green") has atomic number 17 and symbol Cl. It is a halogen, found in the periodic table in group 17. As the chloride ion, which is part of common salt and other compounds, it is abundant in nature and necessary to most forms of life, including humans. In its elemental form under standard conditions, it is a pale green gas about 2.5 times as dense as air.
Group, Period, Block: 17, 3, p
Atomic mass: 35.453(2) g/mol
Electron configuration: $3s^2\ 3p^5$
Electrons per shell: 2, 8, 7

Bromine (from Gr. brómos, meaning "stench") has the symbol Br and atomic number 35.
Group, Period, Block: 17, 4, p
Atomic mass: 79.904(1) g/mol
Electron configuration: $3d^{10}\ 4s^2\ 4p^5$
Electrons per shell: 2, 8, 18, 7

Iodine (from the Greek word Iodes, meaning "violet") has the symbol I and atomic number 53.
Group, Period, Block: 17, 5, p
Atomic mass: 126.90447(3) g/mol
Electron configuration: $4d^{10}\ 5s^2\ 5p^5$
Electrons per shell: 2, 8, 18, 18, 7

Halogens are highly reactive, and as such can be harmful or lethal to biological organisms in sufficient

quantities. Fluorine is the most reactive element in existence, even attacking glass, and forming compounds with the heavier noble gases. It is a corrosive, highly toxic gas. Chlorine and iodine are both used as disinfectants for such things as drinking water, swimming pools, fresh wounds, dishes, and surfaces. They kill bacteria and other potentially harmful microorganisms, a process known as sterilization. Their reactive properties are also put to use in bleaching. Chlorine is the active ingredient of most fabric bleaches and is used in the production of most paper products.

Halide ions combined with single hydrogen atoms form the *hydrohalic* acids (i.e., HF, HCl, HBr, HI), a series of particularly strong acids. (HAt, or "hydrastatic acid", should also qualify, but it is not typically included in discussions of hydrohalic acid due to astatine's extreme instability toward alpha decay.)

They react with each other to form interhalogen compounds. Diatomic interhalogen compounds (BrF, ICl, ClF, etc.) bear strong superficial resemblance to the pure halogens.

Many synthetic organic compounds such as plastic polymers, and a few natural ones, contain halogen atoms; these are known as *halogenated* compounds or organic halides. Chlorine is by far the most abundant of the halogens, and the only one needed in relatively large amounts (as chloride ions) by humans. For example, chloride ions play a key role in brain function by mediating the action of the inhibitory transmitter GABA and are also used by the body to produce stomach acid. Iodine is needed in trace amounts for the production of thyroid hormones such as thyroxine. On the other hand, neither fluorine nor bromine are believed to be really essential for humans, although small amounts of fluoride can make tooth enamel resistant to decay.

They show a number of trends when moving down the group - for instance, decreasing electronegativity and reactivity, increasing melting and boiling point.

The incorporation of halogen atoms into a lead results in analogues that are more lipophilic and so less water soluble. Consequently, halogen atoms are used to improve the penetration of lipid membranes. However, there is an undesirable tenedency for halogenated drugs to accumulate in lipid tissue.

The chemical reactivity of halogen atoms depends on both their point of attachment to the lead and the nature of the halogen. Aromatic halogen groups are far less reactive than aliphatic halogen groups, which can exhibit considerable chemical reactivity. For aliphatic carbon-halogen bonds the C-F bond is the strongest and ussually less chemically reactive than aliphatic C-H bonds. The other aliphatic-halogen bonds are weaker, their reactivity increasing down the periodic table. They are usually more chemically reactive than aliphatic C-H bonds. Consequently, the most popular halogen substitutions are the less reactive aromatic fluorine and chlorine groups.

The hydrogen atom

Hydrogen (Latin: 'hydrogenium', from Ancient Greek: hydro: "water" and genes: "forming") has the symbol H and atomic number 1.

Group, Period, Block: 1, 1, s
Atomic mass: 1.00794(7) g/mol
Electron configuration: $1s^1$
Electrons per shell: 1

Electron energy levels

The ground state energy level of the electron in a hydrogen atom is 13.6 eV, which is equivalent to an ultraviolet photon of roughly 92 nm.

The energy levels of hydrogen can be calculated fairly accurately using the Bohr model of the atom, which conceptualizes the electron as "orbiting" the proton in analogy to the Earth's orbit of the sun. However, electrons and protons are attracted to one another by the electromagnetic force, while planets and celestial objects are attracted to each other by gravity. Because of the discretization of angular momentum postulated in early quantum mechanics by Bohr, the electron in the Bohr model can only occupy certain allowed distances from the proton, and therefore only certain allowed energies. A more accurate description of the hydrogen atom comes from a purely quantum mechanical treatment that uses the Schrödinger equation to calculate the probability density of the electron around the proton. Treating the electron as a matter wave reproduces chemical results such as shape of the hydrogen atom more naturally than the particle-based Bohr model, although the energy and spectral results are the same. Modeling the system fully using the reduced mass of nucleus and electron (as one would do in the two-body problem in celestial mechanics) yields an even better formula for the hydrogen spectra, and also the correct spectral shifts for the isotopes deuterium and tritium. Very small adjustments in energy levels in the hydrogen atom, which correspond to actual spectral effects, may be determined by using a full quantum mechanical theory which corrects for the effects of special relativity, and by accounting for quantum effects arrising from production of virtual particles in the vacuum and as a result of electric fields.

In hydrogen gas, the electronic ground state energy level is split into hyperfine structure levels because of magnetic effects of the quantum mechanical spin of the electron and proton. The energy of the atom when the proton and electron spins are aligned is higher than when they are not aligned. The transition between these two states can occur through emission of a photon through a magnetic dipole transition. Radio telescopes can detect the radiation produced in this process, which is used to map the distribution of hydrogen in the galaxy.

Isotopes

Hydrogen has three naturally occurring isotopes, denoted ^{1}H, ^{2}H, and ^{3}H. Other, highly unstable nuclei (^{4}H to ^{7}H) have been synthesized in the laboratory but not observed in nature.

- **^{1}H** is the most common hydrogen isotope with an abundance of more than 99.98%. Because the nucleus of this isotope consists of only a single proton, it is given the descriptive but rarely used formal name *protium*.

- **^{2}H**, the other stable hydrogen isotope, is known as *deuterium* and contains one proton and one neutron in its nucleus. Deuterium comprises 0.0026-0.0184% of all hydrogen on Earth. It is not radioactive, and does not represent a significant toxicity hazard. Water enriched in molecules that include deuterium instead of normal hydrogen is called heavy water. Deuterium and its compounds are used as a nonradioactive label in chemical experiments and in solvents for ^{1}H-NMR spectroscopy. Heavy water is used as a neutron moderator and coolant for nuclear reactors. Deuterium is also a potential fuel for commercial nuclear fusion.

- **^{3}H** is known as *tritium* and contains one proton and two neutrons in its nucleus. It is radioactive, decays through beta decay with a half-life of 12.32 years. Small amounts of tritium occur naturally because of the interaction of cosmic rays with atmospheric gases; tritium has also been released during nuclear weapons tests. It is used in nuclear fusion reactions, as a tracer in isotope geochemistry, and specialized in self-powered lighting devices. Tritium was also used in chemical and biological labeling experiments as radioactive label.

Hydrogen is the only element that has different names for its isotopes in common use today. (During the early study of radioactivity, various heavy radioactive isotopes were given names, but such names are no longer used). The symbols D and T (instead of ^{2}H and ^{3}H) are sometimes used for deuterium and tritium, but the corresponding symbol P is already in use for phosphorus and thus is not available for protium). IUPAC states that while this use is common it is not preferred.

Compounds

Covalent and organic compounds

While H_2 is not very reactive under standard conditions, it does form compounds with most elements.

Millions of hydrocarbons are known, but they are not formed by the direct reaction of elementary hydrogen and carbon. Hydrogen can form compounds with elements that are more electronegative, such as halogens (e.g., F, Cl, Br, I) and chalcogens (O, S, Se); in these compounds hydrogen takes on a partial positive charge. When bonded to fluorine, oxygen, or nitrogen, hydrogen can participate in a form of strong noncovalent bonding called hydrogen bonding, which is critical to the stability of many biological molecules. Hydrogen also forms compounds with less electronegative elements, such as the metals and metalloids, in which it takes on a partial negative charge. These compounds are often known as hydrides.

Hydrogen forms a vast array of compounds with carbon. Because of their general association with living things, these compounds camed to be called organic compounds; the study of their properties is known as organic chemistry and their study in the context of living organisms is known as biochemistry. By some definitions "organic" compounds are only required to contain carbon (as a classic historical example, urea); however most of them also contain hydrogen, and since it is the carbon-hydrogen bond which gives this class of compounds most of its particular chemical characteristics, carbon-hydrogen bonds are requred in some definitions of the word "organic," in chemistry (this latter definition is not perfect, however, as in this definition urea would *not* be included as an organic compound).

In inorganic chemistry, hydrides can also serve as bridging ligands that link two metal centers in a coordination complex. This function is particularly common in group 13 elements, especially in boranes (boron hydrides) and aluminum complexes, as well as in clustered carboranes.

Hydrides

Compounds of hydrogen are often called hydrides, a term that is used fairly loosely. To chemists, the term "hydride" usually implies that the H atom has acquired a negative or anionic character, denoted H^-. The hydride anion is a convenient bookkeeping tool but does not exist *per se* - alkali metal hydrides, e.g. sodium hydride (NaH), are polymeric and have no solution chemistry. Electrolysis of molten lithium hydride (LiH) produced a stoichiometric quantity of hydrogen at the anode. In lithium aluminum hydride, the AlH_4^- anion carries hydridic centers firmly attached to the Al(III). Although hydrides can be formed with almost all main-group elements, the number and combination of possible compounds varies widely; for example, there are over 100 binary borane hydrides known, but only one binary aluminum hydride. Binary indium hydride has not yet been identified, although larger complexes exist.

"Protons" and acids

Oxidation of H_2 formally gives the proton, H^+. This species is central to discussion of acids, though the term proton is used loosely to refer to positively charged or cationic hydrogen, denoted H^+. A bare proton H^+ cannot exist in solution because of its strong tendency to attach itself to atoms or molecules with electrons. To avoid the convenient fiction of the naked "solvated proton" in solution, acidic aqueous solutions are sometimes considered to contain the hydronium ion (H_3O^+) organized into clusters to form $H_9O_4^+$. Other oxonium ions are found when water is in solution with other solvents.

Although exotic on earth, one of the most common ions in the universe is the H_3^+ ion, known as protonated molecular hydrogen or the triatomic hydrogen cation.

History

Discovery of H_2

Hydrogen gas, H_2, was first artificially produced and formally described by T. von Hohenheim (also known as Paracelsus, 1493-1541) via the mixing of metals with strong acids. He was unaware that the flammable gas produced by this chemical reaction was a new chemical element. In 1671, Robert Boyle rediscovered and described the reaction between iron filings and dilute acids, which results in the production of hydrogen gas. In 1766, Henry Cavendish was the first to recognize hydrogen gas as a discrete substance, by identifying the gas from a metal-acid reaction as "inflammable air", and further finding that the gas produces water when burned. Cavendish had stumbled on hydrogen when experimenting with acids and mercury. Although he wrongly assumed that hydrogen was a liberated component of the mercury rather than the acid, he was still able to accurately describe several key properties of hydrogen. He is usually given credit for its discovery as an element. In 1783 Antoine Lavoisier gave the element the name of hydrogen when he (with Laplace) reproduced Cavendish's finding that water is produced when hydrogen is burned. Lavoisier's name for the gas won out.

One of the first uses of H_2 was for balloons. The H_2 was obtained by reacting sulfuric acid and metallic iron. Infamously, H_2 was used in the Hindenburg airship that was destroyed in a midair fire.

Role in history of quantum theory

Because of its relatively simple atomic structure, consisting only of a proton and an electron, the hydrogen atom, together with the spectrum of light produced from it or absorbed by it, has been central to the development of the theory of atomic structure. Furthermore, the corresponding simplicity of the hydrogen molecule and the corresponding cation H_2^+ allowed fuller understanding of the nature of the chemical bond, which followed shortly after the quantum mechanical treatment of the hydrogen atom had been developed in the mid-1920s.

One of the first quantum effects to be explicitly noticed (but not understood at the time) was Maxwell's observation, half a century before full quantum mechanical theory arrived. He observed that the specific heat capacity of H_2 unaccountably departs from that of a diatomic gas below room temperature and begins to increasingly resemble that of a monatomic gas at cryogenic temperatures. According to quantum theory, this behavior arises from the spacing of the (quantized) rotational energy levels, which are particularly wide-spaced in H_2 because of its low mass. These widely spaced levels inhibit equal partition of heat energy into rotational motion in hydrogen at low temperatures. Diatomic gases composed of heavier atoms do not have such widely spaced levels and do not exhibit the same effect.

Nitrogen

Nitrogen is a chemical element which has the symbol **N** and atomic number 7 in the periodic table. Elemental nitrogen is a colorless, odorless, tasteless and mostly inert diatomic gas at standard conditions, constituting 78.08% percent of Earth's atmosphere. Nitrogen is a constituent element of all living tissues and amino acids. Many industrially important compounds, such as ammonia, nitric acid, and cyanides, contain nitrogen.

Group, Period, Block: 15, 2, p
Atomic mass: 14.0067(2) g/mol
Electron configuration: $1s^2\ 2s^2\ 2p^3$
Electrons per shell: 2, 5

Notable characteristics

Nitrogen is a non-metal, with an electronegativity of 3.0. It has five electrons in its outer shell and is therefore trivalent in most compounds. Nitrogen condenses at 77 K at atmospheric pressure and freezes at 63 K. Liquid nitrogen is a common cryogen.

Biological role

Nitrogen is an essential part of amino acids and nucleic acids, both of which are essential to all life.

Molecular nitrogen in the atmosphere cannot be used directly by either plants or animals, and needs to be converted to other compounds, or "fixed," in order to be used by life. Precipitation often contains substantial quantities of ammonium and nitrate, both thought to be a result of nitrogen fixation by lightning and other atmospheric electric phenomena. However, because ammonium is preferentially retained by the forest canopy relative to atmospheric nitrate, most of the fixed nitrogen that reaches the soil surface under trees is in the form of nitrate. Soil nitrate is preferentially assimilated by tree roots relative to soil ammonium.

Specific bacteria (e.g. Rhizobium *trifolium*) possess nitrogenase enzymes which can fix atmospheric nitrogen into a form (ammonium ion) which is chemically useful to higher organisms. This process requires a large amount of energy and anoxic conditions. Such bacteria may be free in the soil (e.g. azotobacter) but normally exist in a symbiotic relationship in the root nodules of leguminous plants (e.g. clover or the soya bean plant). Nitrogen fixating bacteria can be symbiotic with a number of unrelated plant species. Common examples are legumes, alders, lichens, casuarina, myrica, liverwort, and gunnera.

As part of the symbiotic relationship, the plant subsequently converts the ammonium ion to nitrogen oxides and amino acids to form proteins and other biologically useful molecules, such as alkaloids. In

return for the usable (fixed) nitrogen, the plant secretes sugars to the symbiotic bacteria.

Some plants are able to assimilate nitrogen directly in the form of nitrates which may be present in soil from natural mineral deposits, artificial fertilizers, animal waste, or organic decay (as the product of bacteria, but not bacteria specifically associated with the plant). Nitrates absorbed in this fashion are converted to nitrites by the enzyme *nitrate* reductase, and then converted to ammonia by another enzyme called *nitrite* reductase.

Nitrogen compounds are basic building blocks in animal biology. Animals use nitrogen-containing amino acids from plant sources, as starting materials for all nitrogen-compound animal biochemistry, including the manufacture of proteins and nucleic acids. Some plant-feeding insects are so dependent on nitrogen in their diet, that varying the amount of nitrogen fertilizer applied to a plant can affect the birth rate of the insects feeding on it (Jahn et al. 2005).

Many saltwater fish manufacture large amounts of trimethylamine oxide to protect them from the high osmotic effects of their environment (conversion of this compound to dimethylamine is responsible for the early odor in unfresh saltwater fish: PMID 15186102). In animals, the free radical molecule nitric oxide (NO), which is derived from an amino acid, serves as an important regulatory molecule for circulation.

Animal metabolism of NO results in production of nitrite. Animal metabolism of nitrogen in proteins generally results in excretion of urea, while animal metabolism of nucleic acids results in excretion of urea and uric acid. The characteristic odor of animal flesh decay is caused by nitrogen-containing long-chain amines, such as putrescine and cadaverine.

Decay of organisms and their waste products may produce small amounts of nitrate, but most decay eventually returns nitrogen content to the atmosphere, as molecular nitrogen.

Occurrence

Nitrogen is the largest single component of the Earth's atmosphere (78.084% by volume, 75.5% by weight).

^{14}Nitrogen is created as part of the fusion processes in stars.

Compounds that contain this element have been observed by astronomers, and molecular nitrogen has been detected in interstellar space by David Knauth and coworkers using the Far Ultraviolet Spectroscopic Explorer. Molecular nitrogen is a major constituent of Titan's thick atmosphere, and occurs in trace amounts of other planetary atmospheres.

Nitrogen is present in all living tissues as proteins, nucleic acids and other molecules. It is a large component of animal waste (for example, guano), usually in the form of urea, uric acid, and compounds

of these nitrogenous products.

Isotopes

There are two stable isotopes of nitrogen: ^{14}N and ^{15}N. By far the most common is ^{14}N (99.634%), which is produced in the CNO cycle in stars and the remaining is ^{15}N. Of the ten isotopes produced synthetically, ^{13}N has a half life of nine minutes and the remaining isotopes have half lives on the order of seconds or less. Biologically-mediated reactions (e.g., assimilation, nitrification, and denitrification) strongly control nitrogen dynamics in the soil. These reactions almost always result in ^{15}N enrichment of the substrate and depletion of the product.

The molecular nitrogen in Earth's atmosphere is 0.73% comprised of the isotopomer $^{14}N^{15}N$ and almost all the rest is $^{14}N_2$

History

Nitrogen (Latin *nitrogenium*, where *nitrum* (from Greek *nitron*) means "native soda", and *genes* means "forming") is formally considered to have been discovered by Daniel Rutherford in 1772, who called it *noxious air* or *fixed air*. That there was a fraction of air that did not support combustion was well known to the late 18th century chemist. Nitrogen was also studied at about the same time by Carl Wilhelm Scheele, Henry Cavendish, and Joseph Priestley, who referred to it as *burnt air* or *phlogisticated air*. Nitrogen gas was inert enough that Antoine Lavoisier referred to it as *azote*, from the Greek meaning "lifeless". Animals died in it, and it was the principal component of air in which animals had suffocated and flames had burned to extinction. This term has become the French word for "nitrogen" and later spread out to many other languages.

Compounds of nitrogen were known in the Middle Ages. The alchemists knew nitric acid as *aqua fortis* (strong water). The mixture of nitric and hydrochloric acids was known as *aqua regia* (royal water), celebrated for its ability to dissolve gold (the *king* of metals). The earliest industrial and agricultural applications of nitrogen compounds used it in the form of saltpeter (sodium- or potassium nitrate), notably in gunpowder, and much later, as fertilizer, and later still, as a chemical feedstock.

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Oxygen

Oxygen is a chemical element with the chemical symbol **O** and atomic number 8. Oxygen is the second most common element on Earth, composing around 49% of the mass of Earth's crust and 28% of the mass of Earth as a whole, and is the third most common element in the universe. On Earth, it is usually covalently or ionically bonded to other elements.

Group, Period, Block: 16, 2, p
Atomic mass: 15.9994(3) g/mol
Electron configuration: $1s^2\ 2s^2\ 2p^4$
Electrons per shell: 2, 6

Compounds

Due to its electronegativity, oxygen forms chemical bonds with almost all other elements hence the origin of the original definition of oxidation. The only elements known to escape the possibility of oxidation are a few of the noble gases, and fluorine. The most famous of these oxides is water (H_2O). Other well known examples include compounds of carbon and oxygen, such as carbon dioxide (CO_2), alcohols (R-OH), carbonyls, (R-CO-H or R-CO-R)), and carboxylic acids (R-COOH). Oxygenated radicals such as chlorates (ClO_3^-), perchlorates (ClO_4^-), chromates (CrO_4^{2-}), dichromates ($Cr_2O_7^{2-}$), permanganates (MnO_4^-), and nitrates (NO_3^-) are strong oxidizing agents in and of themselves. Many metals such as iron bond with oxygen atoms, iron(III) oxide (Fe_2O_3). Ozone (O_3) is formed by electrostatic discharge in the presence of molecular oxygen. A double oxygen molecule $(O_2)_2$ is known and is found as a minor component of liquid oxygen. Epoxides are ethers in which the oxygen atom is part of a ring of three atoms.

One unexpected oxygen compound is dioxygen hexafluoroplatinate $O_2^+PtF_6^-$. It was discovered when Neil Bartlett was studying the properties of PtF_6. He noticed a change in color when this compound was exposed to atmospheric air. Bartlett reasoned that xenon should be oxidized by PtF_6. This led him to the discovery of xenon hexafluoroplatinate $Xe^+PtF_6^-$.

Scientific history

Oxygen was first described by Michal Sedziwój, a Polish alchemist and philosopher in the late 16th century. Sedziwój thought of the gas given off by warm nitre (saltpeter) as "the elixir of life".

Oxygen was more quantitatively discovered by the Swedish pharmacist Carl Wilhelm Scheele sometime before 1773, but the discovery was not published until after the independent discovery by Joseph Priestley on August 1, 1774, who called the gas *dephlogisticated air*. Priestley published discoveries in 1775 and Scheele in 1777; consequently Priestley is usually given the credit. Both Scheele and Priestley produced oxygen by heating mercuric oxide.

The gas was named by Antoine Laurent Lavoisier, after Priestley's publication in 1775, from Greek roots meaning "acid-former". As noted, the name reflects the then-common incorrect belief that acids contain oxygen.

Occurrence

Oxygen is the most common component of the Earth's crust (49% by mass), the second most common component of the Earth as a whole (28.2% by mass), and the second most common component of the Earth's atmosphere (20.947% by volume).

Isotopes

Oxygen has seventeen known isotopes with atomic masses ranging from 12.03 u to 28.06 u. Three are stable, ^{16}O, ^{17}O, and ^{18}O, of which ^{16}O is the most abundant (over 99.7%). The radioisotopes all have half-lives of less than three minutes.

An atomic weight of 16 was assigned to oxygen prior to the definition of the unified atomic mass unit based upon ^{12}C. Since physicists referred to ^{16}O only, while chemists meant the naturally abundant mixture of isotopes, this led to slightly different atomic weight scales.

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Phosphorus

Phosphorus, (from the Greek language *phôs* meaning "light", and *phoros* meaning "bearer") has the symbol **P** and atomic number 15. A multivalent nonmetal of the nitrogen group, phosphorus is commonly found in inorganic phosphate rocks and in all living cells.

Group, Period, Block: 15, 3, p
Atomic mass: 30.973762(2) g/mol
Electron configuration: $3s^2\ 3p^3$
Electrons per shell: 2, 8, 5

Phosphorus exists in several allotropes, most commonly white, red and black. White phosphorus (P_4) contains only four atoms, resulting in very high ring strain and instability. White phosphorus glows in the dark, is highly flammable and pyrophoric (self-igniting) upon contact with air as well as toxic. Red phosphorus has a network form which reduces strain and gives greater stability. Red phosphorus does not catch fire in air at temperatures below 240°C whereas white phosphorus ignites at about 40°C. Black phosphorus is amorphous and is the least reactive allotrope.

Due to its high reactivity, phosphorus is never found as a free element in nature. It emits a faint glow upon exposure to oxygen (hence its Greek derivation and the Latin meaning 'morning star') and is an essential element for living organisms. The most important commercial use of phosphorus-based chemicals is the production of fertilizers. They are also widely used in explosives, nerve agents, friction matches, fireworks, pesticides, toothpaste, and detergents.

Characteristics

Phosphorus, in its common form, is a waxy white (or yellowish) solid that has a characteristic, disagreeable smell similar to that of garlic. Pure forms of the element are colorless and transparent. This nonmetal is not soluble in water, but *is* soluble in carbon disulfide. Pure phosphorus ignites spontaneously in air, burning to produce phosphorus pentoxide.

Glow

The glow from phosphorus was the attraction of its discovery around 1669, but the mechanism for that glow was not fully described until 1974. It was known from early times that the glow would persist for a time in a stoppered jar but then cease. Robert Boyle in the 1680s ascribed it to "debilitation" of the air. In fact it is oxygen being consumed. The reaction with oxygen is interesting. By the 18th century it was known that in pure oxygen phosphorus does not glow at all, there is only a range of partial pressure where it does, too high or too low and the reaction stops. Heat can be applied to drive the reaction at higher pressures.

In 1974 the glow was explained by R. J. van Zee and A. U. Khan. A reaction with oxygen takes place at the surface of the solid (or liquid) phosphorus, forming short-lived molecules HPO and P_2O_2 and they both emit visible light. The reaction is slow and only very little of the intermediates is required to produce the luminescence, hence the extended time the glow continues in a stoppered jar.

Although the term phosphorescence is derived from phosphorus, the reaction is properly called luminescence (glowing by its own reaction, in this case chemoluminescence), not phosphorescence (re-emitting light that previously fell on it).

Biological role

Phosphorus is a key element in all known forms of life. Inorganic phosphorus in the form of the phosphate PO_4^{3-} plays a major role in biological molecules such as DNA and RNA where it forms part of the structural framework of these molecules. Living cells also utilize phosphate to transport cellular energy via adenosine triphosphate (ATP). Nearly every cellular process that uses energy gets it in the form of ATP. ATP is also important for phosphorylation, a key regulatory event in cells. Phospholipids are the main structural components of all cellular membranes. Calcium phosphate salts are used by animals to stiffen their bones. An average person contains a little less than 1 kg of phosphorus, about three quarters of which is present in bones and teeth in the form of apatite. A well-fed adult in the industrialized world consumes and excretes about 1-3 g of phosphorus per day in the form of phosphate. Phosphorus is an essential mineral macronutrient, which is studied extensively in soil conservation in order to understand plant uptake from soil systems.

In ecological terms, phosphorus is often a limiting nutrient in many environments, i.e. the availability of phosphorus governs the rate of growth of many organisms. In ecosystems an excess of phosphorus can be problematic, especially in aquatic systems, see eutrophication and algal blooms.

Isotopes

Radioactive isotopes of phosphorus include:

- ^{32}P; a beta-emitter (1.71 MeV) with a half-life of 14.3 days which is used routinely in life-science laboratories, primarily to produce radiolabeled DNA and RNA probes, *e.g.* for use in Northern blots or Southern blots. Because the high energy beta particles produced penetrate skin and corneas, and because any ^{32}P ingested, inhaled, or absorbed is readily incorporated into bone and nucleic acids, OSHA requires that a lab coat, disposable gloves, and safety glasses or goggles be worn when working with ^{32}P, and that working directly over an open container be avoided in order to protect the eyes. Monitoring personal, clothing, and surface contamination is also required. In addition, due to the high energy of the beta particles, shielding this radiation with the normally used dense materials (*e.g.* lead), gives rise to secondary emission of X-rays via a process known as Bremsstrahlung, meaning braking radiation.

Therefore shielding must be accomplished with low density materials, *e.g.* Plexiglas, acrylic, Lucite, plastic, wood, or water.

- ^{33}P; a beta-emitter (0.25 MeV) with a half-life of 25.4 days. It is used in life-science laboratories in applications in which lower energy beta emissions are advantageous such as DNA sequencing.

History

Phosphorus (Greek *phosphoros* was the ancient name for the planet Venus) was discovered by German alchemist Hennig Brand in 1669 through a preparation from urine. Working in Hamburg, Brand attempted to distill salts by evaporating urine, and in the process produced a white material that glowed in the dark and burned brilliantly. Since that time, phosphorescence has been used to describe substances that shine in the dark without burning.

Phosphorus was first made commercially, for the match industry, in the 19th century, by distilling off phosphorus vapour from precipitated phosphates heated in a retort The precipitated phosphates made from ground-up bones, that had been de-greased and treated with strong acids. This process became obsolete in the late 1890s when the Electric arc furnace was adapted to reduce phosphate rock.

Early matches used white phosphorus in their composition, which was dangerous due to its toxicity. Murders, suicides and accidental poisonings resulted from its use. (An apocryphal tale tells of a woman attempting to murder her husband with white phosphorus in his food, which was detected by the stew giving off luminous steam). In addition, exposure to the vapors gave match workers a necrosis of the bones of the jaw, the infamous "phossy jaw." When a safe process for manufacturing red phosphorus was discovered, with its far lower flammability and toxicity, laws were enacted, under a Berne Convention, requiring its adoption as a safer alternative for match manufacture.

The electric furnace method allowed production to increase to the point phosphorus could be used in weapons of war. In World War I it was used in incendiaries, smoke screens and tracer bullets. A special incendiary bullet was developed to shoot at hydrogen filled Zeppelins over Britain (hydrogen of course being highly flammable if it can be ignited). During World War II Molotov cocktails of benzene and phosphorus were distributed in Britain to specially selected civilians within the British Resistance Operation, for defence; and phosphorus incendiary bombs were used in War on a large scale. Burning phosphorus is difficult to extinguish and if it splashes onto human skin it has horrific effects. People covered in it were known to commit suicide due to the torment.

Today phosphorus production is larger than ever, used as a precursor for various chemicals, in particular the herbicide glyphosate sold under the brand name Roundup. Production of white phosphorus takes place at large facilities and is transported heated in liquid form. Some major accidents have occurred during transportation, train derailments at Brownston, Nebraska and Miamisburg, Ohio lead to large fires. The worst accident in recent times though was an environmental one in 1968 when phosphorus spilt into the sea from a plant at Placentia Bay, Newfoundland.

Occurrence

Due to its reactivity to air and many other oxygen containing substances, phosphorus is not found free in nature but it is widely distributed in many different minerals. Phosphate rock, which is partially made of apatite (an impure tri-calcium phosphate mineral), is an important commercial source of this element. Large deposits of apatite are located in China, Russia, Morocco, Florida, Idaho, Tennessee, Utah, and elsewhere. Albright and Wilson in the United Kingdom and their Niagara Falls plant, for instance, were using phosphate rock in the 1890s and 1900s from Connetable, Tennessee and Florida; however, by 1950 they were using phosphate rock mainly from Tennessee and North Africa. In the early 1990s Albright and Wilson's purified wet phosphoric acid business was being affected by phosphate rock sales by China and the entry of their long standing Moroccan phosphate suppliers into the purified wet phosphoric acid business.

The white allotrope can be produced using several different methods. In one process, tri-calcium phosphate, which is derived from phosphate rock, is heated in an electric or fuel-fired furnace in the presence of carbon and silica. Elemental phosphorus is then liberated as a vapor and can be collected under phosphoric acid

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Sulfur

Sulfur or **sulphur** has the symbol **S** and atomic number 16. It is an abundant, tasteless, odorless, multivalent non-metal. Sulfur, in its native form, is a yellow crystaline solid. In nature, it can be found as the pure element or as sulfide and sulfate minerals. It is an essential element for life and is found in two amino acids.

Group, Period, Block: 16, 3, p
Atomic mass: 20.1797(6) g/mol
Electron configuration: $1s^2\ 2s^2\ 2p^6$
Electrons per shell: 2, 8

Notable characteristics

At room temperature, sulfur is a soft bright yellow solid. Although sulfur is infamous for its smell-frequently compared to rotten eggs-the odor is actually characteristic of hydrogen sulfide (H_2S); elemental sulfur has a faint odor similar to matches. It burns with a blue flame that emits sulfur dioxide, notable for its peculiar suffocating odor. Sulfur is insoluble in water but soluble in carbon disulfide and to a lesser extent in other organic solvents such as benzene. Common oxidation states of sulfur include -2, +2, +4 and +6. Sulfur forms stable compounds with all elements except the noble gases.

Sulfur in the solid state ordinarily exists as cyclic crown-shaped S_8 molecules. Sulfur has many allotropes besides S_8. Removing one atom from the crown gives S_7, which is responsible for sulfur's distinctive yellow color. Many other rings have been prepared, including S_{12} and S_{18}. By contrast, its lighter neighbor oxygen only exists in two states of allotropic significance: O_2 and O_3. Selenium, the heavier analogue of sulfur can form rings but is more often found as a polymer chain.

The crystallography of sulfur is complex. Depending on the specific conditions, the sulfur allotropes form several distinct crystal structures, with **rhombic** and **monoclinic** S_8 best known.

A noteworthy property is that the viscosity of molten sulfur, unlike most other liquids, increases with temperature due to the formation of polymer chains. However, after a specific temperature is reached, the viscosity is reduced because there is enough energy to break the chains.

Amorphous or "plastic" sulfur can be produced through the rapid cooling of molten sulfur. X-ray crystallography studies show that the amorphous form may have a helical structure with eight atoms per turn. This form is metastable at room temperature and gradually reverts back to crystalline form. This process happens within a matter of hours to days but can be rapidly catalyzed.

Biological role

The amino acids cysteine and methionine contain sulfur, as do all polypeptides, proteins, and enzymes which contain these amino acids. This makes sulfur a necessary component of all living cells. Disulfide bonds between polypeptides are very important in protein assembly and structure. Homocysteine and taurine are also sulfur containing amino acids but are not coded for by DNA nor are they part of the primary structure of proteins. Some forms of bacteria use hydrogen sulfide (H_2S) in the place of water as the electron donor in a primitive photosynthesis-like process. Sulfur is absorbed by plants via the roots from soil as the sulfate ion and reduced to sulfide before it is incorporated into cysteine and other organic sulfur compounds (sulfur assimilation). Inorganic sulfur forms a part of iron-sulfur clusters, and sulfur is the bridging ligand in the Cu_A site of cytochrome c oxidase. Sulfur is an important component of coenzyme A.

Compounds

Hydrogen sulfide has the characteristic smell of rotten eggs. Dissolved in water, hydrogen sulfide is acidic and will react with metals to form a series of metal sulfides. Natural metal sulfides are common, especially those of iron. Iron sulfide is called pyrite, the so called *fool's gold*. Interestingly, pyrite can show semiconductor properties. Galena, a naturally occurring lead sulfide, was the first semiconductor discovered, and found a use as a signal rectifier in the "cat's whiskers" of early crystal radios.

Many of the unpleasant odors of organic matter are based on sulfur-containing compounds such as methyl and ethyl mercaptan used to scent natural gas so that leaks are easily detectable. The odor of garlic and "skunk stink" are also caused by sulfur-containing organic compounds. However, not all organic sulfur compounds smell unpleasant; for example, grapefruit mercaptan, a sulfur-containing monoterpenoid is responsible for the characteristic scent of grapefruit.

Polymeric sulfur nitride has metallic properties even though it does not contain any metal atoms. This compound also has unusual electrical and optical properties. This polymer can be made from tetrasulfur tetranitride S_4N_4.

Phosphorus sulfides are important in synthesis. For example, P_4S_{10} and its derivatives Lawesson's reagent and naphthalen-1,8-diyl 1,3,2,4-dithiadiphosphetane 2,4-disulfide are used to replace oxygen from some organic molecules with sulfur.

Isotopes

Sulfur has 18 isotopes, of which four are stable: ^{32}S (95.02%), ^{33}S (0.75%), ^{34}S (4.21%), and ^{36}S (0.02%). Other than ^{35}S, the radioactive isotopes of sulfur are all short lived. ^{35}S is formed from cosmic

ray spallation of ^{40}Ar in the atmosphere. It has a half-life of 87 days.

When sulfide minerals are precipitated, isotopic equilibration among solids and liquid may cause small differences in the δS-34 values of co-genetic minerals. The differences between minerals can be used to estimate the temperature of equilibration. The δC-13 and δS-34 of coexisting carbonates and sulfides can be used to determine the pH and oxygen fugacity of the ore-bearing fluid during ore formation.

In most forest ecosystems, sulfate is derived mostly from the atmosphere; weathering of ore minerals and evaporites also contribute some sulfur. Sulfur with a distinctive isotopic composition has been used to identify pollution sources, and enriched sulfur has been added as a tracer in hydrologic studies. Differences in the natural abundances can also be used in systems where there is sufficient variation in the ^{34}S of ecosystem components. Rocky Mountain lakes thought to be dominated by atmospheric sources of sulfate have been found to have different δS-34 values from lakes believed to be dominated by watershed sources of sulfate.

History

Sulfur (Sanskrit, *sulvere*; Latin *sulpur*) was known in ancient times, and is referred to in the Biblical Pentateuch (Genesis). The word itself is almost certainly from the Arabic *sufra* meaning yellow, from the bright color of the naturally occurring form.

English translations of the Bible commonly refer to sulfur as "brimstone", giving rise to the name of 'Fire and brimstone' sermons, in which listeners are reminded of the fate of eternal damnation that awaits the nonbelieving and unrepented. It is from this part of the Bible that Hell is implied to "smell of sulfur", although as mentioned above sulfur is in fact odorless. The "smell of sulfur" usually refers to the odor of hydrogen sulfide, e.g. from rotten eggs. Burning sulfur produces sulfur dioxide, the smell associated with burnt matches.

Homer mentioned "pest-averting sulfur" in the 8th century BC and in 424 BC, the tribe of Boeotia destroyed the walls of a city by burning a mixture of coal, sulfur, and tar under them. Sometime in the 12th century, the Chinese invented gun powder which is a mixture of potassium nitrate (KNO_3), carbon, and sulfur. Early alchemists gave sulfur its own alchemical symbol which was a triangle at the top of a cross. In the late 1770s, Antoine Lavoisier helped convince the scientific community that sulfur was an element and not a compound. In 1867, sulfur was discovered in underground deposits in Louisiana and Texas. The overlying layer of earth was quicksand, prohibiting ordinary mining operations. Therefore the Frasch process was utilized.

Occurrence

Elemental sulfur can be found near hot springs and volcanic regions in many parts of the world, especially along the Pacific Ring of Fire. Such volcanic deposits are currently exploited in Indonesia,

Chile, and Japan.

Significant desposits of elemental sulfur also exist in salt domes along the coast of the Gulf of Mexico, and in evaporites in eastern Europe and western Asia. The sulfur in these deposits is believed to come from the action of anaerobic bacteria on sulfate minerals, especially gypsum. Such deposits are the basis for commercial production in the United States, Poland, Russia, Turkmenistan, and Ukraine.

Sulfur extracted from oil, gas and the Athabasca Oil Sands has become a glut on the market, with huge stockpiles of sulfur in existence throughout Alberta.

Common naturally occurring sulfur compounds include the metal sulfides, such as pyrite (iron sulfide), cinnabar (mercury sulfide), galena (lead sulfide), sphalerite (zinc sulfide) and stibnite (antimony sulfide); and the metal sulfates, such as gypsum (calcium sulfate), alunite (potassium aluminium sulfate), and barite (barium sulfate). It occurs naturally in volcanic emissions, such as from hydrothermal vents, and from bacterial action on decaying sulfur-containing organic matter.

The distinctive colors of Jupiter's volcanic moon, Io, are from various forms of molten, solid and gaseous sulfur. There is also a dark area near the Lunar crater Aristarchus that may be a sulfur deposit. Sulfur is also present in many types of meteorites.

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Hydrocarbons

Introduction

Aliphatic: Alkane (saturated) | Alkene (unsaturated) | Alkyne (unsaturated) | Cycloalkane (unsaturated)

Conjugated

Aromatic (arenes): Benzene | Hückel's rule

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Aliphatic compound

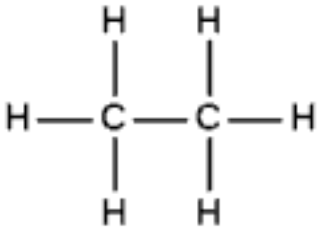
Aliphatic compounds are organic compounds, in which carbon atoms are joined together in straight or branched chains rather than in benzene rings. The simplest aliphatic compound is methane (CH_4).

Aliphatics include not only the fatty acids and other derivatives of paraffin hydrocarbons (alkanes), but also unsaturated compounds, such as ethylene (the alkenes) and acetylene (the alkynes). The most frequently found non-carbon atoms bound to the carbon chain include hydrogen, oxygen, nitrogen, sulfur, and various halides.

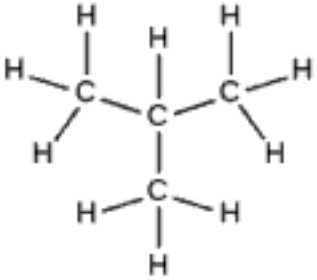
Alicyclic compounds such as cycloalkanes are aliphatic compounds that have one or more non-aromatic cycles in their chemical structure. Bicycloalkanes have two rings of carbon joined at one or two carbons.

Most aliphatic compounds have exothermic combustion reactions, thus allowing hydrocarbons such as methane to fuel Bunsen burners in the laboratory, for example. Due to it being a non-aromatic compound, aliphatic petroleum solvent is used as a starter for barbecues.

Examples



Ethane



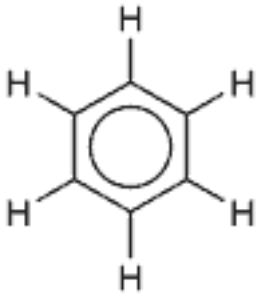
Isobutane

Acetylene

Aromatic hydrocarbon

An **aromatic hydrocarbon** (abbreviated as AH) or **arene** is a hydrocarbon, the molecular structure of which incorporates one or more planar sets of six carbon atoms that are connected by delocalised electrons numbering the same as if they consisted of alternating single and double covalent bonds. The term 'aromatic' was assigned before the physical mechanism determining aromaticity was discovered, and was derived from the fact that many of the compounds have a sweet scent. The configuration of six carbon atoms in aromatic compounds is known as a benzene ring, after the simplest possible aromatic hydrocarbon, benzene. Aromatic hydrocarbons can be *monocyclic* or *polycyclic*.

Benzene ring model



Benzene, C_6H_6, is the simplest AH and was recognized as the first aromatic hydrocarbon, with the nature of its bonding first being recognized by Friedrich August Kekulé von Stradonitz in the 19th century. Each carbon atom in the hexagonal cycle has four electrons to share. One goes to the hydrogen atom, and one each to the two neighboring carbons. This leaves one to share with one of its two neighboring carbon atoms, which is why the benzene molecule is drawn with alternating single and double bonds around the hexagon.

Many chemists draw a circle around the inside of the ring to show that there are six electrons floating around in delocalized molecular orbitals the size of the ring itself. This also accurately represents the equivalent nature of the six bonds all of bond order ~1.5. This equivalency is well explained by resonance forms. The electrons float above and below the ring, and the electromagnetic fields they generate keep the ring flat. General properties:

- Display aromaticity.
- The Carbon-Hydrogen ratio is very large.
- They burn with a sooty yellow flame because of the high carbon-hydrogen ratio.
- They undergo electrophilic substitution reactions and nucleophilic aromatic substitutions.

Arene reactions

The main arene reactions are:

- Electrophilic aromatic substitution
- Nucleophilic aromatic substitution
- Many coupling reactions to biraryls
- Hydrogenation to saturated rings

Benzene and derivatives of benzene

Benzene derivatives have from one to six substituents attached to the central benzene core. Examples of benzene compounds with just one substituent are phenol which carries a hydroxyl group and toluene with a methyl group. When there is more than one substituent present on the ring their spatial relationship becomes important for which the arene substitution patterns *ortho*, *meta* and *para* are devised. For example three isomers exist for cresol because the methyl group and the hydroxyl group can be placed next to each other (ortho), one position removed from each other (meta) or two positions removed from each other (para). Xylenol has two methyl groups in addition to the hydroxyl group and for this structure 6 isomers exist.

Examples of benzene derivative with alkyl substituents (alkylbenzenes) are:

- Ethylbenzene C_6H_5-CH_2-CH_3
- Mesitylene $C_6H_3(-CH_3)_3$
- Toluene C_6H_5-CH_3
- Xylene $C_6H_4(-CH_3)_2$

Examples of other aromatic compounds:

- Aniline C_6H_5-NH_2
- Acetylsalicylic acid $C_6H_4(-O-C(=O)-CH_3)(-COOH)$
- Benzoic acid C_6H_5-$COOH$
- Biphenyl $(C_6H_5)_2$
- Chlorobenzene C_6H_5-Cl
- Nitrobenzene C_6H_5-NO_2
- Paracetamol $C_6H_4(-NH-C(=O)-CH_3)(-OH)$
- Phenacetin $C_6H_4(-NH-C(=O)-CH_3)(-O-CH_2-CH_3)$
- Phenol C_6H_5-OH
- Picric acid $C_6H_2(-OH)(-NO_2)_3$

- Salicylic acid $C_6H_4(-OH)(-COOH)$
- Trinitrotoluene $C_6H_2(-CH_3)(-NO_2)_3$

The arene ring has an ability to stabilize charges. This is seen in, for example, phenol (C_6H_5-OH), which is acidic at the hydroxyl (OH), since a charge on this oxygen (alkoxide $-O^-$) is partially delocalized into the benzene ring.

Polycyclic aromatic hydrocarbons

Some important arenes are the **polycyclic aromatic hydrocarbons** (PAH); they are also called **polynuclear aromatic hydrocarbons**. They are composed of more than one aromatic ring. The simplest PAH is benzocyclobutene (C_8H_6).

Common examples are Naphthalene, Anthracene, Phenanthrene and triphenylene. More exotic examples are helicenes and Corannulene.

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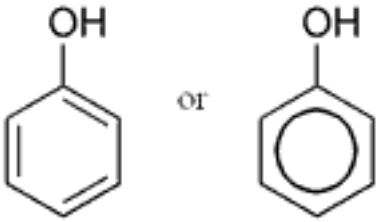
Conjugated system

A chemically **conjugated system** is a system of atoms covalently bonded with alternating single and multiple (e.g. double) bonds (e.g., C=C-C=C-C) in a molecule of an organic compound. This system results in a general delocalization of the electrons, which increases stability and thereby lowers the overall energy of the molecule.



Chemical structure of phenol

The electron delocalisation creates a region where electrons do not belong to a single bond or atom, but rather a group. An example would be phenol (C_6H_5OH, benzene with hydroxyl group) (diagramatically has alternating single and double bonds), which has a system of 6 electrons above and below the flat planar ring, as well as around the hydroxyl group.

Conjugated systems often have unique properties, such as beta carotene's long conjugated hydrocarbon chain resulting in its strong orange color. This is because photons of lower energies can excite the bonds with slightly lower activation enthalpy, allowing photons in the visible region of the electromagnetic spectrum to be absorbed. The color is determined by the length of the conjugated system, since the electron can travel the whole length of the chain. A simple way to visualize this is by thinking of it as a particle in a box where $E=hf \sim 1/L^2$, so the frequency, and thus color, of emitted light is proportional to $1/L^2$. This absorption of light means that conjugated systems are usually analysed using UV/VIS spectroscopy.

Conjugated systems are often present in chromophores, which are light-absorbing parts of a molecule causing a compound to be colored. Such chromophores are often present in various organic compounds and sometimes present in polymers, which are colored or glow in the dark. They are usually caused by conjugated ring systems with bonds such as C=O and N=N in addition to conjugated C-C bonds.

Common examples

- Diene
- Vitamin D
- Vitamin A
- Benzene
- Polyenes

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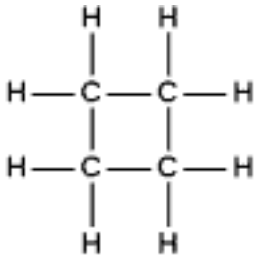
Cycloalkane

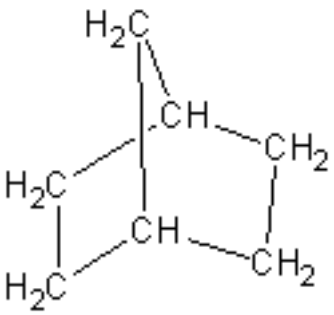
Cycloalkanes are chemical compounds with a one or more rings of carbons to which hydrogens are attached according to the formula C_nH_{2n}. Cycloalkanes with a single ring are named analogously to their normal alkane counterpart of the same carbon count: cyclopropane, cyclobutane, cyclopentane, cyclohexane, etc. The larger cycloalkanes, with greater than 20 carbon atoms are typically called cycloparaffins.


cyclobutane

Cycloalkanes are classified into small, normal and bigger cycloalkanes, where cyclopropane and cyclobutane are the small ones, cyclopentane, cyclohexane, cycloheptane are the normal ones, and the rest are the bigger ones.

Nomenclature

The naming of polycyclic alkanes such as bicyclic alkanes and spiro alkanes is more complex, with the base name indicating the number of carbons in the ring system, a prefix indicating the number of rings (eg, "bicyclo"), and a numeric prefix before that indicating the number of carbons in each part of each ring, exclusive of vertices. For instance, a bicyclooctane which consists of a six-member ring and a four member ring, which share two adjacent carbon atoms which form a shared edge, is [4.2.0]-bicyclooctane. That part of the six-member ring, exclusive of the shared edge has 4 carbons. That part of the four-member ring, exclusive of the shared edge, has 2 carbons. The edge itself, exclusive of the two vertices that define it, has 0 carbons.


bicyclo[2,2,1]heptane

The group of cycloalkanes are also known as **naphthenes**, as they are compounds of petroleum or

naphtha

Reactions

The simple and the bigger cycloalkanes are very stable, like alkanes, and their reactions for example radical chain reactions, are like alkanes.

The small cycloalkanes - particularly cyclopropane - have a lower stability due to Baeyer strain and ring strain. They react similarly to alkenes, though they don't react in electrophilic addition but in nucleophilic aliphatic substitution. These reactions are ring opening reactions or ring cleavage reactions of alkyl cycloalkanes. Cycloalkanes can be formed in a Diels-Alder reaction.

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Hückel's rule

Hückel's rule estimates whether a planar ring molecule will have aromatic properties. The quantum mechanical basis for its formulation was first worked out by physical chemist Erich Hückel in 1931. It was first expressed succinctly as the 4n+2 (actually 2+4n) rule by von Doering in 1951. A cyclic ring molecule follows Hückel's rule when the number of its π electrons equals $4n + 2$ where n is zero or any positive integer (although clearcut examples are really only established for values of n=0 up to about 6).

Hückel's rule is not valid for many compounds containing more than three fused aromatic nuclei in a cyclic fashion like in pyrene or coronene.

The Pariser-Parr-Pople method is a more precise method of estimating whether a cyclic ring molecule is aromatic.

Three-Dimensional Rule

In 2000, chemists in Germany formulated a rule to determine when a fullerene would be aromatic. In particular, they found that if there were $2(n + 1)^2$ π electrons, then the fullerene would display aromatic properties. This follows from the fact that an aromatic fullerene must have full icosahedral (or other appropriate) symmetry, so the molecular orbitals must be entirely filled. This is only possible if there are exactly $2(n + 1)^2$ electrons, where n is a nonnegative integer. In particular, for example, buckminsterfullerene, with 60 π electrons, is non-aromatic, since 60/2=30, which is not a perfect square.

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Hydrocarbon

A **hydrocarbon** is any chemical compound that consists only of the elements **carbon** (C) and **hydrogen** (H). They all contain a carbon backbone, called a carbon skeleton, and have hydrogen atoms attached to that backbone. (Often the term is used as a shortened form of the term aliphatic hydrocarbon.) Most hydrocarbons are combustible.

Examples

The simplest hydrocarbon is methane (swamp/marsh gas), a hydrocarbon with one carbon atom and four hydrogen atoms: CH_4. Ethane is a hydrocarbon (more specifically, an alkane) consisting of two carbon atoms held together with a single bond, each with three hydrogen atoms bonded: C_2H_6. Propane has three carbon atoms (C_3H_8) and butane has four carbons (C_4H_{10}).

Three types of hydrocarbons

There are essentially three types of hydrocarbons:

- **aromatic hydrocarbons**, also known as arenes which have at least one aromatic ring
- **saturated hydrocarbons**, also known as alkanes, which don't have any double, triple or aromatic bonds
- **unsaturated hydrocarbons**, which have one or more double or triple bonds between carbon atoms, are divided into: alkenes and alkynes

The number of hydrogen atoms

The number of hydrogen atoms in hydrocarbons can be determined, if the number of carbon atoms is known, by using these following equations:

- Alkanes: C_nH_{2n+2}
- Alkenes: C_nH_{2n} (assuming only one double bond)
- Alkynes: C_nH_{2n-2} (assuming only one triple bond)
- Cyclic hydrocarbons: C_nH_{2n}

Each of these hydrocarbons must follow the 4-hydrogen rule which states that all carbon atoms must have the maximum number of hydrogen atoms that it can hold (the limit is four). A carbon atom has a

bonding capacity of 4 and therefore must make 4 bonds, whether it be with hydrogen or an adjoining carbon atom. Note, an extra bond removes 2 hydrogen atoms and only saturated hydrocarbons can attain the full four. This is because of the unique positions of the carbon's four electrons.

Molecular graph

Usually carbon backbone is represented as molecular graph in which only carbon atoms are represented as vertices and bonds as edges. Molecular graphs contain the structure of the hydrocarbon in which missing hydrogen atoms can be added in a unique way. Hydrocarbons are extensively studied in mathematical chemistry.

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List of standard amino acids

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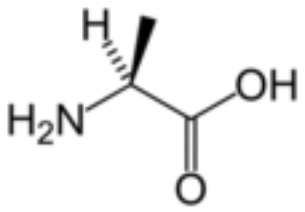
Alanine from MobileReference



Abbrev. A, Ala
Full Name Alanine
Side chain type hydrophobic
Mass 89.09
pl 6.01
pK_1(α-COOH) 2.35

pK_2(α-$^+NH_3$) 9.87

pKr (R)

Side chain -CH_3

Hydro- phobic yes
Polar no
Charged no
Small yes
Tiny yes
Aromatic or Aliphatic no
van der Waals volume 67
Codon GCU, GCC, GCA, GCG
Occurrence in proteins (%) 7.8

Remarks: Very abundant, very versatile. More stiff than glycine, but small enough to pose only small steric limits for the protein conformation. It behaves fairly neutrally, can be located in both hydrophilic regions on the protein outside and the hydrophobic areas inside.

Alanine (Ala) also 2-aminopropanoic acid is a non-essential α-amino acid. It exists as two distinct enantiomers - L-alanine and D-alanine. L-alanine is one of the 20 amino acids most widely used in protein synthesis, second to leucine, accounting for 7.8% of the primary structure in a sample of 1,150 proteins. D-alanine occurs in bacterial cell walls and in some peptide antibiotics.

Structure

The α-carbon atom of alanine is bound with a methyl group (-CH_3), making it one of the simplest α-amino acids with respect to molecular structure and also resulting in alanine being classified as an aliphatic amino acid.

Synthesis

Alanine is most commonly made by transfer of an amine group to pyruvate. Because transamination reactions are readily reversible, alanine can be easily formed from pyruvate and thus has close links to metabolic pathways such as glycolysis, gluconeogenesis, and the citric acid cycle. frg

Function

The methyl group of alanine is very non-reactive, and is thus rarely directly involved in protein function. However, alanine can play a role in substrate recognition or specificity, particularly in interactions with other non-reactive atoms such as carbon. It goes through alanine cycle to generate glucose from protein

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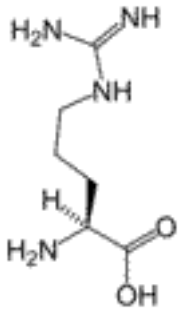
Arginine



Abbrev. R Arg
Full Name Arginine
Side chain type basic
Mass 174.20
pl 10.76
pK_1(α-COOH) 1.82

pK_2(α-$^+NH_3$) 8.99

pKr (R) 12.48

Side chain -$(CH_2)_3NH$-C(NH)NH_2

Hydro- phobic no
Polar yes
Charged positive
Small no
Tiny no
Aromatic or Aliphatic no
van der Waals volume 148
Codon CGU, CGC, CGA, CGG, AGA, AGG
Occurrence in proteins (%) 5.1

Remarks: Functionally similar to lysine.

Arginine (Arg) is an α-amino acid. The L-form is one of the 20 most common natural amino acids. In mammals, arginine is classified as a semiessential or conditionally essential amino acid, depending on the developmental stage and health status of the individual.

Structure

Arginine can be considered to be an amphipathic amino acid as the part of the side chain nearest to the

backbone is long, carbon-containing and hydrophobic, whereas the end of the side chain is a complex guanidinium group. With pK_a > 12, the guanidinium group is positively charged in neutral and acidic environments. Because of the conjugation between the double bond and the nitrogen lone pairs, the positive charge is delocalized. This group is able to form multiple H-bonds.

Synthesis

Arginine is synthesized from citrulline by the sequential action of the cytosolic enzymes argininosuccinate synthetase (ASS) and argininosuccinate lyase (ASL). This is energetically costly, as the synthesis of each molecule of argininosuccinate requires hydrolysis of adenosine triphosphate (ATP) to adenosine monophosphate (AMP); i.e., two ATP equivalents.

Citrulline can be derived from multiple sources:

-from arginine via nitric oxide synthase (NOS);
-from ornithine via catabolism of proline or glutamine/glutamate;
-from asymmetric dimethylarginine (ADMA) via DDAH.
The pathways linking arginine, glutamine, and proline are bidirectional. Thus, the net utilization or production of these amino acids is highly dependent on cell type and developmental stage.

On a whole-body basis, synthesis of arginine occurs principally via the intestinal–renal axis, wherein epithelial cells of the small intestine, which produce citrulline primarily from glutamine and glutamate, collaborate with the proximal tubule cells of the kidney, which extract citrulline from the circulation and convert it to arginine, which is returned to the circulation. Consequently, impairment of small bowel or renal function can reduce endogenous arginine synthesis, thereby increasing the dietary requirement.

Synthesis of arginine from citrulline also occurs at a low level in many other cells, and cellular capacity for arginine synthesis can be markedly increased under circumstances that also induce iNOS. Thus, citrulline, a coproduct of the NOS-catalyzed reaction, can be recycled to arginine in a pathway known as the citrulline-NO or arginine-citrulline pathway. This is demonstrated by the fact that in many cell types, citrulline can substitute for arginine to some degree in supporting NO synthesis. However, recycling is not quantitative because citrulline accumulates along with nitrate and nitrite, the stable end-products of NO, in NO-producing cells.

Function

Arginine plays an important role in cell division, the healing of wounds, removing ammonia from the body, immune function, and the release of hormones.

In proteins

The geometry, charge distribution and ability to form multiple H-bonds make arginine ideal for binding negatively charged groups. For this reason arginine prefers to be on the outside of the proteins where it can interact with the polar environment. Incorporated in proteins, arginine can also be converted to citrulline by PAD enzymes. In addition, arginine can be methylated by protein methyltransferases.

As a precursor

Arginine is the immediate precursor of NO, urea, ornithine and agmatine; is necessary for the synthesis of creatine; and can be used for the synthesis of polyamines (mainly through ornithine and to a lesser degree through agmatine), citrulline, and glutamate. For being a precursor of NO, (relaxes blood vessels), arginine is in used in many conditions where vasodilation is required. The presence of asymmetric dimethylargine (ADMA), a close relative, inhibits the nitric oxide reaction; therefore, ADMA is considered a marker for vascular disease, just as L-arginine is considered a sign of a healthy endothelium.

Implication in herpes simplex viral replication

Tissue culture studies have shown the suppression of viral replication when the lysine to arginine ratio in vitro favours lysine. The therapeutic consequence of this finding is unclear, but dietary arginine may affect the effectiveness of lysine supplementation

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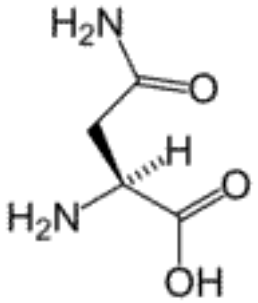
Asparagine



Abbrev. N Asn
Full Name Asparagine
Side chain type hydrophobic
Mass 132.12
pl 5.41
pK_1(α-COOH) 2.14

pK_2(α-$^+NH_3$) 8.72

Side chain -CH_2CONH_2

Hydro- phobic no
Polar yes
Charged no
Small yes
Tiny no
Aromatic or Aliphatic no
van der Waals volume 96
Codon AAU, AAC
Occurrence in proteins (%) 4.3

Remarks: Neutralized version of aspartic acid.

Asparagine is one of the 20 most common natural amino acids on Earth. It has carboxamide as the side chain's functional group. It is considered a non-essential amino acid. Asparagine was the first amino acid to be isolated. It was obtained from asparagus juice(hence the name)

Its three-letter abbreviation is Asn, and its one-letter abbreviation is N. A three-letter designation for either asparagine or aspartic acid is Asx (one-letter abbreviation: B).

A reaction between asparagine and reducing sugars or reactive carbonyls produces acrylamide (acrylic

amide) in food when heated to sufficient temperature, i.e. baking. These occur primarilly in baked goods such as french fries, potato chips, and roasted coffee.

A byproduct of the breakdown of asparagine (asparagine-amino-succinic-acid monoamide) is also blamed for the smell in some people's urine after they have eaten asparagus (Some scientists disagree and implicate other substances in the smell, especially methanethiol). Asparagine was first discovered in asparagus, which has a high concentration of the amino acid. It was the first amino acid to be discovered, in 1806.

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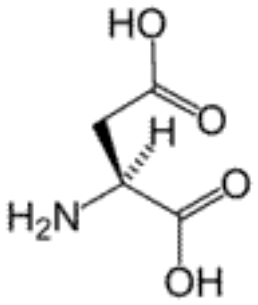
Aspartic acid



Abbrev. D, Asp
Full Name Aspartic acid
Side chain type acidic
Mass 133.10
pl 2.85
pK_1(α-COOH) 1.99

pK_2(α-$^+NH_3$) 9.90

pKr (R) 3.90

Side chain -CH_2COOH

Hydro- phobic no
Polar yes
Charged negative
Small yes
Tiny no
Aromatic or Aliphatic no
van der Waals volume 91
Codon GAU, GAC
Occurrence in proteins (%) 5.3

Remarks: Behaves similarly to glutamic acid. Carries a hydrophilic acidic group with strong negative charge. Usually is located on the outer surface of the protein, making it water-soluble. Binds to positively-charged molecules and ions, often used in enzymes to fix the metal ion. When located inside of the protein, aspartate and glutamate are usually paired with arginine and lysine.

Aspartic acid (Asp), also known as **aspartate**, the name of its anion, is one of the 20 natural proteinogenic amino acids which are the building blocks of proteins.

As with each of the 20 natural amino acids, there are two abbreviations commonly used to designate aspartic acid: Asp (three letter) and D (one letter). The abbreviations signifying a choice of either

aspartic acid or asparagine are Asx (three-letter) and B (one letter).

As its name indicates, aspartic acid is the carboxylic acid analog of asparagine. It is non-essential in mammals, and might serve as an excitatory neurotransmitter in the brain. It is also a metabolite in the urea cycle, and participates in gluconeogenesis.

As a neurotransmitter, aspartic acid may provide resistance to fatigue and thus lead to endurance, although the evidence to support this idea is not strong.

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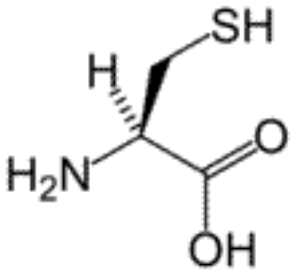
Cysteine



Abbrev. C, Cys
Full Name Cysteine
Side chain type hydrophobic (Nagano, 1999)
Mass 121.16
pl 5.05
pK_1(α-COOH) 1.92

pK_2(α-$^+NH_3$) 10.70

pKr (R) 8.18

Side chain -CH_2SH

Hydro- phobic yes
Polar no
Charged no
Small yes
Tiny no
Aromatic or Aliphatic no
van der Waals volume 67
Codon GCU, GCC, GCA, GCG
Occurrence in proteins (%) 7.8

Remarks: The sulfur atom binds readily to heavy metal ions. Under oxidizing conditions, two cysteines can join together by a disulfide bond to form the amino acid cystine. When cystines are part of a protein, insulin for example, this enforces tertiary structure and makes the protein more resistant to unfolding and denaturation; disulphide bridges are therefore common in proteins that have to function in harsh environments, digestive enzymes (e.g., pepsin and chymotrypsin), structural proteins (e.g., keratin), and proteins too small to hold their shape on their own (eg. insulin).

Cysteine is a naturally occurring hydrophobic amino acid which has a thiol group and is found in most proteins, though only in small quantities. When it is exposed to air it oxidizes to form **cystine**, which is two cysteine molecules joined by a disulfide bond. N-acetyl-L-cysteine (NAC) is derived from cysteine

and is a popular dietary supplement that is metabolized into the antioxidant glutathione. Cysteine takes its name from cystine, named after the Greek *kustis* meaning bladder - cystine was first isolated from kidney stones.

Biochemistry

Cysteine contains a highly nucleophilic thiol group, and one of its primary purposes is to act as a nucleophilic catalyst. Since the pKa of the cysteine thiol approximately 8, its chemical activity is very easily tuned by its environment (compare to histidine which has a pKa of approximately 6.5 and is used similarly). Some important cysteine nucleophiles include ubiquitin ligases, which transfer ubiquitin to its pendant proteins, and caspases which engage in proteolysis in the apoptotic cycle. Inteins often function with the help of a catalytic cysteine. These roles are typically limited to the intracellular milieu, where the environment is reducing, and cysteine is not oxidized to cystine.

Cysteines play a valuable role by crosslinking proteins in an intramolecular sense. This increases the molecular stability in the harsh extracellular environment, and also functions to confer proteolytic resistance (since protein export is a costly process, minimizing its necessity is advantageous). Intracellularly, disulfide bridges between cysteines within a polypeptide support the protein's secondary structure. Insulin is a hallmark of cystine crosslinking, where two separate peptide chains are connected by a pair of disulfide bonds. The arrangement of disulfide bonds in hair arising from cysteine influences its degree of curliness.

Protein Disulfide Isomerases catalyze the formation of disulfide bonds; the cell transfers dehydroascorbic acid to the endoplasmic reticulum which oxidises the environment. In this environment, cysteines are generally oxidized to cystine and no longer functions as a nucleophile.

Dietary Sources

Cysteine can be found in red peppers, garlic, onions, broccoli, brussel sprouts, oats, and wheat germ. However, it is not an essential amino acid, and can be synthesized by the human body if a sufficient quantity of methionine is available.

Production

It is interesting to note that currently cheapest source of material from which food grade L-cysteine may be purified in high yield by hydrolysis from is human hair. Other sources include feathers and pig bristles. The companies producing cysteine by hydrolysis are located mainly in China. Some debate whether consuming L-cysteine derived from human hair is cannibalism. Although many other amino acids were accessible via fermentation for some years, L-Cysteine was unavailable until 2001 when a German company introduced a production route via fermentation (non-human, non-animal origin.)

A source of bonded cysteine (cystine) is ***undenatured*** bovine whey protein; this is the same form as that in human breast milk.

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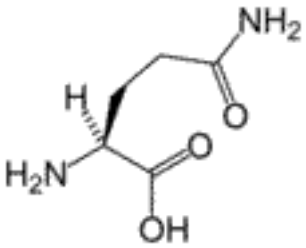
Glutamine



Abbrev. Q Gln
Full Name Glutamine
Side chain type hydrophobic
Mass 146.15
pl 5.65
pK_1(α-COOH) 2.17

pK_2(α-$^+NH_3$) 9.13

Side chain -$CH_2CH_2CONH_2$

Hydro- phobic no
Polar yes
Charged no
Small no
Tiny no
Aromatic or Aliphatic no
van der Waals volume 114
Codon CAA, CAG
Occurrence in proteins (%) 4.2

Remarks: Neutralized version of glutamic acid. Used in proteins and as a storage for ammonia.

Glutamine is one of the 20 amino acids encoded by the standard genetic code. Its side chain is an amide; it is formed by replacing a side-chain hydroxyl of glutamic acid with an amine functional group. Glutamine is genetically coded for by the RNA codons CAA and CAG. Glutamine's three-letter abbreviation is Gln, and its one-letter abbreviation is Q. A three-letter designation for either glutamine or glutamic acid is Glx (one-letter abbreviation: Z).

Like other amino acids, glutamine is biochemically important as a constituent of proteins. Glutamine is also crucial in nitrogen metabolism. Ammonia (formed by nitrogen fixation) is assimilated into organic compounds by converting glutamic acid to glutamine. The enzyme that accomplishes this is called glutamine synthetase. Glutamine can, hence, be used as a nitrogen donor in the biosynthesis of many

compounds, including other amino acids, purines, and pyrimidines.

Usage

Glutamine is a supplement that is used in weightlifting and bodybuilding, as well as by those who suffer for muscular cramps or pain—particularly elderly people. The main use of glutamine within the diet of either groups is as a means of replenishing the body's stores of amino acids that have been used during exercise or everyday activities.

There are still studies which are looking into problems with excessive consumption of glutamine, which thus far have proved inconclusive. However, normal supplementation is healthy mainly because glutamine is supposed to be supplemented after prolonged periods of exercise (for example, a workout or exercise in which amino acids are required for use) and replenishes amino acid stores; this being the main reason glutamine is recommended during fasting or for people who suffer from physical trauma, immune deficiencies, or cancer.

Aiding gastrointestinal function

There have been several recent studies into the effects of glutamine and what properties it posesses, and, there is now a significant body of evidence that links glutamine-enriched diets with intestinal effects; aiding maintenance of gut barrier function, intestinal cell proliferation and differentiation, as well as generally reducing septic morbidity. The reason for such "cleansing" properties is thought to stem from the fact that the intestinal extraction rate of glutamine is higher than that for other amino acids, and is therefore thought to be the most viable option when attempting to alleviate conditions relating to the gut.

These conditions being discovered after comparing plasma concentration within the gut between glutamine-enriched and non glutamine-enriched diets. However, even though Glutamine is thought to have "cleansing" properties and effects, it is unknown to what extent glutamine has clinical benefits, due to the varied concentrations of glutamine in varieties of food.

Aiding recovery after surgery

It is also known that glutamine has various effects in reducing healing time after operations. Hospital waiting times after abdominal surgery are reduced by providing parenteral nutrition regimens containing amounts of glutamine to patients. Clinical trials have revealed that patients on supplimentation regimes containing glutamine have improved nitrogen balances, generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes and improved lymphocyte recovery and intestinal permeability (in postoperative patients) - in comparison to those who had no glutamine within their dietary regime; all without any side-effects.

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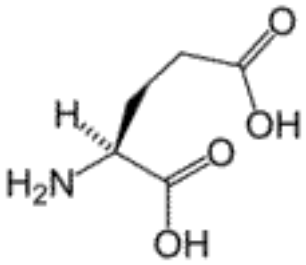
Glutamic acid



Abbrev. E, Glu
Full Name Glutamic acid
Side chain type acidic
Mass 147.13
pl 3.15
pK_1(α-COOH) 2.10

pK_2(α-$^+NH_3$) 9.47

pKr (R) 4.07

Side chain -CH_2SH

Hydro- phobic yes
Polar no
Charged no
Small yes
Tiny no
Aromatic or Aliphatic no
van der Waals volume 91
Codon GAU, GAC
Occurrence in proteins (%) 5.3

Remarks: Behaves similar to aspartic acid. Has longer, slightly more flexible side chain.

Glutamic acid (Glu) or **glutamate** (the anionic form) is one of the 20 standard amino acids used by all organisms in their proteins. Glu is critical for proper cell function, but it is not an essential nutrient in humans because it can be produced from other compounds.

Structure

As its name indicates, it is acidic, with a carboxylic acid component to its side chain.

A three-letter designation for either Gln or Glu is **Glx**. The one-letter abbreviation is E for glutamic acid and Q for glutamine.

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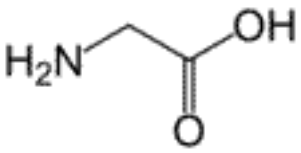
Glycine



Abbrev. G Gly
Full Name Glycine
Side chain type hydrophobic
Mass 75.07
pl 6.06
pK_1(α-COOH) 2.35

pK_2(α-$^+NH_3$) 9.78

Side chain -H
Hydro- phobic yes
Polar no
Charged no
Small yes
Tiny yes
Aromatic or Aliphatic no
van der Waals volume 48
Codon GGU, GGC, GGA, GGG
Occurrence in proteins (%) 7.2

Remarks: Because of the two hydrogen atoms at the α carbon, glycine is not optically active. It is the tiniest amino acid, rotates easily, adds flexibility to the protein chain. It is able to fit into the tightest spaces, e.g., the triple helix of collagen. As too much flexibility is usually not desired, as a structural component it is less common than alanine.

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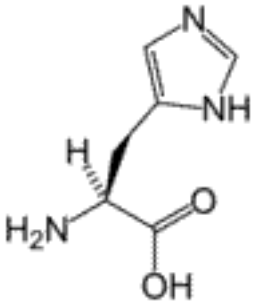
Histidine



Abbrev. H His
Full Name Histidine
Side chain type basic
Mass 155.16
pl 7.60
pK_1(α-COOH) 1.80

pK_2(α-$^+NH_3$) 9.33

pKr (R) 6.04

Side chain -CH_2-$C_3H_3N_2$

Hydro- phobic no
Polar yes
Charged positive
Small no
Tiny no
Aromatic or Aliphatic Aromatic
van der Waals volume 118
Codon CAU, CAC
Occurrence in proteins (%) 2.3

Remarks: In even slightly acidic conditions protonation of the nitrogen occurs, changing the properties of histidine and the polypeptide as a whole. It is used by many proteins as a regulatory mechanism, changing the conformation and behavior of the polypeptide in acidic regions such as the late endosome or lysosome, enforcing conformation change in enzymes. However only a few histidines are needed for this, so it is comparatively scarce.

Histidine is one of the 20 most common natural amino acids present in proteins. In the nutritional sense, in humans, histidine is considered an essential amino acid, but mostly only in children. The imidazole side chains and the relatively neutral pK of histidine (ca 6.0) mean that relatively small shifts in cellular pH will change its charge. For this reason, this amino acid side chain finds its way into considerable use

as a co-ordinating ligand in metalloproteins, and also as a catalytic site in certain enzymes. The imidazole side chain has two nitrogens with different properties: One is bound to hydrogen and donates its lone pair to the aromatic ring and as such is slighty acidic, whereas the other one donates only one electron to the ring so it has a free lone pair and is basic. These properties are exploited in different ways in proteins. In catalytic triads, the basic nitrogen of histidine is used to abstract a proton from serine, threonine or cysteine to activate it as a nucleophile. In a histidine proton shuttle, histidine is used to quickly shuttle protons, it can do this by abstracting a proton with its basic nitrogen to make a positively-charged intermediate and then use another molecule, a buffer, to extract the proton from its acidic nitrogen. In carbonic anhydrases, a histidine proton shuttle is utilized to rapidly shuttle protons away from a zinc-bound water molecule to quickly regenerate the active form of the enzyme.

The amino acid is a precursor for histamine and carnosine biosynthesis.

There are two isoforms: D-histidine and L-histidine

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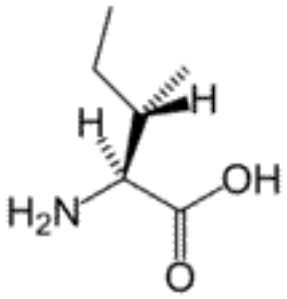
Isoleucine



Abbrev. I Ile
Full Name Isoleucine
Side chain type hydrophobic
Mass 131.17
pl 6.05
pK_1(α-COOH) 2.32

pK_2(α-$^+NH_3$) 9.67

Side chain -$CH(CH_3)CH_2CH_3$

Hydro- phobic yes
Polar no
Charged no
Small no
Tiny no
Aromatic or Aliphatic Aliphatic
van der Waals volume 124
Codon AUU, AUC, AUA
Occurrence in proteins (%) 5.3

Remarks: Essential for humans. Isoleucine, leucine and valine have large aliphatic hydrophobic side chains. Their molecules are rigid, and their mutual hydrophobic interactions are important for the correct folding of proteins, as these chains tend to be located inside of the protein molecule.

Isoleucine is one of the 20 standard amino acids, and is coded for in DNA. Its chemical composition is identical to that of leucine, but the arrangement of its atoms is slightly different, resulting in different properties. Nutritionally, in humans, isoleucine is an essential amino acid. Isoleucine is a hydrophobic amino acid.

Isoleucine has two chiral centers; therefore there are four possible stereoisomers of isoleucine and two possible diastereomers of L-isoleucine. However, isoleucine present in nature exists in one enantiomeric

form, (2S,3S)-2-amino-3-methylpentanoic acid.

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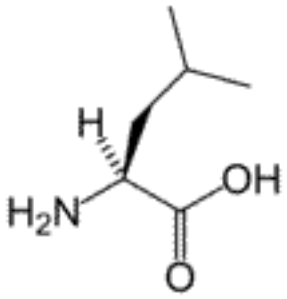
Leucine



Abbrev. L Leu
Full Name Leucine
Side chain type hydrophobic
Mass 131.17
pl 6.01
pK_1(α-COOH) 2.16

pK_2(α-$^+NH_3$) 2.33

pKr (R) 9.74

Side chain -$CH_2CH(CH_3)_2$

Hydro- phobic yes
Polar no
Charged no
Small no
Tiny no
Aromatic or Aliphatic Aliphatic
van der Waals volume 124
Codon UUA, UUG, CUU, CUC, CUA, CUG
Occurrence in proteins (%) 9.1

Remarks: Essential for humans. Behaves similar to isoleucine and valine. See isoleucine.

Leucine is one of the 20 most common amino acids and coded for by DNA. It is isomeric with isoleucine. Nutritionally, in humans, leucine is an essential amino acid.

Leucine is the most common amino acid found in proteins, and is essential for optimal growth in infancy and childhood and for nitrogen equilibrium in adults. It is suspected that Leucine plays a part in maintaining muscles by equalizing synthesis and breakdown of proteins.

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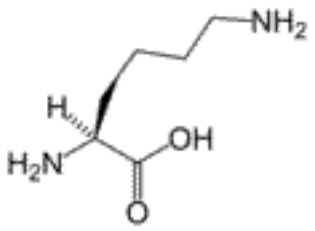
Lysine



Abbrev. K Lys
Full Name Lysine
Side chain type basic
Mass 146.19
pl 9.60
pK_1(α-COOH) 2.16

pK_2(α-$^+NH_3$) 9.06

pKr (R) 10.54

Side chain -$(CH_2)_4NH_2$

Hydro- phobic no
Polar yes
Charged positive
Small no
Tiny no
Aromatic or Aliphatic no
van der Waals volume 135
Codon AAA, AAG
Occurrence in proteins (%) 5.9

Remarks: Essential for humans. Behaves similarly to arginine. Contains a long flexible side-chain with a positively-charged end. The flexibility of the chain makes lysine and arginine suitable for binding to molecules with many negative charges on their surfaces. E.g., DNA-binding proteins have their active regions rich with arginine and lysine. The strong charge makes these two amino acids prone to be located on the outer hydrophilic surfaces of the proteins; when they are found inside, they are usually paired with a corresponding negatively-charged amino acid, e.g., aspartate or glutamate.

Lysine is one of the 20 amino acids normally found in proteins. With its 4-aminobutyl side-chain, it is classified as a basic amino acid, along with arginine and histidine. It is an essential amino acid, and the human nutritional requirement is 1–1.5 g daily. A deficiency in lysine can result in a deficiency in niacin (which is a B Vitamin). This can cause the disease pellagra. Lysine can also be used as a nutritional supplement to help against herpes.

Lysine is the limiting amino acid in all cereal grains, but is plentiful in all pulses (legumes). Fish are also quite rich in lysine. Plants that contain significant amounts of lysine include:

Lysine can undergo posttranslational modification in protein molecules, often by methylation or acetylation. Collagen contains hydroxylysine which is derived from lysine. O-Glycosylation of lysine residues in the endoplasmic reticulum or Golgi apparatus is used to mark certain proteins for secretion from the cell.

Lysine is metabolised in mammals to give Acetyl-CoA, via an initial transamination with α-ketoglutarate. The bacterial degradation of lysine yields cadaverine by decarboxylation.

Some individuals have found that taking lysine supplements may reduce the frequency of canker sores.

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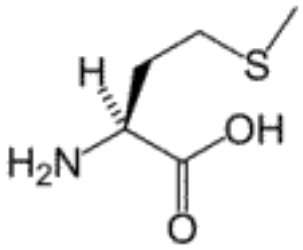
Methionine



Abbrev. M Met
Full Name Methionine
Side chain type hydrophobic
Mass 149.21
pl 5.74
pK_1(α-COOH) 2.13

pK_2(α-$^+NH_3$) 9.28

Side chain -$CH_2CH_2SCH_3$

Hydro- phobic yes
Polar no
Charged no
Small no
Tiny no
Aromatic or Aliphatic no
van der Waals volume 124
Codon AUG
Occurrence in proteins (%) 2.3

Remarks: Essential for humans. Always the first amino acid to be incorporated into a protein; sometimes removed after translation. Like cysteine, contains sulfur, but with a methyl group instead of hydrogen. This methyl group can be activated, and is used in many reactions where a new carbon atom is being added to another molecule.

Methionine is an essential nonpolar amino acid, and a lipotropic.

Methionine and cysteine are the only sulfur-containing proteinogenic amino acids. The methionine derivative S-adenosyl methionine (SAM) serves as a methyl donor. Methionine plays a role in cysteine, carnitine and taurine synthesis by the transsulfuration pathway, lecithin production, the synthesis of phosphatidylcholine and other phospholipids. Improper conversion of methionine can lead to atherosclerosis. Methionine is a chelating agent.

Methionine is one of only two amino acids encoded by a single codon (AUG) in the standard genetic code (tryptophan, encoded by UGG, is the other). The codon AUG is also significant, in that it carries the "Start" message for a ribosome to begin protein translation from mRNA. As a consequence, methionine is incorporated into the N-terminal position of all proteins in eukaryotes and archaea during translation, although it is usually removed by post-translational modification. Methionine can also occur at other positions in the protein.

Foods containing methionine include fruits, meat, vegetables, nuts and legumes. High levels of methionine can be found in spinach, green peas, garlic, some cheeses, corn, brazil nuts, pistachios, cashew nuts, kidney beans, black turtle beans, tofu, and tempeh. Most meat is also a rich source of Methionine including chicken, beef and fish

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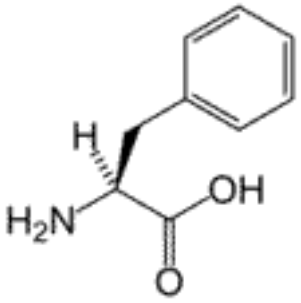
Phenylalanine



Abbrev. F, Phe
Full Name Phenylalanine
Side chain type hydrophobic
Mass 165.19
pl 5.49
pK_1(α-COOH) 2.20

pK_2(α-$^+NH_3$) 9.31

Side chain -$CH_2C_6H_5$

Hydro- phobic yes
Polar no
Charged no
Small no
Tiny no
Aromatic or Aliphatic Aromatic
van der Waals volume 135
Codon UUU, UUC
Occurrence in proteins (%) 3.9

Remarks: Essential for humans. Phenylalanine, tyrosine, and tryptophan contain large rigid aromatic group on the side chain. These are the biggest amino acids. Like isoleucine, leucine and valine, these are hydrophobic and tend to orient towards the interior of the folded protein molecule.

The alpha-amino acid **Phenylalanine** exists in two forms, the *D*- and *L*- forms, which are enantiomers (mirror-image molecules) of each other. It has a benzyl side chain. Its name comes from its chemical structure's consisting of a phenyl group substituted for one of the hydrogens in the side chain of alanine. Because of its phenyl group, phenylalanine is an aromatic compound. At room temperature, it is a white, powdery solid.
L-Phenylalanine (LPA) is an electrically-neutral amino acid, one of the twenty common amino acids used to biochemically form proteins, coded for by DNA. Its enantiomer, *D*-phenylalanine (DPA), can be

synthesized artificially.

L-phenylalanine is used in living organisms, including the human body, where it is an essential amino acid. *L*-phenylalanine can also be converted into *L*-tyrosine, another one of the twenty protein-forming amino acids. *L*-tyrosine is converted into L-DOPA, which is further converted into dopamine, norepinephrine, and epinephrine (latter three are known as the catecholamines). *D*-phenylalanine can be converted only into phenylethylamine.

The genetic disorder phenylketonuria is an inability to metabolize phenylalanine. Individuals with this disorder are known as "phenylketonurics", and must abstain from consumption of phenylalanine. It is present in many sugarless gums, Monster Munch crisps, and other food products, which are labeled: "Phenylketonurics: Contains phenylalanine." The reason is not that phenylalanine is in the food per se. Aspartame (NutraSweet) is an ester that is hydrolyzed in the body to form phenylalanine, aspartic acid and methanol (wood alcohol), and it is the phenylalanine portion of aspartame which then builds up in the person with PKU.

The synthesized mix DL-Phenylalanine (DLPA), which is a combination of the D- and L- forms (e.g. a racemate: a racemic compound or mixture), is used as a nutritional supplement. Research indicates that DLPA can be an effective part of an overall program to fight chronic pain and depression in some cases, including the mood swings of premenstrual syndrome (PMS). Some sources contend that DLPA can increase energy and mental alertness, as well as heighten the ability to focus in individuals with attention deficit hyperactivity disorder (ADHD).

The genetic codon for phenylalanine was the first to be discovered. Marshall W. Nirenberg discovered that, when he inserted *m*-RNA made up of multiple uracil repeats into *E. coli*, the bacterium produced a new protein, made up solely of repeated phenylalanine amino acids.

Phenylalanine uses the same active transport channel as tryptophan to cross the blood-brain barrier, and, in large quantities, interferes with the production of serotonin.

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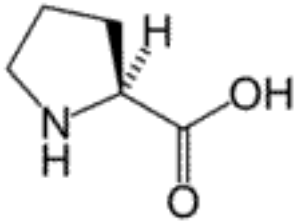
Proline



Abbrev. P Pro
Full Name Proline
Side chain type hydrophobic
Mass 115.13
pl 6.30
pK_1(α-COOH) 1.95

pK_2(α-$^+NH_3$) 10.64

Side chain -$CH_2CH_2CH_2$-

Hydro- phobic yes
Polar no
Charged no
Small yes
Tiny no
Aromatic or Aliphatic no
van der Waals volume 90
Codon CCU, CCC, CCA, CCG
Occurrence in proteins (%) 5.2

Remarks: Contains an unusual ring to the N-end amine group, which forces the CO-NH amide sequence into a fixed conformation. Can disrupt protein folding structures like α helix or β sheet, forcing the desired kink in the protein chain. Common in collagen, where it undergoes a posttranslational modification to hydroxyproline. Uncommon elsewhere.

L-Proline is one of the twenty proteinogenic units which are used in living organisms as the building blocks of proteins. The other nineteen units are all primary amino acids, but due to the (3-carbon) cyclic sidechain binding back to the nitrogen of the backbone, proline lacks a primary amine group ($-NH_2$).

The nitrogen in proline is properly referred to as a secondary amine. Proline is sometimes called an imino acid, but this is not correct, as imines contain a carbon-nitrogen double bond. The side chain binding to the nitrogen prevents rotation around the phi torsion angle, giving proline unique structural properties.

Proline is a non-polar amino acid. In proteins it does not have a hydrogen on the amide group and can therefore not act as a hydrogen bond donor. Proline can act as a structural disruptor for (α) helices, and as a turning point in β sheets. Multiple prolines and/or hydroxyprolines in a row can create a proline helix; this is the predominant structure in collagen. Sequences of proline and 2-aminoisobutyric acid (Aib) form a helical turn structure.

Proline is biosynthetically derived from the amino acid L-glutamate and its direct precursor is the real imino acid (S)-Δ1-pyrroline-5-carboxylate (P5C).

Proline and its derivatives are often used as asymmetric catalysts in organic reactions. The CBS reduction or proline catalysed aldol condensation are prominent examples.

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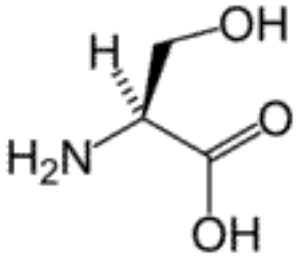
Serine



Abbrev. S, Ser
Full Name Serine
Side chain type hydrophilic
Mass 105.09
pl 5.68
pK_1(α-COOH) 2.19

pK_2(α-$^+NH_3$) 9.21

Side chain -CH_2OH

Hydro- phobic no
Polar yes
Charged no
Small yes
Tiny yes
Aromatic or Aliphatic no
van der Waals volume 73
Codon UCU, UCC, UCA, UCG, AGU,AGC
Occurrence in proteins (%) 6.8

Remarks: Serine and threonine have a short group ended with a hydroxyl group. Its hydrogen is easy to remove, so serine and threonine often act as hydrogen donors in enzymes. Both are very hydrophilic, therefore the outer regions of soluble proteins tend to be rich with them.

Serine, organic compound, one of the 20 amino acids commonly found in animal proteins. Only the L-stereoisomer appears in mammalian protein. It is not essential to the human diet, since it can be synthesized in the body from other metabolites, including glycine. Serine was first obtained from silk protein, a particularly rich source, in 1865. Its name is derived from the Latin for silk, sericum. Serine's structure was established in 1902.

Synthesis

The synthesis of serine and glycine starts with the oxidation of 3-phosphoglycerate forming 3-phosphohydroxypyruvate and NADH. A transamination reaction with glutamic acid forms 3-phosphoserine and removal of P_i yields serine.

Function

Serine is important in metabolism in that it participates in the biosynthesis of purines and pyrimidines, cysteine, tryptophan (in bacteria), and a large number of other metabolites.

When incorporated into the structure of enzymes, serine often plays an important role in their catalytic function. It has been shown to occur in the active sites of chymotrypsin, trypsin, and many other enzymes. The so-called nerve gases and many substances used in insecticides have been shown to act by combining with a residue of serine in the active site of acetylcholine esterase, inhibiting the enzyme completely. Without the esterase activity that usually destroys acetylcholine as soon as it performs its function, dangerously high levels of this neurotransmitter build up, quickly resulting in convulsions and death.

As a constituent (residue) of proteins, its side chain can undergo O-linked glycosylation. This might be important in explaining some of the devastating consequences of diabetes. It is one of three amino acid residues that are commonly phosphorylated by kinases during cell signalling in eukaryotes. Phosphorylated serine residues are often referred to as phosphoserine. Serine proteases are a common type of protease.

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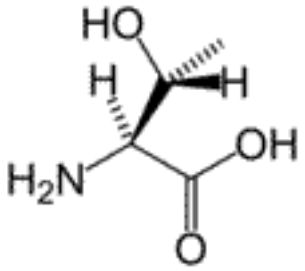
Threonine



Abbrev. T, Thr
Full Name Threonine
Side chain type hydrophilic
Mass 119.12
pl 5.60
pK_1(α-COOH) 2.09

pK_2(α-$^+NH_3$) 9.10

Side chain -$CH(OH)CH_3$

Hydro- phobic yes
Polar yes
Charged no
Small yes
Tiny no
Aromatic or Aliphatic no
van der Waals volume 93
Codon ACU, ACC, ACA, ACG
Occurrence in proteins (%) 5.9

Remarks: Essential for humans. Behaves similarly to serine.

Threonine is one of the 20 natural amino acids. Nutritionally, in humans, threonine is an essential amino acid.

Threonine contains two chiral centers, so there are four possible stereoisomers of threonine, or two possible diastereomers of L-threonine. However, the name **L-threonine** is used for one single enantiomer, (2*S*,3*R*)-2-amino-3-hydroxybutanoic acid. The second diastereomer (2*S*,3*S*), which is rarely present in nature, is called **L-*allo*-threonine**.

The threonine side chain can undergo O-linked glycosylation.

Threonine can become phosphorylated through the action of a threonine kinase. In its phosphorylated form, it can be referred to as **phosphothreonine**.

Foods high in threonine are cottage cheese, poultry, fish, meat, lentils, and sesame seeds.

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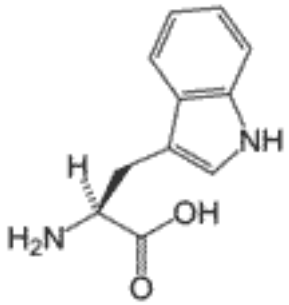
Tryptophan



Abbrev. W, Trp
Full Name Tryptophan
Side chain type hydrophilic
Mass 204.23
pl 5.89
pK_1(α-COOH) 2.46

pK_2(α-$^+NH_3$) 9.41

Side chain -$CH_2C_8H_6N$

Hydro- phobic yes
Polar no
Charged no
Small no
Tiny no
Aromatic or Aliphatic Aromatic
van der Waals volume 163
Codon UGG
Occurrence in proteins (%) 1.4

Remarks: Essential for humans. Behaves similarly to phenylalanine and tyrosine (see phenylalanine). Precursor of serotonin.

Tryptophan is an amino acid and essential in human nutrition. It is one of the 20 amino acids in the genetic code (codon *UGG*). Only the L-stereoisomer appears in mammalian protein.

Function

Tryptophan is an essential amino acid that humans cannot live without consuming. Amino acids function as building blocks in protein biosynthesis.

Tryptophan is a precursor for serotonin (a neurotransmitter), melatonin (a neurohormone), and niacin. The functional group of tryptophan is indole.

Tryptophan has been implicated as a possible cause of schizophrenia in people who cannot metabolize it properly. When improperly metabolized, it creates a waste product in the brain that is toxic, causing hallucinations and delusions. Tryptophan has also been indicated as an aid for schizophrenic patients.

Dietary sources

Tryptophan, found as a component of dietary protein, is particularly plentiful in chocolate, oats, bananas, dried dates, milk, yogurt, cottage cheese, meat, fish, turkey, chicken, sesame and peanuts.

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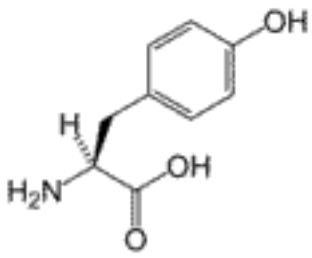
Tyrosine



Abbrev. Y Tyr
Full Name Tyrosine
Side chain type hydrophilic
Mass 181.19
pl 5.64
pK_1(α-COOH) 2.20

pK_2(α-$^+NH_3$) 9.21

pKr (R) 10.46

Side chain -CH_2-C_6H_4OH

Hydro- phobic yes
Polar yes
Charged no
Small no
Tiny no
Aromatic or Aliphatic Aromatic
van der Waals volume 141
Codon UAU, UAC
Occurrence in proteins (%) 3.2

Remarks: Behaves similarly to phenylalanine and tryptophan (see phenylalanine). Precursor of melanin, epinephrine, and thyroid hormones.

Tyrosine (from the Greek *tyros*, meaning *cheese*, as it was first discovered in cheese), **4-hydroxyphenylalanine**, or **2-amino-3(4-hydroxyphenyl)-propanoic acid**, is one of the 20 amino acids that are used by cells to synthesize proteins. It has a phenol side chain.

Tyrosine is converted to DOPA by Tyrosine hydroxylase, an enzyme.

It plays a key role in signal transduction, since it can be *tagged* with a phosphate group (phosphorylated) by protein kinases to alter the functionality and activity of certain enzymes. (In its phosphorylated state,

it is sometimes referred to as **phosphotyrosine**.) Tyrosine is also precursor to the thyroid hormones *thyroxine* and *triiodothyronine*, the pigment *melanin*, and the biologically-active catecholamines *dopamine*, *norepinephrine* and *epinephrine*.

In Papaver somniferum, the opium poppy, it is used to produce morphine.

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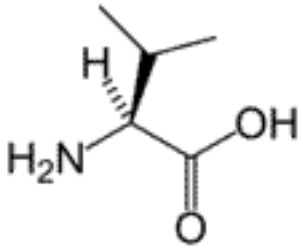
Valine



Abbrev. V Val
Full Name Valine
Side chain type hydrophilic
Mass 117.15
pl 6.00
pK_1(α-COOH) 2.39

pK_2(α-$^+NH_3$) 9.74

Side chain $CH(CH_3)_2$

Hydro- phobic yes
Polar no
Charged no
Small yes
Tiny no
Aromatic or Aliphatic Aliphatic
van der Waals volume 105
Codon GUU, GUC, GUA, GUG
Occurrence in proteins (%) 6.6

Remarks: Essential for humans. Behaves similarly to isoleucine and leucine. See isoleucine.

Valine is one of the 20 natural amino acids, and is coded for in DNA. Nutritionally, valine is also an essential amino acid. It is named after the plant valerian.

In sickle-cell disease, it substitutes for the hydrophilic amino acid glutamic acid in hemoglobin: Because valine is hydrophobic, the hemoglobin does not fold correctly. Valine is uncharged overall, as its R group is neutral, and the charges from its amino and carboxylic acid groups balance out: a zwitterion.

Foods that are good sources of valine include cottage cheese, fish, poultry, beef, peanuts, sesame seeds, and lentils.

In a 1994 report released by five top cigarette companies, valine is one of the 599 additives to cigarettes. Its use or purpose, however, is unknown, like most cigarette additives.

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Functional Groups

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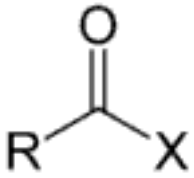
Acyl halide

Chemical class Acyl halide

Group Haloformyl

Formula RCOX

Graphical Formula



Prefix haloformyl-

Suffix -oyl halide

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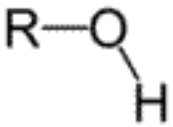
Alcohol

Chemical class Alcohol

Group Hydroxyl

Formula ROH

Graphical Formula



Prefix hydroxy-

Suffix -ol

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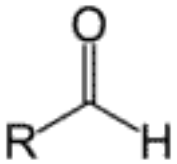
Aldehyde

Chemical class Aldehyde

Group Aldehyde

Formula RCHO

Graphical Formula



Prefix oxo-

Suffix -al

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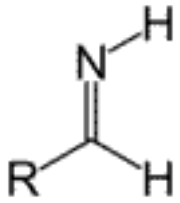
Aldimine

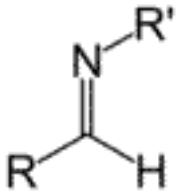
Chemical class Imine

Group Primary aldimine
Formula RC(=NH)H
Graphical Formula



Prefix imino-
Suffix -imine

Group Secondary aldimine
Formula RC(=NR')H
Graphical Formula



Prefix imino-
Suffix -imine

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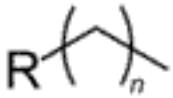
Alkane

Chemical class Alkane

Group Alkyl

Formula RH

Graphical Formula



Prefix alkyl-

Suffix -ane

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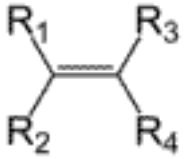
Alkene

Chemical class Alkene

Group Alkenyl

Formula $R_2C=CR_2$

Graphical Formula



Prefix alkenyl-

Suffix -ene

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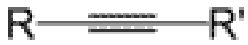
Alkyne

Chemical class Alkyne

Group Alkynyl

Formula RC(triple bond)CR'

Graphical Formula



Prefix alkynyl-

Suffix -yne

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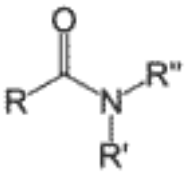
Amide

Chemical class Amide

Group Carboxamide

Formula $RCONR_2$

Graphical Formula



Prefix carboxamido-

Suffix -amide

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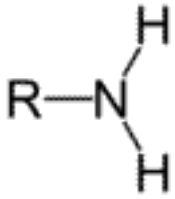
Amines

Chemical class Amines

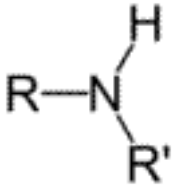
Group Primary amine
Formula RNH_2

Graphical Formula



Prefix amino-
Suffix -amine

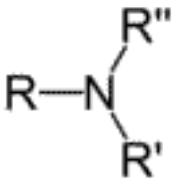
Group Secondary amine
Formula RNHR'
Graphical Formula



Prefix amino-
Suffix -amine

Group Tertiary amine
Formula RNR'_2

Graphical Formula



Prefix amino-
Suffix -amine

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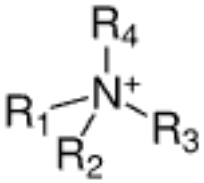
Ammonium ion

Chemical class Amines

Group 4° ammonium ion
Formula $R4N^+$
Graphical Formula



Prefix ammonio-
Suffix -ammonium

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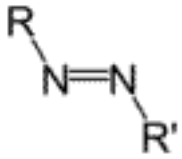
Azo compound

Chemical class Azo compound

Group Azo

Formula RN_2R'

Graphical Formula



Prefix no

Suffix alkyl(alkyl)diazene

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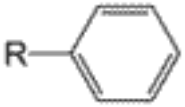
Benzene derivative

Chemical class Benzene derivative

Group Phenyl

Formula RC_6H_5

Graphical Formula



Prefix phenyl-

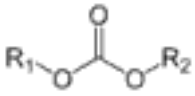
Suffix -benzene

Go to Start | This article uses material from the Wikipedia

Carbonate

Chemical class Carbonate

Group Carbonate ester
Formula ROCOOR
Graphical Formula



Suffix alkyl carbonate

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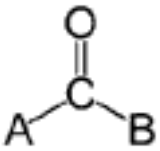
Carbonyl

A **carbonyl group** is a functional group composed of a carbon atom double-bonded to an oxygen atom: C=O.



Carbonyl group

The term carbonyl can also refer to carbon monoxide as a ligand in an inorganic or organometallic complex (e.g. nickel carbonyl); in this situation, carbon is triple-bonded to oxygen: C(triple bond)O.

A carbonyl group characterizes the following types of compounds (where -CO denotes a C=O carbonyl group):
Aldehyde RCHO
Ketone RCOR'
Carboxylic acid RCOOH
Ester RCOOR'
Amide RCONR'R"
Enone RCOC(R')=CR"R"'
Acyl chloride RCOCl
Anhydride (RCO)2O

Reactivity

Oxygen is more electronegative than carbon, and thus pulls electron density away from carbon to increase the bond's polarity. Therefore, the carbonyl carbon becomes electrophilic, and thus more reactive with nucleophiles. Also, the electronegative oxygen can react with an electrophile. For example a proton in an acidified solution.

Carbonyl groups can be reduced by reaction with hydride reagents such as $NaBH_4$ and $LiAlH_4$, and by organometallic reagents such as organolithium reagents and Grignard reagents.

Other important reactions include:
- Wolff-Kishner reduction
- Clemmensen reduction
- Conversion into thioacetals
- Hydration to hemiacetals and hemiketals, and then to acetals and ketals

- Reaction with ammonia and primary amines to form imines
- Reaction with hydroxylamines to form oximes
- Reaction with cyanide anion to form cyanohydrins
- Oxidation with oxaziridines to acyloins
- Reaction with Tebbe's reagent to alkenes.
- Perkins reaction
- Tishchenko reaction
- Aldol condensation
- Cannizaro's reaction

α,β-Unsaturated carbonyl compounds

α,β-Unsaturated carbonyl compounds are an important class of carbonyl compounds with the general structure $C_\beta=C_\alpha-C=O$. In these compounds the carbonyl group is conjugated with an alkene (hence the adjective unsaturated), from which they derive special properties. Examples of unsaturated carbonyls are acrolein, mesityl oxide, acrylic acid and maleic acid. Unsaturated carbonyls can be prepared in the laboratory in an aldol reaction and in the Perkin reaction. The carbonyl group, be it an aldehyde or acid, draws electrons away from the alkene and the alkene group in unsaturated carbonyls are therefore deactived towards an electrophile such as bromine or hydrochloric acid. As a general rule with unsymmetric electrophiles hydrogen attaches itself at the α position in an electrophilic addition. On the other hand, these compounds are activated towards nucleophiles in nucleophilic addition.

Spectroscopy

- Infrared spectroscopy: the C=O double bond absorbs infrared light at wavenumbers between approximately 1680-1750 cm^{-1}. This absorption is known as the "carbonyl stretch" when displayed on an infrared absorption spectrum.
- Nuclear magnetic resonance: the C=O double-bond exhibits different resonances depending on surrounding atoms.
- Mass spectrometry

Other organic carbonyl compounds

- Urea
- Carbamates

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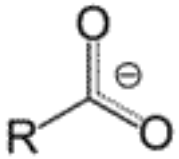
Carboxylate

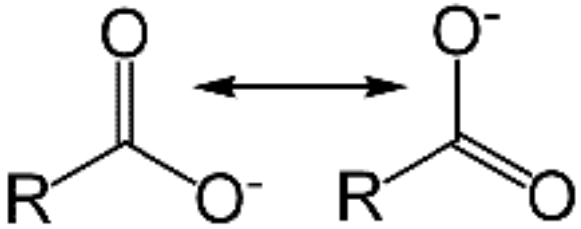
Chemical class Carboxylate

Group Carboxylate

Formula $RCOO^-$

Graphical Formula





Prefix carboxy-

Suffix -oate

Go to Start | This article uses material from the Wikipedia

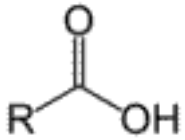
Carboxylic acid

Chemical class Carboxylic acid

Group Carboxyl

Formula RCOOH

Graphical Formula



Prefix carboxy-

Suffix -oic acid

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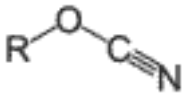
Cyanates acid

Chemical class Cyanates

Group Cyanate
Formula ROCN
Graphical Formula



Prefix isocyanato-
Suffix alkyl **cyanate**

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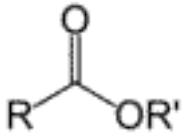
Ester

Chemical class Ester

Group Ester

Formula RCOOR'

Graphical Formula



Prefix no

Suffix -oate

Go to Start | This article uses material from the Wikipedia

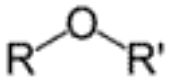
Ether

Chemical class Ether

Group Ether

Formula ROR'

Graphical Formula



Prefix alkoxy-

Suffix alkyl alkyl ether

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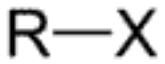
Haloalkane

Chemical class Haloalkane

Group Halo

Formula RX

Graphical Formula



Prefix halo-

Suffix alkyl **halide**

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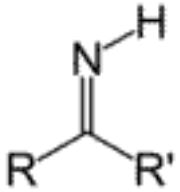
Imine

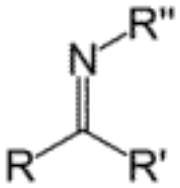
Chemical class Imine

Group Primary ketimine
Formula RC(=NH)R'
Graphical Formula



Prefix imino-
Suffix -imine

Group Secondary ketimine
Formula RC(=NR*)R'*
Graphical Formula



Prefix imino-
Suffix -imine

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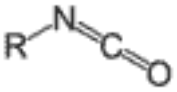
Isocyanates

Chemical class Isocyanates

Group Isocyanate
Formula RNCO
Graphical Formula



Prefix isocyanato-
Suffix alkyl **isocyanate**

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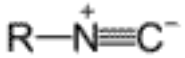
Isocyanide

Chemical class Isocyanide

Group Isocyanide

Formula RNC

Graphical Formula



Prefix isocyano-

Suffix alkyl **isocyanide**

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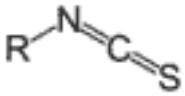
Isothiocyanate

Chemical class Isocyanates

Group Isothiocyanate
Formula RNCS
Graphical Formula



Prefix isothiocyanato-
Suffix alkyl **isothiocyanate**

Go to Start | This article uses material from the Wikipedia

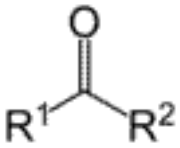
Ketone

Chemical class Ketone

Group Ketone

Formula RCOR'

Graphical Formula



Prefix keto-, oxo-

Suffix -one

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Nitrile

Chemical class Nitrile

Group Nitrile

Formula RCN

Graphical Formula

Prefix cyano-

Suffix alkane**nitrile**, alkyl **cyanide**

Go to Start | This article uses material from the Wikipedia

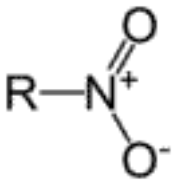
Nitro compound

Chemical class Nitro compound

Group Nitro

Formula RNO_2

Graphical Formula



Prefix nitro-

Go to Start | This article uses material from the Wikipedia

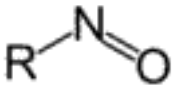
Nitroso compound

Chemical class Nitroso compound

Group Nitroso

Formula RNO

Graphical Formula



Prefix nitroso-

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Functional group

Functional groups are specific groups of atoms within molecules, that are responsible for the characteristic chemical reactions of those molecules. The same functional group will undergo the same or similar chemical reaction(s) regardless of the size of the molecule it is a part of.

The following is a list of common functional groups. In the formulas, the symbols R and R' usually denotes an attached hydrogen, or a hydrocarbon chain of any length, but may sometimes refer to any group of atoms. Below is an image of multiple functional groups found in organic chemistry.

Combining the names of functional groups with the names of the parent alkanes generates a powerful systematic nomenclature for naming organic compounds.

The non-hydrogen atoms of functional groups are always associated with each other and with the rest of the molecule by covalent bonds. When the group of atoms is associated with the rest of the molecule primarily by ionic forces, the group is referred to more properly as a polyatomic ion or complex ion. And all of these are called radicals, by a meaning of the term *radical* that predates the free radical.

The first carbon after the carbon that attaches to the functional group is called the alpha carbon.

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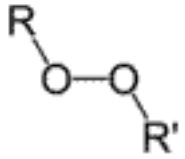
Peroxide

Chemical class Peroxide

Group Peroxy

Formula ROOR

Graphical Formula



Prefix peroxy-

Suffix alkyl **peroxide**

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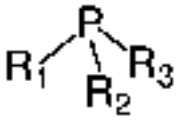
Phosphine

Chemical class Phosphine

Group Phosphino

Formula R_3P

Graphical Formula



Prefix phosphino-

Suffix -phosphane

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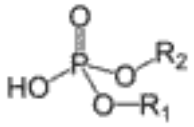
Phosphodiester

Chemical class Phosphodiester

Group Phosphate

Formula $HOPO(OR)_2$

Graphical Formula



Prefix phosphoric acid di(*substituent*) ester

Suffix di(*substituent*) hydrogenphosphate

Go to Start | This article uses material from the Wikipedia

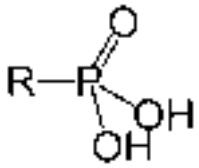
Phosphonic acid

Chemical class Phosphonic acid

Group Phosphono

Formula $RP(=O)(OH)_2$

Graphical Formula



Prefix phosphono-

Suffix *substituent* phosphonic acid

Go to Start | This article uses material from the Wikipedia

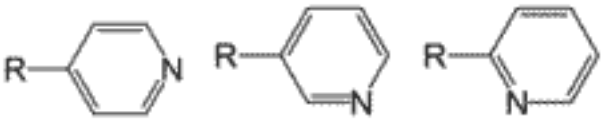
Pyridine derivative

Chemical class Pyridine derivative

Group Pyridyl

Formula RC_5H_4N

Graphical Formula



Prefix
4-pyridyl / pyridin-4-yl
3-pyridyl / pyridin-3-yl
2-pyridyl / pyridin-2-yl

Suffix -pyridine

Go to Start | This article uses material from the Wikipedia

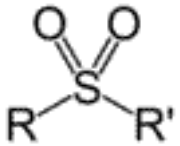
Sulfone

Chemical class Sulfone

Group Sulfonyl

Formula RSO_2R'

Graphical Formula



Prefix sulfonyl-

Suffix di(*substituent*) sulfone

Go to Start | This article uses material from the Wikipedia

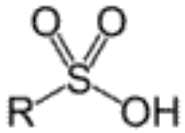
Sulfonic acid

Chemical class Sulfonic acid

Group Sulfo

Formula RSO_3H

Graphical Formula



Prefix sulfo-

Suffix *substituent* sulfonic acid

Go to Start | This article uses material from the Wikipedia

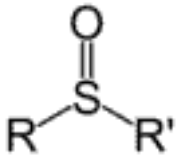
Sulfoxide

Chemical class Sulfoxide

Group Sulfinyl

Formula RSOR'

Graphical Formula



Prefix sulfinyl-

Suffix alkyl alkyl **sulfoxide**

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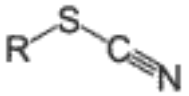
Thiocyanate

Chemical class Cyanates

Group Thiocyanate
Formula RSCN
Graphical Formula



Prefix isothiocyanato-
Suffix alkyl **thiocyanate**

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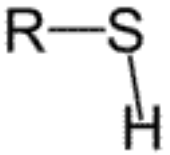
Thiol

Chemical class Thiol

Group Sulfhydryl

FormulaRSH

Graphical Formula



Prefix mercapto-, sulfanyl-

Suffix -thiol

Go to Start | This article uses material from the Wikipedia

Toluene

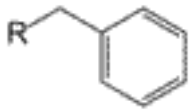
Chemical class Toluene derivative

Group Benzyl

Formula
$RCH_2C_6H_5$

RBn

Graphical Formula



Prefix benzyl-

Suffix no

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Chemical Classes

Go to Start

Alcohol

An **alcohol** is any organic compound in which a hydroxyl group (*-OH*) is bound to a carbon atom of an alkyl or substituted alkyl group. The general formula for a simple acyclic alcohol is $\mathbf{C_nH_{2n+1}OH}$.

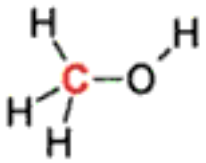
In general usage, **alcohol** (from Arabic *al-kuá*) refers almost always to ethanol, also known as **grain alcohol**, a strongly-smelling, colorless, volatile liquid formed by the fermentation of sugars. It also often refers to any beverage that contains ethanol. This sense underlies the term alcoholism (addiction to alcohol). Other forms of alcohol are usually described with a clarifying adjective, as in *isopropyl alcohol* or by the suffix *-ol*, as in *isopropanol*.

Structure

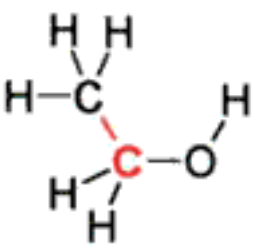
The functional group of an alcohol is a hydroxyl group bonded to an sp^3 hybridized carbon. It can therefore be regarded as a derivative of water, with an alkyl group replacing one of the hydrogens. If an aryl group is present rather than an alkyl, the compound is generally called a phenol rather than an alcohol. Also, if the hydroxyl group is bonded to one of the sp^2 hybridized carbons of an alkenyl group, the compound is referred to as an enol. The oxygen in an alcohol has a bond angle of around 109° (c.f. 104.5° in water), and two nonbonded electron pairs. The O-H bond in methanol (CH_3OH) is around 96 picometres long.

Primary, secondary, and tertiary alcohols

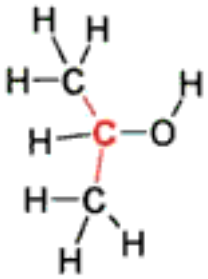
There are three major subsets of alcohols- 'primary' (1°), 'secondary' (2°) and 'tertiary' (3°), based upon the number of carbons the C-OH carbon (shown in red) is bonded to. Methanol is the simplest 'primary' alcohol. The simplest secondary alcohol is isopropanol (propan-2-ol), and a simple tertiary alcohol is *tert*-butanol (2-methylpropan-2-ol).



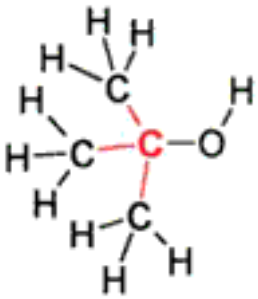
methanol CH_3OH



Ethanl, a 1° alcohol CH_3CH_2OH



Isopropanol, a 2° alcohol $(CH_3)_2CHOH$



tert-Butanol a 3° alcohol $(CH_3)_3COH$

The phenols with parent compound phenol have a hydroxyl group (attached to a benzene ring) just like alcohols but differ sufficiently in properties to warrant a separate treatment.

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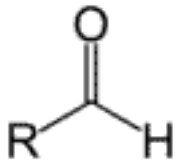
Aldehyde

An **aldehyde** is an organic compound containing a terminal carbonyl group. This functional group, which consists of a carbon atom which is bonded to a hydrogen atom and double-bonded to an oxygen atom (chemical formula -CHO), is called the **aldehyde group**. The aldehyde group is also called the **formyl** or **methanoyl** group.



An aldehyde. -R is the group attached to the carbonyl group.

Nomenclature

IUPAC names for aldehydes

IUPAC prescribes the following nomenclature for aldehydes:
- Acyclic aliphatic aldehydes are named as derivatives of the longest carbon chain containing the aldehyde group. Thus, HCHO is named as a derivative of methane, and $CH_3CH_2CH_2CHO$ is named as a derivative of butane. The name is formed by changing the suffix *-e* of the parent alkane to *-al*, so that HCHO is named *methanal*, and $CH_3CH_2CH_2CHO$ is named *butanal*.

- In other cases, such as when a -CHO group is attached to a ring, the suffix *-carbaldehyde* may be used. Thus, $C_6H_{11}CHO$ is known as *cyclohexanecarbaldehyde*.

- If another functional group is present which IUPAC rules prescribe must be named as a suffix, the aldehyde group is named with the prefix *formyl-*. This prefix is preferred to *methanoyl-*.
- If replacing the aldehyde group with a carboxyl (-COOH) group would yield a carboxylic acid with a trivial name, the aldehyde may be named by replacing the suffix *-ic acid* or *-oic acid* in this trivial name by *-aldehyde*. For example:
- HCHO may be called *formaldehyde*.
- CH_3CHO may be called *acetaldehyde*.

- C_6H_5CHO may be called *benzaldehyde*.

Other nomenclature

The carbon atom adjacent to a carbonyl group is called the α carbon. Carbon atoms further away from the group may be named β for the carbon atom bonded to the α carbon, γ for the next, and so on. Hydrogen atoms bonded to these carbon atoms are named likewise: an α hydrogen is a hydrogen atom bonded to the α carbon and so on.

A reaction that introduces an aldehyde group is known as a *formylation reaction*.

Etymology

The word *aldehyde* seems to have arisen from ***al****cohol* ***dehyd****rogenated*. In the past, aldehydes were sometimes named after the corresponding alcohols, for example *vinous aldehyde* for acetaldehyde. (*Vinous* is from Latin *vinum* = wine, the traditional source of ethanol; compare *vinyl*.)

Examples of aldehydes

- Methanal (Formaldehyde)
- Ethanal (Acetaldehyde)
- Propanal
- Butanal
- Pentanal
- Glucose
- Benzaldehyde
- Cinnamaldehyde

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Alkane

An **alkane** is an acyclic saturated hydrocarbon. In other words, an alkane is a long chain of carbon linked together by single bonds. Alkanes are aliphatic compounds.

The general formula for alkanes is $\mathbf{C_nH_{2n+2}}$; the simplest possible alkane is therefore methane, CH_4. The next simplest is ethane, C_2H_6; the series continues indefinitely. Each carbon atom in an alkane has sp^3 hybridization.

Alkanes are also known as paraffins, or collectively as the *paraffin series*. These terms also used for alkanes whose carbon atoms form a single, unbranched chain. Such branched-chain alkanes are called *isoparaffins*. Nearly all alkanes are combustible.

Isomerism

The atoms in alkanes with more than three carbon atoms can be arranged in multiple ways, forming different isomers. "Normal" alkanes have a linear, unbranched configuration. The number of isomers increases rapidly with the number of carbon atoms; for alkanes with 1 to 12 carbon atoms, the number of isomers equals 1, 1, 1, 2, 3, 5, 9, 18, 35, 75, 159, and 355, respectively (sequence A000602 in OEIS).

Nomenclature of alkanes

The names of all alkanes end with **-ane**.

Alkanes with unbranched carbon chains

The first four members of the series (in terms of number of carbon atoms) are named as follows:
methane, CH_4

ethane, C_2H_6

propane, C_3H_8

butane, C_4H_{10}

Alkanes with five or more carbon atoms are named by adding the suffix **-ane** to the appropriate numerical multiplier with elision of a terminal *-a-* from the basic numerical term. Hence, pentane, C_5H_{12}; hexane, C_6H_{14}; heptane, C_7H_{16}; octane, C_8H_{18}; etc. For a more complete list, see List of alkanes.

Straight-chain alkanes are sometimes indicated by the prefix *n-* (for *normal*) to distinguish them from

branched-chain alkanes having the same number of carbon atoms. Although this is not strictly necessary, the usage is still common in cases where there is an important difference in properties between the straight-chain and branched-chain isomers: e.g. *n*-hexane is a neurotoxin while its branched-chain isomers are not.

Alkanes with branched carbon chains

Branched alkanes are named as follows:

- Identify the longest straight chain of carbon atoms.

- Number the atoms in this chain, starting from 1 at the end nearer to the branching and counting upwards to the other end.

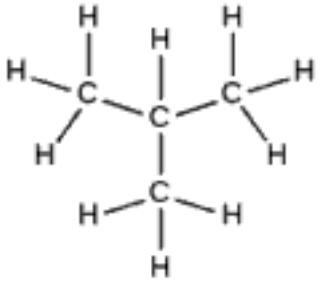
- Examine the groups attached to the chain in order and form their names.

- Form the name by looking at the different attached groups, and writing, for each group, the following:
- The number, or numbers, of the carbon atom, or atoms, where it is attached.
- The prefixes *di-*, *tri-*, *tetra-*, etc. if the group is attached in 2, 3, 4, etc. places, or nothing if it is attached in only one place.
- The name of the attached group.

- The formation of the name is finished by writing down the name of the longest straight chain.

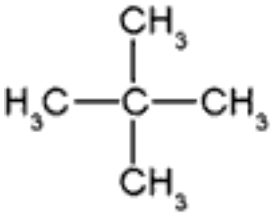
To carry out this algorithm, we must know how to name the substituent groups. This is done by the same method, except that instead of the longest chain of carbon atoms, the longest chain starting from the attachment point is used; also, the numbering is done so that the carbon atom next to the attachment point has the number 1.

For example, the compound



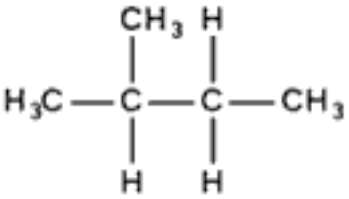
is the only 4-carbon alkane possible, apart from butane. Its formal name is 2-methylpropane.

Pentane, however, has two branched isomers, in addition to its linear, normal form:



2,2-dimethylpropane

and



2-methylbutane.

Trivial names

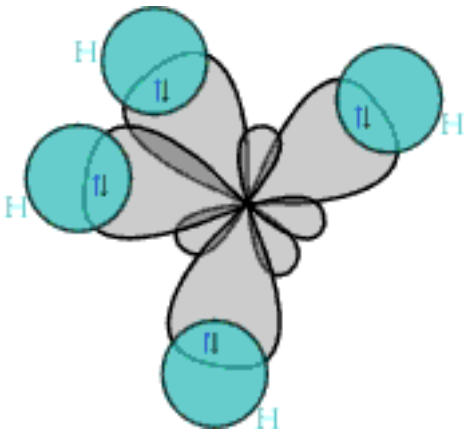
The following nonsystematic names are retained in the IUPAC system:

isobutane for 2-methylpropane isopentane for 2-methylbutane neopentane for 2,2-dimethylpropane

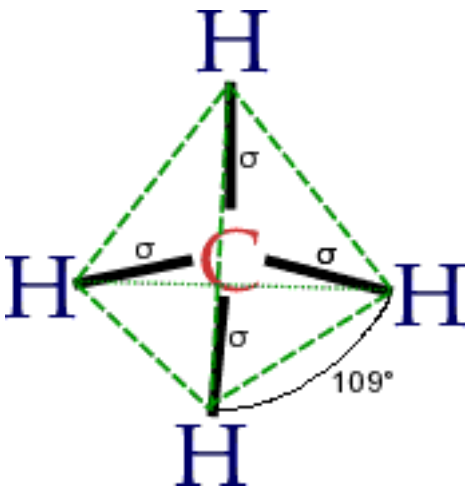
The name *isooctane* is very widely used in the petrochemical industry to refer to 2,2,4-trimethylpentane.

Molecular geometry

The molecular structure of the alkanes directly affects their physical and chemical characteristics. It is derived from the electron configuration of carbon, which has four valence electrons. The carbon atoms in alkanes are always sp^3 hybridised, that is to say that the valence electrons are said to be in four equivalent orbitals derived from the combination of the 2s orbital and the three 2p orbitals. These orbitals, which have identical energies, are arranged spatially in the form of a tetrahedron, the angle of $\cos^{-1}(-1/3) = 109.47°$ between them.



sp³-hybridisation in methane.



The tetrahedral structure of methane.

Bond lengths and bond angles

An alkane molecule has only C-H and C-C single bonds. The former result from the overlap of a sp³-orbital of carbon with the 1s-orbital of a hydrogen; the latter by the overlap of two sp³-orbitals on different carbon atoms. The bond lengths amount to 1.09×10^{-10}m for a C-H bond and 1.54×10^{-10}m for a C-C bond.

The spatial arrangement of the bonds is similar to that of the four sp³-orbitals-they are tetrahedrally arranged, with an angle of 109.47° between them. Structural formulae which represent the bonds as being at right angles to one another, while both common and useful, do not correspond with the reality.

Conformation

The structural formula and the bond angles are not usually sufficient to completely describe the geometry of a molecule. There is a further degree of freedom for each carbon-carbon bond: the torsion angle between the atoms or groups bound to the atoms at each end of the bond. The spatial arrangement described by the torsion angles of the molecule is known as its conformation.

Ethane forms the simplest case for studying the conformation of alkanes, as there is only one C-C bond. If one looks down the axis of the C-C bond, then one will see the so-called Newman projection. The hydrogen atoms on both the front and rear carbon atoms have an angle of 120° between them, resulting from the projection of the base of the tetrahedron onto a flat plane. However, the torsion angle between a given hydrogen atom attached to the front carbon and a given hydrogen atom attached to the rear carbon can vary freely between 0° and 360°. This is a consequence of the free rotation about a carbon-carbon single bond. Despite this apparent freedom, only two limiting conformations are important: eclipsed conformation and staggered conformation.

The two conformations, also known as rotamers, differ in energy: The staggered conformation is 12.6 kJ/mol lower in energy (more stable) than the eclipsed conformation.

This difference in energy between the two conformations, known as the torsion energy, is low compared to the thermal energy of an ethane molecule at ambient temperature. There is constant rotation about the C-C bond, albeit with short "pauses" at each staggered conformation. The time taken for an ethane molecule to pass from one staggered conformation to the next, equivalent to the rotation of one CH_3-group by 120° relative to the other, is of the order of 10^{-11}seconds.

The situation with respect to the two C-C bonds in propane is qualitatively similar to that of ethane: it is more complex, however, for butane and higher alkanes.

If one takes the central C-C bond of butane as the reference axis, each of the two central carbon atoms is bound to two hydrogen atoms and a methyl group. Four different conformations can be defined by the torsion angle between the two methyl groups and, as in the case of ethane, each has its characteristic energy.

The difference in energy between the fully eclipsed conformation and the antiperiplanar conformation is about 19 kJ/mol, and is therefore still relatively small at ambient temperature.

The case of higher alkanes is similar: the antiperiplanar conformation is always the most favoured around each carbon-carbon bond. For this reason, alkanes are usually shown in a zigzag arrangement in diagrams or in models. The actual structure will always differ somewhat from these idealised forms, as the differences in energy between the conformations are small compared to the thermal energy of the molecules: alkane molecules have no fixed structural form, whatever the models may suggest.

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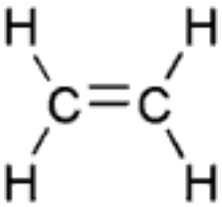
Alkene

An **alkene**, **olefin**, or **olefine** is an unsaturated chemical compound containing at least one carbon-to-carbon double bond. The simplest alkenes, with only one double bond and no other functional groups, form a homologous series of hydrocarbons with the general formula $\mathbf{C_nH_{2n}}$.



The simplest alkene is ethylene (C_2H_4), which has the International Union of Pure and Applied Chemistry (IUPAC) name *ethene*.

Alkenes are also called *olefins* (an archaic synonym, widely used in the petrochemical industry) or vinyl compounds.

Structure of Alkenes

Shape of alkenes

As predicted by the VSEPR model of electron pair repulsion, the molecular geometry of alkenes includes bond angles about each carbon in a double bond of about 120°. The angle may vary because of steric strain introduced by nonbonded interactions created by functional groups attached to the carbons of the double bond. For example, the C-C-C bond angle in propylene is 123.9°. The alkene double bond is stronger than a single covalent bond and also shorter with an average bond length of 133 picometres.

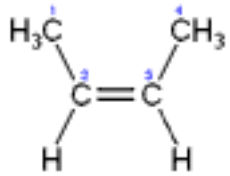
Molecular geometry

Like single covalent bonds, double bonds can be described in terms of overlapping atomic orbitals, except that unlike a single bond (which consists of a single sigma bond), a carbon-carbon double bond consists of one sigma bond and one pi bond.

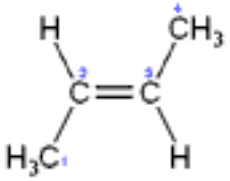
Each carbon of the double bond uses its three sp^2 hybrid orbitals to form sigma bonds to three atoms. The unhybridized *2p* atomic orbitals, which lie perpendicular to the plane created by the axes of the three sp^2 hybrid orbitals, combine to form the pi bond.

Because it requires a large amount of energy to break a pi bond (264 kJ/mol in ethylene), rotation about the carbon-carbon double bond is very difficult and therefore severely restricted. As a consequence substituted alkenes may exist as one of two isomers called a *cis* isomer and a *trans* isomer. For example,

in *cis*-2-butylene the two methyl substituents face the same side of the double bond and in *trans*-2-butylene they face the opposite side.



cis-2-Butylene



trans-2-Butylene

It is certainly not impossible to twist a double bond. In fact, a 90° twist requires an energy approximately equal to half the strength of a pi bond. The misalignment of the p orbitals is less than expected because pyridalization takes place. *trans*-Cyclooctene is a stable strained alkene and the orbital misalignment is only 19° with a dihedral angle of 137° (normal 120°) and a degree of pyramidalization of 18°. This explains the dipole moment of 0.8 D for this compound (cis-isomer 0.4 D) where a value of zero is expected. The *trans* isomer of cycloheptene is only stable at low temperatures.

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Haloalkane (Alkyl halide)

The **haloalkane** (also known as **halogenoalkanes**) are a group of chemical compounds, consisting of alkanes, such as methane or ethane, with one or more halogens linked, such as chlorine or fluorine, making them a type of organic halide. They are known under many chemical and commercial names. As fire extinguishants, propellants and solvents they have or had wide use. Some haloalkanes have negative effects on the environment such as ozone depletion. The most widely known family within this group are the chlorofluorocarbons (CFCs).

A **haloalkane**, also known as **alkyl halogenide**, **halogenalkane** or **halogenoalkane**, and **alkyl halide** is a chemical compound derived from an alkane by substituting one or more hydrogen atoms with halogen atoms. Substitution with fluorine, chlorine, bromine and iodine results in **fluoroalkanes**, **chloroalkanes**, **bromoalkanes** and **iodoalkanes**, respectively. Mixed compounds are also possible, examples are the chlorofluorocarbons (CFCs) which are mainly responsible for ozone depletion. Haloalkanes are used in semiconductor device fabrication, as refrigerants, foam blowing agents, solvents, aerosol spray propellants, fire extinguishing agents, and chemical reagents.

Freon is a trade name for a group of chlorofluorocarbons used primarily as a refrigerant. The word *Freon* is a registered trademark belonging to DuPont.

There are 3 types of haloalkane. In primary haloalkanes (1º), the carbon which carries the halogen atom is only attatched to one other alkyl group. However CH_3Br is also a primary haloalkane, even though there is no alkyl group. In secondary haloalkanes (2º) the carbon that carries the halogen atom is attached to 2 alkyl groups. In a tertiary haloalkanes (3º) the carbon that carries the halogen atom is attached to 3 alkyl groups.

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Alkyne

Alkynes are hydrocarbons that have at least one triple bond between two carbon atoms. The alkynes are traditionally known as **acetylenes** or the **acetylene series**, although the name *acetylene* is also used to refer specifically to the simplest member of the series, known as ethyne (C_2H_2) using formal IUPAC nomenclature.


Acetylene (IUPAC name: ethyne)

Structure

The carbon atoms in an alkyne bond are sp hybridized: they each have 2 p orbitals and 2 sp hybrid orbitals. Overlap of an sp orbital from each atom forms one sp-sp sigma bond. Each p orbital on one atom overlaps one on the other atom, forming two pi bonds, giving a total of three bonds. The remaining sp orbital on each atom can form a sigma bond to another atom, for example to hydrogen atoms in the parent compound acetylene. The two sp orbitals on an atom are on opposite sides of the atom: in acetylene, the H-C-C bond angles are 180°. Because a total of 6 electrons take part in bonding this triple bond is very strong with a bond strength of 837 kJ/mol. The sigma bond contributes 369 kJ/mol, the first pi bond contributes 268 kJ/mol and the second pi bond is weak with 202 kJ/mol bond strength. The CC bond distance with 121 picometers is also much less than that of the alkene bond which is 134 pm or the alkane bond with 153 pm.

The simplest alkyne is ethyne (acetylene):

Terminal and internal alkynes

Terminal alkynes have a hydrogen atom bonded to at least one of the sp hybridized carbons (those involved in the triple bond. An example would be methylacetylene (1-propyne using IUPAC nomenclature).

Internal alkynes have something other than hydrogen attached to the sp hybridized carbons, usually another carbon atom, but could be a heteroatom. A good example is 2-pentyne, in which there is a methyl group on one side of the triple bond and an ethyl group on the other side.

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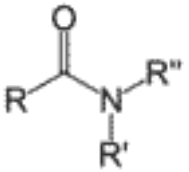
Amide

An ***amide*** is one of two kinds of compounds:
- the organic functional group characterized by a carbonyl group (C=O) linked to a nitrogen atom (N), or a compound that contains this functional group (pictured to the right); or
- a particular kind of nitrogen anion.

In the first sense referred to above, an amide is an amine where one of the nitrogen substituents is an acyl group; it is generally represented by the formula: $R_1(CO)NR_2R_3$, where either or both R_2 and R_3 may be hydrogen. Specifically, an amide can also be regarded as a derivative of a carboxylic acid in which the hydroxyl group has been replaced by an amine or ammonia.
Compounds in which a hydrogen atom on nitrogen from ammonia or an amine is replaced by a metal cation are also known as amides or **azanides**.

The second sense of the word *amide* is the amide anion, which is a deprotonated form of ammonia (NH_3) or an amine. It is generally represented by the formula: $[R_1NR_2]^-$, and is an extremely strong base, due to the extreme weakness of ammonia and its analogues as Brønsted acids.



Amide functional group

Naming conventions

- Example: CH_3CONH_2 is named acetamide or ethanamide
- Other examples: propan-1-amide, N,N-dimethylpropanamide, acrylamide
- For more detail see IUPAC nomenclature of organic chemistry - Amines and Amides

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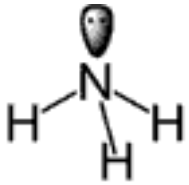
Amine

Amines are organic compounds and a type of functional group that contain nitrogen as the key atom. Structurally amines resemble ammonia, wherein one or more hydrogen atoms are replaced by organic substituents such as alkyl and aryl groups. An important exception to this rule is that compounds of the type $RC(O)NR_2$, where the C(O) refers to a carbonyl group, are called amides rather than amines.

Amides and amines have different structures and properties, so the distinction is chemically important. Somewhat confusing is the fact that amines in which an N-H group has been replaced by an N-M group (M = metal) are also called amides. Thus $(CH_3)_2NLi$ is lithium dimethylamide.

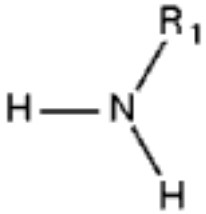


The structure of the ammonia molecule

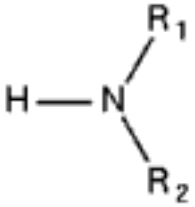
Aliphatic Amines

As displayed in the images below, **primary amines** arise when one of three hydrogen atoms in ammonia is replaced by an organic substituent. **Secondary amines** have two organic substituents bound to N together with one H. In **tertiary amines** all three hydrogen atoms are replaced by organic substituents. Note: the subscripts on the **R** groups are simply used to differentiate the organic substituents. However, the number subscripts on the H atoms show how many H atoms there are in that group. It is also possible to have four alkyl substituents on the nitrogen. These compounds have a charged nitrogen center, and necessarily come with a negative counterion, so they are called quaternary ammonium salts.

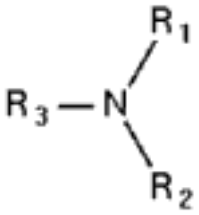
Primary Amine:



Secondary Amine:



Tertiary Amine:



Similarly, an organic compound with multiple amino groups is called a **diamine**, **triamine**, **tetraamine** and so forth.

Aromatic amines

Aromatic amines have the nitrogen atom connected to an aromatic ring as in anilines. The aromatic ring strongly decreases the basicity of the amine, depending on its substituents. Interestingly, the presence of an amine group strongly increases the reactivity of the aromatic ring, due to an electron-donating affect. One organic reaction involving aromatic amines is the Goldberg reaction.

Biological activity

Amines have strong, characteristic, disagreeable odors, and are toxic. The smells of ammonia, fish, urine, rotting flesh and sperm are all mainly composed of amines. Many kinds of biological activity produce amines by breakdown of amino acids.

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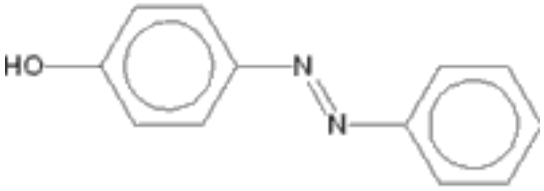
Azo compound

Azo compounds generally have a molecular formula of the form R-N=N-R', in which R and R' can be either aromatic or aliphatic. The N=N group is called an **azo** or **diimide** functional group. This helps to stabilise the N=N group by making it part of an extended delocalised system. This also has the effect of making many azo compounds coloured, as delocalised or *conjugated* systems often absorb visible frequencies of light.



A typical Azo compound, 4-hydroxyphenylazobenzene, a.k.a. yellow azo dye

The name azo comes from *azote*, an old name of nitrogen that originates in French and is derived from the Greek *a* (not) + *zoe* (to live). Aromatic azo compounds (R = R' = aromatic) are usually stable and have vivid colors such as red, orange, and yellow. Therefore, they are used as dyes, which are called **azo dyes**. Some azo compounds, eg. Methyl orange, can also be used as acid-base indicators, due to their ability to function as weak acids, and the different colours of the acid and salt forms. Azobenzene is another typical aromatic azo compound. Their colour originates from absorbance in the visible region of the spectrum due to the delocalization of electrons in the benzene and azo groups forming a conjugated system, whereby the N=N group is the chromophore.

Aliphatic azo compounds (R and/or R' = aliphatic) are rather unstable. At an elevated temperature or by irradiation, two carbon-nitrogen (R-N) bonds are cleaved simultaneously with the loss of nitrogen gas to generate carbon-centered radicals. Owing to this process, some aliphatic azo compounds are utilized as radical initiators. Azobisisobutylonitrile (AIBN) is a typical one and is widely used in industrial processes and in laboratory experiments.

Aromatic azo compounds can be synthesized by using an azocoupling reaction, that is, an electrophilic substitution reaction on aromatic rings with diazonium salts. Diazonium salts decompose at temperatures warmer than about 5 degrees Celsius, so the reaction must take place in solution under freezing conditions:

An oxidation reaction of hydrazine (R-NH-NH-R') also gives an azo compound.

Because of their instability, especially for aliphatic ones, care should be taken with the handling of azo compounds or an explosion may occur.

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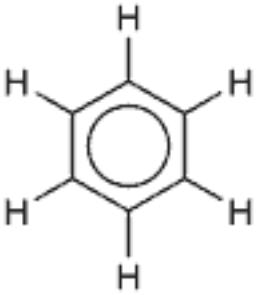
Benzene

Benzene, also known as **benzol**, is an organic chemical compound with the formula C_6H_6. It is sometimes abbreviated PhH. Benzene is a colorless and flammable liquid with a sweet smell and a relatively high melting point. It is carcinogenic and is no longer used as an additive in gasoline, but it is an important industrial solvent and precursor in the production of drugs, plastics, synthetic rubber, and dyes. Benzene is a natural constituent of crude oil, but it is usually synthesized from other compounds present in petroleum. Benzene is an aromatic hydrocarbon and the second [*n*]-annulene (-annulene).

The formula of benzene (C_6H_6) mystified scientists who could not figure out its structure. Friedrich August Kekulé von Stradonitz was the first to deduce the ring structure of benzene. An often-repeated story claims that after years of studying carbon bonding, benzene and related molecules, he dreamt one night of the Ouroboros, a snake eating its own tail, and that upon waking he was inspired to deduce the ring structure of benzene. However, the story first appeared in the *Berichte der Durstigen Chemischen Gesellschaft* (Journal of the Thirsty Chemical Society), a parody of the *Berichte der Deutschen Chemischen Gesellschaft*, which appeared annually in the late-19th century on the occasion of the congress of German chemists; as such, it is probably to be treated with circumspection.

While his (more formal) claims were well-publicized and accepted, by the early-1920s Kekulé's biographer came to the conclusion that Kekulé's understanding of the tetravalent nature of carbon bonding depended on the previous research of Archibald Scott Couper (1831-1892); furthermore, Josef Loschmidt (1821-1895) had earlier posited a cyclic structure for benzene as early as 1861. The cyclic nature of benzene was finally confirmed by the eminent crystallographer Kathleen Lonsdale.

Benzene presents a special problem in that, to account for all the bonds, there must be alternating double carbon bonds. Using X-ray diffraction, researchers discovered that all of the carbon-carbon bonds in benzene are of the same length of 140 picometres (pm). The C-C bond lengths are greater than a double bond (134pm) but shorter than a single bond (147pm). This intermediate distance is explained by electron delocalization: the electrons for C-C bonding are distributed equally between each of the six carbon atoms. One representation is that the structure exists as a superposition of so-called resonance structures, rather than either form individually. This delocalisation of electrons is known as aromaticity, and gives benzene great stability. This enhanced stability is the fundamental property of aromatic molecules that differentiates them from molecules that are non-aromatic. To reflect the delocalised nature of the bonding, benzene is often depicted with a circle inside a hexagonal arrangement of carbon atoms:



As is common in organic chemistry, the carbon atoms in the diagram above have been left unlabeled.

Substituted benzene derivatives

Many important chemicals are derived from benzene, wherein with one or more of the hydrogen atoms is replaced with another functional group. Examples of simple benzene derivatives are phenol, toluene, and aniline, abbreviated PhOH,PhMe, and $PhNH_2$, respectively. Linking benzene rings gives biphenyl, C_6H_5-C_6H_5. Further loss of hydrogen gives "fused" aromatic hydrocarbons, such naphthalene and anthracene. The limit of the fusion process is the hydrogen-free material graphite.

In heterocycles, carbon atoms in the benzene ring are replaced with other elements. The most important derivatives are the rings containing nitrogen. Replacing one CH with N gives the compound pyridine, C_5H_5N. Although benzene and pyridine are *structurally* related, benzene cannot be converted into pyridine. Replacement of a second CH bond with N gives, depending on the location of the second N, pyridazine, pyrimidine, and pyrazine.

History

Benzene has been the subject of many studies by many famous scientists ranging from Michael Faraday to Linus Pauling. In 1825 Faraday reported its isolation from oil gas and gave it the name *bicarburet of hydrogen*. In 1833, Eilhard Mitscherlich produced it via the distillation of benzoic acid (from gum benzoin) and lime. Mitscherlich gave the compound the name *benzin*. In 1845, Charles Mansfield, working under August Wilhelm von Hofmann, isolated benzene from coal tar. Four years later, Mansfield began the first industrial-scale production of benzene, based on the coal-tar method.

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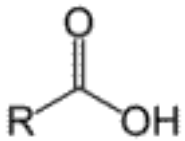
Carboxylic acid

Carboxylic acids are organic acids characterized by the presence of a **carboxyl group**, which has the formula -(C=O)-OH, usually written as **-COOH**. In general, the salts and anions of carboxylic acids are called **carboxylates**.



Structure of a carboxylic acid

The simplest series of carboxylic acids are the **alkanoic acids**, R-COOH, where R is a hydrogen or an alkyl group. Compounds may also have two or more carboxylic acid groups per molecule.

Carboxylic acids are most readily identified as such by infrared spectrometry, the characteristic O-H stretch of the carboxyl group appears as a broad peak in the 2500 to 3000 cm^{-1} region.

In ^{1}H NMR spectrometry the hydroxyl hydrogen appears in the 10-13 ppm region.

Nomenclature and examples

The carboxylate anion $R\text{-}COO^-$ is usually named with the suffix *-ate*, so acetic acid, for example, becomes acetate ion. In IUPAC nomenclature, carboxylic acids have an *-oic acid* suffix (e.g. octadecanoic acid). In common nomenclature, the suffix is usually *-ic acid* (e.g. stearic acid).

Some representative carboxylic acids include:

- Amino acids - the building blocks of proteins

- **Fatty acids** - where R is an alkane in saturated acids or an alkene in unsaturated acids
- Formic acid (methanoic acid) - HCOOH, found in insect stings (*formic* from the Latin word meaning ants)
- Acetic acid (ethanoic acid) - CH_3COOH, the principal component of vinegar
- Acrylic acid (2-propenoic acid) - $CH_2{=}CHCOOH$, used in polymer synthesis
- Propionic acid (propanoic acid) - CH_3CH_2COOH
- Butyric acid (butanoic acid) - $CH_3CH_2CH_2COOH$, found in rancid butter
- Lauric acid (dodecanoic acid) - found in coconut oil
- Docosahexaenoic acid - nutritional supplement

- Eicosapentaenoic acid - nutritional supplement

- **Keto acids** - acids of biochemical significance that contain a ketone group
- Pyruvic acid
- Acetoacetic acid

- **Aromatic carboxylic acids**
- Benzoic acid - C_6H_5COOH. Sodium benzoate, the sodium salt of benzoic acid is used as a food preservative
- Salicylic acid - found in many skin care products

- **Dicarboxylic acids** - containing two carboxyl groups
- Aldaric acid - a family of sugar acids
- Oxalic acid - found in many foods
- Malonic acid
- Malic acid - found in apples
- Succinic acid - a component of the citric acid cycle
- Glutaric acid
- Adipic acid - the monomer used to produce nylon

- **Tricarboxylic acids** - containing three carboxyl groups
- Citric acid - found in citrus fruits

- **Alpha hydroxy acids** - containing a hydroxy group
- Lactic acid (2-hydroxypropanoic acid) - found in sour milk

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Chemical classification

Chemical classification systems attempt to classify elements or compounds according to certain chemical functional or structural properties. Whereas the structural properties are largely intrinsic, functional properties and the derived classifications depend to a certain degree on the type of chemical interaction partners on which the function is exerted. Sometimes other criteria like purely physical ones (e.g. molecular weight) or - on the other hand - functional properties above the chemical level are also used for building chemical taxonomies.

Some systems mix the various levels, resulting in hierarchies where the domains are slightly confused, for example having structural and functional aspects end up on the same level. Whereas chemical function is closely dependent on chemical structure, the situation becomes more involved when e.g. pharmacological function is integrated, because the QSAR can usually not be directly computed from structural qualities.

Physico-chemical classification

- by molecular weight
- by electrical charge: uncharged, positively, negatively, partially charged
- formal charge, oxidation state
- solubility
- pH value

Structural classification

Usually binary classifications and combinations thereof:

- radicals, non-radicals
- cyclic vs. linear
- type of major bond: ionic (salts) vs. covalent
- organic vs. inorganic compounds (depends on whether carbon is the main constituent or not)
- (in organic chemistry)
- aliphatic vs. aromatic compounds

Functional classification

Chemical function

- by functional group

Pharmacological/Biological function

Mostly appropriate only for large biological molecules (as at least one interacting partner), in particular enzymes, depends on chemical functions of their constituent amino acids.

- ligand vs. receptor, coenzyme
- EC number
- TC number
- pharmacophore vs. non-drug

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Cyanate

The **cyanate** ion is an anion consisting of one oxygen atom, one carbon atom, and one nitrogen atom (OCN^-), in that order, and possesses 1 unit of negative charge, borne mainly by the nitrogen atom. In organic compounds the **cyanate group** is a functional group.

The structure of cyanate is resonant between these two structures:

O^- - C (triple bond) N and O = C = N^-

The cyanate ion is isoelectronic with carbon dioxide, and so shares its linear shape.

The cyanate ion is an ambident nucleophile in nucleophilic substitution because it can react to form an alkyl cyanate R-OCN (exception) or an alkyl isocyanate R-NCO (rule). Aryl cyanates (C_6H_5OCN) can be formed by a reaction of phenol with cyanogen chloride (ClCN) in the presence of a base.

Cyanates are salts of cyanic acid for example potassium cyanate (KNCO).

The '*cyanate* ion is relatively non-toxic in comparison to cyanides. Use of this fact is made in cyanide decontamination processes where a permanganate oxidation converts toxic cyanide to cyanate.

The fulminate ion has the same formula but different structure.

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Epoxide

An **epoxide** is a cyclic ether with only three ring atoms. This ring approximately is an equilateral triangle, i.e. its bond angles are about 60°, which makes it highly strained. The strained ring makes epoxides more reactive than other ethers, especially towards nucleophiles. Simple epoxides are named from the parent compound ethylene oxide or oxirane, such as in *chloromethyloxirane*. As a functional group epoxides obtain the **epoxy** prefix such as in the compound *1,2-epoxycycloheptane* which can also be called *cycloheptene epoxide*.

A polymer made of epoxide units is called a *polyepoxide* or an *epoxy*. Epoxy resins are used as adhesives and structural materials. Example: epoxyethane

Reactions

- Nucleophilic addition to an epoxide can be base or acid catalyzed.
- Hydrolysis of an epoxide in presence of an acid catalyst generates a glycol. The hydrolysis process of epoxides can be considered to be the nucleophilic addition of water to the epoxide under acidic conditions.
- Reduction of an epoxide with lithium aluminium hydride and water generates an alcohol. This reduction process can be considered to be the nucleophilic addition of hydride (H-) to the epoxide under basic conditions.
- Reduction with tungsten hexachloride and n-butyllithium generates the alkene. This reaction in effect is a **de-epoxidation.**

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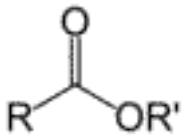
Ester

In chemistry, **esters** are organic compounds in which an organic group (symbolized by **R'** in this article) replaces a hydrogen atom (or more than one) in an oxygen acid. An oxygen acid is an acid whose molecule has an **-OH** group from which the hydrogen (H) can dissociate as an H^+ ion.



General formula of a carboxylate ester

The most common esters are the **carboxylate esters**, where the acid in question is a carboxylic acid. For example, if the acid is acetic acid, the ester is called an acetate. Esters may also be formed with inorganic acids; for example, dimethyl sulfate is an ester, and sometimes called "sulfuric acid, dimethyl ester".

Esters are named similarly to salts; although they don't really have cations and anions, the terminology follows the same pattern: a more electropositive part followed by a more electronegative part.

An ester can be thought of as a product of a condensation reaction of an acid (usually an organic acid) and an alcohol (or phenol compound), although there are other ways to form esters. Condensation is a type of chemical reaction in which two molecules are joined together and eliminate a small molecule, in this case two-**OH** groups are joined eliminating a water molecule. A condensation reaction to form an ester is called esterification. Esterification can be catalysed by the presence of H^+ ions. Sulfuric acid is often used as a catalyst for this reaction. The name ester is derived from the German **Es**sig-Ã**ther**, an old name for acetic acid ethyl ester (ethyl acetate).

Naming of esters

Esters can be produced by an equilibrium reaction between an alcohol and a carboxylic acid. The ester is named according to the *alkyl* group (the part from the alcohol) and then the *alkanoate* (the part from the carboxylic acid) which make it up. For example, the reaction between methanol and butyric acid yields the ester methyl butyrate C_3H_7-COO-CH_3 (as well as water). The simplest ester is H-COO-CH_3 (methyl formate, also called methyl methanoate).

For esters derived from the simplest carboxylic acids, the traditional names are recommended by IUPAC, *viz*, formate, acetate, propionate, butyrate, though out of these only acetate may carry further substituents. For esters from higher acids, the alkane name with an *-oate* ending is generally preferred, e. g., hexanoate. Common esters of aromatic acids include benzoates such as methyl benzoate, and

phthalates, with substitution allowed in the name.

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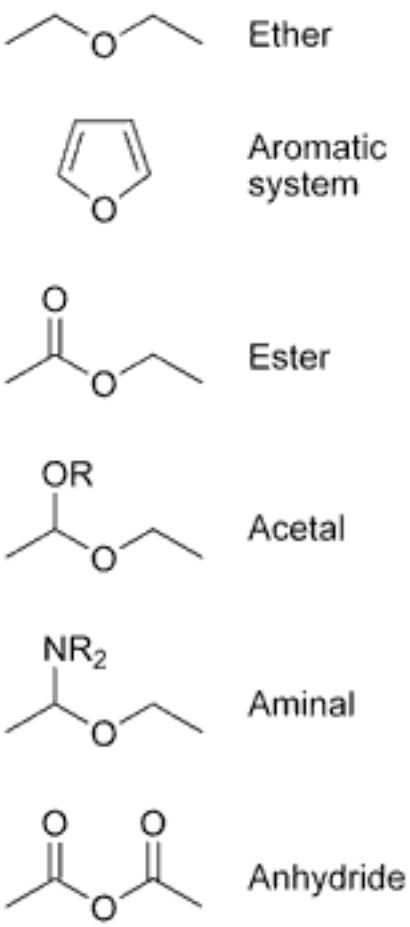
Ether

Ether is the general name for a class of chemical compounds which contain an ether group - an oxygen atom connected to two (substituted) alkyl groups. A typical example is the solvent and anesthetic diethyl ether, commonly referred to simply as "ether", (ethoxyethane, CH_3-CH_2-O-CH_2-CH_3).

Similar structures

Ethers are not to be confused with the following classes of compounds with the same general structure R-O-R.



Not all compounds of the formula R-O-R are ethers

- Aromatic compounds like furan where the oxygen is part of the aromatic system.
- Compounds where one of the carbon atoms next to the oxygen is connected to oxygen, nitrogen, or sulfur:
- Esters R-C(=O)-O-R
- Acetals R-CH(-O-R)-O-R
- Aminals R-CH(-NH-R)-O-R
- Anhydrides R-C(=O)-O-C(=O)-R

Primary, secondary, and tertiary ethers

The terms *"primary ether"*, *"secondary ether"*, and *"tertiary ether"* are occasionally used and refer to the carbon atom next to the ether oxygen. In a *primary ether* this carbon is connected to only one other carbon as in diethyl ether CH_3-CH_2-O-CH_2-CH_3. An example of a *secondary ether* is diisopropyl ether $(CH_3)_2CH$-O-$CH(CH_3)_2$ and that of a *tertiary ether* is di-tert-butyl ether $(CH_3)_3C$-O-$C(CH_3)_3$.

Polyethers

Polyethers are compounds with more than one ether group. While the term generally refers to polymers like polyethylene glycol and polypropylene glycol, low molecular compounds such as the crown ethers may sometimes be included.

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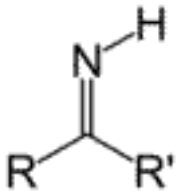
Imine

An **imine** is a functional group or chemical compound containing a carbon-nitrogen double bond. An imine can be synthesised by nucleophilic addition from a ketone or aldehyde and ammonia or an amine to a hemiaminal -C(OH)(NHR)- followed by elimination of water to the imine.



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Isocyanate

Isocyanate is the functional group of atoms -N=C=O (1 nitrogen, 1 carbon, 1 oxygen), not to be confused with the cyanate functional group which is arranged as -O-C(triple bond)N. Any organic compound which contains an isocyanate group may also be referred to in brief as an isocyanate. An isocyanate may have more than one isocyanate group. An isocyanate that has two isocyanate groups is known as a **diisocyanate**. Diisocyanates are manufactured for reaction with polyols in the production of polyurethanes.

The isocyanate group reacts with the hydroxyl functional group to form a urethane linkage. If a diisocyanate is reacted with a compound containing two or more hydroxyl groups (a polyol), long polymer chains are formed, known as polyurethanes.

The isocyanate group also reacts with the amine functional group. Reaction between a diisocyanate and a compound containing two or more amine groups, produces long polymer chains known as polyureas.

The isocyanate group can react with itself. Aliphatic diisocyanates can form trimers, known as biurets.

A monofunctional isocyanate of industrial significance is methyl isocyanate (MIC), which is used in the manufacture of pesticides.

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Isocyanide

An **isocyanide**, also called an **isonitrile**, is an organic compound with the functional group R-N(triple bond)C. The CN functionality is connected to the organic fragment via the nitrogen atom, not via carbon as is found in the isomeric nitriles, which have the connectivity R-C(triple bond)N. Hence the prefix *iso*. Nitrogen and carbon are connected through a triple bond with a positive charge on nitrogen and a negative charge on carbon.

Isocyanides are reactants in two multicomponent reactions: the Ugi reaction and the Passerini reaction.

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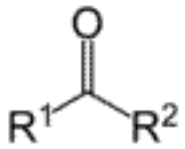
Ketone

A **ketone** is either the functional group characterized by a carbonyl group (O=C) linked to two other carbon atoms or a chemical compound that contains this functional group. A ketone can be generally represented by the formula: $R_1(CO)R_2$.



Ketone group

A carbonyl carbon bonded to two carbon atoms distinguishes ketones from carboxylic acids, aldehydes, esters, amides, and other oxygen-containing compounds. The double-bond of the carbonyl group distinguishes ketones from alcohols and ethers. The simplest ketone is acetone (also called propanone).

The carbon atom adjacent to a carbonyl group is called the α-carbon. Hydrogens attached to this carbon are called α-hydrogens. In the presence of an acid catalyst the ketone is subjected to so-called keto-enol tautomerism. The reaction with a strong base gives the corresponding enolate. A diketone is a compound containing two ketone groups.

Nomenclature

In general, ketones are named using IUPAC nomenclature by changing the suffix *-e* of the parent alkane to *-one*. For common ketones, some traditional names such as acetone and benzophenone predominate, and these are considered retained IUPAC names , although some introductory chemistry texts use names such as 2-propanone or propanone.

Oxo is the formal IUPAC nomenclature for a ketone functional group. However, other prefixes are also used by various books and journals. For some common chemicals (mainly in biochemistry), **keto** or **oxy** is the term used to describe the ketone (also known as alkanone) functional group. **Oxo** also refers to a single oxygen atom coordinated to a transition metal (a metal oxo).

Spectroscopic properties

Spectroscopy is an important means for identifying ketones. Ketones and aldehydes will display a significant peak in infrared spectroscopy, at around 1700 cm^{-1} (slightly higher or lower, depending on the chemical environment)

Ketones in biology

Acetone, acetoacetate and beta-hydroxybutyrate are ketones (or ketone bodies) generated from carbohydrates, fatty acids and amino acids in humans and most vertebrates. Ketones are elevated in blood after fasting including a night of sleep, and in both blood and urine in starvation, hypoglycemia due to causes other than hyperinsulinism, various inborn errors of metabolism, and ketoacidosis (usually due to diabetes mellitus). Although ketoacidosis is characteristic of decompensated or untreated type 1 diabetes, ketosis or even ketoacidosis can occur in type 2 diabetes in some circumstances as well. Acetoacetate and beta-hydroxybutyrate are an important fuel for many tissues, especially during fasting and starvation. The brain, in particular, relies heavily on ketone bodies as a substrate for lipid synthesis and for energy during times of reduced food intake. At the NIH, Dr. Richard Veech refers to ketones as "magic" in their ability to increase metobolic efficiency, while decreasing production of free radicals, the damaging byproducts of normal metabolism. His work has shown that ketone bodies may treat neurological diseases such as Alzheimer's and Parkinson's disease (source), and the heart and brain operate 25% more efficiently using ketones as a source of energy (source).

Applications

Ketones are often used in perfumes and paints to stabilize the other ingredients so that they don't degrade as quickly over time. Other uses are as solvents and intermediates in chemical industry. Examples of ketones are Acetophenone, Butanone (methyl ethyl ketone) and Propanone (acetone).

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Nitrile

A **nitrile** is any organic compound which has a -C**(triple bond)**N functional group. The -C**(triple bond)**N functional group is called a **nitrile group**. In the -CN group, the carbon atom and the nitrogen atom are triple bonded together. The prefix **cyano** is used in chemical nomenclature to indicate the presence of a nitrile group in a molecule. A cyanide ion is a negative ion with the formula CN^-. The -CN group is sometimes, less properly, referred to as a *cyanide group* or *cyano group* and compounds with them are sometimes referred to as cyanides.

Nitriles sometimes release the highly toxic CN^- cyanide ion. See the article on cyanide for a discussion of biological effects and toxicity.

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Nitro compound

Nitro compounds are organic compounds that contain one or more **nitro** functional groups ($-NO_2$).

They are often highly explosive; various impurities or improper handling can easily trigger a violent exothermic decomposition.

Aromatic nitro compounds are typically synthesized by the action of a mixture of nitric and sulfuric acids on a suitable organic molecule. Some examples of such compounds are trinitrophenol (picric acid), trinitrotoluene (TNT), and trinitroresorcinol (styphnic acid).

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Nitroso

Nitroso refers to a functional group in organic chemistry which has the general formula R-NO. Nitroso compounds can be prepared by the reduction of nitro compounds or by the oxidation of hydroxylamines. A good example is $(CH_3)_3CNO$, known formally as 2-methyl-2-nitrosopropane, or *t*-BuNO, which is prepared by the following sequence :

$(CH_3)_3CNH_2$ --> $(CH_3)_3CNO_2$

$(CH_3)_3CNO_2$ --> $(CH_3)_3CNHOH$

$(CH_3)_3CNHOH$ --> $(CH_3)_3CNO$

$(CH_3)_3CNO$ exists in solution as an equilibrium mixture of itself, which is blue, and its dimer, which is colorless, m.p. 80-81 °C.

In the Fischer-Hepp rearrangement aromatic 4-nitroso-anilines are prepared from the corresponding nitrosamines.

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Organic peroxide

Organic peroxides are organic compounds containing the peroxide functional group (ROOR'). If the R' is hydrogen, the compound is called an **organic hydroperoxide** or a **peroxyacid**. **Peresters** have general structure RC(O)OOR.

The O-O bond easily breaks and forms free radicals of the form RO·. This makes organic peroxides useful as catalysts for some types of polymerisation, such as the epoxy resins used in glass-reinforced plastics. MEKP and benzoyl peroxide are commonly used for this purpose. However, the same property also means that organic peroxides can either intentionally or unintentionally initiate explosive polymerisation in materials with unsaturated chemical bonds, and this process has been used in explosives.

Most organic peroxides are highly flammable, explosive materials, often powerful and volatile. As little as 5 milligrams of diethyl ether peroxide can shatter glass chemical apparatuses. Organic peroxides, like their inorganic counterparts, are powerful bleaching agents.

Some peroxide reactions are:
- organic reduction to alcohols with Lithium aluminium hydride or phosphite esters
- cleavage to ketones and alcohols in the base catalyzed Kornblum-DeLaMare rearrangement

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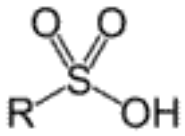
Sulfone

A **sulfone** is a chemical compound containing a sulfonyl functional group attached to two carbon atoms. The central sulfur atom is twice double bonded to oxygen and has two further hydrocarbon substituents. The general structural formula is R-S(=O)(=O)-R' where R and R' are the organic groups.



The use of the alternative name **sulphone** is discouraged by IUPAC. Sulfides are often the starting materials for sulfones by organic oxidation through the intermediate formation of sulfoxides. For example dimethyl sulfide is oxidized to dimethyl sulfoxide and then to dimethyl sulfone.

In the Ramberg-Bäcklund Reaction and the Julia olefination sulfones are converted to alkenes.

A sulfone can also be any of various organic sulfur compounds having a sulfonyl group attached to two carbon atoms, especially such a compound formerly used as an antibiotic to treat leprosy, dermatitis herpetiformis, tuberculosis, or Pneumocystis Carinii Pneumonia (PCP).

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Thioether

A **thioether** (also known as a *sulfide*) is a functional group in organic chemistry that has the structure C-S-C. A thioether is similar to an ether except that it contains a sulfur atom in place of the oxygen. Because the chemical properties of both atoms are similar, as they are in the same group in the periodic table, the chemical properties of ethers and thioethers share some commonalities. This functional group is important in biology, most notably in the amino acid methionine. Like many other sulfur containing compounds, volatile thioethers characteristically have foul odors.

One difference from ethers is that ethers (R-O-R) are not readily oxidized, whereas thioethers (R-S-R) to sulfoxides (R-S(=O)-R), which can themselves be oxidized to sulfones (R-S(=O)$_2$-R). For example, dimethyl sulfide can be oxidized as follows:

$S(CH_3)_2 + O \rightarrow OS(CH_3)_2$

$OS(CH_3)_2 + O \rightarrow O_2S(CH_3)_2$

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Thiol

A **thiol** is a compound that contains the functional group composed of a sulfur atom and a hydrogen atom (-SH). This functional group is referred to either as a *thiol group* or a *sulfhydryl group*. More traditionally, thiols have been referred to as *mercaptans*. In general, the deprotonated form $-S^-$ (called a **thiolate**) is more chemically reactive than the protonated thiol form -SH.

The thiol group is the sulfur analog of the hydroxyl group (-OH) found in alcohols. Since sulfur and oxygen belong to the same periodic table group, they share some similar chemical bonding properties. The chemistry of thiols is thus related to the chemistry of alcohols: thiols form thioethers, thioacetals and thioesters, which are analogous to ethers, acetals, and esters. Furthermore, a thiol group can react with an alkene to create a thioether. (In fact, biochemically, thiol groups may react with vinyl groups to form a thioether linkage.)

The sulfur atom of a thiol is quite nucleophilic, rather more so than the oxygen atom of an alcohol. The thiol group is fairly acidic with a usual pK_a around 10 to 11. In the presence of a base, a thiolate anion is formed which is a very powerful nucleophile. The group and its corresponding anion are readily oxidized by reagents such as bromine to give an organic disulfide (R-S-S-R), or by more powerful reagents such as sodium hypochlorite to yield sulfonic acids (RSO_3H).

Because of the small electronegativity difference between sulfur and hydrogen, an S-H bond is practically nonpolar covalent. Thiols show little association by hydrogen bonding. They have lower boiling points and are less soluble in water and other polar solvents than alcohols of similar molecular weight.

Many thiols are colorless liquids having an odor resembling that of garlic. The odor of thiols is often strong and repulsive, particularly for those of low molecular weight. Thiols bind strongly to skin proteins, and are responsible for the intolerable, persistent odor produced by feces, rotting flesh and the spraying of skunks. Natural gas distributors began adding various forms of pungent thiols, usually ethanethiol, to natural gas, which is naturally odorless, after the deadly 1937 New London School explosion in Texas, United States. Thiols are also responsible for a class of wine faults caused by an unintended reaction between sulfur and yeast. However, not all thiols have unpleasant odors. For example, grapefruit mercaptan, a monoterpenoid thiol, is responsible for the characteristic scent of grapefruit.

Biological importance

As the functional group of the amino acid cysteine, the thiol group plays an important role in biological systems. When the thiol groups of two cysteine residues (as in monomers or constituent units) are brought near each other in the course of protein folding, an oxidation reaction can create a cystine unit

with a disulfide bond (-S-S-). Disulfide bonds can contribute to a protein's tertiary structure if the cysteines are part of the same peptide chain, or contribute to the quaternary structure of multi-unit proteins by forming fairly strong covalent bonds between different peptide chains. The heavy and light chains of antibodies are held together by disulfide bridges. Also, the kinks in curly hair are a product of cystine formation. Permanents take advantage of the oxidizability of cysteine residues. The chemicals used in hair straightening are reductants that reduce cystine disulfide bridges to free cysteine sulfhydryl groups, while chemicals used in hair curling are oxidants that oxidize cysteine sulfhydryl groups to form cystine disulfide bridges. Sulfhydryl groups in the active site of an enzyme can form noncovalent bonds with the enzyme's substrate as well, contributing to catalytic activity. Active site cysteine residues are the functional unit in cysteine proteases.

Nomenclature

When a thiol group is a substituent on an alkane, there are several ways of naming the resulting thiol:

- The preferred method (used by the IUPAC) is to add the suffix *-thiol* to the name of the alkane. Example: CH_3SH would be *methanethiol*.

- An older method, the word *mercaptan* replaces *alcohol* in the name of the equivalent alcohol compound. Example: CH_3SH would be *methyl mercaptan*.

- As a prefix, the term *mercapto-* is used. Example: mercaptopurine.

Etymology

The term *mercaptan* comes from the Latin *mercurius captans*, meaning 'laying hold of mercury,' because the -SH group binds tightly to the element mercury.

Examples of thiols

- Methanethiol - CH_3SH

- Ethanethiol - C_2H_5SH

- Coenzyme A
- Lipoamide
- Glutathione
- Cysteine
- Dithiothreitol/dithioerythritol (an epimeric pair)
- 2-Mercaptoindole

IUPAC nomenclature

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IUPAC nomenclature of organic chemistry

The **IUPAC nomenclature of organic chemistry** is a systematic way of naming organic chemical compounds as recommended by the International Union of Pure and Applied Chemistry (IUPAC). Ideally, every organic compound should have a name from which an unambiguous structural formula can be drawn. There is also an IUPAC nomenclature of inorganic chemistry.

For ordinary communication, to spare a tedious description, the official IUPAC naming recommendations are not always followed in practice except when it is necessary to give a concise definition to a compound, or when the IUPAC name is simpler (viz. ethanol against ethyl alcohol). Otherwise the common or trivial name may be used, often derived from the source of the compound.

Basic principles

In IUPAC nomenclature, a number of prefixes, suffixes and infixes are used to describe the type and position of functional groups in the compound.

For many compounds, naming can begin by determining the name of the parent hydrocarbon and by identifying any functional groups in the molecule that distinguish it from the parent hydrocarbon. The numbering of the parent alkane is used, as modified, if necessary, by application of the Cahn Ingold Prelog priority rules ("CIP") in the case that ambiguity remains after consideration of the structure of the parent hydrocarbon alone. The name of the parent hydrocarbon is modified by the application of the highest-priority functional group suffix, with the remaining functional groups indicated by numbered prefixes, appearing in the name in alphabetical order from first to last.

In many cases, lack of rigor in applying all such nomenclature rules still yields a name that is intelligible - the aim, of course, being to avoid any ambiguity in terms of what substance is being discussed.

For instance, strict application of CIP priority to the naming of the compound

would render the name as 2-aminoethanol, which is preferred. However, the name 2-hydroxyethanamine unambiguously refers to the same compound.

How the name was constructed:

- There are two carbons in the main chain; this gives the root name "eth".
- Since the carbons are singly-bonded, the suffix begins with "an".

- The two functional groups are an alcohol (OH) and an amine (NH_2). The alcohol has the higher atomic number, and takes priority over the amine. The suffix for an alcohol ends in "ol", so that the suffix is "anol".
- The amine group is not on the carbon with the OH (the #1 carbon), but one carbon over (the #2 carbon); therefore we indicate its presence with the prefix "2-amino".
- Putting together the prefix, the root and the suffix, we get "2-aminoethanol".

There is also an older naming system for organic compounds known as common nomenclature, which is often used for simple, well-known compounds, and also for complex compounds whose IUPAC names are too complex for everyday use.

Simplified molecular input line entry specification (SMILES) strings are commonly used to describe organic compounds, and as such are a form of 'naming' them.

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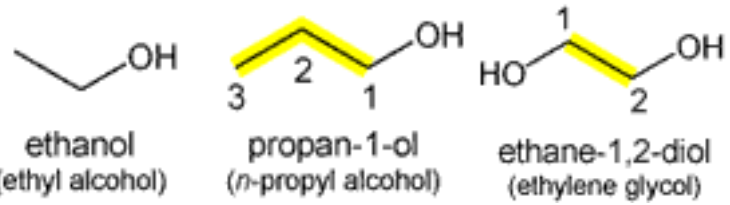
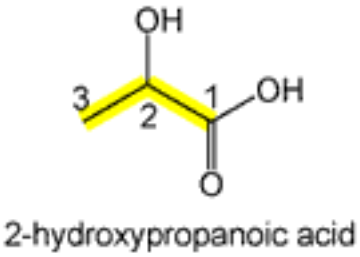
Alcohols

Alcohols (R-OH) drop the terminal "e" from the name of the parent alkane, and take the suffix "-ol" with an infix numerical bonding position: $CH_3CH_2CH_2OH$ is propan-1-ol. (Methanol and ethanol are unambiguous and do not require position numbers). The suffixes -diol, -triol, -tetraol, etc., are used for multiple -OH groups: Ethylene glycol CH_2OHCH_2OH is ethan-1,2-diol.



If higher precedence functional groups are present, the prefix "hydroxy" is used with the bonding position: $CH_3CHOHCOOH$ is 2-hydroxypropanoic acid.



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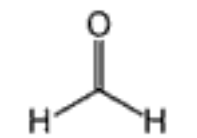
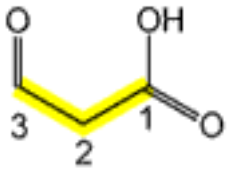
Aldehydes

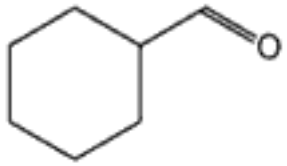
Aldehydes (R-CHO) take the suffix "-al". Since they are always at the end of an alkane chain, they do not need a position number: HCHO (formaldehyde) is methanal, CH_3CHO (acetaldehyde) is ethanal. If other functional groups are present, the chain is numbered such that the aldehyde carbon is in the "1" position.



methanal
(formaldehyde)



3-oxopropanoic acid



cyclohexanecarbaldehyde

If a prefix form is required, "oxo-" is used (as for ketones), with the position number indicating the end of a chain: $CHOCH_2COOH$ is 3-oxopropanoic acid. If the carbon in the carbonyl group cannot be included in the attached chain (for instance in the case of cyclic aldehydes), the prefix "formyl-" or the suffix "-carbaldehyde" is used: $C_6H_{11}CHO$ is cyclohexanecarbaldehyde.

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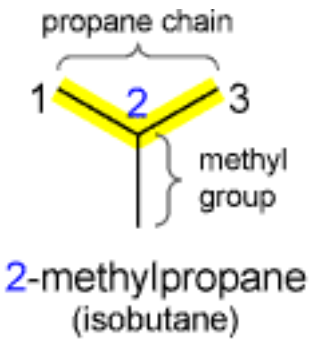
Alkanes

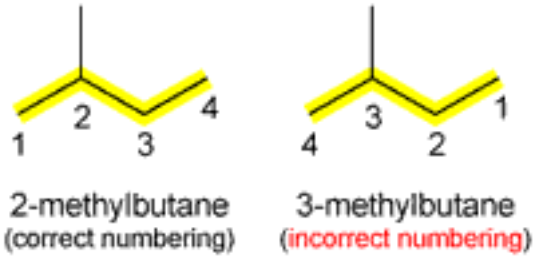
Straight-chain alkanes take the suffix "-ane" and are prefixed depending on the number of carbon atoms in the chain, as given by the following table:

- Meth
- Eth
- Prop
- But
- Pent
- Hex
- Hept
- Oct
- Non
- Dec
- Undec
- Dodec
- Tridec
- Tetradec
- Pentadec
- Eicos

For example, the simplest alkane is CH_4 methane, and the nine-carbon alkane $CH_3(CH_2)_7CH_3$ is named nonane.

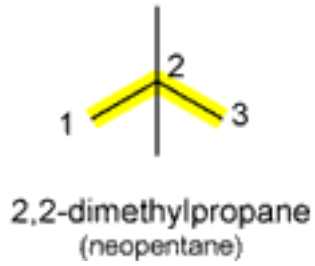
Cyclic alkanes are simply prefixed with "cyclo-", for example C_4H_8 is cyclobutane and C_6H_{12} is cyclohexane.



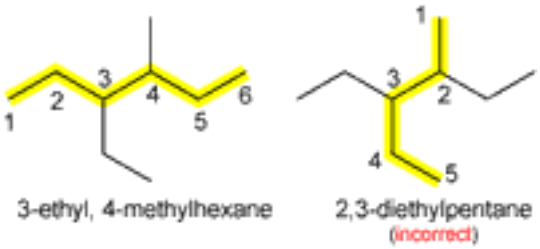


Branched alkanes are named as a straight-chain alkane with attached alkyl groups. They are prefixed with a number indicating the carbon the group is attached to, counting from the end of the alkane chain. Infixed is the name of the substituent, as for alkanes in the table above, plus "-yl". For example, $(CH_3)_2CHCH_3$, commonly known as isobutane, is treated as a propane chain with a methyl group bonded to the middle (2) carbon, and given the systematic name 2-methylpropane. Numbers may be dropped when there is no ambiguity, so 2-methylpropane is just methylpropane. (1-methylpropane would be identical to butane.)

If there is ambiguity in the position of the substituent, depending on which end of the alkane chain is counted as "1", then numbering is chosen so that the smallest number is used. For example, $(CH_3)_2CHCH_2CH_3$ (isopentane) is named 2-methylbutane, not 3-methylbutane. Since this resolves the ambiguity, the number is again dropped in this case.



If there are multiple side-branches of the same size alkyl group, their positions are separated by commas and the group prefixed with di-, tri-, tetra-, etc., depending on the number of branches (e.g. $C(CH_3)_4$ 2,2-dimethylpropane). If there are different groups, they are added in alphabetical order, separated by commas or hyphens: 3-ethyl-4-methylhexane. The longest possible main alkane chain is used; therefore 3-ethyl-4-methylhexane instead of 2,3-diethylpentane, even though these describe equivalent structures. The di-, tri- etc. prefixes are ignored for the purpose of alphabetical ordering of side chains (e.g. 3-ethyl-2,4-dimethylpentane, not 2,4-dimethyl-3-ethylpentane). If multiple chains of the longest possible length exist, the chain that has a larger number of branch points is the chain that is used.



Subsidiary branches off a side-chain are prefixed according to a secondary numbering system specific to that side branch, numbering from the point of attachment to the main chain, and then the whole side-branch is parenthesised and treated as a single substituent. For example, 4-(1-methylethyl)octane is an octane chain with a side chain bonded to the 4th carbon, the side chain consisting of an ethyl group with a methyl group attached to the carbon closest to the main chain.

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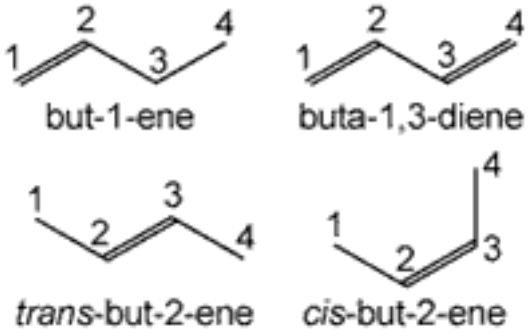
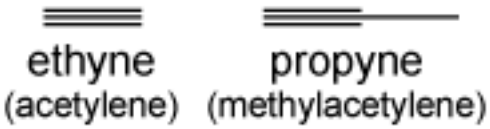
Alkenes and Alkynes

Alkenes are named for their parent alkane chain with the suffix "-ene" and an infixed number indicating the position of the double-bonded carbon in the chain: CH_2=$CHCH_2CH_3$ is but-1-ene. Ethene (ethylene) and propene (propylene) do not require infixed numbers, since there is no ambiguity in the structures. As before, the lowest number is used.



Multiple double bonds take the form -diene, -triene, etc., with the size prefix of the chain taking an extra "a": CH_2=$CHCH$=CH_2 is buta-1,3-diene. Simple cis and trans isomers are indicated with a prefixed *cis*- or *trans*-: *cis*-but-2-ene, *trans*-but-2-ene. More complex geometric isomerisations are described using the Cahn Ingold Prelog priority rules.



Alkynes are named using the same system, with the suffix "-yne" indicating a triple bond: ethyne (acetylene), propyne (methylacetylene).

Nomenclature of Alkenes

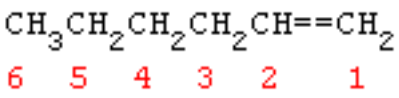
IUPAC Names

To form the root of the IUPAC names for alkenes, simply change the -an- infix of the parent to -en-. For example, **CH_3-CH_3** is the alkane *ethANe*. The name of **CH_2=CH_2** is therefore *ethENe*.

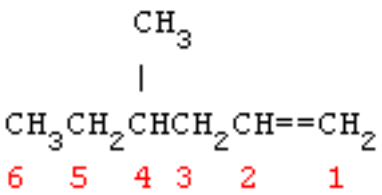
In higher alkenes, where isomers exist that differ in location of the double bond, the following numbering system is used:

1. Number the longest carbon chain that contains the double bond in the direction that gives the carbon

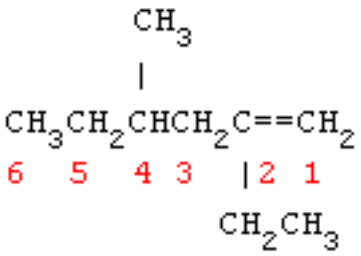
atoms of the double bond the lowest possible numbers.
2. Indicate the location of the double bond by the location of its first carbon
3. Name branched or substituted alkenes in a manner similar to alkanes.
4. Number the carbon atoms, locate and name substituent groups, locate the double bond, and name the main chain



1-Hexene



4-Methyl-1-hexene



2-Ethyl-4-methyl-1-hexene

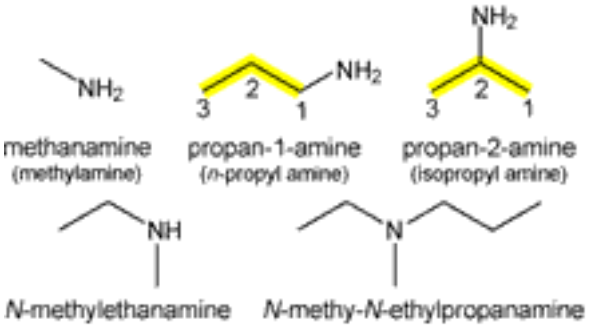
Common Names

Despite the precision and universal acceptance of the IUPAC naming system, some alkenes are known almost exclusively by their common names:
IUPAC name: Ethene
Common name: Ethylene

IUPAC name: Propene
Common name: Propylene

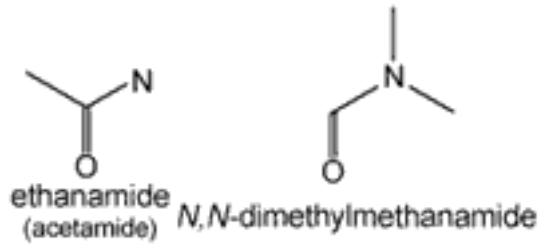
IUPAC name: 2-Methylpropene
Common name: Isobutylene

Amines and Amides



Amines ($R\text{-}NH_2$) are named for the attached alkane chain with the suffix "-amine" (e.g. CH_3NH_2 methanamine). If necessary, the bonding position is infixed: $CH_3CH_2CH_2NH_2$ propan-1-amine, $CH_3CHNH_2CH_3$ propan-2-amine. The prefix form is "amino-".

For secondary amines (of the form R-NH-R), the longest carbon chain attached to the nitrogen atom becomes the primary name of the amine; the other chain is prefixed as an alkyl group with location prefix given as an italic *N*: $CH_3NHCH_2CH_3$ is *N*-methylethanamine. Tertiary amines (R-NR-R) are treated similarly: $CH_3CH_2N(CH_3)CH_2CH_2CH_3$ is *N*-methyl-*N*-ethylpropanamine.



Amides ($R\text{-}CO\text{-}NH_2$) take the suffix "-amide". There is no prefix form, and no location number is required since they always terminate a carbon chain, e.g. CH_3CONH_2 (acetamide) is named ethanamide.

Secondary and tertiary amides are treated similarly to the case of amines: alkane chains bonded to the nitrogen atom are treated as substituents with the location prefix *N*: $HCON(CH_3)_2$ is *N*,*N*-dimethylmethanamide.

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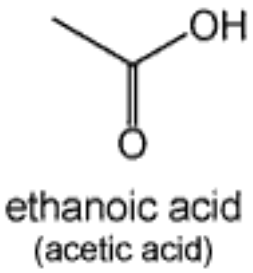
Carboxylic acids



ethanoic acid
(acetic acid)

In general carboxylic acids are named with the suffix *-oic acid* (etymologically a back-formation from benzoic acid). As for aldehydes, they take the "1" position on the parent chain, but do not have their position number indicated. For example, $CH_3CH_2CH_2CH_2COOH$ (valeric acid) is named pentanoic acid. For common carboxylic acids some traditional names such as acetic acid are in such widespread use they are considered retained IUPAC names, although "systematic" names such as ethanoic acid are also acceptable. For carboxylic acids attached to a benzene ring such as Ph-COOH, these are named as benzoic acid or its derivatives.

If there are multiple carboxyl groups on the same parent chain, the suffix "-carboxylic acid" can be used (as -dicarboxylic acid, -tricarboxylic acid, etc.). In these cases, the carbon in the carboxyl group does *not* count as being part of the main alkane chain. The same is true for the prefix form, "carboxyl-". Citric acid is one example; it is named 2-hydroxy-1,2,3-propanetricarboxylic acid, rather than 2-carboxy, 2-hydroxypentanedioic acid.

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Common nomenclature - trivial names

Common nomenclature is an older system of naming organic compounds. Instead of using the prefixes for the carbon skeleton above, another system is used.

Ketones

Common names for ketones can be derived by naming the two alkyl or aryl groups bonded to the carbonyl group as separate words followed by the word *ketone*.

- Acetone
- Acetophenone
- Benzophenone
- Ethyl isopropyl ketone
- Diethyl ketone

The first three of the names shown above are still considered to be acceptable IUPAC names.

Aldehydes

The common name for an aldehyde is derived from the common name of the corresponding carboxylic acid by dropping the word *acid* and changing the suffix from -ic or -oic to -aldehyde.

- Formaldehyde
- Acetaldehyde

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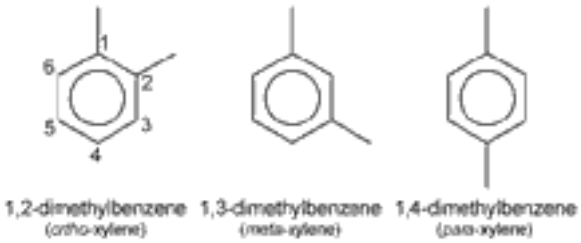
Cyclic compounds



Cycloalkanes and aromatic compounds can be treated as the main parent chain of the compound, in which case the position of substituents are numbered around the ring structure. For example, the three isomers of xylene $CH_3C_6H_4CH_3$, commonly the *ortho*-, *meta*-, and *para*- forms, are 1,2-dimethylbenzene, 1,3-dimethylbenzene, and 1,4-dimethylbenzene. The cyclic structures can also be treated as functional groups themselves, in which case they take the prefix "cyclo*alkyl*-" (e.g. "cyclohexyl-") or for benzene, "phenyl-".

The IUPAC nomenclature scheme becomes rapidly more elaborate for more complex cyclic structures, with notation for compounds containing conjoined rings, and many common names such as phenol, furan, indole, etc. being accepted as base names for compounds derived from them.

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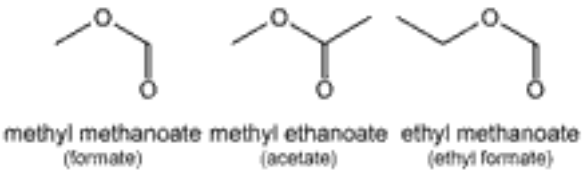
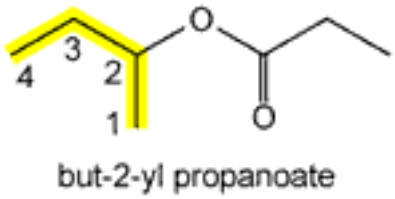
Esters



Esters (R-CO-O-R') are named as alkyl derivatives of carboxylic acids. The alkyl (R') group is named first. The R-CO-O part is then named as a separate word based on the carboxylic acid name, with the ending changed from *oic acid* to *oate*. For example, $CH_3CH_2CH_2CH_2COOCH_3$ is *methyl pentanoate*, and $(CH_3)_2CHCH_2CH_2COOCH_2CH_3$ is *ethyl 4-methylpentanoate*. For esters such as ethyl acetate ($CH_3COOCH_2CH_3$), ethyl formate ($HCOOCH_2CH_3$) or dimethyl phthalate that are based on common acids, IUPAC recommends use of these established names, called retained names. Some simple examples, named both ways, are shown in the figure above.



If the alkyl group is not attached at the end of the chain, the bond position to the ester group is infixed before "-yl": $CH_3CH_2CH(CH_3)OOCCH_2CH_3$ may be called but-2-yl propanoate or but-2-yl propionate.

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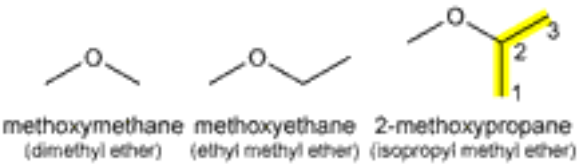
Ethers

Ethers (R-O-R) consist of an oxygen atom between the two attached carbon chains. The shorter of the two chains becomes the first part of the name with the -ane suffix changed to -oxy, and the longer alkane chain become the suffix of the name of the ether. Thus CH_3OCH_3 is methoxymethane, and $CH_3OCH_2CH_3$ is methoxyethane (*not* ethoxymethane). If the oxygen is not attached to the end of the main alkane chain, then the whole shorter alkyl-plus-ether group is treated as a side-chain and prefixed with its bonding position on the main chain. Thus $CH_3OCH(CH_3)_2$ is 2-methoxypropane.



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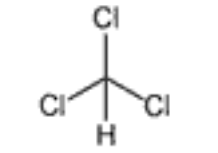
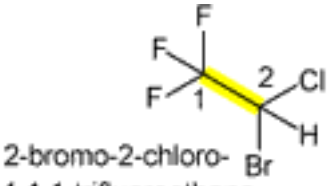
Halogens (Alkyl Halides)

Halogen functional groups are prefixed with the bonding position and take the form fluoro-, chloro-, bromo-, iodo-, etc., depending on the halogen. Multiple groups are dichloro-, trichloro-, etc, and disimilar groups are orded alphabetically as before. For example, $CHCl_3$ (chloroform) is trichloromethane. The anesthetic Halothane ($CF_3CHBrCl$) is 2-bromo-2-chloro-1,1,1-trifluoroethane.



trichloromethane
(chloroform)



2-bromo-2-chloro-
1,1,1-trifluoroethane
(Halothane)

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Ions

The IUPAC nomenclature also provides rules for naming ions.

Hydron

Hydron is a generic term for hydrogen cation; protons, deuterons and tritons are all hydrons.

Parent hydride cations

Simple cations formed by adding a hydron to a hydride of a halogen, chalcogen or nitrogen-family element are named by adding the suffix "-onium" to the element's root: H_4N^+ is ammonium, H_3O^+ is oxonium, and H_2F^+ is fluoronium. Ammonium was adopted instead of nitronium, which commonly refers to NO_2^+.

If the cationic center of the hydride is not a halogen, chalcogen or nitrogen-family element then the suffix "-ium" is added to the name of the neutral hydride after dropping any final 'e'. H_5C^+ is methanium, $HO\text{-}O^+H_2$ is dioxidanium (HO-OH is dioxidane), and $H_2N\text{-}N^+H_3$ is diazanium ($H_2N\text{-}NH_2$ is diazane).

Cations and substitution

The above cations except for methanium are not, strictly speaking, organic, since they do not contain carbon. However, many organic cations are obtained by substituting another element or some functional group for a hydrogen.

The name of each substitution is prepended to the hydride cation name. If many substitutions by the same functional group occur, then the number is indicated by prepending "di-", "tri-" as with halogenation. $(CH_3)_3O^+$ is trimethyloxonium. $CH_3F_3N^+$ is trifluoromethylammonium.

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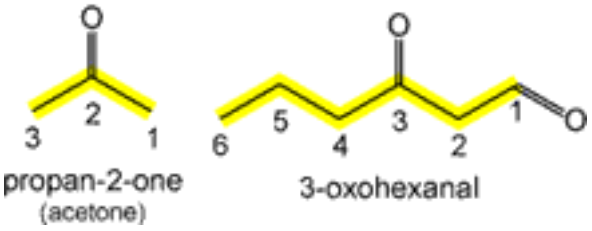
Ketones

In general ketones (R-CO-R) take the suffix "-one" (pronounced *own*, not *won*) with an infix position number: $CH_3CH_2CH_2COCH_3$ is pentan-2-one. For common ketones some traditional names such as acetone and benzophenone predominate, and these are acceptable IUPAC names, although some introductory chemistry texts use alternative names for acetone such as propan-2-one or propanone.



Additionally, in such unambigous cases as propanone, the infixed number can be dropped. If a higher precedence suffix is in use, the prefix "oxo-" is used: $CH_3CH_2CH_2COCH_2CHO$ is 3-oxohexanal.

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Order of precedence of groups

When compounds contain more than one functional group, the order of precedence determines which groups are named with prefix or suffix forms. The highest precedence group takes the suffix, with all others taking the prefix form. However, double and triple bonds only take suffix form (-en and -yn) and are used with other suffixes.

Prefixed substituents are ordered alphabetically (excluding any modifiers such as di-, tri-, etc.), e.g. chlorofluoromethane, *not* fluorochloromethane. If there are multiple functional groups of the same type, either prefixed or suffixed, the position numbers are ordered numerically (thus ethane-1,2-diol, *not* ethane-2,1-diol.) The *N* position indicator for amines and amides comes before "1", e.g. $CH_3CH(CH_3)CH_2NH(CH_3)$ is *N*,2-dimethylpropanamine.

Priority: 1; **Functional group:** Cations, e.g. Ammonium; **Formula:** , $-NH_4^+$; **Prefix:** -onio-, ammonio-; **Suffix:** -onium, -ammonium

Priority: 2; **Functional group:** Carboxylic acids, Thiocarboxylic acids, Selenocarboxylic acids, Sulfonic acids, Sulfinic acids, Sulfenic acids; **Formula:** -COOH, -COSH, -COSeH, $-SO_3H$, $-SO_2H$, -SOH; **Prefix:** carboxy-, thiocarboxy-, selenocarboxy-, sulfo-, sulfino-, sulfeno-; **Suffix:** -oic acid*, -thioic acid*, -selenoic acid*, -sulfonic acid, -sulfinic acid, -sulfenic acid

Priority: 3; **Functional group:** *Carboxylic acid derivatives*, Esters, Acyl chlorides, Amides, Imides, Amidines; **Formula:** , -COOR, -COCl, $-CONH_2$, -CON=C<, $-C(=NH)NH_2$; **Prefix:** , R-oxycarbonyl-, chloroformyl-, carbamoyl-, -imido-, amidino-; **Suffix:** , -oyl chloride*, -amide*, -imide*, -amidine*

Priority: 4; **Functional group:** Nitriles, Isonitriles; **Formula:** -CN, ; **Prefix:** cyano-, isocyano-; **Suffix:** -nitrile*, -isonitrile

Priority: 5; **Functional group:** Aldehydes, Thioaldehydes; **Formula:** -CHO, -CHS; **Prefix:** formyl-, thioformyl-; **Suffix:** -al*, -thial*

Priority: 6; **Functional group:** Ketones, Thioketones; **Formula:** >CO, >CS; **Prefix:** oxo-, thiono-; **Suffix:** -one, -thione

Priority: 7; **Functional group:** Alcohols, Thiols, Selenols, Tellurols; **Formula:** -OH, -SH, -SeH, -TeH; **Prefix:** hydroxy-, sulfyl-, selanyl-, tellanyl-; **Suffix:** -ol, -thiol, -selenol, -tellurol

Priority: 8; **Functional group:** Hydroperoxides; **Formula:** -OOH; **Prefix:** hydroperoxy-; **Suffix:** -

hydroperoxide

Priority: 9; **Functional group:** Amines, Imines, Hydrazines; **Formula:** $-NH_2$, =NH, $-NHNH_2$; **Prefix:** amino-, imino-, hydrazino-; **Suffix:** -amine, -imine, -hydrazine

Priority: 10; **Functional group:** Ethers, Thioethers, Selenoethers; **Formula:** -O-, -S-, -Se-; **Prefix:** -oxy-, -thio-, -seleno-;

Priority: 11; **Functional group:** Peroxides, Disulfides; **Formula:** -OO-, -SS-; **Prefix:** -peroxy-, -disulfanyl-;

**Note*: These suffixes, in which the carbon atom is counted as part of the preceding chain, are the most commonly used.

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Periodic Table of the Chemical Elements

Periodic Table: Standard | Large

List of elements sorted by: Atomic number (including atomic Mass) | Name | Symbol | Boiling Point | Melting Point | Density | Atomic radius | Electronegativity | Electron affinity | Ionization potential | Standard enthalpy change of vaporization | Standard enthalpy change of fusion | Specific heat capacity

About Periodic Table: Arrangement | Periodicity of chemical properties | Electron configuration | Naming of elements | Chemical symbols | History

Appendix: Metric system (SI) | SI writing style | Powers of 10 prefixes | United States units conversion

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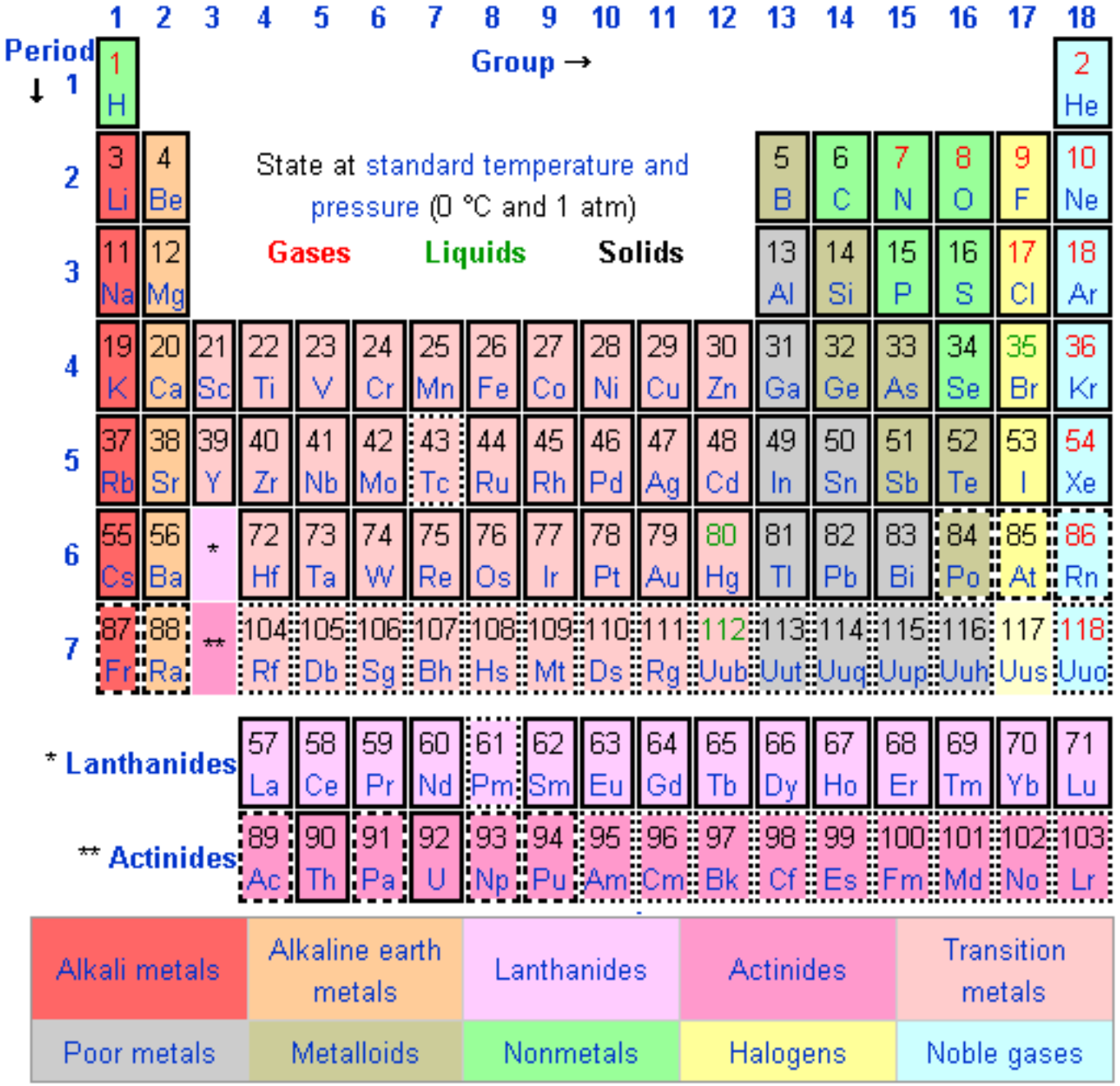

Notes

- Lanthanides are also known as "rare earth elements", a deprecated term.
- Alkali metals, alkaline earth metals, transition metals, actinides, lanthanides, and poor metals are all collectively known as "metals".
- Halogens and noble gases are also non-metals.

State at standard temperature and pressure (0°C and 1atm)

- those numbered in **red** are gaseous
- those numbered in **green** are liquid

- those numbered in **black** are solid

Natural occurrence

- those with **solid borders** are primordial elements, which have stable isotopes older than the Earth.
- those with **dashed borders** arise naturally from decay of other elements, and have no isotopes with a half-life comparable to the age of the Earth; however, some are found in trace amounts in radioactive ores.
- those with **dotted borders** are synthetic elements, which do not occur naturally. *Note:* Although californium (Cf, 98) does not occur naturally on Earth, Cf and its decay products occur in the Universe; their electromagnetic emissions are regularly observed in supernova spectra.
- those **without borders** have not been discovered or synthesised yet.

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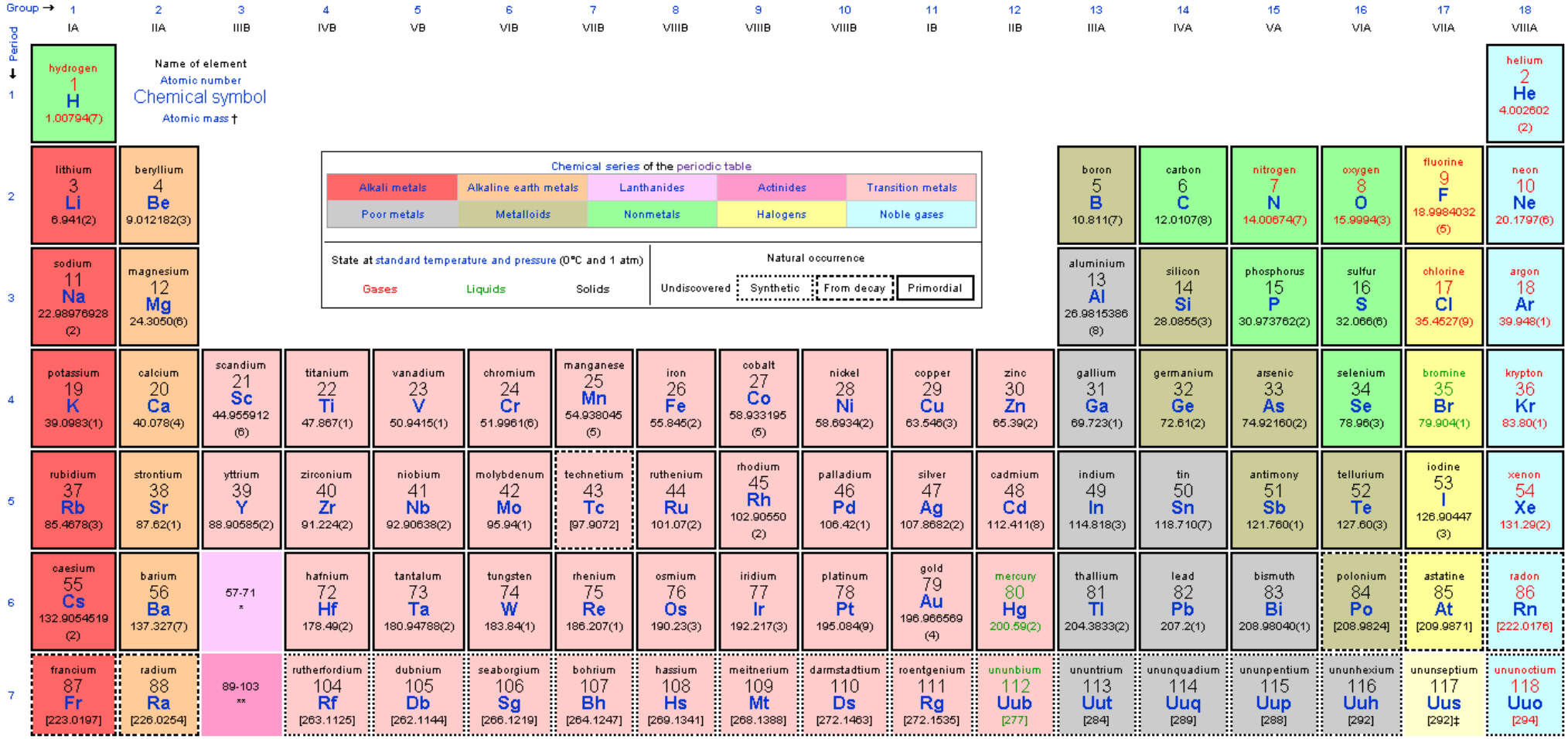

† A value in brackets, such as [259.1011], is the atomic weight of the most stable isotope unless it is an integer, in which case it is the mass number of the most stable isotope. In all other cases, the value is the mean atomic weight of the most stable isotopic composition, according to Atomic Weights of the Elements 2001, and includes its uncertainty in parenthesis. For example, the value of 1.00794(7) for hydrogen means that the most stable isotopic composition of hydrogen has an atomic weight of 1.00794 atomic mass units (amu) with one standard deviation uncertainty of 0.00007 amu.
‡ These atomic masses are only estimates, as these elements have not yet been discovered.

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Arrangement

Earlier attempts to list the elements to show the relationships between them had usually involved putting them in order of atomic mass. Mendeleev's key insight in devising the periodic table was to lay out the elements to illustrate recurring ("periodic") chemical properties (even if this meant some of them were not in mass order), and to leave gaps for "missing" elements. Mendeleev used his table to predict the properties of these "missing elements", and many of them were indeed discovered and fit the predictions well.

With the development of theories of atomic structure (for instance by Henry Moseley) it became apparent that Mendeleev had listed the elements **in order of increasing atomic number** (i.e. the number of protons in the atomic nucleus). This sequence is nearly identical to that resulting from ascending atomic mass.

In order to illustrate recurring properties, Mendeleev began new rows in his table so that elements with similar properties fell into the same vertical columns (**"groups"**).

With the development of modern quantum mechanical theories of electron configuration within atoms, it became apparent that each horizontal row (**"period"**) in the table corresponded to the filling of a quantum shell of electrons. In Mendeleev's original table, each period was the same length. Modern tables have progressively longer periods further down the table, and group the elements into **s-**, **p-**, **d-** and **f-blocks** to reflect our understanding of their electron configuration.

In printed tables, each element is usually listed with its element symbol and atomic number; many versions of the table also list the element's atomic mass and other information, such as its abbreviated electron configuration, electronegativity and most common valence numbers. As of 2005, the table contains 116 chemical elements whose discoveries have been confirmed. Ninety are found naturally on Earth, and the rest are synthetic elements that have been produced artificially in particle accelerators. Elements 43 (technetium) and 61 (promethium), although of lower atomic number than the naturally occurring element 92, uranium, are synthetic; elements 93 (neptunium) and 94 (plutonium) are listed with the synthetic elements, but have been found in trace amounts on earth.

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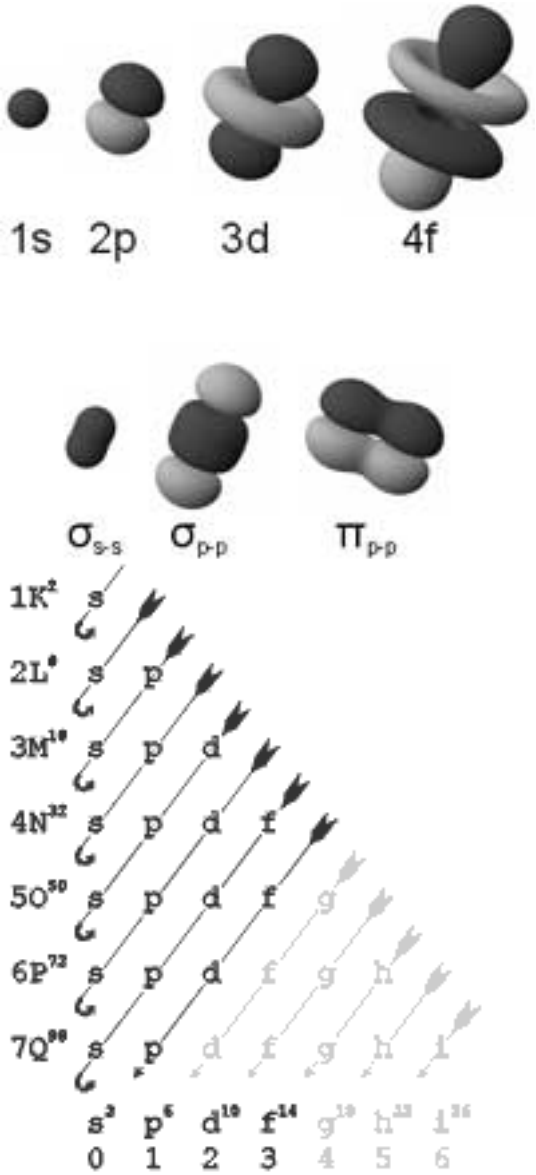
Periodic table structure reflects electron configuration



Electron atomic and molecular orbitals

The primary determinant of an element's chemical properties is its electron configuration, particularly the valence shell electrons. For instance, any atoms with four valence electrons occupying p orbitals will exhibit some similarity. The type of orbital in which the atom's outermost electrons reside determines the "block" to which it belongs. The number of valence shell electrons determines the family, or group, to which the element belongs.

The total number of electron shells an atom has determines the period to which it belongs. Each shell is divided into different subshells, which as atomic number increases are filled in roughly this order (the Aufbau principle):

Subshell:	S	G	F	D	P
Period					
1	1s				
2	2s				2p
3	3s				3p
4	4s			3d	4p
5	5s			4d	5p
6	6s		4f	5d	6p
7	7s		5f	6d	7p
8	8s	5g	6f	7d	8p
9	9s	6g	7f	8d	9p

Hence the structure of the table. Since the outermost electrons determine chemical properties, those with the same number of valence electrons are grouped together.

Progressing through a group from lightest element to heaviest element, the outer-shell electrons (those most readily accessible for participation in chemical reactions) are all in the same type of orbital, with a similar shape, but with increasingly higher energy and average distance from the nucleus. For instance, the outer-shell (or "valence") electrons of the first group, headed by hydrogen all have one electron in an s orbital. In hydrogen, that s orbital is in the lowest possible energy state of any atom, the first-shell orbital (and represented by hydrogen's position in the first period of the table). In francium, the heaviest element of the group, the outer-shell electron is in the seventh-shell orbital, significantly further out on average from the nucleus than those electrons filling all the shells below it in energy. As another example, both carbon and lead have four electrons in their outer shell orbitals.

Note that as atomic number (i.e. charge on the atomic nucleus) increases, this leads to greater spin-orbit coupling between the nucleus and the electrons, reducing the validity of the quantum mechanical orbital approximation model, which considers each atomic orbital as a separate entity.

Because of the importance of the outermost shell, the different regions of the periodic table are sometimes referred to as **periodic table blocks**, named according to the sub-shell in which the "last" electron resides, e.g. the *s*-block, the *p*-block, the *d*-block, etc.

History

In Ancient Greece, it was believed that there were four elements: Air, Fire, Earth and Water. All of these elements could be reacted to create another one; *e.g.*, earth and fire made air. However, this theory was dismissed when the real chemical elements started being discovered. Scientists needed an easily accessible, well organized database through which the elements could be recorded and accessed. This was to be known as the periodic table.

The original table was created before the discovery of subatomic particles or the formulation of current quantum mechanical theories of atomic structure. If one orders the elements by atomic mass, and then plots certain other properties against atomic mass, one sees an undulation or *periodicity* to these properties as a function of atomic mass. The first to recognize these regularities was the German chemist Johann Wolfgang Döbereiner who, in 1829, noticed a number of *triads* of similar elements.

This was followed by the English chemist John Newlands, who noticed in 1865 that the elements of similar type recurred at intervals of eight, which he likened to the octaves of music, though his *law of octaves* was ridiculed by his contemporaries. Finally, in 1869 the Russian chemistry professor Dmitri Ivanovich Mendeleev and four months later the German Julius Lothar Meyer independently developed the first periodic table, arranging the elements by mass. However, Mendeleev plotted a few elements out of strict mass sequence in order to make a better match to the properties of their neighbors in the table, corrected mistakes in the values of several atomic masses, and predicted the existence and properties of a few new elements in the empty cells of his table. Mendeleev was later vindicated by the discovery of the electronic structure of the elements in the late 19th and early 20th century.

In the 1940s Glenn T. Seaborg identified the transuranic lanthanides and the actinides, which may be placed within the table, or below (as shown above).

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Periodicity of chemical properties

The main value of the periodic table is the ability to predict the chemical properties of an element based on its location on the table. It should be noted that the properties vary differently when moving vertically along the columns of the table, than when moving horizontally along the rows.

Groups and Periods

Groups and Periods are the two main ways to view the Periodic Table of the Elements. Take Group 2 for example, all of the elements in that group have similar characteristics as the others.

Groups

- A **group**, also known as a *family*, is a vertical column in the periodic table of the elements.

Groups are considered the most important method of classifying the elements. In some groups, the elements have very similar properties and exhibit a clear trend in properties down the group - these groups tend to be given trivial (non-scientific) names, e.g. the alkali metals, alkaline earth metals, transition metals, halogens and noble gases. Some other groups in the periodic table display fewer similarities and/or vertical trends (for example Groups 14 and 15). Modern quantum mechanical theories of atomic structure explain that elements within the same group have the same electron configurations in their valence shell, which is the largest factor in accounting for their similar chemical properties.

Periods

- A **period** is a horizontal row in the periodic table of the elements.

Although groups are the most common way of classifying elements, there are some regions of the periodic table where the horizontal trends and similarities in properties are more significant than vertical group trends. This can be true in the d-block (or "transition metals"), and especially for the f-block, where the lanthanides and actinides form two substantial horizontal series of elements. The period number also shows how many electron shells there are in an element.

Examples

Noble gases

All the elements of group 18, the noble gases, have full valence shells. This means they do not need to react with other elements to attain a full shell, and are therefore unreactive. Helium is the most inert element among noble gases, since reactivity, in this group, increases with the periods: it is possible to

make heavy noble gases react since they have much larger electronic shells. However, their reactivity remains low in absolute terms.

Halogens

In group 17, known as the halogens, elements are missing just one electron to fill their shell. Therefore, in chemical reactions they tend to acquire electrons (the tendency to acquire electrons is called electronegativity). This property is most evident for fluorine (the most electronegative element of the whole table), and it diminishes with increasing period.

As a result, all halogens form acids with hydrogen, such as hydrofluoric acid, hydrochloric acid, hydrobromic acid and hydroiodic acid, all in the form *HX*. Their acidity increases with higher period, for example, with regard to Iodine and Fluorine, since a large I^- ion is more stable in solution than a small F^-, there is less volume in which to disperse the charge.

Transition metals

In transition metals (groups 3 to 12), the differences between groups are usually not dramatic, and the reactions involve coordinated species. However, it is still possible to make useful predictions.

Lanthanides and actinides

The chemical properties of the lanthanides (elements 57-71) and the actinides (elements 89-103) are even more similar to each other than in transition metals, and separating a mixture of these can be very difficult. This is important in the *chemical* purification of uranium concerning nuclear power.

Nonmetals

This type of element is classified by being neither a gas nor a metal of any sort. Non-metals are the elements in groups 14-16 of the periodic table. Non-metals are not able to conduct electricity or heat very well. As opposed to metals, non-metallic elements are very brittle, and cannot be rolled into wires or pounded into sheets. The non-metals exist in two of the three states of matter at room temperature: gases (such as oxygen) and solids (such as carbon). The non-metals have no metallic luster, and do not reflect light. They have oxidation numbers of ±4, -3, and -2.

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Periodic table

The **periodic table of the chemical elements** is a tabular method of displaying the chemical elements, first devised in 1869 by the Russian chemist Dmitri Mendeleev. Mendeleev intended the table to illustrate recurring ("periodic") trends in the properties of the elements. The layout of the table has been refined and extended over time, as many new elements have been discovered since Mendeleev's time, and new theoretical models have been developed to explain chemical behavior. Various different layouts are possible to emphasize different aspects of behavior; the most common forms, however, are still quite similar to Mendeleev's original design.

The periodic table is now ubiquitous within the academic discipline of chemistry, providing an extremely useful framework to classify, systematize and compare all the many different forms of chemical behavior. The table has also found wide application in physics, biology, engineering, and industry. The current standard table contains 116 confirmed elements.

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List of elements by atomic number

A table of chemical elements ordered by atomic number and given as:
Atomic number. Name, Symbol {Period, Group} Atomic Mass (g/mol)[Notes]

1. Hydrogen, H {1, 1} M=1.00794(7)[2 3 4]
2. Helium, He {1, 18} M=4.002602(2)[2 4]
3. Lithium, Li {2, 1} M=6.941(2)[2 3 4 5]
4. Beryllium, Be {2, 2} M=9.012182(3)
5. Boron, B {2, 13} M=10.811(7)[2 3 4]
6. Carbon, C {2, 14} M=12.0107(8)[2 4]
7. Nitrogen, N {2, 15} M=14.0067(2)[2 4]
8. Oxygen, O {2, 16} M=15.9994(3)[2 4]
9. Fluorine, F {2, 17} M=18.9984032(5)
10. Neon, Ne {2, 18} M=20.1797(6)[2 3]
11. Sodium, Na {3, 1} M=22.98976928(2)
12. Magnesium, Mg {3, 2} M=24.3050(6)
13. Aluminium, Al {3, 13} M=26.9815386(8)
14. Silicon, Si {3, 14} M=28.0855(3)[4]
15. Phosphorus, P {3, 15} M=30.973762(2)
16. Sulfur, S {3, 16} M=32.065(5)[2 4]
17. Chlorine, Cl {3, 17} M=35.453(2)[2 3 4]
18. Argon, Ar {3, 18} M=39.948(1)[2 4]
19. Potassium, K {4, 1} M=39.0983(1)
20. Calcium, Ca {4, 2} M=40.078(4)[2]
21. Scandium, Sc {4, 3} M=44.955912(6)
22. Titanium, Ti {4, 4} M=47.867(1)
23. Vanadium, V {4, 5} M=50.9415(1)
24. Chromium, Cr {4, 6} M=51.9961(6)
25. Manganese, Mn {4, 7} M=54.938045(5)
26. Iron, Fe {4, 8} M=55.845(2)
27. Cobalt, Co {4, 9} M=58.933195(5)
28. Nickel, Ni {4, 10} M=58.6934(2)
29. Copper, Cu {4, 11} M=63.546(3)[4]
30. Zinc, Zn {4, 12} M=65.409(4)
31. Gallium, Ga {4, 13} M=69.723(1)
32. Germanium, Ge {4, 14} M=72.64(1)
33. Arsenic, As {4, 15} M=74.92160(2)
34. Selenium, Se {4, 16} M=78.96(3)[4]
35. Bromine, Br {4, 17} M=79.904(1)

36. Krypton, Kr {4, 18} M=83.798(2)[2] [3]
37. Rubidium, Rb {5, 1} M=85.4678(3)[2]
38. Strontium, Sr {5, 2} M=87.62(1)[2] [4]
39. Yttrium, Y {5, 3} M=88.90585(2)
40. Zirconium, Zr {5, 4} M=91.224(2)[2]
41. Niobium, Nb {5, 5} M=92.906 38(2)
42. Molybdenum, Mo {5, 6} M=95.94(2)[2]
43. Technetium, Tc {5, 7} M=[98.9063][1]
44. Ruthenium, Ru {5, 8} M=101.07(2)[2]
45. Rhodium, Rh {5, 9} M=102.90550(2)
46. Palladium, Pd {5, 10} M=106.42(1)[2]
47. Silver, Ag {5, 11} M=107.8682(2)[2]
48. Cadmium, Cd {5, 12} M=112.411(8)[2]
49. Indium, In {5, 13} M=114.818(3)
50. Tin, Sn {5, 14} M=118.710(7)[2]
51. Antimony, Sb {5, 15} M=121.760(1)[2]
52. Tellurium, Te {5, 16} M=127.60(3)[2]
53. Iodine, I {5, 17} M=126.90447(3)
54. Xenon, Xe {5, 18} M=131.293(6)[2] [3]
55. Caesium, Cs {6, 1} M=132.9054519(2)
56. Barium, Ba {6, 2} M=137.327(7)
57. Lanthanum, La {6} M=138.90547(7)[2]
58. Cerium, Ce {6} M=140.116(1)[2]
59. Praseodymium, Pr {6} M=140.90765(2)
60. Neodymium, Nd {6} M=144.242(3)[2]
61. Promethium, Pm {6} M=[146.9151][1]
62. Samarium, Sm {6} M=150.36(2)[2]
63. Europium, Eu {6} M=151.964(1)[2]
64. Gadolinium, Gd {6} M=157.25(3)[2]
65. Terbium, Tb {6} M=158.92535(2)
66. Dysprosium, Dy {6} M=162.500(1)[2]
67. Holmium, Ho {6} M=164.93032(2)
68. Erbium, Er {6} M=167.259(3)[2]
69. Thulium, Tm {6} M=168.93421(2)
70. Ytterbium, Yb {6} M=173.04(3)[2]
71. Lutetium, Lu {6, 3} M=174.967(1)[2]
72. Hafnium, Hf {6, 4} M=178.49(2)
73. Tantalum, Ta {6, 5} M=180.9479(1)
74. Tungsten, W {6, 6} M=183.84(1)
75. Rhenium, Re {6, 7} M=186.207(1)
76. Osmium, Os {6, 8} M=190.23(3)[2]

77. Iridium, Ir {6, 9} M=192.217(3)
78. Platinum, Pt {6, 10} M=195.084(9)
79. Gold, Au {6, 11} M=196.966569(4)
80. Mercury, Hg {6, 12} M=200.59(2)
81. Thallium, Tl {6, 13} M=204.3833(2)
82. Lead, Pb {6, 14} M=207.2(1)[2 4]
83. Bismuth, Bi {6, 15} M=208.98040(1)
84. Polonium, Po {6, 16} M=[208.9824][1]
85. Astatine, At {6, 17} M=[209.9871][1]
86. Radon, Rn {6, 18} M=[222.0176][1]
87. Francium, Fr {7, 1} M=[223.0197][1]
88. Radium, Ra {7, 2} M=[226.0254][1]
89. Actinium, Ac {7} M=[227.0278][1]
90. Thorium, Th {7} M=232.03806(2)[1 2]
91. Protactinium, Pa {7} M=231.03588(2)[1]
92. Uranium, U {7} M=238.02891(3)[1 2 3]
93. Neptunium, Np {7} M=[237.0482][1]
94. Plutonium, Pu {7} M=[244.0642][1]
95. Americium, Am {7} M=[243.0614][1]
96. Curium, Cm {7} M=[247.0703][1]
97. Berkelium, Bk {7} M=[247.0703][1]
98. Californium, Cf {7} M=[251.0796][1]
99. Einsteinium, Es {7} M=[252.0829][1]
100. Fermium, Fm {7} M=[257.0951][1]
101. Mendelevium, Md {7} M=[258.0986][1]
102. Nobelium, No {7} M=[259.1009][1]
103. Lawrencium, Lr {7, 3} M=[260.1053][1]
104. Rutherfordium, Rf {7, 4} M=[261.1087][1]
105. Dubnium, Db {7, 5} M=[262.1138][1]
106. Seaborgium, Sg {7, 6} M=[263.1182][1]
107. Bohrium, Bh {7, 7} M=[262.1229][1]
108. Hassium, Hs {7, 8} M=[265][1]
109. Meitnerium, Mt {7, 9} M=[266][1]
110. Darmstadtium, Ds {7, 10} M=[269][1]
111. Roentgenium, Rg {7, 11} M=[272][1]
112. Ununbium, Uub {7, 12} M=[285][1]
113. Ununtrium, Uut {7, 13} M=[284][1]
114. Ununquadium, Uuq {7, 14} M=[289][1]
115. Ununpentium, Uup {7, 15} M=[288][1]
116. Ununhexium, Uuh {7, 16} M=[292][1]

117. Ununseptium, Uus {7, 17} M=[1]
118. Ununoctium, Uuo {7, 18} M=[1]

- Note 1: The element does not have any stable nuclides, and a value in brackets, e.g. [209], indicates the mass number of the longest-lived isotope of the element or characteristic isotopic composition.
- Note 2: The isotopic composition of this element varies in some geological specimens, and the variation may exceed the uncertainty stated in the table.
- Note 3: The isotopic composition of the element can vary in commercial materials, which can cause the atomic weight to deviate significantly from the given value.
- Note 4: The isotopic composition varies in terrestrial material such that a more precise atomic weight can not be given.
- Note 5: The atomic weight of commercial Lithium can vary between 6.939 and 6.996—analysis of the specific material is necessary to find a more accurate value.

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Atomic radius

The **atomic radius** is the distance from the atomic nucleus to the outermost stable electron orbital in an atom that is at equilibrium. It is measured in picometers or angstroms. Since electrons are constantly moving, measuring the outermost energy level is difficult. As a result, the atomic radius is more accurately measured as stated in the paragraph below.

Atomic radii are called *covalent radii* (a reference to the types of covalent bonds formed) when referring to non-metallic elements and *metallic radii* when referring to metals. Technically, the atomic radius is one half of the equilibrium internuclear distance between two adjacent atoms (which may either bonded covalently or present in a closely packed crystal lattice) of an element. In simpler terms, it roughly means that the atomic radius is half the distance between the nuclei of two adjacent atoms.

A covalent radius is one-half the distance between nuclei of two of the same atoms that are bonded to each other. Covalent radii for elements whose atoms cannot bond to each another can be estimated by combining radii of those that do with the distances between unlike atoms in various molecules. A metallic radius is one-half of the closest internuclear distance in a metallic crystal.

Radii Trends

In the periodic table, atomic radii increase down a group as new electron shells are added, and decrease left-to-right as the nuclear charge (or number of protons) is increased - an important exception are the noble gases. They do not form bonds, which means one can only measure their van der Waals radius - a case where the atom is "unsquashed".

Each element has a characteristic electronegativity ranging from 0 to 4 on the Pauling scale. The most strongly electronegative element, fluorine, has an electronegativity of 3.98 while weakly electronegative elements, such as lithium, have values close to 1. The least electronegative element is francium at 0.7. *In general*, the degree of electronegativity decreases down each group and increases across the periods, as shown below. Across a period, non-metals tend to gain electrons and metals tend to lose them due to the atom striving to achieve a stable octet. Down a group, the nuclear charge has less effect on the outermost shells. Therefore, the most electronegative atoms can be found in the upper, right hand side of the periodic table, and the least electronegative elements can be found at the bottom left. Consequently, *in general*, atomic radius decreases across the periodic table, but ionization energy increases.

Atomic radii of the elements

Note: All measurements given are in picometres (pm).
Note: The radius of an atom is not a uniquely defined property and depends on the definition. Data derived from other sources with different assumptions cannot be compared.

Note: Empirical radiu are calculated to an accuracy of about 5 pm

1. H (hydrogen): **empirical:** 25; **calculated:** 53; **van der Waals:** 120; **covalent:** 37

2. He (helium): **empirical:** no data; **calculated:** 31; **van der Waals:** 140; **covalent:** 32

3. Li (lithium): **empirical:** 145; **calculated:** 167; **van der Waals:** 182; **covalent:** 134

4. Be (beryllium): **empirical:** 105; **calculated:** 112; **van der Waals:** no data; **covalent:** 90

5. B (boron): **empirical:** 85; **calculated:** 87; **van der Waals:** no data; **covalent:** 82

6. C (carbon): **empirical:** 70; **calculated:** 67; **van der Waals:** 170; **covalent:** 77

7. N (nitrogen): **empirical:** 65; **calculated:** 56; **van der Waals:** 155; **covalent:** 75

8. O (oxygen): **empirical:** 60; **calculated:** 48; **van der Waals:** 152; **covalent:** 73

9. F (fluorine): **empirical:** 50; **calculated:** 42; **van der Waals:** 147; **covalent:** 71

10. Ne (neon): **empirical:** no data; **calculated:** 38; **van der Waals:** 154; **covalent:** 69

11. Na (sodium): **empirical:** 180; **calculated:** 190; **van der Waals:** 227; **covalent:** 154

12. Mg (magnesium): **empirical:** 150; **calculated:** 145; **van der Waals:** 173; **covalent:** 130

13. Al (aluminium): **empirical:** 125; **calculated:** 118; **van der Waals:** no data; **covalent:** 118

14. Si (silicon): **empirical:** 110; **calculated:** 111; **van der Waals:** 210; **covalent:** 111

15. P (phosphorus): **empirical:** 100; **calculated:** 98; **van der Waals:** 180; **covalent:** 106

16. S (sulfur): **empirical:** 100; **calculated:** 88; **van der Waals:** 180; **covalent:** 102

17. Cl (chlorine): **empirical:** 100; **calculated:** 79; **van der Waals:** 175; **covalent:** 99

18. Ar (argon): **empirical:** 71; **calculated:** 71; **van der Waals:** 188; **covalent:** 97

19. K (potassium): **empirical:** 220; **calculated:** 243; **van der Waals:** 275; **covalent:** 196

20. Ca (calcium): **empirical:** 180; **calculated:** 194; **van der Waals:** no data; **covalent:** 174

21. Sc (scandium): **empirical:** 160; **calculated:** 184; **van der Waals:** no data; **covalent:** 144

22. Ti (titanium): **empirical:** 140; **calculated:** 176; **van der Waals:** no data; **covalent:** 136

23. V (vanadium): **empirical:** 135; **calculated:** 171; **van der Waals:** no data; **covalent:** 125

24. Cr (chromium): **empirical:** 140; **calculated:** 166; **van der Waals:** no data; **covalent:** 127

25. Mn (manganese): **empirical:** 140; **calculated:** 161; **van der Waals:** no data; **covalent:** 139

26. Fe (iron): **empirical:** 140; **calculated:** 156; **van der Waals:** no data; **covalent:** 125

27. Co (cobalt): **empirical:** 135; **calculated:** 152; **van der Waals:** no data; **covalent:** 126

28. Ni (nickel): **empirical:** 135; **calculated:** 149; **van der Waals:** 163; **covalent:** 121

29. Cu (copper): **empirical:** 135; **calculated:** 145; **van der Waals:** 140; **covalent:** 138

30. Zn (zinc): **empirical:** 135; **calculated:** 142; **van der Waals:** 139; **covalent:** 131

31. Ga (gallium): **empirical:** 130; **calculated:** 136; **van der Waals:** 187; **covalent:** 126

32. Ge (germanium): **empirical:** 125; **calculated:** 125; **van der Waals:** no data; **covalent:** 122

33. As (arsenic): **empirical:** 115; **calculated:** 114; **van der Waals:** 185; **covalent:** 119

34. Se (selenium): **empirical:** 115; **calculated:** 103; **van der Waals:** 190; **covalent:** 116

35. Br (bromine): **empirical:** 115; **calculated:** 94; **van der Waals:** 185; **covalent:** 114

36. Kr (krypton): **empirical:** no data; **calculated:** 88; **van der Waals:** 202; **covalent:** 110

37. Rb (rubidium): **empirical:** 235; **calculated:** 265; **van der Waals:** no data; **covalent:** 211

38. Sr (strontium): **empirical:** 200; **calculated:** 219; **van der Waals:** no data; **covalent:** 192

39. Y (yttrium): **empirical:** 180; **calculated:** 212; **van der Waals:** no data; **covalent:** 162

40. Zr (zirconium): **empirical:** 155; **calculated:** 206; **van der Waals:** no data; **covalent:** 148

41. Nb (niobium): **empirical:** 145; **calculated:** 198; **van der Waals:** no data; **covalent:** 137

42. Mo (molybdenum): **empirical:** 145; **calculated:** 190; **van der Waals:** no data; **covalent:** 145

43. Tc (technetium): **empirical:** 135; **calculated:** 183; **van der Waals:** no data; **covalent:** 156

44. Ru (ruthenium): **empirical:** 130; **calculated:** 178; **van der Waals:** no data; **covalent:** 126

45. Rh (rhodium): **empirical:** 135; **calculated:** 173; **van der Waals:** no data; **covalent:** 135

46. Pd (palladium): **empirical:** 140; **calculated:** 169; **van der Waals:** 163; **covalent:** 131

47. Ag (silver): **empirical:** 160; **calculated:** 165; **van der Waals:** 172; **covalent:** 153

48. Cd (cadmium): **empirical:** 155; **calculated:** 161; **van der Waals:** 158; **covalent:** 148

49. In (indium): **empirical:** 155; **calculated:** 156; **van der Waals:** 193; **covalent:** 144

50. Sn (tin): **empirical:** 145; **calculated:** 145; **van der Waals:** 217; **covalent:** 141

51. Sb (antimony): **empirical:** 145; **calculated:** 133; **van der Waals:** no data; **covalent:** 138

52. Te (tellurium): **empirical:** 140; **calculated:** 123; **van der Waals:** 206; **covalent:** 135

53. I (iodine): **empirical:** 140; **calculated:** 115; **van der Waals:** 198; **covalent:** 133

54. Xe (xenon): **empirical:** no data; **calculated:** 108; **van der Waals:** 216; **covalent:** 130

55. Cs (caesium): **empirical:** 260; **calculated:** 298; **van der Waals:** no data; **covalent:** 225

56. Ba (barium): **empirical:** 215; **calculated:** 253; **van der Waals:** no data; **covalent:** 198

57. La (lanthanum): **empirical:** 195; **calculated:** no data; **van der Waals:** no data; **covalent:** 169

58. Ce (cerium): **empirical:** 185; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

59. Pr (praseodymium): **empirical:** 185; **calculated:** 247; **van der Waals:** no data; **covalent:** no data

60. Nd (neodymium): **empirical:** 185; **calculated:** 206; **van der Waals:** no data; **covalent:** no data

61. Pm (promethium): **empirical:** 185; **calculated:** 205; **van der Waals:** no data; **covalent:** no data

62. Sm (samarium): **empirical:** 185; **calculated:** 238; **van der Waals:** no data; **covalent:** no data

63. Eu (europium): **empirical:** 185; **calculated:** 231; **van der Waals:** no data; **covalent:** no data

64. Gd (gadolinium): **empirical:** 180; **calculated:** 233; **van der Waals:** no data; **covalent:** no data

65. Tb (terbium): **empirical:** 175; **calculated:** 225; **van der Waals:** no data; **covalent:** no data

66. Dy (dysprosium): **empirical:** 175; **calculated:** 228; **van der Waals:** no data; **covalent:** no data

67. Ho (holmium): **empirical:** 175; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

68. Er (erbium): **empirical:** 175; **calculated:** 226; **van der Waals:** no data; **covalent:** no data

69. Tm (thulium): **empirical:** 175; **calculated:** 222; **van der Waals:** no data; **covalent:** no data

70. Yb (ytterbium): **empirical:** 175; **calculated:** 222; **van der Waals:** no data; **covalent:** no data

71. Lu (lutetium): **empirical:** 175; **calculated:** 217; **van der Waals:** no data; **covalent:** 160

72. Hf (hafnium): **empirical:** 155; **calculated:** 208; **van der Waals:** no data; **covalent:** 150

73. Ta (tantalum): **empirical:** 145; **calculated:** 200; **van der Waals:** no data; **covalent:** 138

74. W (tungsten): **empirical:** 135; **calculated:** 193; **van der Waals:** no data; **covalent:** 146

75. Re (rhenium): **empirical:** 135; **calculated:** 188; **van der Waals:** no data; **covalent:** 159

76. Os (osmium): **empirical:** 130; **calculated:** 185; **van der Waals:** no data; **covalent:** 128

77. Ir (iridium): **empirical:** 135; **calculated:** 180; **van der Waals:** no data; **covalent:** 137

78. Pt (platinum): **empirical:** 135; **calculated:** 177; **van der Waals:** 175; **covalent:** 128

79. Au (gold): **empirical:** 135; **calculated:** 174; **van der Waals:** 166; **covalent:** 144

80. Hg (mercury): **empirical:** 150; **calculated:** 171; **van der Waals:** 155; **covalent:** 149

81. Tl (thallium): **empirical:** 190; **calculated:** 156; **van der Waals:** 196; **covalent:** 148

82. Pb (lead): **empirical:** 180; **calculated:** 154; **van der Waals:** 202; **covalent:** 147

83. Bi (bismuth): **empirical:** 160; **calculated:** 143; **van der Waals:** no data; **covalent:** 146

84. Po (polonium): **empirical:** 190; **calculated:** 135; **van der Waals:** no data; **covalent:** no data

85. At (astatine): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

86. Rn (radon): **empirical:** no data; **calculated:** 120; **van der Waals:** no data; **covalent:** 145

87. Fr (francium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

88. Ra (radium): **empirical:** 215; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

89. Ac (actinium): **empirical:** 195; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

90. Th (thorium): **empirical:** 180; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

91. Pa (protactinium): **empirical:** 180; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

92. U (uranium): **empirical:** 175; **calculated:** no data; **van der Waals:** 186; **covalent:** no data

93. Np (neptunium): **empirical:** 175; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

94. Pu (plutonium): **empirical:** 175; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

95. Am (americium): **empirical:** 175; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

96. Cm (curium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

97. Bk (berkelium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

98. Cf (californium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

99. Es (einsteinium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

100. Fm (fermium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

101. Md (mendelevium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

102. No (nobelium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

103. Lr (lawrencium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

104. Rf (rutherfordium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

105. Db (dubnium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

106. Sg (seaborgium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

107. Bh (bohrium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

108. Hs (hassium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

109. Mt (meitnerium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

110. Ds (darmstadtium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

111. Rg (roentgenium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

112. Uub (ununbium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

113. Uut (ununtrium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

114. Uuq (ununquadium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

115. Uup (ununpentium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

116. Uuh (ununhexium): **empirical:** no data; **calculated:** no data; **van der Waals:** no data; **covalent:** no data

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Electron affinity

Electron affinity is the amount of energy absorbed when an electron is added to a neutral isolated gaseous atom to form a gaseous ion with a -1 charge. It has a negative value if energy is released.

Most elements have a negative electron affinity. This means they do not require energy to gain an electron; instead, they release energy. Atoms more attracted to extra electrons have a more negative electron affinity. Chlorine most strongly attracts extra electrons; mercury most weakly attracts an extra electron.

Although electron affinities vary in a chaotic manner across the table, some patterns emerge. Generally, nonmetals have more negative electron affinities than metals. However, the noble gases are an exception: they have positive electron affinities.

Periodic table of electron affinities, in kJ/mol:

1	H -73																He 21
2	Li -60	Be 19											B -27	C -122	N 7	O -141	F -328	Ne 29
3	Na -53	Mg 19											Al -43	Si -134	P -72	S -200	Cl -349	Ar 35
4	K -48	Ca 10	Sc -18	Ti -8	V -51	Cr -64	Mn	Fe -16	Co -64	Ni -112	Cu -118	Zn 47	Ga -29	Ge -116	As -78	Se -195	Br -325	Kr 39
5	Rb -47	Sr	Y -30	Zr -41	Nb -86	Mo -72	Tc -53	Ru -101	Rh -110	Pd -54	Ag -126	Cd 32	In -29	Sn -116	Sb -103	Te -190	I -295	Xe 41
6	Cs -45	Ba	Lu	Hf	Ta -31	W -79	Re -14	Os -106	Ir -151	Pt -205	Au -223	Hg 61	Tl -20	Pb -35	Bi -91	Po -183	At -270	Rn 41
7	Fr -44	Ra	Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub	Uut	Uuq	Uup	Uuh	Uus	Uuo

Electron affinity trends:

- Electron affinity is influenced by the octet rule. Group 17 elements (fluorine, chlorine, bromine, iodine, and astatine) tend to gain an electron and form -1 anions. The noble gases in group 18 already have a full octet, and thus adding an extra electron requires large amounts of energy, but it is possible.
- Group 2 elements starting with beryllium and group 12 elements starting with zinc also have positive electron affinity values because these elements have a filled s subshell or d subshell.

- The elements in group 15 have low electron affinities and that of nitrogen is even positive. The reason is that stabilization is even gained from half-filled subshells.
- The electron affinities increase across a row (since the radius slightly decreases, because of the increased attraction from the nucleus, and the number of electrons in the top shell increases, helping the atom reach maximum stability) in the periodic table and decrease going down a family (because of a large increase in radius and number of electron that decrease the stability of the atom, repulsing each other).

Electron affinities are not limited to the elements but also apply to molecules. For instance the electron affinity for benzene is positive, that of naphthalene near zero and that of anthracene positive. In silico experiments show that the electron affinity of hexacyanobenzene surpasses that of fullerene.

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Electronegativity

Electronegativity is a measure of the ability of an atom or molecule to attract electrons in the context of a chemical bond. The type of bond formed is largely determined by the difference in electronegativity between the atoms involved. Atoms with similar electronegativities will share an electron with each other and form a covalent bond. However, if the difference is too great, the electron will be permanently transferred to one atom and an ionic bond will form. Furthermore, in a covalent bond if one atom pulls slightly harder than the other, a polar covalent bond will form.

The **Pauling scale** was devised in 1932 by Linus Pauling. On this scale, the most electronegative chemical element (fluorine) is given an electronegativity value of 3.98 (textbooks often state this value to be 4.0); the least electronegative element (francium) has a value of 0.7, and the remaining elements have values in between. On the Pauling scale, hydrogen is arbitrarily assigned a value of 2.1 or 2.2.

'***ΔEN'*** is the difference in electronegativity between two atoms or elements. Bonds between atoms with a large electronegativity difference (greater than or equal to 1.7) are usually considered to be ionic, while values between 1.7 and 0.4 are considered polar covalent. Values below 0.4 are considered non-polar covalent bonds, and electronegativity differences of 0 indicate a completely non-polar covalent bond.

Electronegativity trends

Each element has a characteristic electronegativity ranging from 0 to 4 on the Pauling scale. The most strongly electronegative element, fluorine, has an electronegativity of 3.98 while weakly electronegative elements, such as lithium, have values close to 1. The least electronegative element is francium at 0.7. *In general*, the degree of electronegativity decreases down each group and increases across the periods, as shown below. Across a period, non-metals tend to gain electrons and metals tend to lose them due to the atom striving to achieve a stable octet. Down a group, the nuclear charge has less effect on the outermost shells. Therefore, the most electronegative atoms can be found in the upper, right hand side of the periodic table, and the least electronegative elements can be found at the bottom left. Consequently, *in general*, atomic radius decreases across the periodic table, but ionization energy increases.

List of elemental electronegativity

- Francium - 0.70
- Caesium - 0.79
- Potassium, Rubidium - 0.82
- Barium - 0.89
- Radium - 0.90
- Sodium - 0.93
- Strontium - 0.95
- Lithium - 0.98

- Calcium - 1.00
- Actinium, Lanthanum, Terbium, Ytterbium - 1.10
- Cerium - 1.12
- Americium, Praseodymium, Promethium - 1.13
- Neodymium - 1.14
- Samarium - 1.17
- Europium, Gadolinium - 1.20
- Dysprosium, Yttrium - 1.22
- Holmium - 1.23
- Erbium - 1.24
- Thulium - 1.25
- Lutetium - 1.27
- Plutonium, Curium - 1.28
- Berkelium, Californium, Einsteinium, Fermium, Hafnium, Mendelevium, Nobelium, Thorium - 1.30
- Magnesium - 1.31
- Zirconium - 1.33
- Scandium, Neptunium - 1.36
- Uranium - 1.38
- Tantalum, Protactinium - 1.50
- Titanium - 1.54
- Manganese - 1.55
- Beryllium - 1.57
- Niobium - 1.60
- Aluminum - 1.61
- Thallium - 1.62
- Vanadium - 1.63
- Zinc - 1.65
- Chromium - 1.66
- Cadmium - 1.69
- Indium - 1.78
- Gallium - 1.81
- Iron - 1.83
- Cobalt - 1.88
- Copper, Technetium, Rhenium, Silicon - 1.90
- Nickel - 1.91
- Silver - 1.93
- Tin - 1.96
- Mercury, Polonium - 2.00
- Germanium - 2.01
- Bismuth - 2.02
- Boron - 2.04
- Antimony - 2.05
- Tellurium - 2.10

- Molybdenum - 2.16
- Arsenic - 2.18
- Phosphorus - 2.19
- Astatine, Hydrogen, Iridium, Osmium, Palladium, Ruthenium - 2.20
- Rhenium, Platinum - 2.28
- Lead - 2.33
- Tungsten - 2.36
- Gold - 2.54
- Carbon, Selenium - 2.55
- Sulfur - 2.58
- Xenon - 2.60
- Iodine - 2.66
- Bromine - 2.96
- Krypton - 3.00
- Nitrogen - 3.04
- Chlorine - 3.16
- Oxygen - 3.44
- Fluorine - 4.00

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Ionization potential

The **ionization potential**, or **ionization energy**, of an atom or molecule is the energy required to strip it of an electron. More generally, the *nth ionization energy* is the energy required to strip it of an *n*th electron after the first *n* - 1 have already been removed. It is centrally significant in physical chemistry as a measure of the "reluctance" of an atom or of a molecule to surrender an electron, or the "strength" by which the electron is bound.

Values and trends

Generally speaking, atomic ionization energies decrease down a group (i.e. column) of the periodic table, and increase left-to-right across a period. Ionization energy exhibits a strong negative correlation with atomic radius. Successive ionization energies of any given element increase markedly. Particularly dramatic increases occur after any given block of atomic orbitals is exhausted, except when progressing to the next s orbital. This is because, after all the electrons are removed from an orbital, the next ionization energy involves removing an electron from a closer orbital to the nucleus. Electrons in the closer orbital experience greater forces of electrostatic attraction, and thus, require more energy to be removed.

Ionization energies of the elements

These tables list the ionization energy in kJ/mol necessary to remove an electron from a neutral atom (first energy), respectively from a singly, doubly, etc. ionized atom (second, third, etc. energies).

1st-10th

1. H (hydrogen) **1st:** 1312.0

2. He (helium) **1st:** 2372.3; **2nd:** 5250.5

3. Li (lithium) **1st:** 520.2; **2nd:** 7298.1; **3rd:** 11815.0

4. Be (beryllium) **1st:** 899.5; **2nd:** 1757.1; **3rd:** 14848.7; **4th:** 21006.6

5. B (boron) **1st:** 800.6; **2nd:** 2427.1; **3rd:** 3659.7; **4th:** 25025.8; **5th:** 32826.7

6. C (carbon) **1st:** 1086.5; **2nd:** 2352.6; **3rd:** 4620.5; **4th:** 6222.7; **5th:** 37831; **6th:** 47277.0

7. N (nitrogen) **1st:** 1402.3; **2nd:** 2856; **3rd:** 4578.1; **4th:** 7475.0; **5th:** 9444.9; **6th:** 53266.6; **7th:** 64360

8. O (oxygen) **1st:** 1313.9; **2nd:** 3388.3; **3rd:** 5300.5; **4th:** 7469.2; **5th:** 10989.5; **6th:** 13326.5; **7th:** 71330; **8th:** 84078.0

9. F (fluorine) **1st:** 1681.0; **2nd:** 3374.2; **3rd:** 6050.4; **4th:** 8407.7; **5th:** 11022.7; **6th:** 15164.1; **7th:** 17868; **8th:** 92038.1; **9th:** 106434.3

10. Ne (neon) **1st:** 2080.7; **2nd:** 3952.3; **3rd:** 6122; **4th:** 9371; **5th:** 12177; **6th:** 15238; **7th:** 19999.0; **8th:** 23069.5; **9th:** 115379.5; **10th:** 131432

11. Na (sodium) **1st:** 495.8; **2nd:** 4562; **3rd:** 6910.3; **4th:** 9543; **5th:** 13354; **6th:** 16613; **7th:** 20117; **8th:** 25496; **9th:** 28932; **10th:** 141362

12. Mg (magnesium) **1st:** 737.7; **2nd:** 1450.7; **3rd:** 7732.7; **4th:** 10542.5; **5th:** 13630; **6th:** 18020; **7th:** 21711; **8th:** 25661; **9th:** 31653; **10th:** 35458

13. Al (aluminium) **1st:** 577.5; **2nd:** 1816.7; **3rd:** 2744.8; **4th:** 11577; **5th:** 14842; **6th:** 18379; **7th:** 23326; **8th:** 27465; **9th:** 31853; **10th:** 38473

14. Si (silicon) **1st:** 786.5; **2nd:** 1577.1; **3rd:** 3231.6; **4th:** 4355.5; **5th:** 16091; **6th:** 19805; **7th:** 23780; **8th:** 29287; **9th:** 33878; **10th:** 38726

15. P (phosphorus) **1st:** 1011.8; **2nd:** 1907; **3rd:** 2914.1; **4th:** 4963.6; **5th:** 6273.9; **6th:** 21267; **7th:** 25431; **8th:** 29872; **9th:** 35905; **10th:** 40950

16. S (sulfur) **1st:** 999.6; **2nd:** 2252; **3rd:** 3357; **4th:** 4556; **5th:** 7004.3; **6th:** 8495.8; **7th:** 27107; **8th:** 31719; **9th:** 36621; **10th:** 43177

17. Cl (chlorine) **1st:** 1251.2; **2nd:** 2298; **3rd:** 3822; **4th:** 5158.6; **5th:** 6542; **6th:** 9362; **7th:** 11018; **8th:** 33604; **9th:** 38600; **10th:** 43961

18. Ar (argon) **1st:** 1520.6; **2nd:** 2665.8; **3rd:** 3931; **4th:** 5771; **5th:** 7238; **6th:** 8781; **7th:** 11995; **8th:** 13842; **9th:** 40760; **10th:** 46186

19. K (potassium) **1st:** 418.8; **2nd:** 3052; **3rd:** 4420; **4th:** 5877; **5th:** 7975; **6th:** 9590; **7th:** 11343; **8th:** 14944; **9th:** 16963.7; **10th:** 48610

20. Ca (calcium) **1st:** 589.8; **2nd:** 1145.4; **3rd:** 4912.4; **4th:** 6491; **5th:** 8153; **6th:** 10496; **7th:** 12270; **8th:** 14206; **9th:** 18191; **10th:** 20385

21. Sc (scandium) **1st:** 633.1; **2nd:** 1235.0; **3rd:** 2388.6; **4th:** 7090.6; **5th:** 8843; **6th:** 10679; **7th:** 13310; **8th:** 15250; **9th:** 17370; **10th:** 21726

22. Ti (titanium) **1st:** 658.8; **2nd:** 1309.8; **3rd:** 2652.5; **4th:** 4174.6; **5th:** 9581; **6th:** 11533; **7th:** 13590; **8th:** 16440; **9th:** 18530; **10th:** 20833

23. V (vanadium) **1st:** 650.9; **2nd:** 1414; **3rd:** 2830; **4th:** 4507; **5th:** 6298.7; **6th:** 12363; **7th:** 14530; **8th:** 16730; **9th:** 19860; **10th:** 22240

24. Cr (chromium) **1st:** 652.9; **2nd:** 1590.6; **3rd:** 2987; **4th:** 4743; **5th:** 6702; **6th:** 8744.9; **7th:** 15455; **8th:** 17820; **9th:** 20190; **10th:** 23580

25. Mn (manganese) **1st:** 717.3; **2nd:** 1509.0; **3rd:** 3248; **4th:** 4940; **5th:** 6990; **6th:** 9220; **7th:** 11500; **8th:** 18770; **9th:** 21400; **10th:** 23960

26. Fe (iron) **1st:** 762.5; **2nd:** 1561.9; **3rd:** 2957; **4th:** 5290; **5th:** 7240; **6th:** 9560; **7th:** 12060; **8th:** 14580; **9th:** 22540; **10th:** 25290

27. Co (cobalt) **1st:** 760.4; **2nd:** 1648; **3rd:** 3232; **4th:** 4950; **5th:** 7670; **6th:** 9840; **7th:** 12440; **8th:** 15230; **9th:** 17959; **10th:** 26570

28. Ni (nickel) **1st:** 737.1; **2nd:** 1753.0; **3rd:** 3395; **4th:** 5300; **5th:** 7339; **6th:** 10400; **7th:** 12800; **8th:** 15600; **9th:** 18600; **10th:** 21670

29. Cu (copper) **1st:** 745.5; **2nd:** 1957.9; **3rd:** 3555; **4th:** 5536; **5th:** 7700; **6th:** 9900; **7th:** 13400; **8th:** 16000; **9th:** 19200; **10th:** 22400

30. Zn (zinc) **1st:** 906.4; **2nd:** 1733.3; **3rd:** 3833; **4th:** 5731; **5th:** 7970; **6th:** 10400; **7th:** 12900; **8th:** 16800; **9th:** 19600; **10th:** 23000

31. Ga (gallium) **1st:** 578.8; **2nd:** 1979.3; **3rd:** 2963; **4th:** 6180

32. Ge (germanium) **1st:** 762; **2nd:** 1537.5; **3rd:** 3302.1; **4th:** 4411; **5th:** 9020

33. As (arsenic) **1st:** 947.0; **2nd:** 1798; **3rd:** 2735; **4th:** 4837; **5th:** 6043; **6th:** 12310

34. Se (selenium) **1st:** 941.0; **2nd:** 2045; **3rd:** 2973.7; **4th:** 4144; **5th:** 6590; **6th:** 7880; **7th:** 14990

35. Br (bromine) **1st:** 1139.9; **2nd:** 2103; **3rd:** 3470; **4th:** 4560; **5th:** 5760; **6th:** 8550; **7th:** 9940; **8th:** 18600

36. Kr (krypton) **1st:** 1350.8; **2nd:** 2350.4; **3rd:** 3565; **4th:** 5070; **5th:** 6240; **6th:** 7570; **7th:** 10710; **8th:** 12138; **9th:** 22274; **10th:** 25880

37. Rb (rubidium) **1st:** 403.0; **2nd:** 2633; **3rd:** 3860; **4th:** 5080; **5th:** 6850; **6th:** 8140; **7th:** 9570; **8th:** 13120; **9th:** 14500; **10th:** 26740

38. Sr (strontium) **1st:** 549.5; **2nd:** 1064.2; **3rd:** 4138; **4th:** 5500; **5th:** 6910; **6th:** 8760; **7th:** 10230; **8th:** 11800; **9th:** 15600; **10th:** 17100

39. Y (yttrium) **1st:** 600; **2nd:** 1180; **3rd:** 1980; **4th:** 5847; **5th:** 7430; **6th:** 8970; **7th:** 11190; **8th:** 12450; **9th:** 14110; **10th:** 18400

40. Zr (zirconium) **1st:** 640.1; **2nd:** 1270; **3rd:** 2218; **4th:** 3313; **5th:** 7752; **6th:** 9500

41. Nb (niobium) **1st:** 652.1; **2nd:** 1380; **3rd:** 2416; **4th:** 3700; **5th:** 4877; **6th:** 9847; **7th:** 12100

42. Mo (molybdenum) **1st:** 684.3; **2nd:** 1560; **3rd:** 2618; **4th:** 4480; **5th:** 5257; **6th:** 6640.8; **7th:** 12125; **8th:** 13860; **9th:** 15835; **10th:** 17980

43. Tc (technetium) **1st:** 702; **2nd:** 1470; **3rd:** 2850

44. Ru (ruthenium) **1st:** 710.2; **2nd:** 1620; **3rd:** 2747

45. Rh (rhodium) **1st:** 719.7; **2nd:** 1740; **3rd:** 2997

46. Pd (palladium) **1st:** 804.4; **2nd:** 1870; **3rd:** 3177

47. Ag (silver) **1st:** 731.0; **2nd:** 2070; **3rd:** 3361

48. Cd (cadmium) **1st:** 867.8; **2nd:** 1631.4; **3rd:** 3616

49. In (indium) **1st:** 558.3; **2nd:** 1820.7; **3rd:** 2704; **4th:** 5210

50. Sn (tin) **1st:** 708.6; **2nd:** 1411.8; **3rd:** 2943.0; **4th:** 3930.3; **5th:** 7456

51. Sb (antimony) **1st:** 834; **2nd:** 1594.9; **3rd:** 2440; **4th:** 4260; **5th:** 5400; **6th:** 10400

52. Te (tellurium) **1st:** 869.3; **2nd:** 1790; **3rd:** 2698; **4th:** 3610; **5th:** 5668; **6th:** 6820; **7th:** 13200

53. I (iodine) **1st:** 1008.4; **2nd:** 1845.9; **3rd:** 3180

54. Xe (xenon) **1st:** 1170.4; **2nd:** 2046.4; **3rd:** 3099.4

55. Cs (caesium) **1st:** 375.7; **2nd:** 2234.3; **3rd:** 3400

56. Ba (barium) **1st:** 502.9; **2nd:** 965.2; **3rd:** 3600

57. La (lanthanum) **1st:** 538.1; **2nd:** 1067; **3rd:** 1850.3; **4th:** 4819; **5th:** 5940

58. Ce (cerium) **1st:** 534.4; **2nd:** 1050; **3rd:** 1949; **4th:** 3547; **5th:** 6325; **6th:** 7490

59. Pr (praseodymium) **1st:** 527; **2nd:** 1020; **3rd:** 2086; **4th:** 3761; **5th:** 5551

60. Nd (neodymium) **1st:** 533.1; **2nd:** 1040; **3rd:** 2130; **4th:** 3900

61. Pm (promethium) **1st:** 540; **2nd:** 1050; **3rd:** 2150; **4th:** 3970

62. Sm (samarium) **1st:** 544.5; **2nd:** 1070; **3rd:** 2260; **4th:** 3990

63. Eu (europium) **1st:** 547.1; **2nd:** 1085; **3rd:** 2404; **4th:** 4120

64. Gd (gadolinium) **1st:** 593.4; **2nd:** 1170; **3rd:** 1990; **4th:** 4250

65. Tb (terbium) **1st:** 565.8; **2nd:** 1110; **3rd:** 2114; **4th:** 3839

66. Dy (dysprosium) **1st:** 573.0; **2nd:** 1130; **3rd:** 2200; **4th:** 3990

67. Ho (holmium) **1st:** 581.0; **2nd:** 1140; **3rd:** 2204; **4th:** 4100

68. Er (erbium) **1st:** 589.3; **2nd:** 1150; **3rd:** 2194; **4th:** 4120

69. Tm (thulium) **1st:** 596.7; **2nd:** 1160; **3rd:** 2285; **4th:** 4120

70. Yb (ytterbium) **1st:** 603.4; **2nd:** 1174.8; **3rd:** 2417; **4th:** 4203

71. Lu (lutetium) **1st:** 523.5; **2nd:** 1340; **3rd:** 2022.3; **4th:** 4370; **5th:** 6445

72. Hf (hafnium) **1st:** 658.5; **2nd:** 1440; **3rd:** 2250; **4th:** 3216

73. Ta (tantalum) **1st:** 761; **2nd:** 1500

74. W (tungsten) **1st:** 770; **2nd:** 1700

75. Re (rhenium) **1st:** 760; **2nd:** 1260; **3rd:** 2510; **4th:** 3640

76. Os (osmium) **1st:** 840; **2nd:** 1600

77. Ir (iridium) **1st:** 880; **2nd:** 1600

78. Pt (platinum) **1st:** 870; **2nd:** 1791

79. Au (gold) **1st:** 890.1; **2nd:** 1980

80. Hg (mercury) **1st:** 1007.1; **2nd:** 1810; **3rd:** 3300

81. Tl (thallium) **1st:** 589.4; **2nd:** 1971; **3rd:** 2878

82. Pb (lead) **1st:** 715.6; **2nd:** 1450.5; **3rd:** 3081.5; **4th:** 4083; **5th:** 6640

83. Bi (bismuth) **1st:** 703; **2nd:** 1610; **3rd:** 2466; **4th:** 4370; **5th:** 5400; **6th:** 8520

84. Po (polonium) **1st:** 812.1

85. At (astatine) **1st:** 920

86. Rn (radon) **1st:** 1037

87. Fr (francium) **1st:** 380

88. Ra (radium) **1st:** 509.3; **2nd:** 979.0

89. Ac (actinium) **1st:** 499; **2nd:** 1170

90. Th (thorium) **1st:** 587; **2nd:** 1110; **3rd:** 1930; **4th:** 2780

91. Pa (protactinium) **1st:** 568

92. U (uranium) **1st:** 597.6; **2nd:** 1420

93. Np (neptunium) **1st:** 604.5

94. Pu (plutonium) **1st:** 584.7

95. Am (americium) **1st:** 578

96. Cm (curium) **1st:** 581

97. Bk (berkelium) **1st:** 601

98. Cf (californium) **1st:** 608

99. Es (einsteinium) **1st:** 619

100. Fm (fermium) **1st:** 627

101. Md (mendelevium) **1st:** 635

102. No (nobelium) **1st:** 642

103. Lr (lawrencium) **1st:** 470

104. Rf (rutherfordium) **1st:** 580

11th-20th

11. Na (sodium) **11th:** 159076

12. Mg (magnesium) **11th:** 169988; **12th:** 189368

13. Al (aluminium) **11th:** 42647; **12th:** 201266; **13th:** 222316

14. Si (silicon) **11th:** 45962; **12th:** 50502; **13th:** 235196; **14th:** 257923

15. P (phosphorus) **11th:** 46261; **12th:** 54110; **13th:** 59024; **14th:** 271791; **15th:** 296195

16. S (sulfur) **11th:** 48710; **12th:** 54460; **13th:** 62930; **14th:** 68216; **15th:** 311048; **16th:** 337138

17. Cl (chlorine) **11th:** 51068; **12th:** 57119; **13th:** 63363; **14th:** 72341; **15th:** 78095; **16th:** 352994; **17th:** 380760

18. Ar (argon) **11th:** 52002; **12th:** 59653; **13th:** 66199; **14th:** 72918; **15th:** 82473; **16th:** 88576; **17th:** 397605; **18th:** 427066

19. K (potassium) **11th:** 54490; **12th:** 60730; **13th:** 68950; **14th:** 75900; **15th:** 83080; **16th:** 93400; **17th:** 99710; **18th:** 444880; **19th:** 476063

20. Ca (calcium) **11th:** 57110; **12th:** 63410; **13th:** 70110; **14th:** 78890; **15th:** 86310; **16th:** 94000; **17th:** 104900; **18th:** 111711; **19th:** 494850; **20th:** 527762

21. Sc (scandium) **11th:** 24102; **12th:** 66320; **13th:** 73010; **14th:** 80160; **15th:** 89490; **16th:** 97400; **17th:** 105600; **18th:** 117000; **19th:** 124270; **20th:** 547530

22. Ti (titanium) **11th:** 25575; **12th:** 28125; **13th:** 76015; **14th:** 83280; **15th:** 90880; **16th:** 100700; **17th:** 109100; **18th:** 117800; **19th:** 129900; **20th:** 137530

23. V (vanadium) **11th:** 24670; **12th:** 29730; **13th:** 32446; **14th:** 86450; **15th:** 94170; **16th:** 102300; **17th:** 112700; **18th:** 121600; **19th:** 130700; **20th:** 143400

24. Cr (chromium) **11th:** 26130; **12th:** 28750; **13th:** 34230; **14th:** 37066; **15th:** 97510; **16th:** 105800; **17th:** 114300; **18th:** 125300; **19th:** 134700; **20th:** 144300

25. Mn (manganese) **11th:** 27590; **12th:** 30330; **13th:** 33150; **14th:** 38880; **15th:** 41987; **16th:** 109480; **17th:** 118100; **18th:** 127100; **19th:** 138600; **20th:** 148500

26. Fe (iron) **11th:** 28000; **12th:** 31920; **13th:** 34830; **14th:** 37840; **15th:** 44100; **16th:** 47206; **17th:** 122200; **18th:** 131000; **19th:** 140500; **20th:** 152600

27. Co (cobalt) **11th:** 29400; **12th:** 32400; **13th:** 36600; **14th:** 39700; **15th:** 42800; **16th:** 49396; **17th:** 52737; **18th:** 134810; **19th:** 145170; **20th:** 154700

28. Ni (nickel) **11th:** 30970; **12th:** 34000; **13th:** 37100; **14th:** 41500; **15th:** 44800; **16th:** 48100; **17th:** 55101; **18th:** 58570; **19th:** 148700; **20th:** 159000

29. Cu (copper) **11th:** 25600; **12th:** 35600; **13th:** 38700; **14th:** 42000; **15th:** 46700; **16th:** 50200; **17th:** 53700; **18th:** 61100; **19th:** 64702; **20th:** 163700

30. Zn (zinc) **11th:** 26400; **12th:** 29990; **13th:** 40490; **14th:** 43800; **15th:** 47300; **16th:** 52300; **17th:** 55900; **18th:** 59700; **19th:** 67300; **20th:** 71200

36. Kr (krypton) **11th:** 29700; **12th:** 33800; **13th:** 37700; **14th:** 43100; **15th:** 47500; **16th:** 52200; **17th:** 57100; **18th:** 61800; **19th:** 75800; **20th:** 80400

38. Sr (strontium) **11th:** 31270

39. Y (yttrium) **11th:** 19900; **12th:** 36090

42. Mo (molybdenum) **11th:** 20190; **12th:** 22219; **13th:** 26930; **14th:** 29196; **15th:** 52490; **16th:**

55000; **17th:** 61400; **18th:** 67700; **19th:** 74000; **20th:** 80400

21st-30th

21. Sc (scandium) **21st:** 582163

22. Ti (titanium) **21st:** 602930; **22nd:** 639294

23. V (vanadium) **21st:** 151440; **22nd:** 661050; **23rd:** 699144

24. Cr (chromium) **21st:** 157700; **22nd:** 166090; **23rd:** 721870; **24th:** 761733

25. Mn (manganese) **21st:** 158600; **22nd:** 172500; **23rd:** 181380; **24th:** 785450; **25th:** 827067

26. Fe (iron) **21st:** 163000; **22nd:** 173600; **23rd:** 188100; **24th:** 195200; **25th:** 851800; **26th:** 895161

27. Co (cobalt) **21st:** 167400; **22nd:** 178100; **23rd:** 189300; **24th:** 204500; **25th:** 214100; **26th:** 920870; **27th:** 966023

28. Ni (nickel) **21st:** 169400; **22nd:** 182700; **23rd:** 194000; **24th:** 205600; **25th:** 221400; **26th:** 231490; **27th:** 992718; **28th:** 1039668

29. Cu (copper) **21st:** 174100; **22nd:** 184900; **23rd:** 198800; **24th:** 210500; **25th:** 222700; **26th:** 239100; **27th:** 249660; **28th:** 1067358; **29th:** 1116105

30. Zn (zinc) **21st:** 179100

36. Kr (krypton) **21st:** 85300; **22nd:** 90400; **23rd:** 96300; **24th:** 101400; **25th:** 111100; **26th:** 116290; **27th:** 282500; **28th:** 296200; **29th:** 311400; **30th:** 326200

42. Mo (molybdenum) **21st:** 87000; **22nd:** 93400; **23rd:** 98420; **24th:** 104400; **25th:** 121900; **26th:** 127700; **27th:** 133800; **28th:** 139800; **29th:** 148100; **30th:** 154500

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List of elements by boiling point

This is a list of the chemical elements, sorted by boiling point measured .

2. helium: -269°C°C
1. hydrogen: -253°C°C
10. neon: -246°C
7. nitrogen: -196°C
9. fluorine: -188°C
18. argon: -186°C
8. oxygen: -183°C
36. krypton: -152°C
54. xenon: -107°C
86. radon: -62°C
17. chlorine: -34°C
35. bromine: 59°C
53. iodine: 184°C
15. white phosphorus: 280°C
80. mercury: 357°C
85. astatine: 370°C
16. sulfur: 445°C
33. arsenic: 613°C
55. caesium: 671°C
87. francium: 677°C
34. selenium: 685°C
37. rubidium: 688°C
97. berkelium: 710°C
19. potassium: 754°C
48. cadmium: 767°C
11. sodium: 890°C
30. zinc: 907°C
84. polonium: 962°C
52. tellurium: 990°C
12. magnesium: 1105°C
70. ytterbium: 1194°C
3. lithium: 1317°C
51. antimony: 1380°C
38. strontium: 1384°C
81. thallium: 1457°C
98. californium: 1470°C
20. calcium: 1487°C

83. bismuth: 1560°C
63. europium: 1597°C
56. barium: 1640°C
88. radium: 1737°C
82. lead: 1744°C
62. samarium: 1791°C
69. thulium: 1947°C
49. indium: 2000°C
25. manganese: 2041°C
47. silver: 2212°C
50. tin: 2270°C
14. silicon: 2355°C
32. germanium: 2355°C
31. gallium: 2403°C
4. beryllium: 2487°C
5. boron: 2550°C
66. dysprosium: 2562°C
29. copper: 2582°C
95. americium: 2607°C
24. chromium: 2642°C
13. aluminium: 2647°C
67. holmium: 2695°C
61. promethium: 2700°C
21. scandium: 2831°C
28. nickel: 2837°C
68. erbium: 2863°C
27. cobalt: 2877°C
26. iron: 2887°C
46. palladium: 2970°C
60. neodymium: 3068°C
79. gold: 3080°C
65. terbium: 3123°C
96. curium: 3190°C
89. actinium: 3200°C
64. gadolinium: 3266°C
22. titanium: 3277°C
94. plutonium: 3330°C
39. yttrium: 3338°C
23. vanadium: 3377°C
71. lutetium: 3394°C
58. cerium: 3426°C
57. lanthanum: 3457°C
59. praseodymium: 3512°C

45. rhodium: 3727°C
92. uranium: 3818°C
78. platinum: 3827°C
44. ruthenium: 3900°C
6. Graphite (carbon): 3900°C
91. protactinium: 4027°C
93. neptunium: 4090°C
77. iridium: 4130°C
40. zirconium: 4377°C
72. hafnium: 4602°C
41. niobium: 4742°C
90. thorium: 4787°C
6. Diamond (carbon): 4827°C
43. technetium: 4877°C
76. osmium: 5297°C
73. tantalum: 5427°C
42. molybdenum: 5560°C
75. rhenium: 5627°C
74. tungsten: 5660°C

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List of elements by density

This is a list of the chemical elements, sorted by density (g/cm³) measured at standard temperature (273.15 K) and pressure (100 kPa=1 bar).

Hydrogen, H: 0.00008988
Helium, He: 0.0001785
Neon, Ne: 0.0008999
Nitrogen, N: 0.0012506
Oxygen, O: 0.001429
Fluorine, F: 0.001696
Argon, Ar: 0.0017837
Chlorine, Cl: 0.003214
Krypton, Kr: 0.003733
Xenon, Xe: 0.005887
Radon, Rn: 0.00973
Lithium, Li: 0.534
Potassium, K: 0.862
Sodium, Na: 0.971
Rubidium, Rb: 1.532
Calcium, Ca: 1.54
Magnesium, Mg: 1.738
Phosphorus, P: 1.82
Beryllium, Be: 1.85
Francium, Fr: 1.87
Caesium, Cs: 1.873
Sulfur, S: 2.067
Carbon, C: 2.267
Silicon, Si: 2.3296
Boron, B: 2.34
Strontium, Sr: 2.64
Aluminium, Al: 2.698
Scandium, Sc: 2.989
Bromine, Br: 3.122
Barium, Ba: 3.594
Yttrium, Y: 4.469
Titanium, Ti: 4.540
Selenium, Se: 4.809
Iodine, I: 4.93
Europium, Eu: 5.243
Germanium, Ge: 5.323

Radium, Ra: 5.50
Arsenic, As: 5.776
Gallium, Ga: 5.907
Vanadium, V: 6.11
Lanthanum, La: 6.145
Tellurium, Te: 6.232
Zirconium, Zr: 6.506
Antimony, Sb: 6.685
Cerium, Ce: 6.770
Praseodymium, Pr: 6.773
Ytterbium, Yb: 6.965
Astatine, At: Approximately 7
Neodymium, Nd: 7.007
Zinc, Zn: 7.134
Chromium, Cr: 7.15
Promethium, Pm: 7.26
Tin, Sn: 7.287
Indium, In: 7.310
Manganese, Mn: 7.44
Samarium, Sm: 7.52
Iron, Fe: 7.874
Gadolinium, Gd: 7.895
Terbium, Tb: 8.229
Dysprosium, Dy: 8.55
Niobium, Nb: 8.570
Cadmium, Cd: 8.69
Holmium, Ho: 8.795
Cobalt, Co: 8.86
Nickel, Ni: 8.912
Copper, Cu: 8.933
Erbium, Er: 9.066
Polonium, Po: 9.32
Ununhexium, Uuh: >9.32
Thulium, Tm: 9.321
Bismuth, Bi: 9.807
Ununpentium, Uup: >9.807
Lutetium, Lu: 9.84
Lawrencium, Lr: >9.84
Actinium, Ac: 10.07
Molybdenum, Mo: 10.22
Silver, Ag: 10.501
Lead, Pb: 11.342
Ununquadium, Uuq: >11.342

Technetium, Tc: 11.50
Thorium, Th: 11.72
Thallium, Tl: 11.85
Ununtrium, Uut: >11.85
Palladium, Pd: 12.020
Ruthenium, Ru: 12.37
Rhodium, Rh: 12.41
Hafnium, Hf: 13.31
Einsteinium, Es: 13.5 (Estimate)
Curium, Cm: 13.51
Mercury, Hg: 13.5336
Ununbium, Uub: >13.5336
Americium, Am: 13.69
Berkelium, Bk: 14.79
Californium, Cf: 15.10
Protactinium, Pa: 15.37
Tantalum, Ta: 16.654
Rutherfordium, Rf: 18.1
Uranium, U: 18.95
Tungsten, W: 19.25
Gold, Au: 19.282
Roentgenium, Rg: >19.282
Plutonium, Pu: 19.84
Neptunium, Np: 20.25
Rhenium, Re: 21.02
Platinum, Pt: 21.46
Darmstadtium, Ds: >21.46
Osmium, Os: 22.610
Iridium, Ir: 22.650
Seaborgium, Sg: 35 (Estimate)
Meitnerium, Mt: 35 (Estimate)
Bohrium, Bh: 37 (Estimate)
Dubnium, Db: 39 (Estimate)
Hassium, Hs: 41 (Estimate)
Fermium, Fm: Unknown
Mendelevium, Md: Unknown
Nobelium, No: Unknown

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List of elements by melting point

This is a list of the chemical elements, sorted by melting point measured at normal pressure.

Helium, He: (Does not solidify-at normal pressure-even at absolute zero)°C
Hydrogen, H: -258.975°C°C
Neon, Ne: -248.447°C
Oxygen, O: -222.65°C
Fluorine, F: -219.52°C
Nitrogen, N: -209.86°C
Argon, Ar: -189.19°C
Krypton, Kr: -157.22°C
Xenon, Xe: -111.7°C
Chlorine, Cl: -100.84°C
Radon, Rn: -71°C
Mercury, Hg: -38.72°C
Bromine, Br: -7.1°C
Francium, Fr: 27°C
Caesium, Cs: 28.55°C
Gallium, Ga: 29.76°C
Rubidium, Rb: 39.64°C
Phosphorus (white), P: 44.1°C
Potassium, K: 63.35°C
Sodium, Na: 98°C
Iodine, I: 113.5°C
Sulfur, S: 115.36°C
Indium, In: 156.76°C
Lithium, Li: 180.7°C
Selenium, Se: 221°C
Tin, Sn: 232.06°C
Polonium, Po: 254°C
Bismuth, Bi: 271.52°C
Astatine, At: 302°C
Thallium, Tl: 304°C
Cadmium, Cd: 321.18°C
Lead, Pb: 327.6°C
Zinc, Zn: 419.73°C
Tellurium, Te: 449.65°C
Antimony, Sb: 630.9°C
Neptunium, Np: 640°C
Plutonium, Pu: 640°C

Magnesium, Mg: 650°C
Aluminium, Al: 660.25°C
Radium, Ra: 700°C
Barium, Ba: 729°C
Strontium, Sr: 769°C
Cerium, Ce: 798°C
Arsenic, As: 817°C
Europium, Eu: 822°C
Ytterbium, Yb: 824°C
Calcium, Ca: 839°C
Einsteinium, Es: 860°C
Lanthanum, La: 920°C
Praseodymium, Pr: 931°C
Promethium, Pm: 931°C
Germanium, Ge: 938.3°C
Silver, Ag: 961°C
Berkelium, Bk: 986°C
Americium, Am: 994°C
Neodymium, Nd: 1016°C
Actinium, Ac: 1050°C
Gold, Au: 1064.58°C
Curium, Cm: 1067°C
Samarium, Sm: 1072°C
Copper, Cu: 1084.6°C
Uranium, U: 1132°C
Manganese, Mn: 1246°C
Beryllium, Be: 1278°C
Gadolinium, Gd: 1312°C
Terbium, Tb: 1357°C
Dysprosium, Dy: 1407°C
Silicon, Si: 1410°C
Nickel, Ni: 1453°C
Holmium, Ho: 1470°C
Cobalt, Co: 1495°C
Erbium, Er: 1522°C
Yttrium, Y: 1526°C
Iron, Fe: 1535°C
Scandium, Sc: 1539°C
Thulium, Tm: 1545°C
Palladium, Pd: 1552°C
Protactinium, Pa: 1600°C
Titanium, Ti: 1660°C
Lutetium, Lu: 1663°C

Thorium, Th: 1755°C
Platinum, Pt: 1772°C
Zirconium, Zr: 1852°C
Chromium, Cr: 1857°C
Vanadium, V: 1902°C
Rhodium, Rh: 1966°C
Technetium, Tc: 2200°C
Hafnium, Hf: 2227°C
Ruthenium, Ru: 2250°C
Boron, B: 2300°C
Iridium, Ir: 2443°C
Niobium, Nb: 2468°C
Molybdenum, Mo: 2617°C
Tantalum, Ta: 2996°C
Osmium, Os: 3027°C
Rhenium, Re: 3180°C
Tungsten, W: 3407°C
Carbon (diamond), C: 3550°C
Carbon (graphite), C: 3675°C
Carbon (amorphous), C: 3675

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List of elements by name

Actinium Ac
Aluminium (Aluminum) Al
Aluminum (Aluminium) Al
Americium Am
Antimony (Stibium) Sb
Argentum (Silver) Ag
Argon Ar
Arsenic As
Astatine At
Aurum (Gold) Au
Barium Ba
Berkelium Bk
Beryllium Be
Bismuth Bi
Bohrium Bh
Boron B
Bromine Br
Cadmium Cd
Caesium (Cesium) Cs
Calcium Ca
Californium Cf
Carbon C
Cerium Ce
Cesium (Caesium) Cs
Chlorine Cl
Chromium Cr
Cobalt Co
Copper (Cuprum) Cu
Curium Cm
Darmstadtium Ds
Dubnium Db
Dysprosium Dy
Einsteinium Es
Erbium Er
Europium Eu
Fermium Fm
Ferrum (Iron) Fe
Fluorine F
Francium Fr
Gadolinium Gd

Gallium Ga
Germanium Ge
Gold (Aurum) Au
Hafnium Hf
Hassium Hs
Helium He
Holmium Ho
Hydrargyrum (Mercury) Hg
Hydrogen H
Indium In
Iodine I
Iridium Ir
Iron (Ferrum) Fe
Kalium (Potassium) K
Krypton Kr
Lanthanum La
Lawrencium Lr
Lead (Plumbum) Pb
Lithium Li
Lutetium Lu
Magnesium Mg
Manganese Mn
Meitnerium Mt
Mendelevium Md
Mercury (Hydrargyrum) Hg
Molybdenum Mo
Natrium (Sodium) Na
Neodymium Nd
Neon Ne
Neptunium Np
Nickel Ni
Niobium Nb
Nitrogen N
Nobelium No
Osmium Os
Oxygen O
Palladium Pd
Plumbum (Lead) Pb
Phosphorus P
Platinum Pt
Plutonium Pu
Polonium Po
Potassium (Kalium) K

Praseodymium Pr
Promethium Pm
Protactinium Pa
Radium Ra
Radon Rn
Rhenium Re
Rhodium Rh
Roentgenium Rg
Rubidium Rb
Ruthenium Ru
Rutherfordium Rf
Samarium Sm
Scandium Sc
Seaborgium Sg
Selenium Se
Silicon Si
Silver (Argentum) Ag
Sodium (Natrium) Na
Stannum (Tin) Sn
Stibium (Antimony) Sb
Strontium Sr
Sulfur S
Tantalum Ta
Technetium Tc
Tellurium Te
Terbium Tb
Thallium Tl
Thorium Th
Thulium Tm
Tin (Stannum) Sn
Titanium Ti
Tungsten (Wolfram) W
Ununbium Uub
Ununhexium Uuh
Ununpentium Uup
Ununquadium Uuq
Ununtrium Uut
Uranium U
Vanadium V
Wolfram (Tungsten) W
Xenon Xe
Ytterbium Yb
Yttrium Y

Zinc Zn
Zirconium Zr

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List of elements by symbol

Ac Actinium
Ag Silver
Al Aluminium (Aluminum)
Am Americium
Ar Argon
As Arsenic
At Astatine
Au Gold
B Boron
Ba Barium
Be Beryllium
Bh Bohrium
Bi Bismuth
Bk Berkelium
Br Bromine
C Carbon
Ca Calcium
Cd Cadmium
Ce Cerium
Cf Californium
Cl Chlorine
Cm Curium
Co Cobalt
Cr Chromium
Cs Caesium (Cesium)
Cu Copper
Db Dubnium
Ds Darmstadtium
Dy Dysprosium
Er Erbium
Es Einsteinium
Eu Europium
F Fluorine
Fe Iron
Fm Fermium
Fr Francium
Ga Gallium
Gd Gadolinium
Ge Germanium
H Hydrogen

He Helium
Hf Hafnium
Hg Mercury
Ho Holmium
Hs Hassium
I Iodine
In Indium
Ir Iridium
K Potassium (Kalium)
Kr Krypton
La Lanthanum
Li Lithium
Lr Lawrencium
Lu Lutetium
Md Mendelevium
Mg Magnesium
Mn Manganese
Mo Molybdenum
Mt Meitnerium
N Nitrogen
Na Sodium
Nb Niobium
Nd Neodymium
Ne Neon
Ni Nickel
No Nobelium
Np Neptunium
O Oxygen
Os Osmium
P Phosphorus
Pa Protactinium
Pb Lead
Pd Palladium
Pm Promethium
Po Polonium
Pr Praseodymium
Pt Platinum
Pu Plutonium
Ra Radium
Rb Rubidium
Re Rhenium
Rf Rutherfordium
Rg Roentgenium

Rh Rhodium
Rn Radon
Ru Ruthenium
S Sulfur (Sulphur)
Sb Antimony
Sc Scandium
Se Selenium
Sg Seaborgium
Si Silicon
Sm Samarium
Sn Tin
Sr Strontium
Ta Tantalum
Tb Terbium
Tc Technetium
Te Tellurium
Th Thorium
Ti Titanium
Tl Thallium
Tm Thulium
U Uranium
Uub Ununbium
Uuh Ununhexium
Uup Ununpentium
Uuq Ununquadium
Uut Ununtrium
V Vanadium
W Tungsten
Xe Xenon
Y Yttrium
Yb Ytterbium
Zn Zinc
Zr Zirconium

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Standard enthalpy change of vaporization

The **standard enthalpy change of vaporization**, $\Delta_v H^o$, also (less correctly) known as the **heat of vaporization** is the energy required to transform a given quantity of a substance into a gas. It is measured at the boiling point of the substance, although tabulated values are usually corrected to 298K: the correction is small, and is often smaller than the uncertainty in the measured value. Values are usually quoted in kJ/mol, although kJ/kg, kcal/mol, cal/g and Btu/lb (obsolete) are also possible, among others.

The **standard enthalpy change of condensation** (or **heat of condensation**) is numerically exactly equal to the standard enthalpy change of vaporisation, but has the opposite sign: enthalpy changes of vaporisation are always positive (heat is absorbed by the substance), whereas enthalpy changes of condensation are always negative (heat is released by the substance).

The enthalpy change of vaporisation can be viewed as the energy required to overcome the intermolecular interactions in the liquid (or solid, in the case of sublimation). Hence helium has a particularly low standard enthalpy change of vaporisation, 0.0845kJ/mol, as the van der Waals forces between helium atoms are particularly weak. One the other hand, the molecules in liquid water are held together by relatively strong hydrogen bonds, and its standard enthalpy change of vaporisation, 40.8kJ/mol, is more than five times the energy required to heat the same quantity of water from 0°C to 100°C (c_p= 75.3JK^{-1}mol^{-1}). Care must be taken, however, when using enthaply changes of vaporization to *measure* the strength of intermolecular forces, as these forces may persist in the gas phase (as is the case with water), and so the calculated value of the bond strength will be too low. This is particularly true of metals, which often form covalently bonded molecules in the gas phase: in these cases, the standard enthalpy change of atomization must be used to obtain a true value of the bond energy.

An alternative description is to view the enthalpy change of condensation as the heat which must be released to the surroundings to compensate for the drop in entropy when a gas condenses to a liquid. As the liquid and gas are in equilibrium at the boiling point (T_b), $\Delta_v G$=0, which leads to:

$$\Delta_v S = S_{gas} - S_{liquid} = \Delta_v H/T_b$$

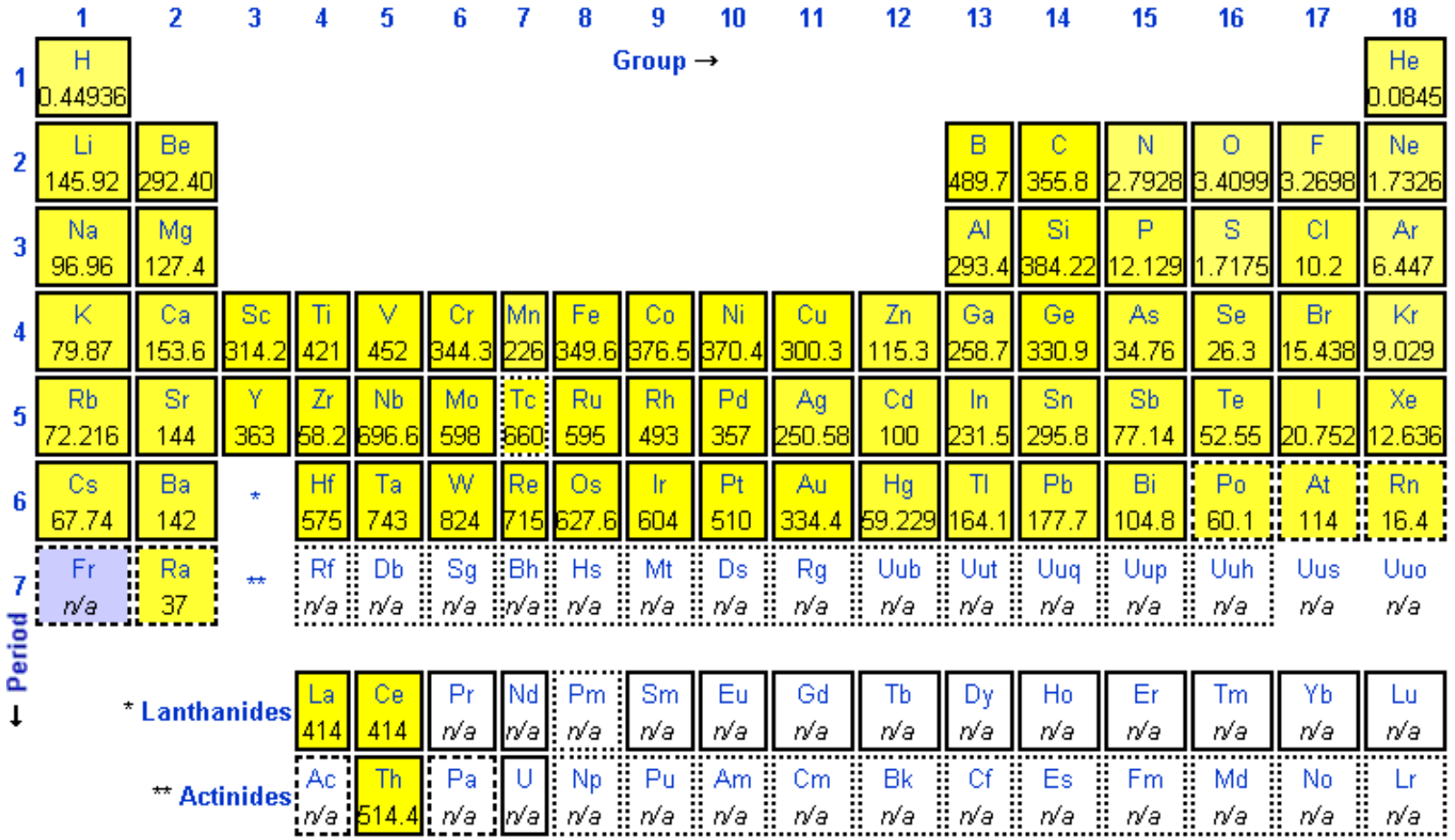
As neither entropy nor enthalpy vary greatly with temperature, it is normal to use the tabulated standard values without any correction for the difference in temperature from 298K. A correction must be made if the pressure is different from 100kPa, as the entropy of a gas is proportional to its pressure (or, more precisely, to its fugacity): the entropies of liquids vary little with pressure, as the compressibility of a liquid is small.

These two definitions are equivalent: the boiling point is the temperature at which the increased entropy of the gas phase overcomes the intermolecular forces. As a given quantity of matter always has a higher entropy in the gas phase than in a condensed phase ($\Delta_v S$ is always positive), and from

$$\Delta G = \Delta H - T\Delta S,$$

the Gibbs free energy change falls with increasing temperature: gases are favored at higher temperatures, as is observed in practice.

Standard enthalpy change of vaporization at 298 K:



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Standard enthalpy change of fusion

The **standard enthalpy change of fusion,** also known as the **heat of fusion,** is the amount of thermal energy which must be absorbed or lost for 1 gram of a substance to change states from a solid to a liquid or vice versa. It is also called the **latent heat of fusion** or the **enthalpy of fusion**, and the temperature at which it occurs is called the melting point.

When you withdraw thermal energy from a liquid or solid, the temperature falls. When you add heat energy the temperature rises. However, at the transition point between solid and liquid (the melting point), extra energy is required (the heat of fusion). To go from liquid to solid, the molecules of a substance must become more ordered. For them to maintain the order of a solid, extra heat must be withdrawn. In the other direction, to create the disorder from the solid crystal to liquid, extra heat must be added.

The heat of fusion can be observed if you measure the temperature of water as it freezes. If you plunge a closed container of room temperature water into a very cold environment (say -20 °C), you will see the temperature fall steadily until it drops just below the freezing point (0 °C). The temperature then rebounds and holds steady while the water crystalises. Once completely frozen, the temperature will fall steadily again.

The temperature stops falling at (or just below) the freezing point due to the heat of fusion. The energy of the heat of fusion must be withdrawn (the liquid must turn to solid) before the temperature can continue to fall.

The units of heat of fusion are usually expressed as:

- joules per mole (the SI units)
- calories per gram (old metric units now little used, except for a different, larger calorie used in nutritional contexts)
- British thermal units per pound or Btu per pound-mole

- Note: These are not the calories found in food. The calories found in food are more properly known as kilocalories-equal to 1000 calories. 1000 calories = 1 kilocalorie = 1 food calorie. Food calories are sometimes abbreviated as kcal as if small calories were being used, while calories are abbreviated as cal. Another distinguishing method, though often confusing, uses capitalisation. A Calorie is a food calorie, or 1000 calories. So 1 Cal = 1000 cal.

Values

The heat of fusion of water is: 79.72 calories per gram or 334.5 kilojoules per kilogram

The heat of fusion of a few more common substances in cal/g and (kJ/kg) in brackets:
methane: 13.96 (58.41)
ethane: 22.73 (95.10)
propane: 19.11 (79.96)
methanol: 23.70 (99.16)
ethanol: 26.05 (108.99)
glycerol: 47.95 (200.62)
formic acid: 66.05 (276.35)
acetic acid: 45.91 (192.09)
acetone: 23.42 (97.99)
benzene: 30.45 (127.40)
myristic acid: 47.49 (198.70)
palmitic acid: 39.18 (163.93)
stearic acid: 47.54 (198.91)

Application

To heat one kilogram (about 1 liter) of water 20 °C from 10 °C to 30 °C requires 20 kcal.
However, to melt ice and raise the resulting water temperature 20 °C requires extra energy. To heat ice from 0 °C to water at 20 °C requires:

(1) 80 cal/g (heat of fusion of ice) = 80 kcal for 1 kg
PLUS
(2) 1 cal/(g·°C) = 20 kcal for 1 kg to go up 20 °C
= 100 kcal

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Specific heat capacity

Specific heat capacity, also known simply as **specific heat** (Symbol: *C* or *c*) is the measure of the heat energy required to raise the temperature of a specific quantity of a substance (thus, the name "specific" heat) by certain amount, usually one kelvin. A kelvin is a unit increment of thermodynamic temperature and is precisely equal to an increment of one degree Celsius. Virtually any substance may have its specific heat capacity measured, including pure chemical elements, compounds, alloys, solutions, and composites.

Symbols and standards

When measuring specific heat capacity, the specified quantity of the substance can be in terms of either mass or *moles* (which is a certain number of atoms or molecules). When mass is the unit quantity, the symbol for specific heat capacity is lowercase *c*. When the mole is the unit quantity, the symbol is uppercase *C* (and it is also known as **molar heat capacity**). Alternatively-especially in chemistry as opposed to engineering-the uppercase version for specific heat, *C*, may be used in combination with the symbol for *enthalpy* (*H* or *h*) as a suffix. When the mole is the unit quantity, the enthalpy symbol is uppercase *H* and when mass is the unit quantity, the symbol is lowercase *h*.

The modern SI units for measuring specific heat capacity are either the *joule per gram per kelvin* ($Jg^{-1}K^{-1}$) or the *joule per mole per kelvin* ($Jmol^{-1}K^{-1}$). The various SI prefixes can create variations of these units (such as $kJkg^{-1}K^{-1}$ and $kJmol^{-1}K^{-1}$). Other units of measure are often employed in the measure of specific heat capacity. These include calories and BTUs for energy, pounds-mass for quantity, and degree Fahrenheit (°F) for the increment of temperature.

There are two distinctly different experimental conditions under which specific heat capacity is measured and these are denoted with a subscripted suffix modifying the symbols *C* or *c*. The specific heat of substances are typically measured under constant pressure (Symbols: C_p or c_p). However, fluids (gases and liquids) are typically also measured at constant volume (Symbols: C_v or c_v). Measurements under constant pressure produces greater values than those at constant volume because work must be performed in the former. This difference is particularly great in gases where values under constant pressure are typically 30% to 66.7% greater than those at constant volume

Thus, the symbols for specific heat capacity are as follows:

	Under constant pressure	At constant volume
Unit quantity = mole	C_p or C_pH	C_v or C_vH
Unit quantity = mass	c_p or C_ph	c_v or C_vh

The specific heat capacities of substances comprised of molecules (distinct from the monatomic gases) are not fixed constants and vary somewhat depending on temperature. Accordingly, the temperature at which the measurement is made is usually also specified. Examples of two common ways to cite the specific heat of a substance are as follows:

Water (liquid): $c_p = 4.1855\ \text{J g}^{-1}\ \text{K}^{-1}$ (15 °C), and

Water (liquid): $C_vH = 74.539\ \text{J mol}^{-1}\ \text{K}^{-1}$ (25 °C)

The pressure at which specific heat capacity is measured is especially important for gases and liquids. The standard pressure was once virtually always "one standard atmosphere" which is defined as the sea level-equivalent value of precisely 101.325kPa (760torr). In the case of water, 101.325kPa is still typically used due to water's unique role in temperature and physical standards. However, in 1985, the International Union of Pure and Applied Chemistry (IUPAC) recommended that for the purposes of specifying the physical properties of substances, "*the standard pressure*" should be defined as precisely 100kPa (750.062torr). Besides being a round number, this had a very practical effect: relatively few people live and work at precisely sea level; 100kPa equates to the mean pressure at an altitude of about 112 meters (which is closer to the 194-meter world-wide median altitude of human habitation). Accordingly, the pressure at which specific heat capacity is measured should be specified since one can not assume its value. An example of how pressure is specified is as follows:

Water (gas): $C_vH = 28.03\ \text{J mol}^{-1}\ \text{K}^{-1}$ (100°C, 101.325kPa)

Note in the above specification that the experimental condition is at constant volume. Still, the pressure within this fixed volume is controlled and specified.

Why different materials have different specific heat capacities

- Different substances have different molar masses: When the specific heat capacity, *c*, of a material

is measured (lowercase *c* means the unit quantity is in terms of mass), different values arise because different substances have different *molar masses* (essentially, the weight of the individual atoms or molecules). Heat energy arises, in part, due to the *number* of atoms or molecules that are vibrating. If a substance has a lighter molar mass, then each gram of it has more atoms or molecules available to store heat energy. This is why hydrogen-the lightest substance there is-has such a high specific heat capacity on a gram basis; one gram of it contains a relatively great many molecules. If specific heat capacity is measured on a *molar* basis (uppercase *C),* the differences between substances is less pronounced and hydrogen's molar heat capacity is quite unremarkable.

- **Molecular-based substances have more degrees of freedom:** Molecules are quite different from the monatomic gases like helium and argon. With monatomic gases, heat energy is comprised only of *translational* motions. Translational motions are ordinary, whole-body movements in 3D space whereby particles move about and exchange energy in collisions (like rubber balls in a vigorously shaken container). These simple movements in the three X, Y, and Z-axis dimensions of space means monatomic atoms have three translational *degrees of freedom.* Molecules, however, have various *internal* vibrational and rotational degrees of freedom because they are complex objects; they are a population of atoms that can move about within a molecule in different ways. Heat energy is stored in these internal motions. Water for instance, can absorb a large amount of heat energy per mole with only a modest temperature change because it has *six* active degrees of freedom, the maximum available. Not surprisingly, water gas molecules (steam molecules) have twice the specific heat capacity per mole as do the monatomic gases which move only within the six degrees of freedom comprising translational motion. See *Thermodynamic temperature* for more on translational motions, kinetic (heat) energy, and their relationship to temperature.

- **Some materials have hydrogen bonds:** Hydrogen-containing molecules like ethanol, ammonia, and water have powerful, intermolecular *hydrogen bonds* when in their liquid phase. These bonds provide yet another place where kinetic (heat) energy is stored.

Equations

- The equation relating heat energy to specific heat capacity, where the unit quantity is in terms of mass is:
$Q = m\,c\,\Delta T$ where Q is the heat energy put into or taken out of the substance, m is the mass of the substance, c is the specific heat capacity, and ΔT is the temperature differential.
- Where the unit quantity is in terms of moles, the equation relating heat energy to specific heat capacity (also known as *molar heat capacity*) is
$Q = n\,C\,\Delta T$ where Q is the heat energy put into or taken out of the substance, n is the number moles, C is the specific heat capacity, and ΔT is the temperature differential.

Table of specific heat capacities in J g-1 K-1 and [J mol-1 K-1]

Air (Sea level, dry, 0 °C) (gas)1.0035 [29.07]
Air (typical room conditions*) (gas) 1.012 [29.19]

Aluminium (solid) 0.897 [24.2]
Ammonia(liquid) 4.700 [80.08]
Argon (gas) 0.5203 [20.7862]
Beryllium (solid) 1.82 [16.4]
Copper (solid) 0.385 [24.47]
Diamond (solid) 0.5091 [6.115]
Ethanol (liquid) 2.44 [112]
Gold (solid) 0.1291 [25.42]
Graphite (solid) 0.710 [8.53]
Helium (gas) 5.1932 [20.7862]
Hydrogen (gas) 14.30 [28.82]
Iron (solid) 0.450 [25.1]
Lithium (solid) 3.58 [24.8]
Mercury (liquid) 0.1395 [27.98]
Nitrogen (gas) 1.040 [29.12]
Neon (gas) 1.0301 [20.7862]
Oxygen (gas) 0.918 [29.38]
Silica (fused) (solid) 0.703 [42.2]
Uranium (solid) 0.116 [27.7]
Water (gas) (100 °C)2.080 [37.47]
Water (liquid) (25 °C)4.1813 [75.327]
Water (solid) (0 °C)2.114 [38.09]

*Assuming an altitude of 194 meters above mean sea level (the world-wide median altitude of human habitation), an indoor temperature of 23 °C, a dewpoint of 9 °C (40.85% relative humidity), and 760 mm-Hg sea level-corrected barometric pressure (molar water vapor content = 1.16%).

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Powers of 10 prefixes

Factor Prefix Symbol

- 10^{24} yotta Y
- 10^{21} zetta Z
- 10^{18} exa E
- 10^{15} peta P
- 10^{12} tera T
- 10^{9} giga G
- 10^{6} mega M
- 10^{3} kilo k
- 10^{2} hecto h
- 10^{1} deka da
- 10^{-1} deci d
- 10^{-2} centi c
- 10^{-3} milli m
- 10^{-6} micro µ
- 10^{-9} nano n
- 10^{-12} pico p
- 10^{-15} femto f
- 10^{-18} atto a
- 10^{-21} zepto z
- 10^{-24} yocto y

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International System of Units

The **International System of Units** (abbreviated **SI** from the French language name *Système international d'unités*) is the modern form of the metric system. It is the world's most widely used system of units, both in everyday commerce and in science.

The older metric system included several groupings of units. The SI was developed in 1960 from the metre-kilogram-second (mks) system, rather than the centimetre-gram-second (cgs) system which, in turn, had many variants.

The SI introduced several newly named units. The SI is not static; it is a living set of standards where units are created and definitions are modified with international agreement as measurement technology progresses.

With few exceptions, the system is used in every country in the world, and many countries do not maintain official definitions of other units. In the United States, industrial use of SI is increasing, but popular use is still limited. In the United Kingdom, conversion to metric units is official policy but not yet complete. Those countries that still recognize non-SI units (e.g. the U.S. and UK) have redefined their traditional non-SI units in terms of SI units.

Units

The international system of units consists of a set of units together with a set of prefixes. The units of SI can be divided into two subsets. There are the seven base units. Each of these base units are nominally dimensionally independent. From these seven base units several other units are derived.

metre **m** Length
kilogram **kg** Mass
second **s** Time
ampere **A** Electrical current
kelvin **K** Thermodynamic temperature
mole **mol** Amount of substance
candela **cd** Luminous intensity

A prefix may be added to units to produce a multiple of the original unit. All multiples are integer powers of ten. For example, *kilo-* denotes a multiple of a thousand and *milli-* denotes a multiple of a thousandth hence there are one thousand millimetres to the metre and one thousand metres to the kilometre. The prefixes are **never** combined: a millionth of a kilogram is a *milligram* not a *microkilogram*.

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SI writing style

- Symbols are written in lower case, except for symbols derived from the name of a person. For example, the unit of pressure is named after Blaise Pascal, so its symbol is written "Pa" whereas the unit itself is written "pascal".
- The one exception is the litre, whose original symbol "l" is unsuitably similar to the numeral "1", at least in many English-speaking countries. The American National Institute of Standards and Technology recommends that "L" be used instead, a usage which is common in the U.S., Canada and Australia (but not elsewhere). This has been accepted as an alternative by the CGPM in 1979. The cursive l is occasionally seen, especially in Japan, but this is not currently recommended by any standards body.

- Abbreviated symbols, unlike spelled-out full names of units, should not be pluralized-for example "25 kg", not "25 kgs"-though they sometimes are. For spelled-out unit names in English, all are made plural by adding an 's', *except* lux, hertz, and siemens, all of which are the same in singular and plural.

- In the SI international system of units there should never be a period after or inside the unit, i.e. both 10 k.m. and 10 k.m are wrong - the only correct form is 10 km (only followed with a period when at the end of a sentence).

- It is preferable to write symbols in upright Roman type (m for metres, L for litres), so as to differentiate from the italic type used for mathematical variables (*m* for mass, *l* for length).

- A space should separate the number and the symbol, e.g. "2.21 kg", "7.3x10^2 m^2", "22 °C". Exceptions are the symbols for plane angular degrees, minutes and seconds (°,'and"), which are placed immediately after the number with no intervening space.

- Spaces may be used to group decimal digits in threes, e.g. 1 000 000 or 342142 (in contrast to the commas or dots used in other systems, e.g. 1,000,000 or 1.000.000). This is presumably to reduce confusion. In print, the space used for this purpose is typically narrower than that between words.

- The 10th resolution of CGPM in 2003 declared that "the symbol for the decimal marker shall be either the point on the line or the comma on the line". In practice, the decimal point is used in English, and the comma in most other European languages.

- Symbols for derived units formed from multiple units by multiplication are joined with a space or centre dot (·), e.g. N m or N·m.

- Symbols formed by division of two units are joined with a solidus (/), or given as a negative exponent. For example, the "metre per second" can be written "m/s", "ms^{-1}", "$m \cdot s^{-1}$" or $\frac{m}{s}$. A solidus should not be used if the result is ambiguous, i.e. "$kg \cdot m^{-1} \cdot s^{-2}$" is preferable to "$kg/m \cdot s^2$".

- In countries using ideographic writing systems such as Chinese and Japanese, often the full symbol for

the unit, including prefixes, is placed in one square.

Spelling variations

- Several nations, notably the United States, typically use the spellings 'meter' and 'liter' instead of 'metre' and 'litre' in keeping with standard American English spelling. In addition, the official US spelling for the SI prefix 'deca' is 'deka'.

- The unit 'gram' is often spelled 'gramme' outside of the United States.

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United States customary units

Units of length

1 inch (in) = 25.4 mm
1 foot (ft) = 12 in = 30.48 cm
1 yard (yd) = 3 ft = 91.44 cm
1 mile (mi) = 5,280 ft = 1.609 344 km

Units of area

1 square inch (sq in) = 6.451 6 cm^2
1 square foot (sq ft) = 144 sq in = 929.030 4 cm^2
1 square yard (sq yd) = 9 sq ft = 8,361.273 6 cm^2
1 square mile (sq mi) = 3,097,600 sq yd = 2.589988110336 km^2

Units of capacity and volume

Volume in general

1 cubic inch (cu in) = = 16.387 064 mL
1 cubic foot (cu ft) = 1 728 cu in = 28.316 846 592 L
1 cubic yard (cu yd) = 27 cu ft = 764.554 857 984 L

Liquid volume

1 minim (min) = = 0.061 611 52 mL
1 fluid dram (fl dr) = 60 min = 3.696 691 mL
1 **fluid ounce (fl oz)** = 8 fl dr = 29.573 53 mL
1 gill (gi) = 4 **fl oz** = 118.294 1 mL
1 **cup (cp) or (c)** = 8 **fl oz** = 236.588 2 mL
1 (liquid) **pint (pt)** = 4 gi = 16 **fl oz** = 473.176 5 mL
1 (liquid) **quart (qt)** = 2 **pt** = 32 **fl oz** = 946.352 9 mL
1 **gallon (gal)** = 4 **qt** =128 **fl oz** =231 **in^3** = 3.785 412 L

Dry volume

1 (dry) pint (pt) = 33.6003125 cu in (exactly) = 550.610 5 mL
1 (dry) quart (qt) = 2 pt = 1.101 221 L
1 (dry) gallon = 4 qt = 4.404 884 L

1 peck (pk) = 2 (dry) gallons = 8.809 768 L
1 bushel (bu) = 4 pk = 35.239 07 L

Units of mass

1 ounce (oz) = 28.349 523 125 g
1 pound (lb) = 16 oz = 453.592 37 g
1 hundredweight (cwt) = 100 lb = 45.359 237 kg
1 (short) ton = 20 cwt = 907.184 74 kg

Cooking measures

1 teaspoon (tsp) = = 5 mL
1 tablespoon (tbsp) = 3 tsp = 15 mL
1 cup = 16 tbsp = 240 mL
1 stick = 4 oz = 115 g

Grain measures

- 1 bushel (maize) = 56 lb = 25.401 kg
- 1 bushel (wheat) = 60 lb = 27.216 kg

Units of temperature

Fahrenheit to Celsius: °C = (°F - 32) / 1.8
Celsius to Fahrenheit: °F = (°C) × 1.8 + 32

- Pure water freezes at 32 °F and boils at 212 °F at 1 atm.
- Water saturated with common salt freezes at -6.02 °F.

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Covalent bond

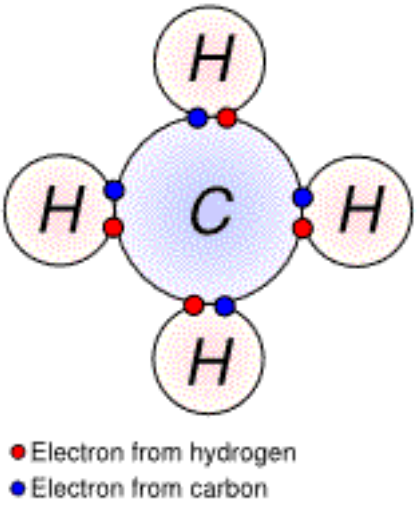
History | Bond Polarity | Bond order | Coordinate covalent bonds | Resonance | Current theory

Covalent bonding is an intramolecular form of chemical bonding characterized by the sharing of one or more pairs of electrons between two components, producing a mutual attraction that holds the resultant molecule together. Atoms tend to share electrons in such a way that their outer electron shells are filled. Such bonds are always stronger than the intermolecular hydrogen bond and similar in strength to or stronger than the ionic bond.

In contrast to the ionic and metalic bond, the covalent bond is directional. I.e. the bond angles have a great impact on the strength of the bond. Because of the directional character of the bond, covalently bound materials are more difficult to deform than metals. The cause of the directionallity is the form of the S, P, and SP-hybrid orbitals.

Covalent bonding most frequently occurs between atoms with similar electronegativities. For this reason, non-metals tend to engage in covalent bonding more readily since metals have access to metallic bonding, where the easily-removed electrons are more free to roam about. For non-metals, liberating an electron is more difficult, so sharing is the only option when confronted with another species of similar electronegativity.

However, covalent bonding involving metals is particularly important, especially in industrial catalysis and process chemistry. Many polymerization techniques require catalysis involving metal-organic covalent bonds. In their more useful applications, metals often engage in more exotic covalent bonding, such as those between a metal and the σ bond of molecular hydrogen, or between a metal and the π bond of an alkane or alkene.



Covalently bonded hydrogen and carbon in a molecule of methane. One way of representing covalent bonding in a molecule is with a dot and cross diagram.

History

The idea of covalent bonding can be traced to Gilbert N. Lewis, who in 1916 described the sharing of electron pairs between atoms. He introduced the so called *Lewis Notation* or *Electron Dot Notation* in which valence electrons (those in the outer shell) are represented as dots around the atomic symbols. Pairs of electrons located between atoms represent covalent bonds. Multiple pairs represent multiple bonds, such as double and triple bonds. Some examples of Electron Dot Notation are shown in the following figure. An alternative form, in which bond-forming electron pairs are represented as solid lines, is shown alongside.

While the idea of shared electron pairs provides an effective qualitative picture of covalent bonding, quantum mechanics is needed to understand the nature of these bonds and predict the structures and properties of simple molecules. Walter Heitler and Fritz London are credited with the first successful quantum mechanical explanation of a chemical bond, specifically that of molecular hydrogen, in 1927. Their work was based on the valence bond model, which assumes that a chemical bond is formed when there is good overlap between the atomic orbitals of participating atoms. These atomic orbitals are known to have specific angular relationships between each other, and thus the valence bond model can successfully predict the bond angles observed in simple molecules.

Bond Polarity

There are two types of covalent bonds: Polar covalent bonds, and non-polar (or pure) covalent bonds. The most widely-accepted definition of polar covalence is the occurrence of the atoms involved of an electronegativity difference less than 1.67 (though some texts read 1.7), but greater than zero. A pure covalent bond is a bond that occurs when the atoms involved have an electronegativity difference of zero (though some texts read less than 0.2).

Pure covalent bonds (which are usually non-soluble, are electrically non-conductive, and tend to exist as individual molecules), and ionic bonds (which are soluble, are electrically conductive when molten or in solution, and, in general, tend to exist in a crystalline form) are on two opposite ends of the spectrum and have different properties. Polar covalent bonds fall in the middle and have properties of both.

Bond order

Bond order is a term that describes the number of pairs of electrons shared between atoms forming a covalent bond.

1) The most common type of covalent bond is the **single bond**, sharing only one pair of electrons between two atoms. It usually consists of one sigma bond.

All bonds with more than one shared pair are called **multiple covalent bonds**.

2) Sharing two pairs is called a **double bond**. An example is in ethylene (between the carbon atoms). It usually consists of one sigma bond and one pi bond.

3) Sharing three pairs is called a **triple bond**. An example is in hydrogen cyanide (between C and N). It usually consists of one sigma bond and two pi bonds.

4) Quadruple bonds, though rare, exist. Both carbon and silicon can theoretically form these; however, the formed molecules are explosively unstable. Stable quadruple bonds are observed as transition metal-metal bonds, usually between two transition metal atoms in organometallic compounds. Molybdenum and Ruthenium are the elements most commonly observed with this bonding configuration. An example of a quadruple bond is also found in Di-tungsten tetra(hpp).

5) Quintuple bonds are found to exist in certain chromium dimers.

6) Sextuple bonds, of order 6, have also been observed in transition metals in the gaseous phase at very low temperatures and are extremely rare.

Other more exotic bonds, such as three center bonds are known and defy the conventions of bond order. It is also important to note that bond order is an integer value only in the elementary sense and is often fractional in more advanced contexts.

Coordinate covalent bonds

A special case is called a dative covalent bond, also known as a coordinate covalent bond, which occurs when one atom gives both of the electrons in the bond.

Resonance

Some structures can have more than one valid Lewis Dot Structure (for example, ozone, O_3). In an LDS diagram of O_3, the center atom will have a single bond with one atom and a double bond with the other. The LDS diagram cannot tell us which atom has the double bond; the first and second adjoining atoms have equal chances of having the double bond. These two possible structures are called resonance structures. In reality, the structure of ozone is a **resonance hybrid** between its two possible resonance structures. Instead of having one double bond and one single bond, there are actually two 1.5 bonds with approximately three electrons in each at all times.

A special resonance case is exhibited in aromatic rings of atoms (for example, benzene). Aromatic rings are composed of atoms arranged in a circle (held together by covalent bonds) that alternate between single and double bonds according to their LDS. In actuality, the electrons tend to be disambiguously and evenly spaced within the ring. Electron sharing in aromatic structures is often represented with a

ring inside the circle of atoms.

Current theory

Today the valence bond model has been supplemented with the molecular orbital model. In this model, as atoms are brought together, the *atomic* orbitals interact to form **hybrid** *molecular* orbitals. These molecular orbitals are a cross between the original atomic orbitals and generally extend between the two bonding atoms.

Using quantum mechanics it is possible to calculate the electronic structure, energy levels, bond angles, bond distances, dipole moments, and frequency spectra of simple molecules with a high degree of accuracy. Currently, bond distances and angles can be calculated as accurately as they can be measured (distances to a few pm and bond angles to a few degrees). For small molecules, energy calculations are sufficiently accurate to be useful for determining thermodynamic heats of formation and kinetic activation energy barriers.

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Hydrogen bond

Hydrogen bond in water | Hydrogen bond in proteins and DNA | Symmetric hydrogen bond | Dihydrogen bond | Advanced theory of the hydrogen bond

In chemistry, a hydrogen bond is a type of attractive intermolecular force that exists between two partial electric charges of opposite polarity. Although stronger than most other intermolecular forces, the typical hydrogen bond is much weaker than both the ionic bond and the covalent bond. Within macromolecules such as proteins and nucleic acids, it can exist between two parts of the same molecule, and figures as an important constraint on such molecules' overall shape.

As the name "hydrogen bond" implies, one part of the bond involves a hydrogen atom. The hydrogen must be attached to a strongly electronegative heteroatom, such as oxygen, nitrogen or fluorine, which is called the hydrogen-bond *donor*. This electronegative element attracts the electron cloud from around the hydrogen nucleus and, by decentralizing the cloud, leaves the atom with a positive partial charge. Because of the small size of hydrogen relative to other atoms and molecules, the resulting charge, though only partial, nevertheless represents a large charge density. A hydrogen bond results when this strong positive charge density attracts a lone pair of electrons on another heteroatom, which becomes the hydrogen-bond *acceptor*.

The hydrogen bond is not like a simple attraction between point charges, however. It possesses some degree of orientational preference, and can be shown to have some of the characteristics of a covalent bond. This covalency tends to be more extreme when acceptors bind hydrogens from more electronegative donors.

Strong covalency in a hydrogen bond raises the questions: "To which molecule or atom does the hydrogen nucleus belong?" and "Which should be labelled 'donor' and which 'acceptor'?" According to chemical convention, the donor generally is that atom to which, on separation of donor and acceptor, the retention of the hydrogen nucleus (or proton) would cause no increase in the atom's positive charge. The acceptor meanwhile is the atom or molecule that would become more positive by retaining the positively charged proton. Liquids that display hydrogen bonding are called **associated liquids**.

Hydrogen bonds can vary in strength from very weak (1-2 kJ mol^{-1}) to so strong (40 kJ mol^{-1}) so as to be indistinguishable from a covalent bond, as in the ion HF_2^-. Typical values include:

- O-H···:N (7 kcal/mol)
- O-H···:O (5 kcal/mol)
- N-H···:N (3 kcal/mol)
- N-H···:O (2 kcal/mol)

The length of hydrogen bonds depends on bond strength, temperature and pressure. The typical length of a hydrogen bond in water is 197 pm (1.97 Angstrom).

Hydrogen bond in water

The most ubiquitous, and perhaps simplest, example of a hydrogen bond is found between water molecules. In a discrete water molecule, water has two hydrogen atoms and one oxygen atom. Two molecules of water can form a hydrogen bond between them; the simplest case, when only two molecules are present, is called the water dimer and is often used as a model system. When more molecules are present, as is the case in liquid water, more bonds are possible because the oxygen of one water molecule has two lone pairs of electrons, each of which can form a hydrogen bond with hydrogens on two other water molecules. This can repeat so that every water molecule is H-bonded with up to four other molecules (two through its two lone pairs, and two through its two hydrogen atoms.)

Liquid water's high boiling point is due to the high number of hydrogen bonds each molecule can have relative to its low molecular mass. Water is unique because its oxygen atom has two lone pairs and two hydrogen atoms, meaning that the total number of bonds of a water molecule is up to four. For example, hydrogen fluoride - which has three lone pairs on the F atom but only one H atom - can have a total of only two bonds (ammonia has the opposite problem: three hydrogen atoms but only one lone pair).

H-F···H-F···H-F

The exact number of hydrogen bonds in which a molecule in liquid water participates fluctuates with time and depends on the temperature. From TIP4P liquid water simulations at 25 °C, it was estimated that each water molecule participates in an average of 3.59 hydrogen bonds. At 100 °C, this number decreases to 3.24 due to the increased molecular motion and decreased density, while at 0 °C, the average number of hydrogen bonds increases to 3.69. A more recent study found a much smaller number of hydrogen bonds: 2.357 at 25 °C. The differences may be due to the use of a different method for defining and counting the hydrogen bonds.

Were the bond strengths more equivalent, one might instead find the atoms of two interacting water molecules partitioned into two polyatomic ions of opposite charge, specifically hydroxide (OH^-) and hydronium (H_3O^+) (Hydronium ions are also known as 'hydroxonium' ions.)

$H\text{-}O^-$ H_3O^+

Indeed, in pure water under conditions of standard temperature and pressure, this latter formulation is applicable only rarely; on average about one in every 5.5×10^8 molecules gives up a proton to another water molecule, in accordance with the value of the dissociation constant for water under such conditions. It is a crucial part of uniqness of water

Hydrogen bond in proteins and DNA

Hydrogen bonding also plays an important role in determining the three-dimensional structures adopted by proteins and nucleic bases. In these macromolecules, bonding between parts of the same macromolecule cause it to fold into a specific shape, which helps determine the molecule's physiological or biochemical role. The double helical structure of DNA, for example, is due largely to hydrogen bonding between the base pairs, which link one complementary strand to the other and enable replication.

In proteins, hydrogen bonds form between the backbone oxygens and amide hydrogens. When the spacing of the amino acid residues participating in a hydrogen bond occurs regularly between positions *i* and *i*+4, an alpha helix is formed. When the spacing is less, between positions *i* and *i*+3, then a 3_{10} helix is formed. When two strands are joined by hydrogen bonds involving alternating residues on each participating strand, a beta sheet is formed. Hydrogen bondings also play a part in forming the tertiary structure of protein through interaction of R-groups.

Symmetric hydrogen bond

Symmetric hydrogen bonds have been observed recently spectroscopically in formic acid at high pressure (>GPa). Each hydrogen atom forms a partial covalent bond with two atoms rather than one. Symmetric hydrogen bonds have been postulated in ice at high pressure (ice-X).

Dihydrogen bond

The hydrogen bond can be compared with the closely related dihydrogen bond, which is also an intermolecular bonding interaction involving hydrogen atoms. These structures have been known for some time, and well characterized by crystallography; however, an understanding of their relationship to the conventional hydrogen bond, ionic bond, and covalent bond remains unclear. Generally, the hydrogen bond is characterized by a proton acceptor that is a lone pair of electrons in nonmetallic atoms (most notably in the nitrogen, and chalcogen groups). In some cases, these proton acceptors may be pi-bonds or metal complexes. In the dihydrogen bond, however, a metal hydride serves as a proton acceptor; thus forming a hydrogen-hydrogen interaction. Neutron diffraction has shown that the molecular geometry of these complexes are similar to hydrogen bonds, in that the bond length is very adaptable to the metal complex/hydrogen donor system.

Advanced theory of the hydrogen bond

The hydrogen bond remains a fairly mysterious object in the theoretical study of quantum chemistry and physics. Most generally, the hydrogen bond can be viewed as a metric dependent electrostatic scalar field between two or more intermolecular bonds. This is slightly different than the intramolecular bound states of, for example, covalent or ionic bonds; however, hydrogen bonding is generally still a bound

state phenomenon, since the interaction energy has a net negative sum. The question of the relationship between the covalent bond and the hydrogen bond remains largely unsettled, though the initial theory proposed by Linus Pauling suggests that the hydrogen bond has a partial covalent nature. While a lot of experimental data has been recovered for hydrogen bonds in water, for example, that provide good resolution on the scale of intermolecular distances and molecular thermodynamics, the kinetic and dynamical properties of the hydrogen bond in dynamic systems remains largely mysterious.

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Hydrophobic forces

Hydrophobic forces are not actually bonds, so this list has four items, but still just three bond types. In a way hydrophobic forces are the negation of the hydrogen bonds of a polar solute, usually water, enclosing a nonpolar molecule. For a polar solute like water, it is energetically unfavourable to "waste" a possible hydrogen bond by exposing it towards a nonpolar molecule. Thus, water will arrange itself around any nonpolar molecule in such a way that no hydrogen bonds point towards that molecule. This results in a higher order, compared to "freely" moving water, which leads to a lower entropy level and is thus energetically unfavourable. If there is more than one nonpolar molecule in the solute, it is favourable for the nonpolar molecules to aggregate in one place, reducing their surrounding, ordered "shell" of water to a minimal surface. Also, in large molecules, such as proteins, the hydrophobic (nonpolar) parts of the molecule will tend to turn towards the inside, while the polar parts will tend to turn towards the surface of the molecule.

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Ionic bond

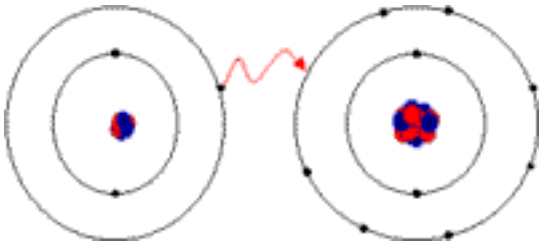
Polarization effects | Ionic Structure | Ionic versus covalent bonds

Ionic bonds are a type of chemical bond based on electrostatic forces between two oppositely-charged ions. In ionic bond formation, a metal donates an electron, due to a low electronegativity to form a positive ion or cation. In ordinary table salt, the bonds between the sodium and chlorine ions are ionic bonds. Often ionic bonds form between metals and non-metals. The non-metal atom has an electron configuration just short of a noble gas structure. They are electronegative, and so readily gain electrons to form negative ions or anions. The two or more ions are then attracted to each other by electrostatic forces. Such bonds are stronger than hydrogen bonds, but similar in strength to covalent bonds.

$$\begin{aligned} Li + F &\rightarrow Li^+F^- \\ 3Na + P &\rightarrow Na_3^+P^{3-} \end{aligned}$$

Ionic bonding occurs only if the overall energy change for the reaction is favourable when the bonded atoms have a lower energy than the free ones. The larger the resulting energy change the stronger the bond.

Pure ionic bonding is not known to exist. All ionic bonds have a degree of covalent bonding or metallic bonding. The larger the difference in electronegativity between two atoms the more ionic the bond. Ionic compounds conduct electricity when molten or in solution. They generally have a high melting point and tend to be soluble in water.



Electron configurations of lithium and fluorine. Lithium has one electron in its outer shell, held rather loosely because the ionisation energy is low. Fluorine carries 7 electrons in its outer shell. When one electron moves from lithium to fluorine, each ion acquires the noble gas configuration. The bonding energy from the electrostatic attraction of the two oppositely-charged ions has a large enough negative value that the overall bonded state energy is lower than the unbonded state

Polarization effects

Ions in crystal lattices of purely ionic compounds are spherical, but, if the positive ion is small and/or highly charged, it will distort the electron cloud of the negative ion. This polarization of the negative ion leads to a build-up of extra charge density between the two nuclei, i.e., to partial covalency. Larger

negative ions are more easily polarized, but the effect is usually only important when positive ions with charges of 3+ (e.g., Al^{3+}) are involved (e.g., pure $AlCl_3$ is a covalent molecule). However, 2+ ions (Be^{2+}) or even 1+ (Li^{+}) show some polarizing power because their sizes are so small (e.g., LiI is ionic but has some covalent character). The **Polarizing Power** depends on the ratio of charge and size of the ion, often called the **charge density**.

Ionic Structure

Ionic compounds in the solid state form a continuous ionic lattice structure in an ionic crystal. When all the ions are approximately the same size, they can form a structure that is face-centered cubic, but, when the ions are different sizes, the structure is often body-centered cubic. In ionic lattices the coordination number refers to the number of ions that each is connected, too.

Ionic versus covalent bonds

In an ionic bond, the atoms are bound by attraction of opposite ions, whereas, in a covalent bond, atoms are bound by sharing electrons. In covalent bonding, the molecular geometry around each atom is determined by VSEPR rules, whereas, in ionic materials, the geometry follows maximum packing rules. **Thus**, a compound can be classified as ionic or covalent based on the **geometry of the atoms**.

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Non-covalent bonds

Ionic bonds | Hydrogen bonds | Van der Waals attractions | Hydrophobic forces

The destruction of covalent bonds takes up huge amounts of energy. The breakdown of an O_2 molecule into two oxygen atoms needs ~460 kJ mol^{-1}. Thus, nowhere in "living" biochemistry are covalent bonds actually destroyed; if one is broken, another one is created. Nonetheless, many biochemical functions are using so-called weak/secondary/non-covalent bonds.

Weak bonds are created and destroyed much more easily than covalent ones. The typical range of energy needed to destroy such a weak bond is 4-30 kJ mol^{-1}. Thus, the formation of weak bonds is energetically favorable, but these bonds are also easily broken by kinetic (thermal) energy (the normal movement of molecules). Biochemical interactions are often temporary (e.g., a substrate has to leave an enzyme quickly after being processed), for which the weakness of these bonds is essential. Also, biochemical specificity (e.g., enzyme-substrate-recognition) is achieved through weak bonds, utilizing two of their major properties:

- Since individual weak bonds are, well, weak, several of them have to occur in a specific pattern at the same time in roughly the same place.

- The short range of weak bonds.

There are three basic types of weak bonds, and a fourth "pseudo-bond":

Ionic bonds

Ionic bonds are electrostatic attractions between permanently charged groups. Ionic bonds are not directed. Example:

$$X\text{-}CO_2^- \cdots H_3^+N\text{-}Y$$

~ 20 kJ mol^{-1}

Hydrogen bonds

Hydrogen bonds are also established by electrostatic attraction, though not between permanently charged groups, but rather between atoms temporarily charged by a *dipole moment*, resulting from the different electronegativity of atoms within a group. Hydrogen bonds are even weaker than ionic bonds, and they are highly directional, usually along a straight line. The most common hydrogen bonds in biochemistry are:

X-OH ····· O-Y
X-OH ····· N-Y
X-NH ····· O-Y
X-NH ····· N-Y

Hydrogen bonds equal an energy between 12-29 kJ mol^{-1}

Van der Waals attractions

Van der Waals attractions are established between electron density-induced dipoles. They form when the outer electron shells of two atoms *almost* (but not quite) touch. The distance of the atoms is very important for these weak interactions. If the atoms are too far apart, the interactions are too weak to establish; if the atoms are too close to each other, their electron shells will repell each other. Van der Waals attractions are highly unspecific; they can occur between virtually any two atoms. Their energy is between 4-8 kJ mol^{-1}.

Hydrophobic forces

Hydrophobic forces are not actually bonds, so this list has four items, but still just three bond types. In a way hydrophobic forces are the negation of the hydrogen bonds of a polar solute, usually water, enclosing a nonpolar molecule. For a polar solute like water, it is energetically unfavourable to "waste" a possible hydrogen bond by exposing it towards a nonpolar molecule. Thus, water will arrange itself around any nonpolar molecule in such a way that no hydrogen bonds point towards that molecule. This results in a higher order, compared to "freely" moving water, which leads to a lower entropy level and is thus energetically unfavourable. If there is more than one nonpolar molecule in the solute, it is favourable for the nonpolar molecules to aggregate in one place, reducing their surrounding, ordered "shell" of water to a minimal surface. Also, in large molecules, such as proteins, the hydrophobic (nonpolar) parts of the molecule will tend to turn towards the inside, while the polar parts will tend to turn towards the surface of the molecule.

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Hydrophile

Hydrophile, from the Greek *(hydros)* "water" and *(philia)* "friendship," refers to a physical property of a molecule that can transiently bond with water (H_2O) through hydrogen bonding. This is thermodynamically favorable, and makes these molecules soluble not only in water, but also in other polar solvents.

A hydrophilic molecule or portion of a molecule is one that is typically charge-polarized and capable of hydrogen bonding, enabling it to dissolve more readily in water than in oil or other hydrophobic solvents. Hydrophilic and hydrophobic molecules are also known as polar molecules and nonpolar molecules, respectively.

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Hydrophobe

Hydrophobe (from the Greek *(hydros)* "water" and *(phobos)* "fear") in chemistry refers to the physical property of a molecule that is repelled by water. Hydrophobic molecules in water often cluster together.

Hydrophobic or **lipophilic** species, or hydrophobes, tend to be electrically neutral and nonpolar, and thus prefer other neutral and nonpolar solvents or molecular environments. *Hydrophobic* is often used interchangeably with "oily" or "lipophilic."

The term **hydrophobic interaction** (**HI**) has been used in the context of several closely-related phenomena to hydrophobic species.

According to thermodynamics, matter seeks to be in a low-energy state, and bonding reduces chemical energy. Water is electrically polarized, and is able to form hydrogen bonds internally, which gives it many of its unique physical properties. But, since hydrophobes are not electrically polarized, and because they are unable to form hydrogen bonds, water repels hydrophobes, in favour of bonding with itself. It is this effect that causes the hydrophobic interaction - which in itself is incorrectly named as the energetic force comes from the hydrophilic molecules. Thus the two immiscible phases (hydrophilic vs. hydrophobic) will change so that their corresponding interfacial area will be minimal. This effect can be visualized in the phenomenon called phase separation.

Examples of **hydrophobic** molecules include the alkanes, oils, fats, and greasy substances in general. Hydrophobic materials are used for oil removal from water, the management of oil spills, and chemical separation processes to remove non-polar from polar compounds.

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Chemical polarity

Theory | Polarity of molecules | Properties and examples | Predicting Polar and Nonpolar Molecules | **Polar** | Nonpolar

Chemical polarity, also known as **bond polarity** or just **polarity**, is a concept in chemistry which describes how equally bonding electrons are shared between atoms. It is a physical property of compounds and affects other physical properties such as solubility, melting points and boiling points. Polarity also affects intermolecular forces, leading to some compounds or molecules within compounds being labelled as polar or non-polar.

A commonly-used example of a polar compound is water (H2O). The electrons of water's hydrogen atoms are strongly attracted to the oxygen atom, and are actually closer to oxygen's nucleus than to the hydrogen nuclei; thus, water has a relatively strong negative charge in the middle (red shade), and a positive charge at the ends (blue shade).

Theory

Electrons are not always shared equally between two bonding atoms: one atom might exert more of a "pull" on the electron cloud than the other. This "pull" is termed electronegativity and measures the attraction for electrons a particular atom has. The unequal sharing of electrons within a bond leads to the formation of an electric dipole: a separation of positive and negative electric charge.

Atoms with high electronegativities - such as fluorine, oxygen, and nitrogen - exert a greater pull on electrons than atoms with lower electronegativities. In a bonding situation this can lead to unequal sharing of electrons between atoms as electrons will spend more time closer to the atom with the higher electronegativity.

Bonds can fall between one of two extremes - being completely non-polar or completely polar. A completely non-polar bond occurs when the electronegativities are identicle and therefore possess a difference of zero. A completely polar bond is more correctly termed ionic bonding and occurs when the difference between electronegativities is large enough that one atom takes an electron from the other. The terms "polar" and "non-polar" bonds usually refer to covalent bonds. To determine the polarity of a covalent bond using numerical means, the difference between the electronegativity of the atoms is taken, if the result is below 1.7 and above 0.5 then the bond is polar.

Polarity of molecules

A compound is comprised of one or more chemical bonds between atoms. The polarity of each bond within the compound determines the *overall polarity* of the compound: how polar or non-polar it is. A polar molecule contains polar bonds - bonds which have unequal sharing of electrons between the two atoms involved in bonding. A non-polar compound contains non-polar bonds - bonds which have identical or similar sharing of electrons.

However, a compound's symmetricity and net polarity must also be considered when determining the polarity of the overall molecule . Even if a compound contains only polar bonds, it may be non-polar overall as the direction of the polarities cancel each other out, giving the molecule a net polarity of zero. This occurs in boron trifluoride, which contains three identicle polar bonds all cancelling each other out due to their symmetrical arrangement. Trigonal planar, tetrahedral and linear bonding arrangements often lead to symmetrical, non-polar molecules which contain polar bonds.

Properties and examples

Whilst molecules can be described as "polar" or "non-polar" it must be noted that this is often a relative term, with one molecule simply being *more polar* or *more non-polar* than another. As such, there are no ultimate properties which can be ascribed to polar or non-polar molecules. However, the following properties are typical of such molecules.

Polar molecules
Examples of household polar molecules include table salt, ammonia and sugar (glucose). Polar molecules are generally able to dissolve in water (hydrophilic) due to the polar nature of water - *like dissolves like*.

Non-polar molecules
Examples of household non-polar compounds include fats, oil and petrol. Most non-polar molecules are water insoluable (hydrophobic) at room temperature. However many non-polar organic solvents, such as turpentine, are able to dissolve non-polar substances - like dissolves like.

When comparing a polar and nonpolar molecule with similar molar mass, the polar one generally has a higher boiling point.

Predicting Polar and Nonpolar Molecules

Polar

Formula: AB **| Description:** Linear Molecules | **Example**: CO

Formula: HA_x| **Description:** Molecules with a single H | **Example**: HCl

Formula: A_xOH | **Description:** Molecules with an OH at one end | **Example**: C_2H_5OH

Formula: O_xA_y | **Description:** Molecules with an O at one end | **Example**: H_2O

Formula: N_xA_y | **Description:** Molecules with an N at one end | **Example**: NH_3

Nonpolar

Formula: A_x | **Description:** All elements | **Example**: O_2

Formula: C_xA_y | **Description:** Most carbon compounds | **Example**: CO_2

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Acid

An **acid** (often represented by the generic formula **HA**) is traditionally considered any chemical compound that when dissolved in water, gives a solution with a pH of less than 7. That approximates the modern definition of Bronsted and Lowry, who defined an acid as a compound which donates a hydrogen ion (H^+) to another compound (called a base). Common examples include acetic acid (in vinegar) and sulfuric acid (used in car batteries). Acids generally taste sour; however, tasting acids, particularly concentrated acids, can be dangerous and is not recommended.

Definitions of acids and bases

The word "acid" comes from the Latin *acidus* meaning "sour," but in chemistry the term acid has a more specific meaning. There are three common ways to define an acid, namely, the **Arrhenius**, the **Bronsted-Lowry** and the **Lewis** definitions, in order of increasing generality.

- **Arrhenius**: According to this definition, an acid is a substance that increases the concentration of hydronium ion (H_3O^+) when dissolved in water, while bases are substances that increase the concentration of hydroxide ions (OH^-). This definition limits acids and bases to substances that can dissolve in water. Around 1800, many French chemists, including Antoine Lavoisier, incorrectly believed that all acids contained oxygen. English chemists, including Sir Humphry Davy at the same time believed all acids contained hydrogen. The Swedish chemist Svante Arrhenius used this belief to develop this definition of acid.
- **Bronsted-Lowry**: According to this definition, an acid is a proton donor and a base is a proton acceptor. The acid is said to be dissociated after the proton is donated. An acid and the corresponding base are referred to conjugate acid-base pairs. Bronsted and Lowry formulated this definition, which includes water-insoluble substances not in the Arrhenius definition.
- **Lewis**: According to this definition, an acid is an electron-pair acceptor and a base is an electron-pair donor. (These are frequently referred to as "Lewis acids" and "Lewis bases," and are electrophiles and nucleophiles, respectively, in organic chemistry; Lewis bases are also ligands in coordination chemistry.) Lewis acids include substances with no protons (i.e. hydrogen), such as iron(III) chloride. The Lewis definition can also be explained with molecular orbital theory. In general, an acid can receive an electron pair in its lowest unoccupied orbital (LUMO) from the highest occupied orbital (HOMO) of a base. That is, the HOMO from the base and the LUMO from the acid combine to a bonding molecular orbital. This definition was developed by Gilbert N. Lewis.

Although not the most general theory, the Bronsted-Lowry definition is the most widely used definition.

The strength of an acid may be understood by this defintion by the stability of hydronium and the solvated conjugate base upon dissociation. Increasing stability of the conjugate base will increase the acidity of a compound. This concept of acidity is used frequently for organic acids such as carboxylic acid. The molecular orbital description, where the unfilled proton orbital overlaps with a lone pair, is connected to the Lewis definition.

Solutions of weak acids and salts of their conjugate bases form buffer solutions.

Acid/base systems are different from redox reactions in that there is no change in oxidation state.

Generally, acids have the following chemical and physical properties:

- **Taste**: Acids generally are sour when dissolved in water.
- **Touch**: Acids produce a stinging feeling, particularly strong acids.
- **Reactivity**: Acids react aggressively with or corrode most metals.
- **Electrical conductivity**: Acids are electrolytes.

Strong acids are dangerous, causing severe burns for even minor contact. Generally, acid burns are treated by rinsing the affected area abundantly with water and followed up with immediate medical attention.

Nomenclature

Acids are named according to the ending of their anion. That ionic ending is dropped and replaced with a new suffix according to the table below. For example, HCl has chloride as its anion, so the -ide suffix makes it take the form hydrochloric acid.

Anion Ending: per-anion-ate
Acid Prefix: per
Acid Suffix: ic acid

Anion Ending: ate
Acid Prefix: -
Acid Suffix: ic acid

Anion Ending: ite
Acid Prefix: -
Acid Suffix: ous acid

Anion Ending: hypo-anion-ite
Acid Prefix: hypo

Acid Suffix: ous acid

Anion Ending: ide
Acid Prefix: ide
Acid Suffix: ic acid

Chemical characteristics

In water the following equilibrium occurs between an acid (HA) and water, which acts as a base:

$HA(aq) <--> H_3O^+(aq) + A^-(aq)$

The acidity constant (or acid dissociation constant) is the equilibrium constant for the reaction of HA with water:

$$K_a = \frac{[H_3O^+] \cdot [A^-]}{[HA]}$$

Strong acids have large K_a values (i.e. the reaction equilibrium lies far to the right; the acid is almost completely dissociated to H_3O^+ and A^-). Strong acids include the heavier hydrohalic acids: hydrochloric acid (HCl), hydrobromic acid (HBr), and hydroiodic acid (HI). (However, hydrofluoric acid, HF, is relatively weak.) For example, the K_a value for hydrochloric acid (HCl) is 10^7.

Weak acids have small K_a values (i.e. at equilibrium significant amounts of HA and A^- exist together in solution; modest levels of H_3O^+ are present; the acid is only partially dissociated). For example, the K_a value for acetic acid is 1.8×10^{-5}. Most organic acids are weak acids. Oxoacids, which tend to contain central atoms in high oxidation states surrounded by oxygen may be quite strong or weak. Nitric acid, sulfuric acid, and perchloric acid are all strong acids, whereas nitrous acid, sulfurous acid and hypochlorous acid are all weak.

Note the following:

- The terms "hydrogen ion" and "proton" are used interchangeably; both refer to H^+.
- In aqueous solution, the water is protonated to form hydronium ion, $H_3O^+(aq)$. This is often abbreviated as $H^+(aq)$ even though the symbol is not chemically correct.
- The strength of an acid is measured by its acid dissociation constant (K_a) or equivalently its pK_a (pK_a=

- $\log(K_a)$.

- The pH of a solution is a measurement of the concentration of hydronium. This will depend of the concentration and nature of acids and bases in solution.

Polyprotic acids

Polyprotic acids are able to donate more than one proton per acid molecule, in contrast to monoprotic acids that only donate one proton per molecule. Specific types of polyprotic acids have more specific names, such as **diprotic acid** (two potential protons to donate) and **triprotic acid** (three potential protons to donate)

A monoprotic acid can undergo one dissociation (sometimes called ionization) as follows and simply has one acid dissociation constant (K_a):

$HA(aq) + H_2O(l) \text{<--> } H_3O^+(aq) + A^-(aq)$

A diprotic acid (here symbolized by H_2A) can undergo one or two dissociations depending on the pH. Each dissociation has its own dissociation constant, K_{a1} and K_{a2}.

$H_2A(aq) + H_2O(l) \text{<--> } H_3O^+(aq) + HA^-(aq)$

$HA^-(aq) + H_2O(l) \text{<--> } H_3O^+(aq) + A^{2-}(aq)$

The first dissociation constant is typically greater than the second; i.e., $K_{a1} > K_{a2}$. For example, sulfuric acid (H_2SO_4) can donate one proton to form the bisulfate anion (HSO_4^-), for which K_{a1} is very large; then it can donate a second proton to form the sulfate anion (SO_4^{2-}), wherein the K_{a2} is intermediate strength. The large K_{a1} for the first dissociation makes sulfuric a strong acid. In a similar manner, the weak unstable carbonic acid (H_2CO_3) can lose one proton to form bicarbonate anion (HCO_3^-) and lose a second to form carbonate anion (CO_3^{2-}). Both K_a values are small, but $K_{a1} > K_{a2}$.

A triprotic acid (H_3A) can undergo one, two, or three dissociations and has three dissociation constants, where $K_{a1} > K_{a2} > K_{a3}$.

$H_3A(aq) + H_2O(l) \text{<--> } H_3O^+(aq) + H_2A^-(aq) \qquad K_{a1}$

$H_2A^-(aq) + H_2O(l) <--> H_3O^+(aq) + HA^{2-}(aq)$ K_{a2}

$HA^{2-}(aq) + H_2O(l) <--> H_3O^+(aq) + A^{3-}(aq)$ K_{a3}

An inorganic example of a triprotic acid is orthophosphoric acid (H_3PO_4), usually just called phosphoric acid. All three protons can be successively lost to yield $H_2PO_4^-$, then HPO_4^{2-}, and finally PO_4^{3-} , the orthophosphate ion, usually just called phosphate. An organic example of a triprotic acid is citric acid, which can successively lose three protons to finally form the citrate ion. Even though the positions of the protons on the original molecule may be equivalent, the successive K_a values will differ since it is energetically less favorable to lose a proton if the conjugate base is more negatively charged.

Neutralization

Neutralization is the reaction between equal amounts of an acid and a base, producing a salt and water; for example, hydrochloric acid and sodium hydroxide form sodium chloride and water:

$HCl(aq) + NaOH(aq) -> H_2O(l) + NaCl(aq)$

Neutralization is the basis of titration, where a pH indicator shows equivalence point when the equivalent number of moles of a base have been added to an acid.

Common acids

Strong inorganic acids

- Hydrobromic acid
- Hydrochloric acid
- Hydroiodic acid
- Nitric acid
- Sulfuric acid
- Perchloric acid

Medium to weak inorganic acids

- Boric acid
- Carbonic acid
- Chloric acid
- Hydrofluoric acid
- Phosphoric acid

- Pyrophosphoric acid

Weak organic acids

- Acetic acid
- Benzoic acid
- Butyric acid
- Citric acid
- Formic acid
- Lactic acid
- Malic acid
- Mandelic acid
- Methanethiol
- Propionic acid
- Pyruvic acid
- Valeric acid

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Alkali

In chemistry, an **alkali** is a specific type of base, formed as a carbonate, hydroxide or other basic (pH greater than 7) ionic salt of an alkali metal or alkali earth metal element. The word alkali or the adjective **alkaline** are frequently used to refer to all bases, since most common bases are alkalis, although strictly speaking this is inaccurate.

Common properties of alkalis

Alkalis are all Arrhenius bases and share many properties with other chemicals in this group (Arrhenius bases form hydroxide ions when dissolved in water). Common properties of alkaline solutions include:

- All alkalis have a pH greater than seven and hence can be detected with litmus paper (litmus will turn blue on contact with an alkali).
- Most alkalis have a pH of 10 or greater. This means that they will turn phenolphthalein from colorless to pink.
- Caustic (causing chemical burns).
- Alkaline solutions are slippery or soapy to the touch (due to the caustic reaction dissolving the surface of the skin and fingerprint).
- Alkalis normally form aqueous solutions (although some like barium carbonate are only soluble when reacting with an acidic aqueous solution).

Confusion between base and alkali

The terms "base" and "alkali" are often used interchangeably, since most common bases are alkalis. It is common to speak of "measuring the alkalinity of soil" when what is actually meant is the measurement of the pH (base property). Similarly, bases which are not alkalis, such as ammonia, are sometimes erroneously referred to as alkaline.

Note that not all or even most salts formed by alkali metals are alkaline; this designation applies only to those salts which are basic.

While most electropositive metal oxides are basic, only the soluble alkali metal and alkali earth metal oxides can be correctly called alkalis.

This definition of an alkali as the salt of an alkali metal or alkali earth metal does appear to be the most common, based on dictionary definitions , however conflicting definitions of the term alkali do exist.

These include:

- Any base that is water soluble . This is more accurately called an Arrhenius base.
- The solution of a base in water .

Alkali salts

Most basic salts are alkali salts, of which common examples are:

- sodium hydroxide (often called "caustic soda")
- potassium hydroxide (commonly called "potash")
- lye (generic term, for either of the previous two, or even for a mixture)
- calcium carbonate (sometimes called "free lime")

Alkaline soil

Soil with a pH above 7.4 is normally referred to as alkaline. This soil property can occur naturally, due to the presence of alkali salts. Although some plants do prefer slightly basic soil (including cabbage family vegetables and buffalograss), most plants prefer a mildly acidic soil (pH between 6.0 and 6.8), and high pH levels can cause a problem.

In alkali lakes (a type of salt lake), evaporation concentrates the naturally occurring alkali salts, often forming a crust of mildly basic salt across a large area.

Examples of alkali lakes:

- Redberry Lake, Saskatchewan, Canada.
- Tramping Lake, Saskatchewan, Canada.

Etymology

The word "alkali" is derived from Arabic - "the calcined ashes", referring to the original source of alkaline substance. Ashes were used in conjunction with animal fat to produce soap, a process known as saponification.

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Base (chemistry)

The common definition of a **base** is a chemical compound that absorbs hydronium ions when dissolved in water (a proton acceptor). An **alkali** is a special example of a base, where in an aqueous environment, hydroxide ions are donated. Bases and acids are seen as opposites because the effect of an acid is to increase the hydronium ion (H_3O^+) concentration in water, whereas bases reduce this concentration.

Arrhenius bases are water-soluble and these solutions always have a pH greater than 7.

There are other more generalized and advanced definitions of acids and bases.

Common bases

- Carbonates - Baking soda (sodium hydrogen carbonate) and Sodium carbonate
- Ammonia and amines
- Pyridine and other basic aromatic rings
- Metal hydroxides like sodium hydroxide or potassium hydroxide
- Many metal oxides form basic hydroxides with water (anhydrides)
- Soap

Bases and pH

The pH of (impure) water is a measure of its acidity. In pure water, about one in ten million molecules dissociate into hydronium ions (H_3O^+) and hydroxide ions (OH^-), according to the following equation:

$$2H_2O(l) \text{ <--> } H_3O^+(aq) + OH^-(aq)$$

The concentration, measured in molarity (*M*), or the equivalent moles per liter, of the ions is indicated as $[H_3O^+]$ and $[OH^-]$; their product is the dissociation constant of water with and has the value 10^{-14} *M*.

The pH is defined as $-\log [H_3O^+]$; thus, pure water has a pH of 7. (These numbers are correct at 23°C and slightly different at other temperatures.)

A base accepts (removes) hydronium ions (H_3O^+) from the solution, or donates hydroxide ions (OH^-) to the solution. Both actions will lower the concentration of hydronium ions, and thus raise pH. By contrast, an acid donates H_3O^+ ions to the solution or accepts OH^-, thus lowering pH.

The pH of a solution can be calculated. For example, if 1 mole of sodium hydroxide (40 g) is dissolved in 1 liter of water, the concentration of hydroxide ions becomes $[OH^-] = 1$ mol/l. Therefore $[H^+] = 10^{-14}$ mol/l, and pH = -log $10^{-14} = 14$.

Characteristics of bases

Bases are slightly less viscous than pure water, have a bitter taste and are soapy to the touch. They react with acids to form salts.

Neutralization of acids

When dissolved in water, the base sodium hydroxide decomposes into hydroxide and sodium ions:

$$\mathrm{NaOH} \rightarrow \mathrm{Na^+ + OH^-}$$

and similarly, in water hydrogen chloride forms hydronium and chloride ions:

$$\mathrm{HCl + H_2O \rightarrow H_3O^+ + Cl^-}.$$

When the two solutions are mixed, the H_3O^+ and OH^- ions combine to form water molecules:

$$\mathrm{H_3O^+ + OH^- \rightarrow 2H_2O}$$

If equal quantities of NaOH and HCl are dissolved, the base and the acid exactly neutralize, leaving only NaCl, effectively table salt, in solution.

Alkalinity of non-hydroxides

Both sodium carbonate and ammonia are bases, although neither of these substances contains OH^- groups. That is because both compounds accept H^+ when dissolved in water:

$$\mathrm{Na_2CO_3 + H_2O \rightarrow 2Na^+ + HCO_3^- + OH^-}$$

$$\mathrm{NH_3 + H_2O \rightarrow NH_4^+ + OH^-}.$$

Bases as heterogeneous catalysts

Basic substances can be used as insoluble heterogeneous catalysts for chemical reactions. Examples are metal oxides such as magnesium oxide, calcium oxide, and barium oxide as well as potassium fluoride on alumina and some zeolites. A great deal of transition metals make good catalysts, many of which form basic substances. Basic catalysts have been used for hydrogenations, the migration of double bonds, Meerwein-Ponndorf-Verlay reduction, the Michael reaction, and many other reactions.

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pH

pH (potential of hydrogen) is a measure of the activity of hydrogen ions (H^+) in a solution and, therefore, its acidity or alkalinity. In aqueous systems, the hydrogen ion activity is dictated by the dissociation constant of water (K_w = 1.011 x 10^{-14} at 25 °C) and interactions with other ions in solution.

Due to this dissociation constant a neutral solution (hydrogen ion activity equals hydroxide ion activity) has a pH of approximately 7. Aqueous solutions with pH values lower than 7 are considered acidic, while pH values higher than 7 are considered alkaline.

The concept was introduced by S.P.L. Sorensen in 1909, and is purported to mean "pondus hydrogenii" in Dutch. However, most other sources attribute the name to the French term *pouvoir hydrogène.* In English, pH can stand for "hydrogen power," "power of hydrogen," or "potential of hydrogen." All of these terms are technically correct.

Definition

Though a pH value has no unit, it is not an arbitrary scale; the number arises from a definition based on the activity of hydrogen ions in the solution.

The precise formula for calculating pH is:

$$\mathrm{pH} = -\log_{10}\left(a_{\mathrm{H}^+}\right)$$

a_{H^+} denotes the activity of H^+ ions , and is unitless. In dilute solutions (like river or tap water) the activity is approximately equal to the numeric value of the concentration of the H^+ ion, denoted as $[H^+]$ (or more accurately written, $[H_3O^+]$), measured in moles per litre (also known as molarity): Therefore, it is often convenient to define pH as:

$$\mathrm{pH} \approx -\log_{10}\left[\mathrm{H}^+\right]$$

For both definitions, $\log_{10}$ denotes the base-10 logarithm, therefore pH defines a logarithmic scale of acidity. For example, a solution of pH = 8.2 will have an $[H^+]$ activity (concentration) of $10^{-8.2}$ mol/L, or about 6.31 x 10^{-9} mol/L; a solution with an $[H^+]$ activity of 4.5 x 10^{-4} mol/L will have a pH value of $-\log_{10}(4.5 \times 10^{-4})$, or about 3.35.

In solution at 25 °C, a pH of 7 indicates neutrality (i.e. the pH of pure water) because water naturally

dissociates into H^+ and OH^- ions with equal concentrations of 1 x 10^{-7} mol/L. A lower pH value (for example pH 3) indicates increasing strength of acidity, and a higher pH value (for example pH 11) indicates increasing strength of alkalinity.

Neutral pH is not *exactly* 7; this would imply that the H^+ ion concentration is *exactly* 1x10^{-7} mol/L, which is not the case. The value is close enough, however, for neutral pH to be 7.00 to two significant figures, which is near enough for most people to assume that it is exactly 7. At temperatures other than 25 °C, or room temperature, the pH of pure water will not be 7. (Note also that pure water, when exposed to the atmosphere, will take in carbon dioxide, some of which reacts with water to form carbonic acid and H^+, thereby lowering the pH to about 5.7.)

Most substances have a pH in the range 0 to 14, although extremely acidic or basic substances may have pH less than 0 or greater than 14.

Cell potential

pH can also be measured by measuring the cell potential of the sample:

$$\mathrm{pH} = \frac{\epsilon}{0.059}$$

where epsilon (ε) is the electromotive force (EMF) or cell potential of a galvanic cell.

The formula for pH was derived from the application of the Nernst Equation to concentration cells, or galvanic cells where the half cells are at different concentrations. In the Nernst Equation,

$$\epsilon = \epsilon^o - \frac{0.059}{n} \times log(Q)$$

However, in a concentration cell both e^o are equal so the equation becomes

$$\epsilon = -\frac{0.059}{n} \times log(Q)$$

By using the standard hydrogen electrode, with H_2 gas at 1 atm and an unknown molarity of H^+ ions, and in which 2 moles of electrons are transferred for every mole of reaction, the equation may be set up as follows:

$$\epsilon = -\frac{0.059}{2} \times \log\left(\frac{[\mathrm{H}^+]^2}{1^2}\right)$$

$$\epsilon = -\frac{0.059}{2} \times 2 \times \log([\mathrm{H}^+])$$

$$\epsilon = 0.059 \times -\log([\mathrm{H}^+])$$

Arbitrarily, the potential of hydrogen, or pH, is defined as -\log ([\mbox{H}$^+$]). Therefore,

pH = - $\log_{10}[H^+]$

or, by substitution,

$$\mathrm{pH} = \frac{\epsilon}{0.059}$$

The "pH" of any other substance may also be found (e.g. the potential of silver ions, or pAg^+) by deriving a similar equation using the same process. These other equations for potentials will not be the same, however, as the number of moles of electrons transferred (n) will differ for the different reactions.

Measuring

pH can be measured:

- by addition of a pH indicator into the studying solution. The indicator color varies depending on the pH of the solution. Using indicators, qualitative determinations can be made with universal indicators that have broad color variability over a wide pH range and quantitative determinations can be made using indicators that have strong color variability over a small pH range. Extremely precise measurements can be made over a wide pH range using indicators that have multiple equilibriums (ie H_2I) in conjunction with spectrophotometric methods to determine the relative abundance of each pH dependent component that make up the color of solution.
- by using a pH meter together with pH-selective electrodes (pH glass electrode, hydrogen electrode, quinhydrone electrode, ion sensitive field effect transistor and other).

pH

Substance	pH
Acid mine runoff	-3.6 – 1.0
Battery acid	-0.5
Gastric acid	2.0
Lemon juice	2.4
Cola	2.5
Vinegar	2.9
Orange or apple juice	3.5
Beer	4.5
Acid Rain	<5.0
Coffee	5.0
Tea	5.5
Milk	6.5
Pure water	7.0
Healthy human saliva	6.5 – 7.4
Blood	7.34 – 7.45
Sea water	8.0
Hand soap	9.0 – 10.0
Household ammonia	11.5
Bleach	12.5
Household lye	13.5

pOH

There is also pOH, in a sense the opposite of pH, which measures the concentration of OH^- ions. Since water self ionizes, and notating $[OH^-]$ as the concentration of hydroxide ions, we have

$$K_w = a_{\mathrm{H}}\ a_{\mathrm{OH}^-} = 10^{-14} \quad (*)$$

where K_w is the ionization constant of water.

Now, since

$$\log_{10} K_w = \log_{10} a_{\mathrm{H}^+} + \log_{10} a_{\mathrm{OH}^-}$$

by logarithmic identities, we then have the relationship:

$$-14 = \log_{10} a_{H^+} + \log_{10} a_{OH^-}$$

and thus

$pOH = -\log_{10} a_{OH^-} = 14 + \log_{10} a_{H^+} = 14 - pH$ (*)

(*) This formula is valid exactly for temperature = 298.15 K (25 °C) only, acceptable for most lab calculations.

Calculation of pH for weak and strong acids

Values of pH for weak and strong acids can be approximated using certain assumptions.

Under the Bronsted-Lowry theory, stronger or weaker acids are a relative concept. But here we define a strong acid as a species which is a much stronger acid than the hydronium (H_3O^+) ion. In that case the dissociation reaction (strictly $HX+H_2O<-->H_3O^++X^-$ but simplified as $HX<-->H^++X^-$) goes to completion, i.e. no unreacted acid remains in solution. Dissolving the strong acid HCl in water can therefore be expressed:

$HCl(aq) --> H^+ + Cl^-$

This means that in a 0.01 mol/L solution of HCl it is approximated that there is a concentration of 0.01 mol/L dissolved hydrogen ions. From above, the pH is: $pH = -\log_{10} [H^+]$:

$pH = -\log (0.01)$

which equals 2.

For weak acids, the dissociation reaction does not go to completion. An equilibrium is reached between the hydrogen ions and the conjugate base. The following shows the equilibrium reaction between methanoic acid and its ions:

$HCOOH(aq) <-->H^+ + HCOO^-$

It is necessary to know the value of the equilibrium constant of the reaction for each acid in order to calculate its pH. In the context of pH, this is termed the *acidity constant* of the acid but is worked out in the same way:

K_a = [hydrogen ions][acid ions] / [acid]

For HCOOH, $K_a = 1.6 \times 10^{-4}$

When calculating the pH of a weak acid, it is usually assumed that the water does not provide any hydrogen ions. This simplifies the calculation, and the concentration provided by water, 1×10^{-7} mol, is usually insignificant.

With a 0.1 mol/L solution of methanoic acid (HCOOH), the acidity constant is equal to:

$K_a = [H^+][HCOO^-] / [HCOOH]$

Given that an unknown amount of the acid has dissociated, [HCOOH] will be reduced by this amount, while $[H^+]$ and $[HCOO^-]$ will each be increased by this amount. Therefore, [HCOOH] may be replaced by 0.1 - *x*, and $[H^+]$ and $[HCOO^-]$ may each be replaced by *x*, giving us the following equation:

$$1.6 \times 10^{-4} = \frac{x^2}{0.1 - x}$$

Solving this for *x* yields 3.9×10^{-3}, which is the concentration of hydrogen ions after dissociation. Therefore the pH is $-\log(3.9 \times 10^{-3})$, or about 2.4.

Indicators

An indicator is used to measure the pH of a substance. Common indicators are litmus paper, phenolphthalein, methyl orange, phenol red, and bromothymol blue.

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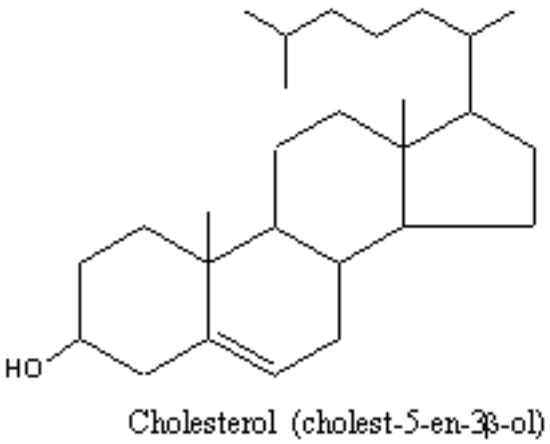
Cholesterol

Cholesterol is a sterol (a combination steroid and alcohol) and a lipid found in the cell membranes of all body tissues, and transported in the blood plasma of all animals. The name originates from the Greek *chole-* (bile) and *stereos* (solid), and the chemical suffix *-ol* for an alcohol, as researchers first identified cholesterol ($C_{27}H_{45}OH$) in solid form in gallstones in 1784.

Most cholesterol is not dietary in origin; it is synthesized internally. Cholesterol is present in higher concentrations in tissues which either produce more or have more densely-packed membranes, for example, the liver, spinal cord and brain, and also in atheroma. Cholesterol plays a central role in many biochemical processes, but is best known for the association of cardiovascular disease with various lipoprotein cholesterol transport patterns and high levels of cholesterol in the blood.

Often, when most doctors talk to their patients about the health concerns of cholesterol, they are referring to "bad cholesterol", or low-density lipoprotein (LDL). "Good cholesterol" is high-density lipoprotein (HDL).



Cholesterol chemical structure

Physiology

Function

Cholesterol is required to build and maintain cell membranes; it makes the membrane's fluidity - degree of viscosity - stable over bigger temperature intervals (the hydroxyl group on cholesterol interacts with the phosphate head of the membrane, and the bulky steroid and the hydrocarbon chain is embedded in

the membrane). Cholesterol also aids in the manufacture of bile (which helps digest fats), and is also important for the metabolism of fat soluble vitamins, including vitamins A, D, E and K. It is the major precursor for the synthesis of vitamin D, of the various steroid hormones, including cortisol and aldosterone in the adrenal glands, and of the sex hormones progesterone, estrogen, and testosterone. Further recent research shows that cholesterol has an important role for the brain synapses as well as in the immune system, including protecting against cancer.

Recently, cholesterol has also been implicated in cell signalling processes, where it has been suggested that it forms lipid rafts in the plasma membrane. It also reduces the permeability of the plasma membrane to proton and sodium ions (Haines 2001).

Properties

Cholesterol is minimally soluble in water; it cannot dissolve and travel in the water-based bloodstream. Instead, it is transported in the bloodstream by lipoproteins - protein "molecular-suitcases" that are water-soluble and carry cholesterol and fats internally. The proteins forming the surface of the given lipoprotein particle determine from what cells cholesterol will be removed and to where it will be supplied.

The largest lipoproteins, which primarily transport fats from the intestinal mucosa to the liver, are called chylomicrons. They carry mostly triglyceride fats and cholesterol (that are from food and especially internal cholesterol secreted by the liver into the bile). In the liver, chylomicron particles give up triglycerides and some cholesterol, and are converted into low-density lipoprotein (LDL) particles, which carry triglycerides and cholesterol on to other body cells. In healthy individuals the LDL particles are large and relatively few in number. In contrast, large numbers of small LDL particles are strongly associated with promoting atheromatous disease within the arteries. (Lack of information on LDL particle number and size is one of the major problems of conventional lipid tests.)

High-density lipoprotein (HDL) particles transport cholesterol back to the liver for excretion, but vary considerably in their effectiveness for doing this. Having large numbers of large HDL particles correlates with better health outcomes. In contrast, having small amounts of large HDL particles is strongly associated with atheromatous disease progression within the arteries. (Note that the concentration of total HDL does not indicate the actual number of functional large HDL particles, another of the major problems of conventional lipid tests.)

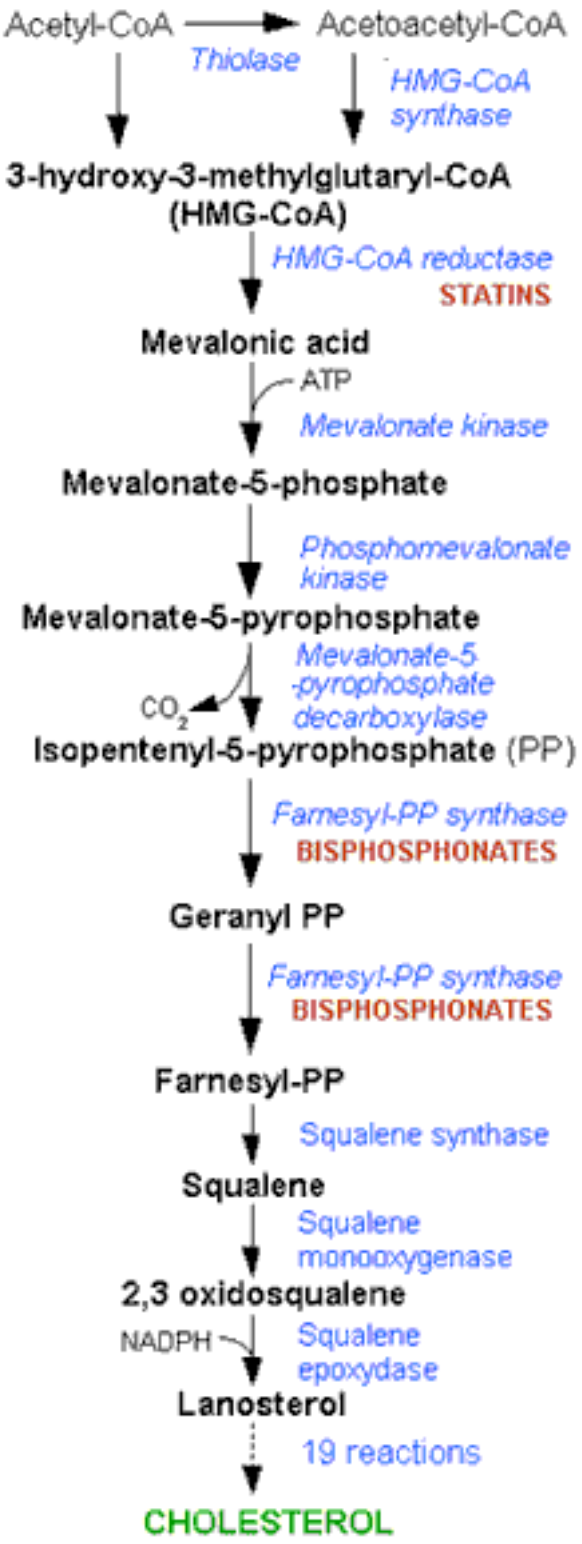
The cholesterol molecules present in *LDL cholesterol* and *HDL cholesterol* are identical. The difference between the two types of cholesterol derives from the carrier protein molecules; the lipoprotein component.

Synthesis and intake

Cholesterol is primarily synthesized from acetyl CoA through the HMG-CoA reductase pathway in

many cells and tissues. About 20–25% of total daily production (~1 g/day) occurs in the liver; other sites of higher synthesis rates include the intestines, adrenal glands and reproductive organs. For a person of about 150 pounds (68 kg), typical total body content is about 35 g, typical daily internal production is about 1 g and typical daily dietary intake is 200 to 300 mg. Of the 1,200 to 1,300 mg input to the intestines (via bile production and food intake), about 50% is reabsorbed into the bloodstream.

Konrad Bloch and Feodor Lynen shared the Nobel Prize in Physiology or Medicine in 1964 for their discoveries concerning the mechanism and regulation of the cholesterol and fatty acid metabolism.



The HMG-CoA reductase pathway

Regulation

Biosynthesis of cholesterol is directly regulated by the cholesterol levels present, though the homeostatic mechanisms involved are only partly understood. A higher intake from food leads to a net decrease in endogenous production, while lower intake from food has the opposite effect. The main regulatory mechanism is the sensing of intracellular cholesterol in the endoplasmic reticulum by the protein SREBP (Sterol Regulatory Element Binding Protein 1 and 2). In the presence of cholesterol, SREBP is bound to two other proteins: SCAP (SREBP-cleavage activating protein) and Insig-1. When cholesterol levels fall, Insig-1 dissociates from the SREBP-SCAP complex, allowing the complex to migrate to the Golgi apparatus, where SREBP is cleaved by S1P and S2P (site 1/2 protease), two enzymes that are activated by SCAP when cholesterol levels are low. The cleaved SREBP then migrates to the nucleus and acts as a transcription factor to bind to the SRE (Sterol regulatory element) of a number of genes to stimulate their transcription. Among the genes transcribed are the LDL receptor and HMG-CoA reductase. The former scavenges circulating LDL from the bloodstream, whereas HMG-CoA reductase leads to an increase of endogenous production of cholesterol. An excess of cholesterol can build up in the bloodstream and accumulates on the walls of arteries. This build up is what can lead to clogged ateries and eventually to heart attacks and strokes.

A large part of this mechanism was clarified by Dr Michael S. Brown and Dr Joseph L. Goldstein in the 1970s. They received the Nobel Prize in Physiology or Medicine for their work in 1985.

The average amount of blood cholesterol varies with age, typically rising gradually until one is about 60 years old. A study by Ockene et al. showed that there are seasonal variations in cholesterol levels in humans, more, on average, in winter.

Excretion

Cholesterol is excreted from the liver in bile and reabsorbed from the intestines. Under certain circumstances, when more concentrated, as in the gallbladder, it crystallises and is the major constituent of most gallstones, although lecithin and bilirubin gallstones also occur less frequently.

Role in atheromatous disease

In conditions with elevated concentrations of oxidized LDL particles, especially small LDL particles, cholesterol promotes atheroma plaque deposits in the walls of arteries, a condition known as *atherosclerosis*, which is a major contributor to coronary heart disease and other forms of cardiovascular disease. (In contrast, HDL particles have been the only identified mechanism by which cholesterol can be removed from atheroma. Increased concentrations of large HDL particles, not total HDL particles, correlate with lower rates of atheroma progressions, even regression.)

There is a world-wide trend to believe that lower total cholesterol levels tend to correlate with lower atherosclerosis event rates (though many studies refute this idea). Due to this reason, cholesterol has become a very large focus for scientific researchers trying to determine the proper amount of cholesterol needed in a healthy diet. However, the primary association of atherosclerosis with cholesterol has always been specifically with cholesterol transport patterns, not total cholesterol per se. For example, total cholesterol can be low, yet made up primarily of small LDL and small HDL particles and atheroma growth rates are high. In contrast, however, if LDL particle number is low (mostly large particles) and a large percentage of the HDL particles are large (HDL is actively reverse transporting cholesterol), then atheroma growth rates are usually low, even negative, for any given total cholesterol concentration. These effects are further complicated by the relative concentration of aymmetric dimethylarginin (ADMA) in the endothelium, since ADMA down-regulates production of nitric oxide, a relaxant of the endothelium. Thus, high levels of ADMA, associated with high oxidized levels of LDL pose a heightened risk factor for vascular disease.

Multiple human trials utilizing HMG-CoA reductase inhibitors or *statins*, have repeatedly confirmed that changing lipoprotein transport patterns from unhealthy to healthier patterns significantly lower cardiovascular disease event rates, even for people with cholesterol values currently considered low for adults; However, no statistically significant mortality benefit has been derived to date by lowering cholesterol using medications in *asymptomatic* people, i.e., no heart disease, no history of heart attack, etc.

Some of the better recent randomized human outcome trials studying patients with coronary artery disease or its risk equivalents include the Heart Protection Study (HPS), the PROVE IT trial, and the TNT trial. In addition, there are trials that have looked at the effect of lowering LDL as well as raising HDL and atheroma burden using intravascular ultrasound. Small trials have shown prevention of progression of coronary artery disease and possibly a slight reduction in atheroma burden with successful treatment of an abnormal lipid profile.

The American Heart Association provides a set of guidelines for total (fasting) blood cholesterol levels and risk for heart disease:

Levelmg/dL <200 **Level**mmol/L (<5.2 mmol/L) **Interpretation** Desirable level

Levelmg/dL 200-239 **Level**mmol/L (5.2-6.2 mmol/L) **Interpretation** Borderline high

Levelmg/dL >240 **Level**mmol/L (>6.2 mmol/L) **Interpretation** High risk

However, as today's testing methods determine LDL ("bad") and HDL ("good") cholesterol separately, this simplistic view has become somewhat outdated. The desirable LDL level is considered to be less than 100 mg/dL (2.6 mmol/L), although a newer target of <70 mg/dL can be considered in higher risk individuals based on some of the above-mentioned trials. A ratio of total cholesterol to HDL —another useful measure— of far less than 5:1 is thought to be healthier. Of note, typical LDL values for children

before fatty streaks begin to develop is 35 mg/dL.

Patients should be aware that most testing methods for LDL do not actually measure LDL in their blood, much less particle size. For cost reasons, LDL values have long been estimated using the formula: Total-cholesterol - total-HDL - 20% of the triglyceride value = estimated LDL.

Increasing clinical evidence has strongly supported the greater predictive value of more-sophisticated testing that directly measures both LDL and HDL particle concentrations and size, as opposed to the more usual estimates/measures of the total cholesterol carried within LDL particles or the total HDL concentration. There are three commercial labs in the United States that offer more-sophisticated analysis using different methodologies. As outlined above, the real key is cholesterol transport, which is determined by both the proteins that form the lipoprotein particles and the proteins on cell surfaces with which they interact.

Hypocholesterolemia

Although relatively rare, an excessively low cholesterol level (hypocholesterolemia) (readings below 160 mg/dL) can increase the risk of depression, cancer, hemorrhagic stroke, respiratory diseases.

Possible causes of low cholesterol are:
* hyperthyroidism, or an overactive thyroid gland
* liver disease
* malabsorption
* inadequate absorption of nutrients from the intestines
* malnutrition
* celiac disease
* abetalipoproteinemia - A rare genetic disease that causes cholesterol readings below 50mg/dl. It is found mostly in jewish populations.
* hypobetalipoproteinemia-A genetic disease that causes cholesterol readings below 50mg/dl
* Manganese deficiency

Cholesteric liquid crystals

Some cholesterol derivatives, (among others simple cholesteric lipids) are known to generate liquid crystalline phase called *cholesteric*. The cholesteric phase is in fact a chiral nematic phase, and changes colour when its temperature changes. Therefore, cholesterol derivatives are commonly used as temperature-sensitive dyes, in liquid crystal thermometers, and in temperature-sensitive paints.

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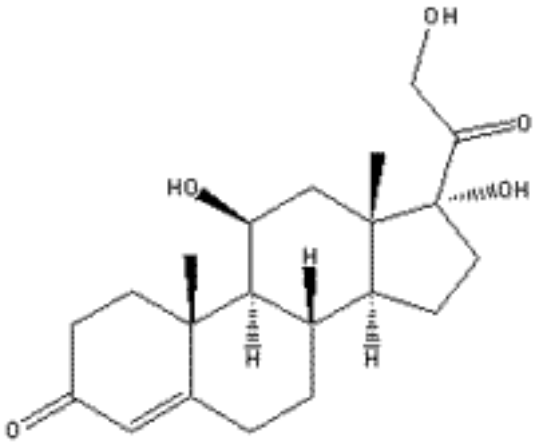
Cortisol

Synthesis | Physiology | Pharmacology | Diseases



Cortisol (hydrocortisone)

Cortisol is a corticosteroid hormone that is involved in the response to stress; it increases blood pressure and blood sugar levels and suppresses the immune system. Synthetic cortisol, also known as **hydrocortisone**, is used as a drug mainly to fight allergies and inflammation.

Synthesis

Cortisol is synthesized from pregnenolone. The conversion involves hydroxylation of C-11, C-17, and C-21, the oxidation of C-3, and the isomerization of the C-5 double bond to C-4. The synthesis takes place in the *zona fasciculata* of the cortex of the adrenal glands. While the adrenal cortex also produces aldosterone (in the *zona glomerulosa*) and some sex hormones (in the *zona reticulosa*), cortisol is its main secretion. (The name *cortisol* comes from *cortex*.)

The synthesis of cortisol in the adrenal gland is stimulated by the anterior lobe of the pituitary gland with adrenocorticotropic hormone (ACTH); production of ACTH is in turn stimulated by corticotropin-releasing hormone (CRH), released by the hypothalamus.

Physiology

The amount of cortisol present in the serum undergoes diurnal variation, with the highest levels present in the early morning, and lower levels in the evening, several hours after the onset of sleep. Information about the light/dark cycle is transmitted from the retina to the paired suprachiasmatic nuclei in the hypothalamus. Changed patterns of the serum cortisol levels have been observed in connection with

abnormal ACTH levels, clinical depression, psychological stress, and such physiological stressors as hypoglycemia, illness, fever, trauma, surgery, fear, pain, physical exertion or extremes of temperature. There is also significant individual variation, although a given person tends to have consistent rhythms.

Cortisol also inhibits the secretion of corticotropin releasing hormone (CRH), resulting in feedback inhibition of ACTH secretion. Some researchers believe that this normal feedback system may break down when animals are exposed to chronic stress.

In normal release, cortisol has widespread actions which help restore homeostasis after stress. It acts as a physiological antagonist to insulin by promoting gluconeogenesis, breakdown of lipids, and proteins, and mobilization of extrahepatic amino acids and ketone bodies. This leads to increased blood glucose concentrations, resulting in increased glycogen formation in the liver. It also increases blood pressure. The hormone lowers the activity of the immune system in the blood. It reflects leukocyte redistribution to LNs, bone marrow, and skin. Acute administration of corticosterone (the endogenous Type I and Type II receptor agonist), or RU28362 (a specific Type II receptor agonist), to adrenalectomized animals induced changes in leukocyte distribution. Bone formation is also lowered by cortisol.

These normal endogenous functions are the basis for the physiological consequences of chronic stress - prolonged cortisol secretion causes muscle wastage, hyperglycemia, and suppresses immune / inflammatory responses. The same consequences arise from long-term use of glucocorticoid drugs.

Also, long-term exposure to cortisol results in damage to cells in the hippocampus. This damage results in impaired learning. However, short-term exposure of cortisol helps to create memories; this is the proposed mechanism for storage of flash bulb memories.

Most serum cortisol, all but about 4%, is bound to proteins including corticosteroid binding globulin (**CBG**), and albumin. Only free cortisol is available to most receptors.

Pharmacology

As an oral or injectable drug, cortisol is also known as hydrocortisone. It is used as an immunosuppressive drug, given by injection in the treatment of severe allergic reactions such as anaphylaxis and angioedema, in place of prednisolone in patients who need steroid treatment but cannot take oral medication, and peri-operatively in patients on long-term steroid treatment to prevent an Addisonian crisis.

It is given by topical application for its anti-inflammatory effect in allergic rashes, eczema and certain other inflammatory conditions. It may also be injected into inflamed joints resulting from diseases such as gout.

Compared to prednisolone, hydrocortisone is about 1/4th the strength. Dexamethasone is about 40 times stronger than hydrocortisone.

Diseases

- **Hypercortisolism**: Excessive levels of cortisol in the blood result in Cushing's syndrome.
- **Hypocortisolism, or adrenal insufficiency**: If on the other hand the adrenal glands do not produce sufficient amounts of cortisol, Addison's disease is the consequence.

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Enzymes: Definition

An **enzyme** is a protein that catalyzes, or speeds up, a chemical reaction. The word comes from the Greek, which comes from *én* ("at" or "in") and *simo* ("leaven" or "yeast"). Certain RNAs also have catalytic activity, but to differentiate them from protein enzymes, they are referred to as RNA enzymes or ribozymes.

Enzymes are essential to sustain life because most chemical reactions in biological cells would occur too slowly, or would lead to different products without enzymes. A malfunction (mutation, overproduction, underproduction or deletion) of a single critical enzyme can lead to a severe disease. For example, the most common type of phenylketonuria is caused by a single amino acid mutation in the enzyme phenylalanine hydroxylase, which catalyzes the first step in the degradation of phenylalanine. The resulting build-up of phenylalanine and related products can lead to mental retardation if the disease is untreated.

Like all catalysts, enzymes work by providing an alternate pathway of lower activation energy of a reaction, thus allowing the reaction to proceed much faster. Enzymes may speed up reactions by a factor of many millions. An enzyme, like any catalyst, remains unaltered by the completed reaction and can therefore continue to function. Because enzymes do not affect the relative energy between the products and reagents, they do not affect equilibrium of a reaction. However, the advantage of enzymes compared to most other catalysts is their sterio-, regio- and chemoselectivity and specificity.

Enzyme activity can be affected by other molecules. Inhibitors are naturally occurring or synthetic molecules that decrease or abolish enzyme activity; activators are molecules that increase activity. Some irreversible inhibitors bind enzymes very tightly, effectively inactivating them. Many drugs and poisons act by inhibiting enzymes. Aspirin inhibits the COX-1 and COX-2 enzymes that produce the inflammation messenger prostaglandin, thus suppressing pain and inflammation. The poison cyanide inhibits cytochrome c oxidase, which effectively blocks cellular respiration.

While all enzymes have a biological role, some enzymes are used commercially for other purposes. Many household cleaners use enzymes to speed up chemical reactions (*e.g.*, breaking down protein or starch stains in clothes).

More than 5,000 enzymes are known. Typically the suffix *-ase* is added to the name of the substrate (*e.g.*, lactase is the enzyme that catalyzes the cleavage of lactose) or the type of reaction (*e.g.*, DNA polymerase catalyzes the formation of DNA polymers). However, this is not always the case, especially when enzymes modify multiple substrates. For this reason Enzyme Commission or EC numbers are used to classify enzymes based on the reactions they catalyze. Even this is not a perfect solution, as enzymes from different species or even very similar enzymes in the same species may have identical EC numbers.

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Dehydrogenase

A **dehydrogenase** is an enzyme that oxidizes a substrate by transferring one or more protons and a pair of electrons to an acceptor, usually NAD/NADP or a flavin coenzyme such as FAD or FMN.

Common examples of dehydrogenase enzymes in the TCA cycle are pyruvate dehydrogenase, isocitrate dehydrogenase, and alpha-ketoglutarate dehydrogenase.

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Enzymes: Etymology and history

The word enzyme comes from Greek: *"in leaven"*. As early as the late 1700s and early 1800s, the digestion of meat by stomach secretions and the conversion of starch to sugars by plant extracts and saliva were observed.

Studying the fermentation of sugar to alcohol by yeast, Louis Pasteur came to the conclusion that this fermentation was catalyzed by "ferments" in the yeast, which were thought to function only in the presence of living organisms.

In 1897, Hans and Eduard Buchner inadvertently used yeast extracts to ferment sugar, despite the absence of living yeast cells. They were interested in making extracts of yeast cells for medical purposes, and, as one possible way of preserving them, they added large amounts of sucrose to the extract. To their surprise, they found that the sugar was fermented, even though there were no living yeast cells in the mixture. The term "enzyme" was used to describe the substance(s) in yeast extract that brought about the fermentation of sucrose. It was not until 1926, however, that the first enzyme was obtained in pure form.

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Enzymes: Inhibition

Enzymes reaction rates can be decreased by competitive, non-competitive, partially competitive, uncompetitive inhibition, and mixed inhibition.

Competitive inhibition

In competitive inhibition, the inhibitor binds to the substrate binding site as shown (*right* part b), thus preventing substrate binding. Malonate is a competitive inhibitor of the enzyme succinate dehydrogenase, which catalyzes the oxidation of succinate to fumarate.

Competitive inhibition causes the K_m value to increase, but does not effect V_{max}.

Non-competitive inhibition

Non-competitive inhibitors never bind to the active center, but to other parts of the enzyme that can be far away from the substrate binding site, consequently, there is no competition between the substrate and inhibitor for the enzyme. The extent of inhibition depends entirely on the inhibitor concentration and will not be affected by the substrate concentration. For example, cyanide combines with the copper prosthetic groups of the enzyme cytochrome c oxidase, thus inhibiting cellular respiration. This type of inhibition is typically irreversible, meaning that the enzyme will no longer function.

By changing the conformation (the three-dimensional structure) of the enzyme, the inhibitors either disable the ability of the enzyme to bind or turn over its substrate. The enzyme-inhibitor (EI) and enzyme-inhibitor-substrate (EIS) complex have no catalytic activity.

Non-Competitive inhibition causes a decrease in V_{max}, but does not change the K_m value.

Partially competitive inhibition

The mechanism of partially competitive inhibition is similar to that of non-competitive, except that the EIS-complex has catalytic activity, which may be lower or even higher (partially competitive activation) than that of the enzyme-substrate (ES) complex.

This inhibition typically displays a lower V_{max}, but an unaffected K_m value.

Uncompetitive inhibition

Uncompetitive inhibition occurs when the inhibitor binds only to the enzyme-substrate complex, not to the free enzyme, the EIS complex is catalytically inactive. This mode of inhibition is rare and causes a decrease in both V_{max} and the K_m value.

Mixed inhibition

Mixed inhibitors can bind to both the enzyme and the ES complex. It has the properties of both competitive and uncompetitive inhibition.

Both a decrease in V_{max} and an increase in the K_m value are seen in mixed inhibition.

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Enzymes: Kinetics

In 1913, Leonor Michaelis and Maud Menten proposed a quantitative theory of enzyme kinetics, which is referred to as Michaelis-Menten kinetics. Their work was further developed by G. E. Briggs and J. B. S. Haldane, who derived numerous kinetic equations that are still widely used today.

Enzymes can perform up to several million catalytic reactions per second; to determine the maximum speed of an enzymatic reaction, the substrate concentration is increased until a constant rate of product formation is achieved. This is the maximum velocity (V_{max}) of the enzyme. In this state, all enzyme active sites are saturated with substrate. However, V_{max} is only one kinetic parameter that biochemists are interested in. The amount of substrate needed to achieve a given rate of reaction is also of interest. This can be expressed by the Michaelis-Menten constant (K_m), which is the substrate concentration required for an enzyme to reach one half its maximum velocity. Each enzyme has a characteristic K_m for a given substrate.

The efficiency of an enzyme can be expressed in terms of k_{cat}/K_m. The quantity k_{cat}, also called the turnover number, incorporates the rate constants for all steps in the reaction, and is the quotient of V_{max} and the total enzyme concentration. k_{cat}/K_m is a useful quantity for comparing different enzymes against each other, or the same enzyme with different substrates, because it takes both affinity and catalytic ability into consideration. The theoretical maximum for k_{cat}/K_m, called the diffusion limit, is about 10^8 to 10^9 (M^{-1} s^{-1}). At this point, every collision of the enzyme with its substrate will result in catalysis and the rate of product formation is not limited by the reaction rate but by the diffusion rate. Enzymes that reach this k_{cat}/K_m value are called *catalytically perfect* or *kinetically perfect*. Example of such enzymes are triose-phosphate isomerase, carbonic anhydrase, acetylcholinesterase, catalase, fumarase, beta-lactamase, and superoxide dismutase.

Some enzymes operate with kinetics which are faster than diffusion rates, which would seem to be impossible. Several mechanisms have been invoked to explain this phenomenon. Some proteins are believed to accelerate catalysis by drawing their substrate in and preorienting them by using dipolar electric fields. Some invoke a quantum-mechanical tunneling explanation whereby a proton or an electron can tunnel through activation barriers, although for protons tunneling remains somewhat controversial.

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Enzymes: Metabolic pathways and allosteric enzymes

Several enzymes can work together in a specific order, creating metabolic pathways. In a metabolic pathway, one enzyme takes the product of another enzyme as a substrate. After the catalytic reaction, the product is then passed on to another enzyme. The end product(s) of such a pathway are often inhibitors for one of the first enzymes of the pathway (usually the first irreversible step, called *committed step*), thus regulating the amount of end product made by the pathways. Such a regulatory mechanism is called a negative feedback mechanism, because the amount of the end product produced is regulated by its own concentration. Negative feedback mechanism can effectively adjust the rate of synthesis of intermediate metabolites according to the demands of the cells. This helps with effective allocations of materials and energy economy, and it prevents the excess manufacture of end products. Like other homeostatic devices, the control of enzymatic action helps to maintain a stable internal environment in living organisms.

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Enzymes: Enzyme-naming conventions

By common convention, an enzyme's name consists of a description of what it does, with the word ending in *-ase*. Examples are alcohol dehydrogenase and DNA polymerase. Kinases are enzymes that transfer phosphate groups. This results in different enzymes with the same function having the same basic name; they are therefore distinguished by other characteristics, such as their optimal pH (alkaline phosphatase) or their location (membrane ATPase). Furthermore, the reversibility of chemical reactions means that the normal physiological direction of an enzyme's function may not be that observed under laboratory conditions. This can result in the same enzyme being identified with two different names: one stemming from the formal laboratory identification as described above, the other representing its behavior in the cell. For instance the enzyme formally known as *xylitol:NAD+ 2-oxidoreductase (D-xylulose-forming)* is more commonly referred to in the cellular physiological sense as *D-xylulose reductase*, reflecting the fact that the function of the enzyme in the cell is actually the reverse of what is often seen under *in vitro* conditions.

The International Union of Biochemistry and Molecular Biology has developed a nomenclature for enzymes, the EC numbers; each enzyme is described by a sequence of four numbers, preceded by "EC". The first number broadly classifies the enzyme based on its mechanism:

The toplevel classification is

- EC 1 *Oxidoreductases*: catalyze oxidation/reduction reactions

- EC 2 *Transferases*: transfer a functional group (e.g. a methyl or phosphate group)

- EC 3 *Hydrolases*: catalyze the hydrolysis of various bonds

- EC 4 *Lyases*: cleave various bonds by means other than hydrolysis and oxidation

- EC 5 *Isomerases*: catalyze isomerization changes within a single molecule

-EC 6 *Ligases*: join two molecules with covalent bonds

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Enzymes: Thermodynamics

As with all catalysts, all reactions catalyzed by enzymes must be "spontaneous" (containing a net negative Gibbs free energy). With the enzyme, they run in the same direction as they would without the enzyme, just more quickly. However, the uncatalyzed, "spontaneous" reaction might lead to different products than the catalyzed reaction. Furthermore, enzymes can couple two or more reactions, so that a thermodynamically favorable reaction can be used to "drive" a thermodynamically unfavorable one. For example, the cleavage of the high-energy compound ATP is often used to drive other, energetically unfavorable chemical reactions.

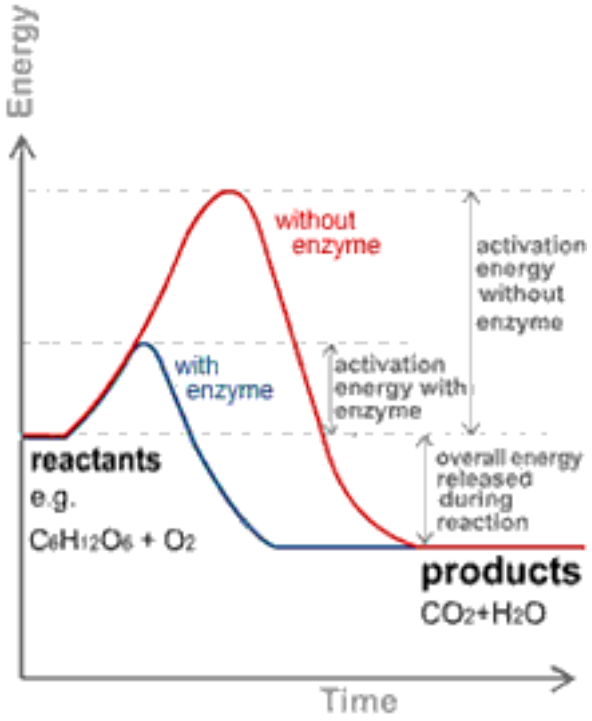

Diagram of a catalytic reaction, showing the energy niveau at each stage of the reaction. The substrates usually need a large amount of energy to reach the transition state, which then reacts to form the end product. The enzyme stabilizes the transition state, reducing the energy of the transition state and thus the energy required to get over this barrier.

Enzymes catalyze the forward and backward reactions equally. They do not alter the equilibrium itself, but only the speed at which it is reached. Carbonic anhydrase catalyzes its reaction in either direction depending on the conditions. $CO_2 + H_2O \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3$ (in tissues - high CO_2 concentration)

$H_2CO_3 \xrightarrow{\text{Carbonic anhydrase}} CO_2 + H_2O$ (in lungs - low CO_2 concentration)

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Enzymes: 3D Structure

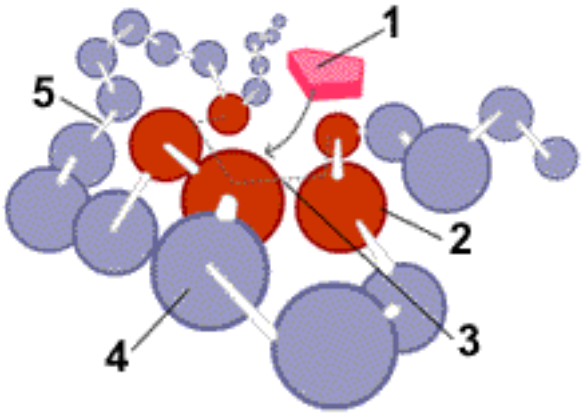
In enzymes, as with other proteins, function is determined by structure. An enzyme can be:

- A monomeric protein, *i.e.*, containing only one polypeptide chain, typically one hundred or more amino acids; or

- an oligomeric protein consisting of several polypeptide chains, different or identical, that act together as a unit.

As with any protein, each monomer is actually produced as a long, linear chain of amino acids, which folds in a particular fashion to produce a three-dimensional product. Individual monomers may then combine via non-covalent interactions to form a multimeric protein. Many enzymes can be unfolded or inactivated by heating, which destroys the three-dimensional structure of the protein.

A polypetide chain folded into a three-dimensional enzyme molecule



1. substrate molecule bound to the active site of the enzyme molecule
2. amino acid molecule involved in active site formation
3. active site
4. amino acid molecule
5. peptide bond

Most enzymes are larger than the substrates they act on and only a very small portion of the enzyme, around 10 amino acids, come into direct contact with the substrate(s). This region, where binding of the substrate(s) and then the reaction occurs, is known as the active site of the enzyme. Some enzymes contain sites that bind cofactors, which are needed for catalysis. Certain enzymes have binding sites for small molecules, which are often direct or indirect products or substrates of the reaction catalyzed. This binding can serve to increase or decrease the enzyme's activity (depending on the molecule and enzyme), providing a means for feedback regulation.

Modifications

Many enzymes contain not only a protein part but need additionally various modifications. These modifications are made *posttranslational*, *i.e.*, after the polypeptide chain is synthesized. Additional groups can be synthesized onto the polypeptide chain, *e.g.*, phosphorylation or glycosylation of the enzyme.

Another kind of posttranslational modification is the cleavage and splicing of the polypeptide chain. Chymotrypsin, a digestive protease, is produced in inactive form as chymotrypsinogen in the pancreas and transported in this form to the stomach where it is activated. This prevents the enzyme from harmful digestion of the pancreas or other tissue. This type of inactive precursor to an enzyme is known as a zymogen.

Enzyme cofactors

Some enzymes do not need any additional components to exhibit full activity. However, others require non-protein molecules to be bound for activity. Cofactors can be either inorganic (*e.g.*, metal ions and Iron-sulfur clusters) or organic compounds, which are also known as coenzymes.

Enzymes that require a cofactor, but do not have one bound are called apoenzymes. An apoenzyme together with its cofactor(s) constitutes a holoenzyme (*i.e*, the active form). Most cofactors are not covalently bound to an enzyme, but are closely associated. However, some cofactors known as prosthetic groups are covalently bound (*e.g.*, thiamine pyrophosphate in certain enzymes).

Most cofactors are either regenerated or chemically unchanged at the end of the reactions. Many cofactors are vitamin-derivatives and serve as carriers to transfer electrons, atoms, or functional groups from an enzyme to a substrate. Common examples are NAD and NADP, which are involved in electron transfer and coenzyme A, which is involved in the transfer of acetyl groups.

Allosteric modulation

Allosteric enzymes change their structure in response to binding of effectors. Modulation can be direct, where effectors bind directly to binding sites in the enzyme, or indirect, where the effector binds to other proteins or protein subunits that interact with the allosteric enzyme and thus influence catalytic activity.

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Ubiquitin

Ubiquitin is a small regulatory protein that is *ubiquitous* in eukaryotes. **Ubiquitination** (or **Ubiquitylation**) refers to the Post-translational modification of a protein by the covalent attachment (via an isopeptide bond) of one or more ubiquitin monomers. Ubiquitin (originally, **Ubiquitous Immunopoeitic Polypeptide**) was first identified in 1975 as an 8.5 kDa protein of unknown function expressed universally in living cells. The basic functions of ubiquitin and the components of the ubiquitination pathway were elucidated in the early 1980s in groundbreaking work performed by Aaron Ciechanover, Avram Hershko and Irwin Rose for which the Nobel Prize in Chemistry was awarded in 2004.

The ubiquitylation system was initially characterised as an ATP-dependent proteolytic system present in cellular extracts. A heat-stable polypeptide present in these extracts, ATP-dependent proteolysis factor 1 (APF-1), was found to become covalently attached to the model protein substrate lysozyme in an ATP and Mg^{2+}-dependent process. Multiple APF-1 molecules were linked to a single substrate molecule by an isopeptide linkage and conjugates were found to be rapidly degraded with the release of free APF-1. Soon after APF-1-protein conjugation was characterised, APF-1 was identified as ubiquitin. The carboxyl group of the C-terminal glycine residue of ubiquitin (Gly76) was identified as the moiety conjugated to substrate lysine residues.

The protein

Ubiquitin properties (human)

Number of residues: 76

Molecular mass: 8564.47 Da

Isoelectric point (pI): 6.79

Gene names: RPS27A (UBA80, UBCEP1), UBA52 (UBCEP2), UBB, UBC

Ubiquitin is a small protein that occurs in all eukaryotic cells. Its main function is to mark other proteins for destruction, known as proteolysis. Several ubiquitin molecules attach to the condemned protein (polyubiquitination), and it then moves to a proteasome, a barrel-shaped structure where the proteolysis occurs. Ubiquitin can also mark transmembrane proteins (for example, receptors) for removal from membranes and fulfill several signalling roles within the cell.

Ubiquitin consists of 76 amino acids and has a molecular mass of about 8500 Da. It is highly conserved among eukaryotic species: Human and yeast ubiquitin share 96% sequence identity. The human ubiquitin sequence is:

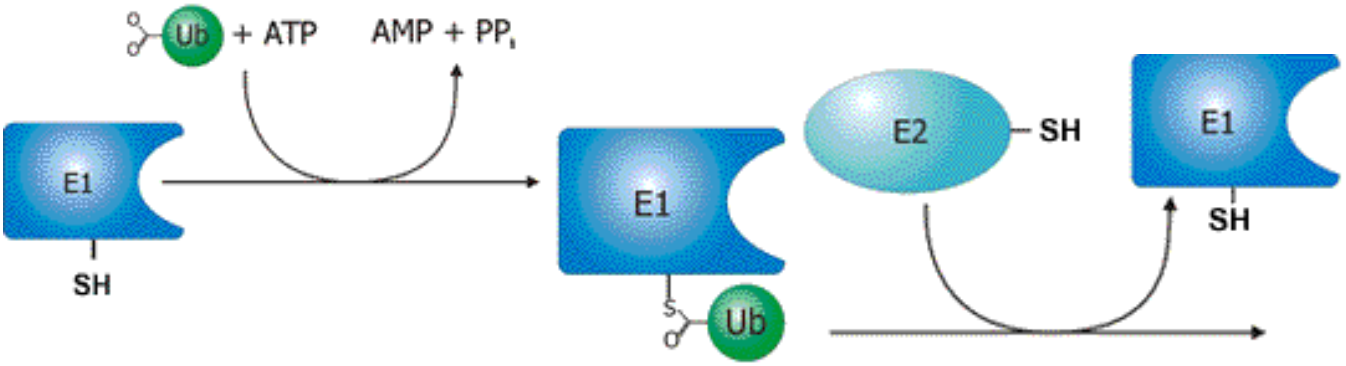
```
MQIFVKTLTGKTITLEVEPSDTIENVKAKIQDKEGIPPDQQRLIFAGKQLEDGRTLSDYNIQKESTLHLVLRLRGG
```

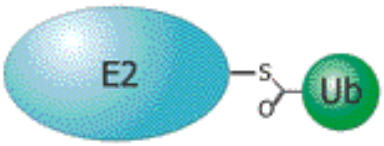
Ubiquitylation

The process of marking a protein with ubiquitin (ubiquitylation or ubiquitination) consists of a series of steps:

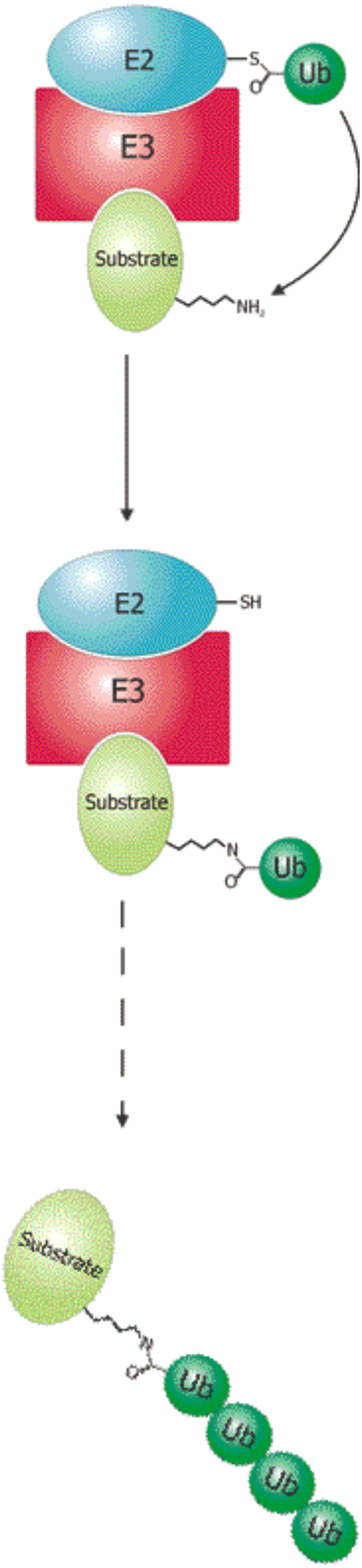
- Activation of ubiquitin - Ubiquitin is activated in a two-step reaction by an E1 ubiquitin-activating enzyme in a process requiring ATP as an energy source. The initial step involves production of an ubiquitin-adenylate intermediate. The second step transfers ubiquitin to the E1 active site cysteine residue, with release of AMP. This step results in a thioester linkage between the C-terminal carboxyl group of ubiquitin and the E1 cysteine sulfhydryl group.
- Transfer of ubiquitin from E1 to the active site cysteine of an ubiquitin-conjugating enzyme E2 via a trans(thio) esterification reaction.
- The final step of the ubiquitylation cascade generally requires the activity of an E3 ubiquitin-protein ligase (often termed simply ubiquitin ligase). E3 enzymes function as the substrate recognition modules of the system and are capable of interaction with both E2 and substrate. E3 enzymes possess one of two domains: - The **HECT** (Homologous to the E6-AP Carboxyl Terminus) domain
- The **RING** domain (or the closely related **U-box** domain)

Transfer can occur in two ways: - Directly from E2, catalysed by RING domain E3s.
- Via an E3 enzyme, catalysed by HECT domain E3s. In this case, a covalent E3-ubiquitin intermediate is formed prior to transfer of ubiquitin to the substrate protein.





Ubiquitin


E2
S
O
Ub
E3
Substrate
NH2
E2
SH
E3
Substrate
N
O
Ub
Substrate
N
O
Ub
Ub
Ub
Ub

In many cases, ubiquitin molecules are further added on to previously-conjugated ubiquitin molecules to forms a polyubiquitin chain. If the chain is longer than 3 ubiquitin molecules, the tagged protein is rapidly degraded by the 26S-proteasome into small peptides (usually 3-24 amino acid residues in length). Ubiquitin moieties are cleaved off the protein by deubiquitinating enzymes and are recycled for further use.

Cell-surface transmembrane molecules that are tagged with ubiquitin are often mono-ubiquitinated, and this modification alters the subcellular localization of the protein, often targeting the protein for destruction in lysosomes.

The ubiquitin pathway is thought to be the method of cellular egress for a number of retroviruses, including HIV and Ebola, but the exact mechanism by which this occurs has yet to be deduced.

The Anaphase-promoting complex (APC) and the SCF complex (for Skp1-Cullin-F-box protein complex) are two examples of multi-subunit E3s involved in recognition and ubiquitination of specific target proteins for degradation by the proteasome.

Disease association

Genetic disorders

- The gene whose disruption causes Angelman syndrome, *UBE3A*, encodes an ubiquitin ligase (E3) enzyme termed E6-AP.
- The gene disrupted in Von Hippel-Lindau syndrome encodes an ubiquitin E3 ligase termed the VHL tumor suppressor or VHL gene.

Immunohistochemistry

Antibodies to ubiquitin are used in histology to identify abnormal accumulations of protein inside cells that are markers of disease. These accumulations are called inclusion bodies. Examples of such abnormal inclusions in cells are

- Neurofibrillary tangles in Alzheimer's disease
- Lewy body in Parkinson's disease
- Pick bodies in Pick's disease
- Inclusions in motor neuron disease
- Mallory's Hyalin in alcoholic liver disease
- Rosenthal fibres in astrocytes

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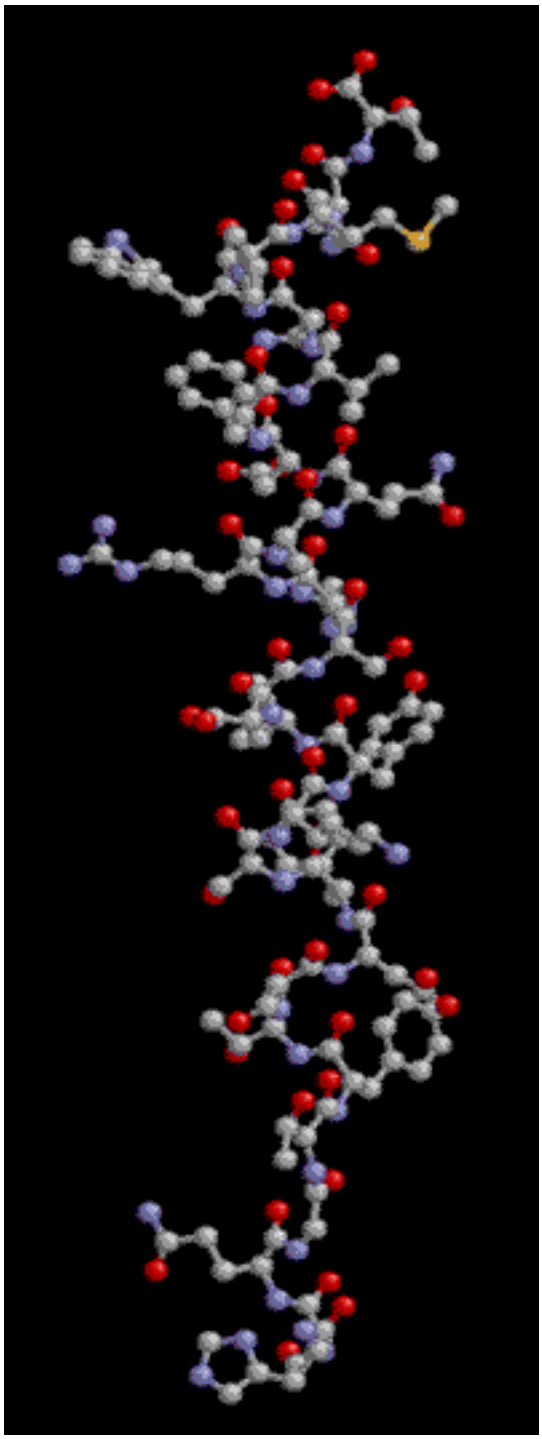
Glucagon



Glucagon *is a 29-amino acid polypeptide acting as an important hormone in carbohydrate metabolism. The polypeptide has a molecular weight of 3485 daltons and was discovered in 1923 by Kimball and*

Murlin.

Its primary structure is: NH_2-His-Ser-Gln-Gly-Thr-Phe- Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu- Met-Asn-Thr-COOH

History

In the 1920s, Kimball and Murlin studied pancreatic extracts and found an additional substance with hyperglycemic properties. Glucagon was sequenced in the late-1950s, but a more complete understanding of its role in physiology and disease was not established until the 1970s, when a specific radioimmunoassay was developed.

Physiology

The hormone is synthesized and secreted from alpha cells (α-cells) of the Islets of Langerhans, which are located in the endocrine portion of the pancreas. The alpha cells are located in the outer rim of the islet.

Regulation

Stimulus for increased secretion of glucagon

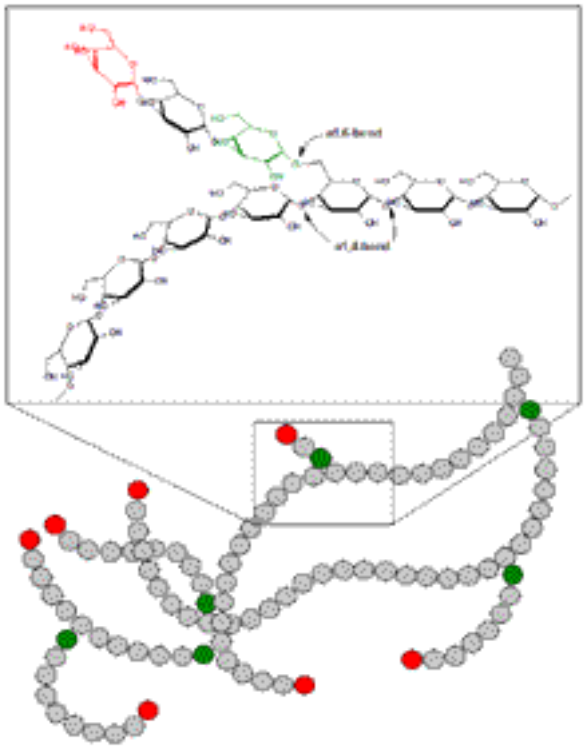
- Decreased plasma glucose
- Increased catecholamines
- Increased plasma amino acids (to protect from hypoglycemia if an all protein meal consumed)
- Sympathetic nervous system

Stimulus for decreased secretion of glucagon (Inhibition)

- Somatostatin
- Insulin

Function

- Glucagon helps maintain the level of glucose in the blood by binding to specific receptors on hepatocytes, causing the liver to release glucose - stored in the form of glycogen - through a process known as glycogenolysis.



Glycogen structure

As these stores become depleted, glucagon then encourages the liver to synthesize additional glucose by gluconeogenesis. This glucose is released into the bloodstream. Both of these mechanisms lead to glucose release by the liver, preventing the development of hypoglycemia.
- Increased free fatty acids and ketoacids into the blood
- Increased urea production

Mechanism of action

- Acts via cAMP generation

Pathology

Abnormally-elevated levels of glucagon may be caused by pancreatic cancers such as glucagonoma, symptoms of which include necrolytic migratory erythema (NME).

Pharmacological application of glucagon

An injectable form of glucagon is essential first aid in cases of severe hypoglycemia. The glucagon is given by intramuscular injection, and quickly raises blood glucose levels.

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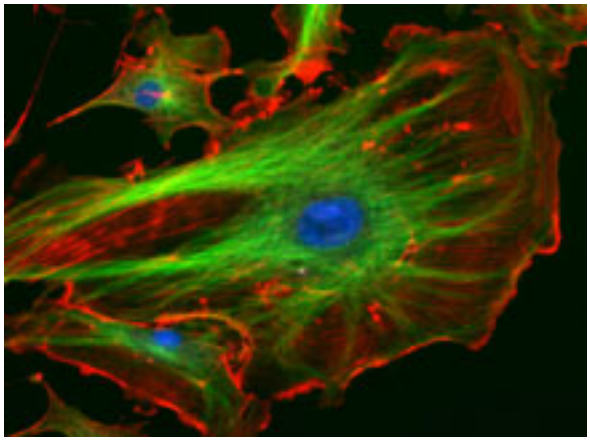
Cytoskeleton



The eukaryotic cytoskeleton. **Actin** filaments are shown in red, **microtubules** in green, and the **nuclei** are in blue.

The **cytoskeleton** is a cellular "scaffolding" or "skeleton" contained, as all other organelles, within the cytoplasm. It is contained in all cells, including plant and animal cells as well as prokaryotic and eukaryotic cells. It is a dynamic structure that maintains cell shape, enables some cell motion (using structures such as flagella and cilia), and plays important roles in both intra-cellular transport (the movement of vesicles and organelles, for example) and cellular division.

The eukaryotic cytoskeleton

Eukaryotic cells contain three kinds of cytoskeletal filaments.

Actin filaments

Around 7 nm in diameter, this filament is composed of two actin chains oriented in an helicoidal shape. They are mostly concentrated just beneath the plasma membrane, as they keep cellular shape, form cytoplasmatic protuberances (like pseudopodia and microvilli), and participate in some cell-to-cell or cell-to-matrix junctions and in the transduction of signals. They are also important for cytokinesis and, along with myosin, muscular contraction.

Intermediate filaments

These filaments, 8 to 11 nanometers in diameter, are the more stable (strongly bound) and heterogeneous constitutents of the cytoskeleton. They organize the internal tridimensional structure of the cell (they are structural components of the nuclear envelope or the sarcomeres for example). They also participate in some cell-cell and cell-matrix junctions.

Different intermediate filaments are:
• made of vimentins, being the common structural support of many cells.
• made of keratin, found in skin cells, hair and nails.
• neurofilaments of neural cells.
• made of lamin, giving structural support to the nuclear envelope.

Microtubules

They are hollow cylinders of about 25 nm, formed by 13 protofilaments which, in turn, are polymers of alpha and beta tubulin. They have a very dynamic behaviour, binding GTP for polymerization. They are organized by the centrosome.

They play key roles in:
• intracellular transport (associated with dyneins and kinesins they transport organelles like mitochondria or vesicles).
• the axoneme of cilia and flagella.
• the mitotic spindle.
• synthesis of the cell wall in plants.

A fourth eukaryotic cytoskeletal element, microtrabeculae, were proposed by Keith Porter in the 1960s. Porter's lab observed short, filamentous structures of unknown molecular composition in electron micrographs of whole cells. Due to their filamentous appearance and association with known cytoplasmic structures, microtrabeculae were speculated to represent a novel filamentous network distinct from microtubules, filamentous actin, or intermediate filaments. However, they were later shown to be an artifact of certain types of fixation treatments by Hans Ris and others.

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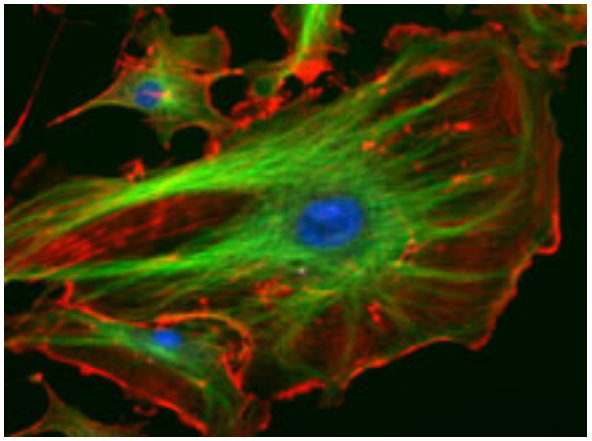
Actin

Microfilaments assembly | Organization | Bundles | Muscular contraction | Networks | Genetics | History



The eukaryotic cytoskeleton. **Actin** filaments are shown in red, **microtubules** in green, and the **nuclei** are in blue.

Actin is a globular structural protein that polymerizes in a helically fashion to form actin filaments (or microfilaments). These form the cytoskeleton - a three-dimensional network inside an eukaryotic cell. Actin filaments provide mechanical support for the cell, determine the cell shape, enable cell movements (through lamellipodia, filopodia, or pseudopodia); and participate in certain cell junctions, in cytoplasmic streaming and in contraction of the cell during cytokinesis. In muscle cells they play an essential role, along with myosin, in muscle contraction. In the cytosol, actin is predominantly bound to ATP, but can also bind to ADP. An ATP-actin complex polymerizes faster and dissociates slower than an ADP-actin complex. Actin is one of the most abundant proteins in many eukaryotic cells, with concentrations of over 100 μM. It is also one of the most highly conserved proteins, differing by no more than 5% in species as diverse as algae and humans.

F-Actin; surface representation of 13 subunit repeat based on Ken Holmes' actin filament model

Microfilaments assembly

The individual subunits of actin are known as globular actin (G-actin), while the filamentous polymer composed of G-actin subunits (a microfilament), is called F-actin. The microfilaments are the thinnest component of the cytoskeleton, measuring only 7 nm in diameter. Much like the microtubules, actin filaments are polar, with a fast growing plus (+) or barbed end and a slow growing minus (-) or pointed end. The terms *barbed* and

pointed end

come from the arrow-like appearance of microfilaments decorated with the motor domain of myosin as seen in electronmicrographs. Filaments elongate approximately 10 times faster at the plus (+) end than the minus (-) end. This phenomenon is known as the treadmill effect. The process of actin polymerization, nucleation, starts with the association of three G-actin monomers into a trimer. ATP-actin then binds the plus (+) end, and the ATP is subsequently hydrolyzed, which reduces the binding strength between neighboring units and generally destabilizes the filament. ADP-actin dissociates from the minus end and the increase in ADP-actin stimulates the exchange of bound ADP for ATP, leading to more ATP-actin units. This rapid turnover is important for the cell's movement. End-capping proteins such as CapZ prevent the addition or loss of monomers at the filament end where actin turnover is unfavourable like in the muscle apparatus.

The protein cofilin binds to ADP-actin units and promotes their dissociation from the minus end and prevents their reassembly. The protein profilin reverses this effect by stimulating the exchange of bound ADP for ATP. In addition, ATP-actin units bound to profilin will dissociate from cofilin and are then free to polymerize. Another important component in filament production is the Arp2/3 complex, which nucleates new actin filaments while bound to existing filaments, thus creating a branched network. All of these three proteins are regulated by cell signaling mechanism.

Organization

Actin filaments are assembled in two general types of structures: bundles and networks. Actin-binding proteins dictate the formation of either structure since they cross-link actin filaments. Actin filaments have the appearance of a double-stranded helix.

Bundles

In non-muscle actin bundles, the filaments are held together such that they are parallel to each other by actin-bundling proteins and/or cationic species. Bundles play a role in many cellular processes such as cell division (cytokinesis) and cell movement. For example, in vertebrates, the actin-bundling protein villin is almost entirely responsible for causing bundle formations in the microvilli of intestinal cells.

Muscular contraction

Actin, together with myosin filaments, form actomyosin, which provides the mechanism for muscle contraction. Muscular contraction uses ATP for energy. The ATP allows, through hydrolysis, the myosin head to extend up and bind with the actin filament. The myosin head then releases after moving the actin filament in a relaxing or contracting movement by usage of ADP.

In contractile bundles, the actin-bundling protein actinin separates each filament by 40 nm. This increase in distance allows the motor protein myosin to interact with the filament, enabling deformation or

contraction. In the first case, one end of myosin is bound to the plasma membrane while the other end walks towards the plus end of the actin filament. This pulls the membrane into a different shape relative to the cell cortex. For contraction, the myosin molecule is usually bound to two separate filaments and both ends simultaneously walk towards their filament's plus end, sliding the actin filaments over each other. This results in the shortening, or contraction, of the actin bundle (but not the filament). This mechanism is responsible for muscle contraction and cytokinesis, the division of one cell into two.

Networks

Actin networks, along with many actin-binding proteins (such as the Arp2/3 complex and filamin) form a complex network at the cortical regions of the cell. Recent studies have also suggested that actin network on the cell cortex serve as barriers for molecular diffusion within the plasmic membrane.

Genetics

Actin is one of the most highly conserved proteins, with 80.2% sequence conservation at the gene level between Homo sapiens and Saccharomyces cerevisiae, and 95% conservation of the primary structure of the protein product.

Although most yeasts have only a single actin gene, higher eukaryotes generally express several isoforms of actin encoded by a family of related genes. Mammals have at least six actins, which are divided into three classes (alpha, beta and gamma) according to their isoelectric point. Alpha actins are generally found in muscle, whereas beta and gamma isoforms are prominent in non-muscle cells. Although there are small differences in sequence and properties between the isoforms, all actins assemble into microfilaments and are essentially identical in the majority of tests performed in vitro.

The typical actin gene has an approximately 100 nucleotide 5' UTR, a 1200 nucleotide translated region, and a 200 nucleotide 3' UTR. The majority of actin genes are interrupted by introns, with up to 6 introns in any of 19 well-characterised locations. The high conservation of the family makes actin the favoured model for studies comparing the introns-early and introns-late models of intron evolution.

All non-spherical prokaryotes appear to possess genes such as MreB which encode homologues of actin; these genes are required for the cell's shape to be maintained. The plasmid-derived gene ParM encodes an actin-like protein whose polymerised form is dynamically unstable, and appears to partition the plasmid DNA into the daughter cells during cell division by a mechanism analogous to that employed by microtubules in eukaryotic mitosis.

History

Actin was first observed experimentally in 1887 by W.D. Halliburton, who extracted a protein from muscle which 'coagulated' preparations of myosin, and which he dubbed "myosin-ferment". However, Halliburton was unable to further characterise his findings and the discovery of actin is generally

credited instead to Brúnó F. Straub, a young biochemist working in Albert Szent-Gyorgyi's laboratory at the Institute of Medical Chemistry at the University of Szeged, Hungary.

In 1942 Straub developed a novel technique for extracting muscle protein that allowed him to isolate substantial amounts of relatively pure actin. Straub's method is essentially the same as that used in laboratories today. Szent-Gyorgyi had previously described the more viscous form of myosin produced by slow muscle extractions as 'activated' myosin, and since Straub's protein produced the activating effect, it was dubbed 'actin'. The hostilities of World War II meant that Szent-Gyorgyi and Straub were unable to publish the work in Western scientific journals; it became well-known in the West only in 1945, when it was published as a supplement to the Acta Physiologica Scandinavica.

Straub continued to work on actin and in 1950 reported that actin contains bound ATP and that, during polymerisation of the protein into microfilaments, the nucleotide is hydrolysed to ADP and inorganic phosphate (which remain bound in the microfilament). Straub suggested that the transformation of ATP-bound actin to ADP-bound actin played a role in muscular contraction. In fact this is only true in smooth muscle, and was not experimentally supported until 2001.

The crystal structure of G-actin was solved in 1990 by Kabsch and colleagues. In the same year a model for F-actin was proposed by Holmes and colleagues. The model was derived by fitting a helix of G-actin structures according to low-resolution fibre diffraction data from the filament. Several models of the filament have been proposed since. However there is still no x-ray structure of F-actin.

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Flagellin

Flagellin is a protein that arranges itself in a hollow cylinder to form the filament in bacterial flagellum. It has a mass of about 30,000 to 60,000 daltons. Flagellin is the principal substituent of bacterial flagellum, and is present in large amounts on nearly all flagellated bacteria.

The structure of flagellin is responsible for the helical shape of the flagellar filament, which is important for its proper function.

The N- and C-termini of flagellin form the inner core of the flagellin protein, and is responsible for flagellin's ability to polymerize into a filament. The central portion of the protein makes up the outer surface of the flagellar filament. While the termini of the protein is quite similar between all bacterial flagellins, the central portion is wildly variable. Mammals often have acquired immune responses (T-cell and antibody responses) to flagellated bacterium occurs frequently to flagellar antigens. Some bacteria are able to switch between multiple flagellin genes in order to evade this response.

The propensity of the immune response to flagellin may be explained by two facts - first, flagellin is an extremely abundant protein in flagellated bacteria. Secondly, there exists a specific innate immune receptor that recognizes flagellin, Toll-like receptor 5 (TLR5).

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Intermediate filament

Intermediate filaments (IFs) are a component of the cytoskeleton - important structural components of living cells. Their size is intermediate between that of microfilaments and microtubules. They are assembled from several different proteins. IFs crisscross the cytosol from the nuclear envelope to the cell membrane.

Each IF molecule has a globular domain at both ends, separated by a long alpha-helical region. IFs are formed of dimers in which the two monomers are joined by the winding of their alpha-helical parts into a coiled coil, oriented in the same direction. Two dimers join side-by-side, anti-parallel, forming a tetramer. Each dimer is 48 nanometers long; because the dimers are staggered the tetramer is somewhat longer. The anti-parallel orientation of tetramers means that, unlike microtubules and microfilaments which have a plus end and a minus end, IFs lack polarity.

Although they cannot undergo treadmilling as microtubules and microfilaments, IFs are dynamic, continually disassembled into soluble tetramers and reassembled into filaments. Until 2003 IFs were thought to be static structural components.

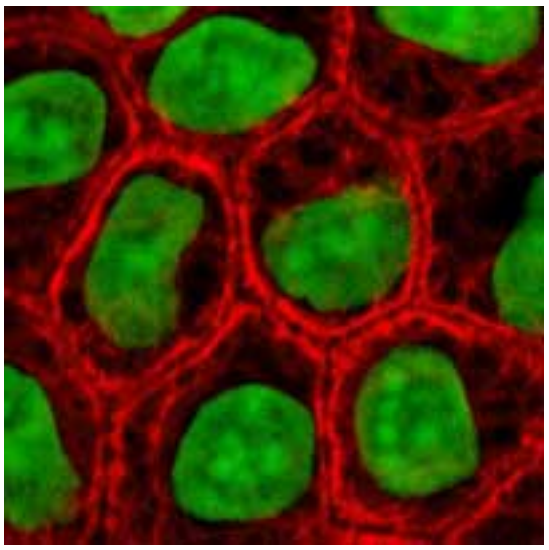
Types

Different kinds of IFs share basic characteristics: they are from 9 to 11 nm. in diameter and are very stable; their main function being a structural one. Different types of IFs are distinguished by the protein each is made of.

Lamin IFs

These proteins localize to two distict regions of the nuclear compartment. The first is the nuclear lamina, a proteinaceous layer located at the inner surface of the inner nuclear envelope membrane. The second is throughout the nucleoplasm in a structure termed the nucleoplasmic veil. Human cells express two types of lamin, A and B, from three differentially regulated genes. Lamin A and C are the most common A-type lamins and are splice variants of the LMNA gene found at 1q21. B type lamins, B1 and B2, are expressed from the LMNB1 and LMNB2 genes on 5q23 and 19q13, respectively.

Keratin IFs


keratin intermediate filaments

These proteins are the most diverse among IFs. The many isoforms are divided in two groups: "soft" keratins (cytokeratins) in epithelial cells (image to right), and "hard" keratins (hair keratins) which make up hair, nails, horns and reptilian scales. Regardless of the group, keratin can be acidic or basic. Acidic and basic keratins can bind each other to form acidic-basic heterodimers, these heterodimers can then associate to make a keratin filament.

Type III IFs

• **Desmin** IFs are structural components of the sarcomeres in muscle cells.
• **Vimentin** IFs can be found in fibroblasts and endothelial cells, they support the cell membrane and keep some organelles in a fixed place within the cytoplasm.
• **Peripherin** found in peripheral neurons.
• **GFAP** (glial fibrillary acidic protein) is found in astrocytes.

Neurofilaments

• a-Internexin
• Neurofilament-L (designated NF-L for 'light')
• Neurofilament-M (designated NF-M for 'medium')
• Neurofilament-H (designated NF-H for 'heavy')

Neurofilaments are a family of intermediate filaments that is found in high concentrations along the axons of vertebrate neurons. The three types of neurofilament proteins coassemble in vivo, forming a heteropolymer that contain NF-L plus one of the others. The NF-H and NF-M proteins have lengthy C-terminal tail domains that bind to neighboring filaments, generating aligned arrays with a uniform interfilament spacing. During axonal growth, new neurofilament subunits are incorporated all along the axon in a dynamic process that involves the addition of subunits along the filament length, as well as the addition of subunits at the filament ends. After an axon has grown and connected with its target cell, the

diameter of the axon may increase as much as fivefold. The level of neurofilament gene expression seems to directly control axonal diameter, which in turn controls how fast electrical signals travel down the axon.

Axonal structure also depends on microtubules as well as actin filaments. Actin filaments line the cortex of the axon, just beneath the plasma membrane, and actin-based motor proteins such as myosin V are also abundant in the axon, perhaps to help move materials, although their exact function is still unclear. The specialized neurofilaments of nerve cells provide the most important structural support in the axon. A disruption in neurofilament structure, or in the cross-linking proteins that attach the neurofilaments to the microtubules and actin filaments distributed along the axon, can result in axonal disorganization and eventually axonal degeneration.

Plectin-like cross-links between microtubules and neurofilaments are seen in micrographs of nerve cell axons. They may represent intermediate filament associated proteins whose function is to cross-link neurofilaments and microtubules into a stable cytoskeleton. Alternatively, these connections to microtubules may be the long arms of the NF-H, which is known to bind microtubules.

Nestin

Intermediate filament type VI. It is found in neural stem cells.

Cell adhesion

At the plasma membrane, IFs are attached by adapter proteins forming desmosomes (cell-cell adhesion) and hemidesmosomes (cell-matrix adhesion).

Associated proteins

Filaggrin binds to keratin fibers in epidermal cells. Plectin links vimentin to other vimentin fibers, as well as to microfilaments, microtubules, and myosin II.

Keratin filaments in epithelial cells link to desmosomes through plakoglobin, desmoplakin, desmogleins and desmocollins. Similar for desmin filaments in heart muscle cells.

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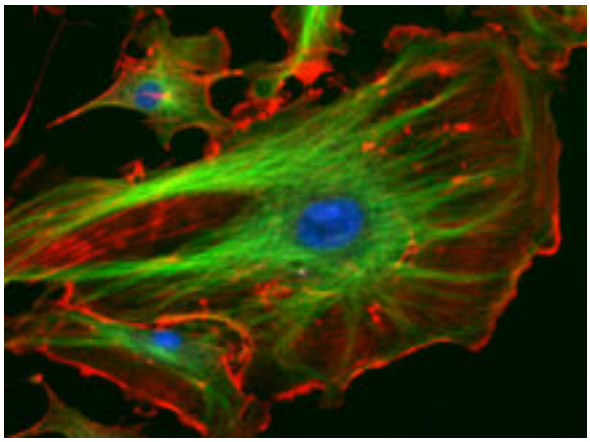
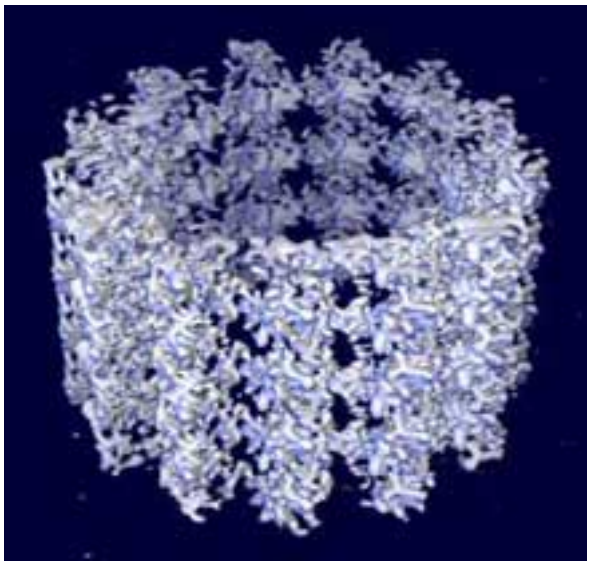
Microtubule



The eukaryotic cytoskeleton. **Actin** filaments are shown in red, **microtubules** in green, and the **nuclei** are in blue.

Microtubules are protein structures found within cells, one of the components of the cytoskeleton. They have diameter of ~ 24 nm and varying length from several micrometers to possible millimeters in axons of nerve cells. Microtubules serve as structural components within cells and are involved in many cellular processes including mitosis, cytokinesis, and vesicular transport.



Structure

Microtubules are polymers of α- and β-tubulin dimers. The tubulin dimers polymerize end to end in protofilaments. The protofilaments then bundle in a hollow cylindrical filaments. Typically, the protofilaments arrange themselves in an imperfect helix with one turn of the helix containing 13 tubulin

dimers each from a different protofilament. The image above illustrates a small section of microtubule, a few αβ dimers in length.

Another important feature of microtubule structure is polarity. Tubulin polymerizes end to end with the a subunit of one tubulin dimer contacting the &ha;β subunit of the next. Therefore, in a protofilament, one end will have the a subunit exposed while the other end will have the β subunit exposed. These ends are designated (-) and (+) respectively. The protofilaments bundle parallel to one another, so in a microtubule, there is one end, the (+) end, with only β subunits exposed while the other end, the (-) end, only has a subunits exposed.

Organization within Cells

Microtubules are nucleated and organized by the microtubule organizing centers (MTOCs), such as centrosomes and basal bodies. They are part of a structural network (the cytoskeleton) within the cell's cytoplasm, but, in addition to structural support, microtubules are used in many other processes, as well. They are capable of growing and shrinking in order to generate force, and there are also motor proteins that move along the microtubule. A notable structure involving microtubules is the mitotic spindle used by eukaryotic cells to segregate their chromosomes correctly during cell division. Microtubules are also part of the cilia and flagella of eukaryotic cells (prokaryote flagella are entirely different).

Nucleation and growth

Polymerization of microtubules is nucleated in a microtubule organizing center. Contained within the MTOC is another type of tubulin, Y-tubulin, which is distinct from the alpha and beta subunits which compose the microtubules themselves. The Y-tubulin combines with several other associated proteins to form a circular structure known as the "Y-tubulin ring complex." This complex acts as a scaffold for α/β tubulin dimers to begin polymerization; it acts as a cap of the (-) end while mictrotubule growth continues away from the MTOC in the (+) direction.

Chemical effects on microtubule dynamics

Microtubule dynamics can also be altered by drugs. For example, the taxane drug class (e.g. paclitaxel or docetaxel), used in the treatment of cancer, blocks dynamic instability by stabilizing GDP-bound tubulin in the microtubule. Thus, even when hydrolysis of GTP reaches the tip of the microtubule, there is no depolymerization and the microtubule does not shrink back. Nocodazole and Colchicine have the opposite effect, blocking the polymerization of tubulin into microtubules.

Motor proteins

In addition to movement generated by the dynamic instability of the microtubule itself, the fibers are substrates along which motor proteins can move. The major microtubule motor proteins are kinesin,

which generally moves towards the [+] end of the microtubule, and dynein, which generally moves towards the [-] end.

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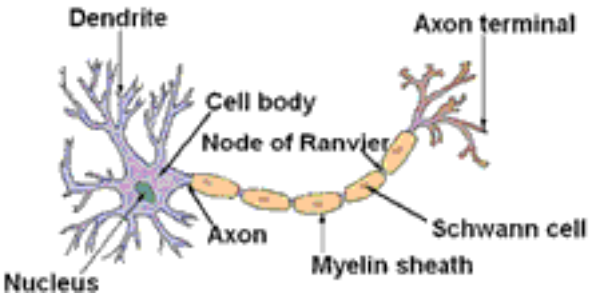
Myelin

In neuroscience, **myelin** is an electrically insulating phospholipid layer that surrounds the axons of many neurons. It is an outgrowth of glial cells: Schwann cells supply the myelin for peripheral neurons while oligodendrocytes supply it to those of the central nervous system. The myelin produced by the different cell types varies in its chemical composition or configuration, but performs the same function. Myelinated neurons are white in appearance, hence the "white matter" of the brain.

Myelin is composed of about 80% lipid fat and about 20% protein. Some of the proteins that make up myelin are Myelin Basic Protein (MBP), Myelin Oligodendrocyte Glycoprotein (MOG) and Proteolipid Protein (PLP). Myelin is made up primarily of a sphingolipid called sphingomyelin, and it is thought that the intertwining of the hydrocarbon chains of sphingomyelin serve to strengthen the myelin sheath.



The main consequence of a myelin layer (or *sheath*) is an increase in the speed at which impulses propagate along the *myelinated* fiber. Along *unmyelinated* fibers, impulses move continuously as waves, but, in myelinated fibers, they hop (or "propagate by saltation"). Myelin increases resistance by a factor of 5,000 and decreases capacitance by a factor of 50. Myelination also helps prevent the electrical current from leaving the axon and causing a short-circuit in the brain. When a peripheral fiber is severed, the myelin sheath provides a track along which regrowth can occur. Unmyelinated fibers and myelinated axons of the mammalian central nervous system do not regenerate.

Demyelination is a loss of myelin and is the root cause of symptoms experienced by patients with diseases such as multiple sclerosis and transverse myelitis. The immune system may play a role in demyelination associated with such diseases. Heavy metal poisoning may also lead to demyelination. When an axon's myelin degrades due to these diseases, conduction can be impaired or lost.

Research is currently being undertaken to repair damaged myelin sheaths. These techniques include surgically implanting oligodendrocyte precursor cells in the central nervous system and inducing myelin repair with certain antibodies. While there have been some encouraging results in mice, it is still unknown whether this research will provide a cure for demyelination-related diseases.

Other research implicates exogenous and endogenous glycations and Advanced Glycation Endproducts are important in the age-related destruction of myelin, particularly in peripheral neuropathy. It is

reasonable to suspect that all nerves, especially high activity nerves such as the sensory nerves in the eye and ear, are similarly affected. Until effective therapies are developed, dietary restriction of exogenous AGEs and strongly glycation forming sugars, such as fructose and galactose, is the best available approach.

Adrenoleukodystrophy (ALD) is a disease that is found in young boys at around age six. This is a degenerative disease that strips myelin off of the nerves. Carriers may become blind, unable to move, and lose control of many other functions. Myelin is important in the function of these abilities.

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Myosin

Myosins are a large family of motor proteins found in eukaryotic tissues. They are responsible for actin-based motility.

Structure and function

Most myosin molecules are composed of both a head and a tail domain. The head domain binds the filamentous actin, and uses ATP hydrolysis to generate force and to "walk" along the filament towards the (+) end (with the exception of one family member, myosin VI, which moves towards the (-) end). The tail domain generally mediates interaction with cargo molecules and/or other myosin subunits. Myosin II, responsible for skeletal muscle contraction, is perhaps the best-studied example of these properties. Myosin II contains two heavy chains, each about 2000 amino acids in length, which constitute the head and tail domains. Each of these heavy chains contains the N-terminal head domain, while the C-terminal tails take on a coiled-coil morphology, holding the two heavy chains together (imagine two snakes wrapped around each other, such as in a caduceus). Thus, myosin II has two heads. It also contains 4 light chains (2 per head), which bind the heavy chains in the "neck" region between the head and tail.

In muscle cells, it is myosin II that is responsible for producing the contractile force. Here, the long coiled-coil tails of the individual myosin molecules join together, forming the thick filaments of the sarcomere. The force-producing head domains stick out from the side of the thick filament, ready to walk along the adjacent actin-based thin filaments in response to the proper chemical signals.

The polarity of an actin filament can be determined by decorating the microfilament with myosin "S1" fragments, creating and barbed (+) and pointed (-) end on the filament. An S1 fragment is composed of the head and neck domains of the myosin II.

Evolution and Family Tree

Myosin II, the most conspicuous of the myosin superfamily due to its abundance in muscle fibers, was the first to be discovered. However, beginning in the 1970s researchers began to discover new myosin variants, with one head as opposed to myosin II's two and largely divergent tail domains. These new superfamily members have been grouped according to their structural similarities, with each subfamily being assigned a Roman numeral. The now diverse array of myosins has evolved from an ancestral precursor. Analysis of the amino acid sequences of different myosins shows great variability among the tail domains but almost perfect retention of the same head sequence. Presumably this is so the myosins may interact, via their tails, with a large number of different cargoes, while the goal in each case - to move along actin filaments - remains the same and therefore requires the same machinery in the motor. For example, the human genome contains over 40 different myosin genes.

These differences in shape also determine the speed at which myosins can move along actin filaments. The hydrolysis of ATP and the subsequent release of the phosphate group causes the "power stroke," in which the "lever arm" or "neck" region of the heavy chain is dragged forward. Since the power stoke always move the lever arm by the same angle, the length of the lever arm determines how fast the cargo will move. A longer lever arm will cause the cargo to traverse a greater distance even though the lever arm undergoes the same angular displacement - just as a person with longer legs can move farther with each individual step. Myosin V, for example, has a much longer neck region than myosin II, and therefore moves 30-40 nanometers with each stroke as opposed to only 5-10.

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Peptidoglycan

Peptidoglycan, also known as **murein**, is a polymer consisting of sugars and amino acids that forms a homogeneous layer outside the plasma membrane of eubacteria. Archaea have a similar layer of pseudopeptidoglycan. Peptidoglycan serves a structural role in the bacterial cell wall, giving the wall shape and structural strength, as well as counteracting the osmotic pressure of the cytoplasm. Peptidoglycan is also involved in binary fission during bacterial cell reproduction.

The peptidoglycan layer is substantially thicker in Gram-positive bacteria (20 to 80 nm) than in Gram-negative bacteria (7 to 8 nm), with the attachment of the S-layer. Peptidoglycan forms around 90% of the dry weight of Gram-positive bacteria but only 10% of Gram-negative strains.

Antibiotic inhibition

Antibacterial drugs such as penicillin target the peptidoglycan layer by interfering with its formation, specifically the crosslinking enzyme transpeptidase. Mutations in the transpeptidase enzyme (also known as *penicillin binding protein* or PBP) which lead to reduced interactions between an antibiotic and the bacterial PBPs are a significant cause of emerging antibiotic resistance.

Structure

The peptidoglycan layer in the bacterial cell wall is a crystal lattice structure formed from linear chains of two alternating amino sugars, namely N-acetyl glucosamine (GlcNAc) and N-acetyl muramic acid (MurNAc). Each MurNAc is attached to a short (4 to 5 residue) amino acid chain. Cross-linking between amino acids in different linear amino sugar chains by an enzyme known as transpeptidase result in a 3-dimensional structure that is strong and rigid. The specific amino acid sequence and molecular structure vary with the bacterial species.

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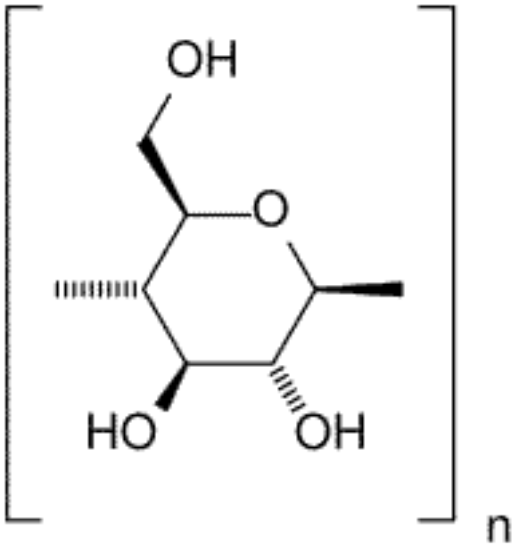
Cellulose

History and applications | Chemistry | Derivatives

Cellulose $(C_6H_{10}O_5)n$ is a long-chain polymeric polysaccharide carbohydrate, of beta-glucose. It forms the primary structural component of green plants. The primary cell wall of green plants is made primarily of cellulose; the secondary wall contains cellulose with variable amounts of lignin. Lignin and cellulose, considered together, are termed lignocellulose, which (as wood) is the most common biopolymer on Earth.



History and applications

Cellulose is a common material in plant cell walls and was first noted as such in 1838. It occurs naturally in almost pure form in cotton fiber. In combination with lignin and hemicellulose, it is found in all plant material. Cellulose is the most abundant form of living terrestrial biomass.

Some animals, particularly ruminants and termites, can digest cellulose with the help of symbiotic micro-organisms. Cellulose is not digestible by humans, and is often referred to as 'dietary fibre' or 'roughage', acting as a hydrophilic bulking agent for faeces.

Cellulose is the major constituent of paper; further processing can be performed to make cellophane and rayon, and more recently Modal, a textile derived from beechwood cellulose. Cellulose is used within the laboratory as a solid-state substrate for thin layer chromatography, and cotton linters, is used in the manufacture of nitrocellulose, historically used in smokeless gunpowder.

Chemistry

Cellulose monomers (β-glucose) are linked together through 1-->4 glycosidic bonds by condensation. Cellulose is a straight chain polymer: unlike starch, no coiling occurs, and the molecule adopts an extended rod-like conformation. In microfibrils, the multiple hydroxyl groups on the glucose residues hydrogen bond with each other, holding the chains firmly together and contributing to their high tensile strength. This strength is important in cell walls, where they are meshed into a carbohydrate matrix, helping keep plant cells rigid.

Given a cellulose material, the portion that does not dissolve in a 17.5% solution of sodium hydroxide at 20 °C is α *cellulose*, which is true cellulose; the portion that dissolves and then precipitates upon acidification is β *cellulose*; and the proportion that dissolves but does not precipitate is γ *cellulose*.

Cellulose can be assayed using a method described by Updegraff in 1969, where the fiber is dissolved in acetic and nitric acid, and allowed to react with anthrone in sulfuric acid. The resulting coloured compound is assayed spectrophotometrically at a wavelength of approximately 635 nm.

Derivatives

The hydroxyl groups of cellulose can be partially or fully reacted with various chemicals to provide derivates with useful properties. Cellulose esters and cellulose ethers are the most important commercial materials. In principle, though not always in current industrial practice, cellulosic polymers are renewable resources.

Among the esters are cellulose acetate and triacetate, which are film- and fiber-forming materials that find a variety of uses. The inorganic ester nitrocellulose was initially used as an explosive and was an early film forming material.

Ether derivatives include

• Ethylcellulose, a water-insoluble commercial thermoplastic used in coatings, inks, binders, and controlled-release drug tablets;
• Hydroxypropyl cellulose;
• Carboxymethyl cellulose;
• Hydroxypropyl methyl cellulose, E464, used as a viscosity modifier, gelling agent, foaming agent and binding agent;
• Hydroxyethyl methyl cellulose, used in production of cellulose films.

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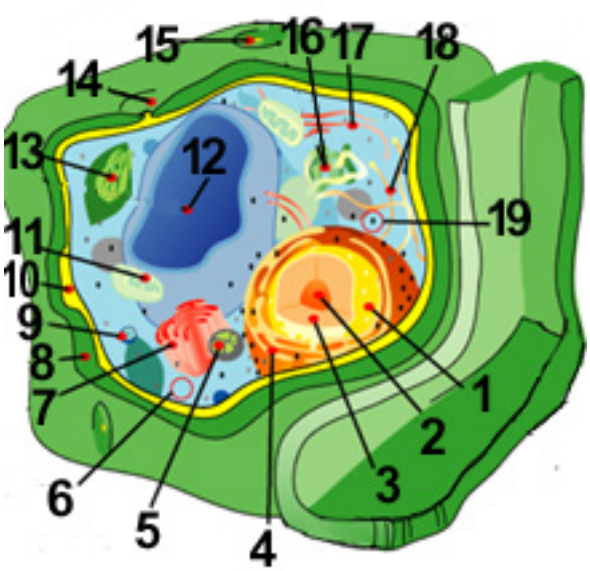
Cell wall

Plant cell walls | Composition of plant cell walls | Algal cell walls | Diatom cell walls | Prokaryotic cell walls | Fungal cell walls

A **cell wall** is a more or less solid layer surrounding a cell. They are found in bacteria, archaea, fungi, plants, and algae. Animals and most other protists have cell membranes without surrounding cell walls. When a cell wall is removed using cell wall degrading enzymes, what is left of the cell and its surrounding plasma membrane is called a protoplast. The cell wall's main purpose is to actually protect the interior from any physical movement that may damage the cell.

Plant cell walls



1. Nuclear envelope
2. Nucleolus
3. Nucleus
4. Rough endoplasmic retuculum
5. Leukoplast
6. Cytoplasm
7. Golgi vesicles (golge apparatus)
8. Cell wall
9. Peroxisome
10. Plasma membrane
11. Mitochodrion (mitochondria)
12. Vacuole
13. Chloroplast
14. Plasmodesmata
15. Plasmodesmata

16. Smooth endoplasmic reticulum
17. Filamentous cytoskeleton
18. Small membranous vesicles
19. Ribosomes

Plant cell walls have a number of functions: they provide rigidity to the cell for structural and mechanical support, maintaining cell shape, the direction of cell growth and ultimately the architecture of the plant. The cell wall also prevents expansion when water enters the cell. The term turgor is used to describe this pressure that is induced by excess water inside the plant cell. Cell walls protect against pathogens and the environment and are a store of carbohydrates for the plant. The cell wall is constructed primarily from a carbohydrate polymer called cellulose.

The *primary cell wall*, built by the plant first, is composed of cellulose microfibrils aligned at all angles. Microfibrils are held together by hydrogen bonds to provide a high tensile strength. Cell walls of neighbouring cells are held together by a shared gelatinous membrane called the *middle lamella*, which contains magnesium and calcium pectates (salts of pectic acid).Cells interact though plasmodesma(ta), which are inter-connecting channels of cytoplasm that connect to the protoplasts of adjacent cells across the cell wall.

In some plants and cell types, after a maximum size or point in development has been reached, a *secondary wall* is constructed between the plant cell and primary wall. Unlike the primary wall, the microfibrils are aligned mostly in the same direction, and with each additional layer the orientation changes slightly. Cells with secondary cell walls are rigid. Cell to cell communication is possible through pits in the secondary cell wall that allow plasmodesma to connect cells through the secondary cell walls.

Composition of plant cell walls

The major carbohydrates making up the primary cell wall are cellulose, pectin and hemicellulose. Insoluble cellulose fibers are meshed in to a matrix called pectin and hemicelluloses; they give the plant strength and support.

Plant cells walls also incorporate a number of proteins; the most abundant include hydroxyproline-rich glycoproteins (HRGP), also called the extensins, the arabinogalactan proteins (AGP), the glycine-rich proteins (GRPs), and the proline-rich proteins (PRPs). With the exception of glycine-rich proteins, all the previously mentioned proteins are glycosylated and contain hydroxyproline (Hyp). Each class of glycoprotein is defined by a characteristic, highly repetitive protein sequence. Chimeric proteins contain two or more different domains, each with a sequence from a different class of glycoprotein. Most cell wall proteins are cross-linked to the cell wall and may have structural functions.

Secondary cell walls may contain lignin and suberin, making the walls rigid.

The relative composition of carbohydrates, secondary compounds and protein varies between plants and between the cell type and age.

Algal cell walls

Like plants, algae have cell walls. Algal cell walls contain cellulose and a variety of glycoproteins. The inclusion of additional polysaccharides in algal cells walls is used as a feature for algal taxonomy.

• Manosyl form microfibrils in the cell walls of a number of marine green algae including those from the genera *Codium*, *Dasycladus*, and *Acetabularia* as well as in the walls of some red algae, like *Porphyra* and *Bangia*.
• Xylanes
• Alginic acid is a common polysaccharide in the cell walls of brown algae
• Sulfonated polysaccharides occur in the cell walls of most algae; those common in red algae include agarose, carrageenan, porphyran, furcelleran and funoran.

Other compounds that may accumulate in algal cell walls include sporopollenin and calcium.

Diatom cell walls

The group of algae known as the diatoms synthesise their cell walls (also known as frustules or valves) from silicic acid (specifically orthosilicic acid, H_4SiO_4). The acid is polymerised intra-cellularly, then the wall is extruded to protect the cell. Significantly, relative to the organic cell walls produced by other groups, silica frustules require less energy to synthesize (approximately 8%), potentially a major saving on the overall cell energy budget.

Prokaryotic cell walls

Cell walls of bacteria are primarily used for protection against hostile environments or, in the case of pathogenic bacteria, against the immune system of the host. They contain peptidoglycan, which can be made visible in Gram-positive bacteria by Gram staining. The cell walls of bacteria are also vital for containing the high osmotic pressure inside bacterial cells caused by the high concentration of solutes in the cytoplasm. This pressure can often be as high as 15 atmospheres. Many antibiotics, including penicillin and its derivatives, target the cell wall of bacteria.

The cell walls of archaea are not made of peptidoglycan, but some archaea may contain pseudopeptidoglycan, which is composed of N-acetyltalosaminuronic acid, instead of N-acetyl muramic acid in peptidoglycan.

Fungal cell walls

Not all species of fungi have cell walls but in those that do, the cell walls are composed of cellulose, glucosamine, and chitin, the same carbohydrate that gives strength to the exoskeletons of insects. They serve a similar purpose to those of plant cells, giving fungal cells rigidity and strength to hold their shape and preventing osmotic lysis. It also limits the entry of molecules that may be toxic to the fungus, like plant-produced and synthetic fungicides.

The composition, properties, and form of the fungal cell wall change during the cell cycle and depend on growth conditions.

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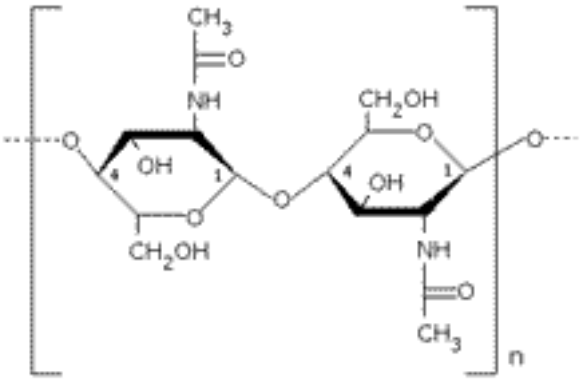
Chitin

Chitin (pronounced *kai-tin*) is one of the main components in the cell walls of fungi, the exoskeletons of insects and other arthropods, and in some other animals. It is considered a polysaccharide; it is constructed from units of acetylglucosamine (more completely, N-acetyl-D-glucos-2-amine). These are linked together in β-1,4 fashion (in a similar manner to the glucose units which form cellulose). In effect chitin may be described as cellulose with one hydroxyl group on each monomer replaced by an acetylamine group. This allows for increased hydrogen bonding between adjacent polymers, giving the polymer increased strength.



Structure of chitin molecule

"Chitin" and "chiton" (a marine animal) both derive from the same Greek word meaning "tunic", referring to the hardness of the shell.

In the honeybee the color of chitin may be yellow, golden, brown or black.

Other uses

• The strength and flexibility of chitin make it the material of choice for surgical thread, which decomposes over time after the wound heals.
• Chitin can be used to produce chitosan, which has a variety of biomedical applications.

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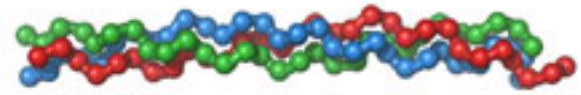
Collagen

Collagen is the main protein of connective tissue in animals and the most abundant protein in mammals, making up about 40% of the total. It is one of the long, fibrous structural proteins whose functions are quite different from those of globular proteins such as enzymes. It is tough and inextensible, with great tensile strength, and is the main component of cartilage, ligaments and tendons, and the main protein component of bone and teeth. Along with soft keratin, it is responsible for skin strength and elasticity, and its degradation leads to wrinkles that accompany aging. It strengthens blood vessels and plays a role in tissue development. It is present in the cornea and lens of the eye in crystalline form. It is also used in cosmetic surgery — for example lip enhancement — although hyaluronic acid is now often used instead.



Tropocollagen triple helix.

Synthesis

Collagen has an unusual amino acid composition and sequence. Glycine (Gly) is found at almost every third residue, and collagen contains large amounts of proline, (Pro) — as well as two uncommon derivative amino acids not directly inserted during translation of mRNA: hydroxyproline (Hypro) and hydroxylysine. Prolines and lysines at specific locations relative to glycine are modified post-translationally by different enzymes, both of which require vitamin C as a cofactor. Vitamin C deficiency causes scurvy, a serious and painful disease in which defective collagen prevents the formation of strong connective tissue. Gums deteriorate and bleed, with loss of teeth; skin discolors, and wounds do not heal. This was notorious in the British Royal Navy, where sailors were deprived of fresh fruits and vegetables during long voyages. Depending on the type of collagen, varying numbers of hydroxylysines have disaccharides attached to them.

Composition and structure

The *tropocollagen* subunit is a rod about 300 nm long and 1.5 nm in diameter, made up of three polypeptide strands, each of which is a left-handed helix. They are twisted together into a right-handed coiled coil, a triple helix, a cooperative quaternary structure stabilized by numerous hydrogen bonds. Tropocollagen subunits spontaneously self-assemble, with regularly staggered ends, into even larger arrays in the extracellular spaces of tissues. There is some covalent crosslinking within the triple helices, and a variable amount of covalent crosslinking between tropocollagen helices, to form the different types of collagen found in different mature tissues — similar to the situation found with the α-keratins in hair. Collagen's insolubility was a barrier to study until it was found that tropocollagen from young

animals can be extracted because it is not yet fully crosslinked.

A distinctive feature of collagen is the regular arrangement of amino acids in each of the three chains of these collagen subunits. The sequence often follows the pattern Gly-X-Pro or Gly-X-Hypro, where X may be any of various other amino acid residues. Gly-Pro-Hypro occurs frequently. This kind of regular repetition and high glycine content is found in only a few other fibrous proteins, such as silk fibroin. 75-80% of silk is (approximately) -Gly-Ala-Gly-Ala- with 10% serine — and elastin is rich in glycine, proline, and alanine (Ala), whose side group is a small, inert methyl. Such high glycine and regular repetitions are never found in globular proteins. Chemically-reactive side groups are not needed in structural proteins as they are in enzymes and transport proteins. The high content of Pro and Hypro rings, with their geometrically constrained carboxyl and (secondary) amino groups, accounts for the tendency of the individual polypeptide strands to form left-handed helices spontaneously, without any intrachain hydrogen bonding. The triple helix tightens under tension, resisting stretching, making collagen inextensible.

Because glycine is the smallest amino acid, it plays a unique role in fibrous structural proteins. In collagen, Gly is required at every third position because the assembly of the triple helix puts this residue at the interior (axis) of the helix, where there is no space for a larger side group than glycine's single hydrogen atom. For the same reason, the rings of the Pro and Hypro must point outward. These two amino acids thermally stabilize the triple helix — Hypro even more so than Pro — and less of them is required in animals such as fish, whose body temperatures are low.

In bone, entire collagen triple helices lie in a parallel, staggered array. 40 nm gaps between the ends of the tropocollagen subunits probably serve as nucleation sites for the deposition of long, hard, fine crystals of the mineral component, which is (approximately) hydroxyapatite, $Ca_5(PO_4)_3(OH)$, with some phosphate. It is in this way that certain kinds of cartilage turn into bone. Collagen gives bone its elasticity and contributes to fracture resistance.

Industrial uses

If collagen is solubilized and heated, the three tropocollagen strands separate into globular, random coils, producing gelatin, which is used in many foods, including flavored desserts. It is not a good dietary source for synthesizing bodily proteins in general because it lacks adequate amounts of most of the essential amino acids. However, collagen hydrolysates (collagen denatured into single strands and broken down into polypeptides) do find nutritional use, where it is suggested they can improve skin quality and aid joint health. These products are particularly popular in Japan.

Collagen means "glue producer" (*kolla* is Greek for glue), derived from the early process of boiling the skin, hooves and sinews of horses and other animals to obtain glue. Collagen adhesive was used by Egyptians about 4,000 years ago, and Native Americans used it in bows about 1,500 years ago. The oldest glue in the world, carbon dated as more than 8,000 years old, was found to be collagen — used as a protective lining on rope baskets and embroidered fabrics, and to hold utensils together; also in

crisscross decorations on human skulls. Collagen normally converts to gelatin, but survived due to the dry conditions. Animal glues are thermoplastic, softening again upon reheating, and so they are still used in making musical instruments such as fine violins and guitars, which may have to be reopened for repairs — an application incompatible with tough, synthetic plastic adhesives, which are permanent. Animal sinews and skins, including leather, have been used to make useful articles for millennia.

Medical Uses

Collagen has been widely used is cosmetic surgery and certain skin substitutes for burns patients. The cosmetic use of collagens is declining because:
1. There is a fairly high rate of allergic reactions causing prolonges redness and requiring inconspicuous patch testing prior to cosmetic use, and
2. Most medical collagen is derrived from cows and the risk of transmitting prion diseases like BSE

Collagens are still employed in the construction of artificial skin substitutes used in the management of severe burns.

Types of collagen

Collagen occurs in many places throughout the body, and occurs in different forms known as types, which include:
• Type I collagen - This is the most abundant collagen of the human body. It is present in scar tissue, the end product when tissue heals by repair. It is found in tendons and the organic part of bone.
• Type II collagen - Articular cartilage
• Type III collagen - This is the collagen of granulation tissue, and is produced quickly by young fibroblasts before the tougher type I collagen is synthesized.
• Type IV collagen - basal lamina; eye lens
• Type V collagen - most interstitial tissue, assoc. with type I, associated with placenta
• Type VI collagen - most interstitial tissue, assoc. with type I
• Type VII collagen - epithelia
• Type VIII collagen - some endothelial cells
• Type IX collagen - cartilage, assoc. with type II
• Type X collagen - hypertrophic and mineralizing cartilage
• Type XI collagen - cartilage
• Type XII collagen - interacts with types I and III
• Type XIII collagen - interacts with types I and II

There are 27 types of collagen in total.

Staining

In histology, the dye methyl violet is used to stain the collagen in tissue samples. The dye methyl blue

can also be used to stain collagen.

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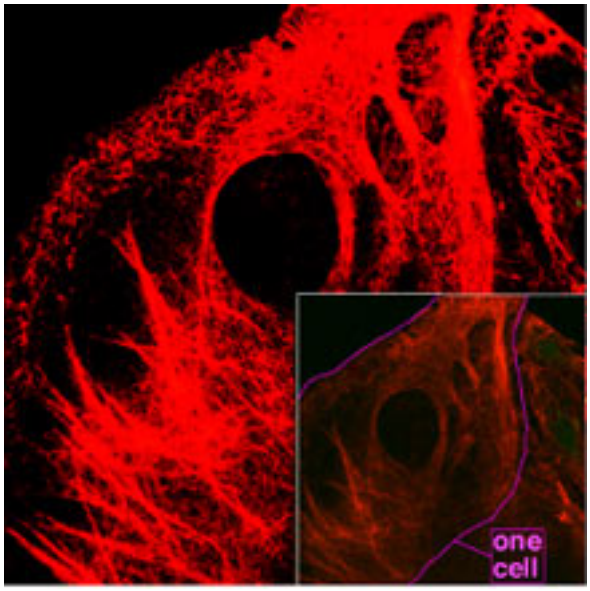
Keratin

Keratins are a family of fibrous structural proteins; tough and insoluble, they form the hard but nonmineralized structures found in reptiles, birds and mammals. The baleen plates of filter-feeding whales are made of them. Keratins are also found in the gastrointestinal tracts of many animals, including roundworms. They are rivaled in biological toughness only by chitin, a cellulose-like polymer of glucosamine and the main constituent of the exoskeletons of arthropods. There are various types of keratins, even within a single animal. Some infectious fungi, such as those which cause athlete's foot and ringworm, feed on keratin. The silk fibroins produced by insects and spiders are often classified as keratins, though it is unclear whether they are phylogenetically related to vertebrate keratins.



Microscopy of keratin filaments inside cells.

Keratin in the Kingdom Animalia

Cells in the epidermis contain a structural matrix of keratin which makes this outermost layer of the skin almost waterproof, and along with collagen and elastin, gives skin its strength. Rubbing and pressure cause keratin to proliferate with the formation of protective calluses — useful for athletes and on the fingertips of musicians who play stringed instruments. Keratinized epidermal cells are constantly shed and replaced.

In mammals there are soft epithelial keratins, the cytokeratins, and harder hair keratins. As certain skin cells differentiate and cornify, pre-keratin polypeptides are incorporated into intermediate filaments. Eventually the nucleus and cytoplasmic organelles disappear, metabolism ceases, and cells undergo a programmed death as they become fully keratinized.

Keratins are the main constituent of structures that grow from the skin: the α-keratins in the hair (including wool), horns, nails, claws and hooves of mammals; also the harder β-keratins in the scales

and claws of reptiles, and their shells (tortoises), and in the feathers, beaks, and claws of birds. These hard, integumentary structures are formed by intercellular cementing of fibers formed from the dead, cornified cells generated by specialized beds deep within the skin. Hair grows continuously and feathers moult and regenerate. The constituent proteins may be phylogenetically homologous but differ somewhat in chemical structure and supermolecular organization. The evolutionary relationships are complex and only partially known. Multiple genes have been identified for the β-keratins in feathers, and this is probably characteristic of all keratins.

Molecular biology and biochemistry

The properties which make structural proteins like keratins useful depend on their supermolecular aggregation. These depend on the properties of the individual polypeptide strands, which depend in turn on their amino acid composition and sequence. The α-helix and β-sheet motifs, and disulfide bridges, are crucial to the conformations of globular, functional proteins like enzymes, many of which operate semi-independently, but they take on a completely dominant role in the architecture and aggregation of keratins.

Keratins contain a high proportion of the smallest of the 20 amino acids, glycine, whose "side group" is a single hydrogen atom; also the next smallest, alanine, with a small and uncharged methyl group. In the case of β-sheets, this allows sterically-unhindered hydrogen bonding between the amino and carboxyl groups of peptide bonds on adjacent protein chains, facilitating their close alignment and strong binding. Fibrous keratin molecules can twist around each other to form helical intermediate filaments.

Limited interior space is the reason why the triple helix of the (unrelated) structural protein collagen, found in skin, cartilage and bone, likewise has a high percentage of glycine. The connective tissue protein elastin also has a high percentage of both glycine and alanine. Silk fibroin, considered a β-keratin, can have these two as 75-80% of the total, with 10-15% serine, with the rest having bulky side groups. The chains are antiparallel, with an alternating C --> N orientation. A preponderance of amino acids with small, unreactive side groups is characteristic of structural proteins, for which H-bonded close packing is more important than chemical specificity.

In addition to intra- and intermolecular hydrogen bonds, keratins have large amounts of the sulfur-containing amino acid cysteine, required for the disulfide bridges that confer additional strength and rigidity by permanent, thermally-stable crosslinking — a role sulfur bridges also play in vulcanized rubber. Human hair is approximately 14% cysteine. The pungent smells of burning hair and rubber are due to the sulfur compounds formed. Extensive disulfide bonding contributes to the insolubility of keratins, except in dissociating or reducing agents such as urea.

The more flexible and elastic keratins of hair have fewer interchain disulfide bridges than the keratins in mammalian fingernails, hooves and claws (homologous structures), which are harder and more like their analogs in other vertebrate classes. Hair and other α-keratins consist of α-helically-coiled single protein strands (with regular intra-chain H-bonding), which are then further twisted into superhelical ropes that

may be further coiled. The β-keratins of reptiles and birds have β-pleated sheets twisted together, then stabilized and hardened by disulfide bridges.

Silk found in insect pupae, and in spider webs and egg casings, also has twisted β-pleated sheets incorporated into fibers wound into larger supermolecular aggregates. The structure of the spinnerets on spiders' tails, and the contributions of their interior glands, provide remarkable control of fast extrusion. Spider silk is typically about 1 to 2 micrometres (μm) thick, compared with about 60 μm for human hair, and more for some mammals. (Hair, or fur, occurs only in mammals.) The biologically and commercially useful properties of silk fibers depend on the organization of multiple adjacent protein chains into hard, crystalline regions of varying size, alternating with flexible, amorphous regions where the chains are randomly coiled. A somewhat analogous situation occurs with synthetic polymers such as nylon, developed as a silk substitute. Silk from the hornet cocoon contains doublets about 10 μm across, with cores and coating, and may be arranged in up to 10 layers; also in plaques of variable shape. Adult hornets also use silk as a glue, as do spiders.

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Lignin

Biological function | Economic significance | Structure and biosynthesis

Lignin (sometimes "**lignen**") is a chemical compound that is most commonly derived from wood and is an integral part of the cell walls of plants, especially in tracheids, xylem fibres and sclereids. It is the second most abundant organic compound on earth after cellulose. Lignin makes up about one-quarter to one-third of the dry mass of wood.

Biological function

Lignin fills the spaces in the cell wall between cellulose, hemicellulose and pectin components. It confers mechanical strength to the cell wall and therefore the entire plant. It is particularly abundant in compression wood, but curiously scarce in tension wood.

Lignin plays a crucial part in conducting water in plant stems. The polysaccharide components of plant cell walls are highly hydrophilic and thus permeable to water. Lignin makes it possible to form vessels which conduct water efficiently.

Lignin is difficult to degrade and is therefore an efficient physical barrier against pathogens which would invade plant tissues. For example an infection by a fungus causes the plant to deposit more lignin near the infection site.

Economic significance

Highly lignified wood is durable and therefore a good raw material for many applications. It is also an excellent fuel, since lignin yields more energy when burned than cellulose. However, lignin is detrimental to paper manufacture and must be removed from pulp before paper can be manufactured. This is costly both in terms of energy and environment.

In the sulfite and sulfate (also called kraft) chemical pulping processes, lignin is removed from wood pulp as sulphates. These materials have several uses:

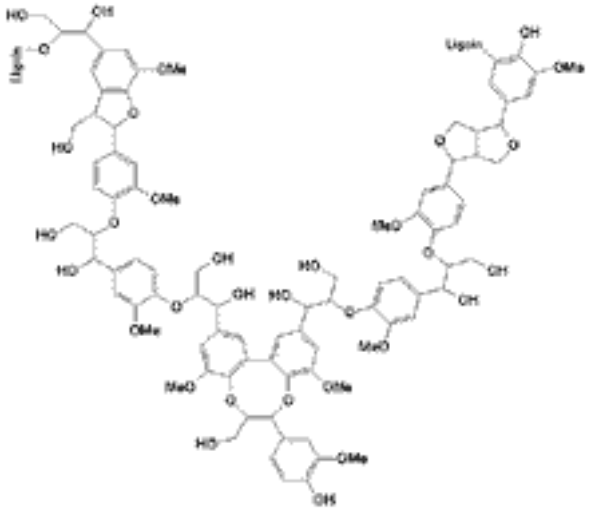
• Dispersants in high performance cement applications, water treatment formulations and textile dyes
• Additives in specialty oil field applications and agricultural chemicals
• Raw materials for several chemicals, such as vanillin, DMSO, ethanol, torula yeast, xylitol sugar and humic acid
• Environmentally friendly dust supression agent for roads

The first investigations into commercial use of lignin were done by Marathon Corporation in Rothschild,

Wisconsin (USA), starting in 1927. The first class of products which showed promise were leather tanning agents. The lignin chemical business of Marathon is now known as LignoTech USA, Inc., and is owned by the Norwegian company, Borregaard.

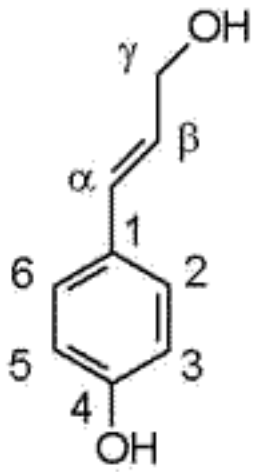
Structure and biosynthesis

Lignin is a large macromolecule with molecular mass in excess of 10,000 amu. It is hydrophobic and aromatic in nature. The molecule consists of various types of substructures which repeat in random manner.

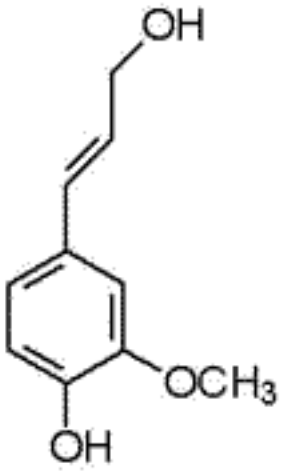


Structure of a small piece of lignin polymer

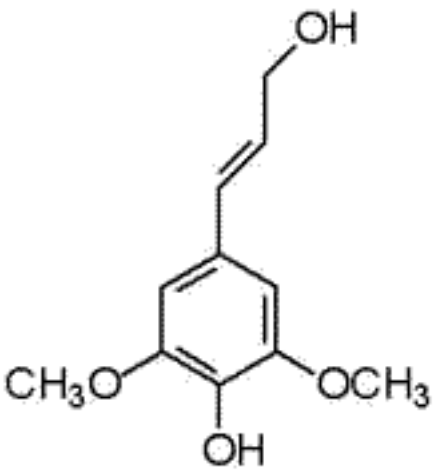
Lignin biosynthesis begins with the synthesis of monolignols. The starting material is the amino acid phenylalanine. The first reactions in the biosynthesis are shared with the phenylpropanoid pathway, and monolignols are considered to be a part of this group of compounds. There are three types of monolignols: coniferyl alcohol, sinapyl alcohol and paracoumaryl alcohol. Different plants use different monolignols. For example, Norway spruce lignin is almost entirely coniferyl alcohol while paracoumaryl alcohol is found almost exclusively in grasses.



p-coumaryl alcohol



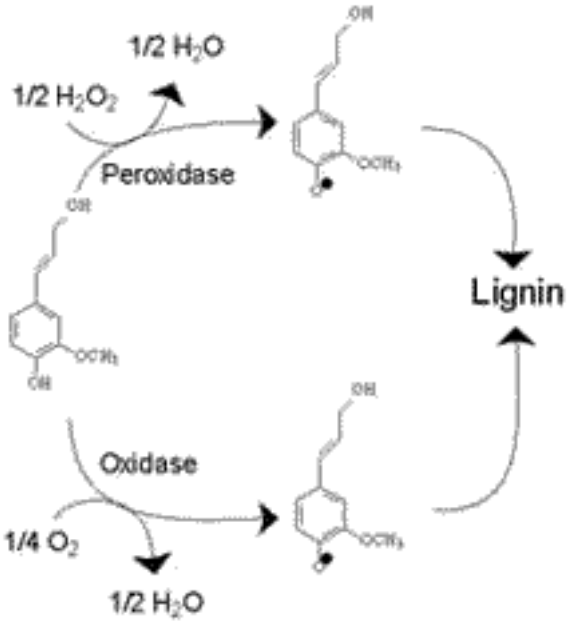
Coniferyl alcohol



Sinapyl alcohol

Structures of the three commonly occurring monolignols

Monolignols are synthetised in the cytosol as glucosides. The glucose is added to the monolignol to make them water soluble and to reduce their toxicity. The glucosides are transported through the cell membrane to the apoplast. The glucose is then removed and the monolignols are polymerised into lignin.



Polymerisation of coniferyl alcohol to lignin. The reaction has two alternative routes catalysed by two different oxidative enzymes, peroxidases or oxidases.

The polymerisation step is catalysed by oxidative enzymes. Both peroxidase and laccase enzymes are present in the plant cell walls, and it is not known whether one or both of these groups participates in the polymerisation. The oxidative enzyme catalyses the formation of monolignol radicals. These radicals then undergo chemical coupling to form the lignin polymer. The details of this final step are being debated, since it is not known how the abundance of various possible bond types between monolignols in controlled. Some theories favour pure chemical coupling, while other state that dirigent proteins control this step.

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Silk

Silk is a natural protein fiber that can be woven into textiles. It is obtained from the cocoon of the silkworm larva, in the process known as *sericulture*, which kills the larvae. The shimmering appearance for which it is prized comes from the fibers' triangular prism-like structure, which allows silk cloth to refract incoming light at different angles.

Early history

Silk was first developed in early China, possibly as early as 6000 BC and definitely by 3000 BC. Legend gives credit to a Chinese Empress Xi Ling-Shi. Though first reserved for the Emperors of China, its use spread gradually through Chinese culture both geographically and socially. From there, silken garments began to reach regions throughout Asia. Silk rapidly became a popular luxury fabric in the many areas accessible to Chinese merchants, because of its texture and lustre. Because of the high demand for the fabric, silk was one of the staples of international trade prior to industrialization.

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Enzymes: Definition

An **enzyme** is a protein that catalyzes, or speeds up, a chemical reaction. The word comes from the Greek, which comes from *én* ("at" or "in") and *simo* ("leaven" or "yeast"). Certain RNAs also have catalytic activity, but to differentiate them from protein enzymes, they are referred to as RNA enzymes or ribozymes.

Enzymes are essential to sustain life because most chemical reactions in biological cells would occur too slowly, or would lead to different products without enzymes. A malfunction (mutation, overproduction, underproduction or deletion) of a single critical enzyme can lead to a severe disease. For example, the most common type of phenylketonuria is caused by a single amino acid mutation in the enzyme phenylalanine hydroxylase, which catalyzes the first step in the degradation of phenylalanine. The resulting build-up of phenylalanine and related products can lead to mental retardation if the disease is untreated.

Like all catalysts, enzymes work by providing an alternate pathway of lower activation energy of a reaction, thus allowing the reaction to proceed much faster. Enzymes may speed up reactions by a factor of many millions. An enzyme, like any catalyst, remains unaltered by the completed reaction and can therefore continue to function. Because enzymes do not affect the relative energy between the products and reagents, they do not affect equilibrium of a reaction. However, the advantage of enzymes compared to most other catalysts is their sterio-, regio- and chemoselectivity and specificity.

Enzyme activity can be affected by other molecules. Inhibitors are naturally occurring or synthetic molecules that decrease or abolish enzyme activity; activators are molecules that increase activity. Some irreversible inhibitors bind enzymes very tightly, effectively inactivating them. Many drugs and poisons act by inhibiting enzymes. Aspirin inhibits the COX-1 and COX-2 enzymes that produce the inflammation messenger prostaglandin, thus suppressing pain and inflammation. The poison cyanide inhibits cytochrome c oxidase, which effectively blocks cellular respiration.

While all enzymes have a biological role, some enzymes are used commercially for other purposes. Many household cleaners use enzymes to speed up chemical reactions (*e.g.*, breaking down protein or starch stains in clothes).

More than 5,000 enzymes are known. Typically the suffix *-ase* is added to the name of the substrate (*e.g.*, lactase is the enzyme that catalyzes the cleavage of lactose) or the type of reaction (*e.g.*, DNA polymerase catalyzes the formation of DNA polymers). However, this is not always the case, especially when enzymes modify multiple substrates. For this reason Enzyme Commission or EC numbers are used to classify enzymes based on the reactions they catalyze. Even this is not a perfect solution, as enzymes from different species or even very similar enzymes in the same species may have identical EC numbers.

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Dehydrogenase

A **dehydrogenase** is an enzyme that oxidizes a substrate by transferring one or more protons and a pair of electrons to an acceptor, usually NAD/NADP or a flavin coenzyme such as FAD or FMN.

Common examples of dehydrogenase enzymes in the TCA cycle are pyruvate dehydrogenase, isocitrate dehydrogenase, and alpha-ketoglutarate dehydrogenase.

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Enzymes: Etymology and history

The word enzyme comes from Greek: *"in leaven"*. As early as the late 1700s and early 1800s, the digestion of meat by stomach secretions and the conversion of starch to sugars by plant extracts and saliva were observed.

Studying the fermentation of sugar to alcohol by yeast, Louis Pasteur came to the conclusion that this fermentation was catalyzed by "ferments" in the yeast, which were thought to function only in the presence of living organisms.

In 1897, Hans and Eduard Buchner inadvertently used yeast extracts to ferment sugar, despite the absence of living yeast cells. They were interested in making extracts of yeast cells for medical purposes, and, as one possible way of preserving them, they added large amounts of sucrose to the extract. To their surprise, they found that the sugar was fermented, even though there were no living yeast cells in the mixture. The term "enzyme" was used to describe the substance(s) in yeast extract that brought about the fermentation of sucrose. It was not until 1926, however, that the first enzyme was obtained in pure form.

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Enzymes: Inhibition

Enzymes reaction rates can be decreased by competitive, non-competitive, partially competitive, uncompetitive inhibition, and mixed inhibition.

Competitive inhibition

In competitive inhibition, the inhibitor binds to the substrate binding site as shown (*right* part b), thus preventing substrate binding. Malonate is a competitive inhibitor of the enzyme succinate dehydrogenase, which catalyzes the oxidation of succinate to fumarate.

Competitive inhibition causes the K_m value to increase, but does not effect V_{max}.

Non-competitive inhibition

Non-competitive inhibitors never bind to the active center, but to other parts of the enzyme that can be far away from the substrate binding site, consequently, there is no competition between the substrate and inhibitor for the enzyme. The extent of inhibition depends entirely on the inhibitor concentration and will not be affected by the substrate concentration. For example, cyanide combines with the copper prosthetic groups of the enzyme cytochrome c oxidase, thus inhibiting cellular respiration. This type of inhibition is typically irreversible, meaning that the enzyme will no longer function.

By changing the conformation (the three-dimensional structure) of the enzyme, the inhibitors either disable the ability of the enzyme to bind or turn over its substrate. The enzyme-inhibitor (EI) and enzyme-inhibitor-substrate (EIS) complex have no catalytic activity.

Non-Competitive inhibition causes a decrease in V_{max}, but does not change the K_m value.

Partially competitive inhibition

The mechanism of partially competitive inhibition is similar to that of non-competitive, except that the EIS-complex has catalytic activity, which may be lower or even higher (partially competitive activation) than that of the enzyme-substrate (ES) complex.

This inhibition typically displays a lower V_{max}, but an unaffected K_m value.

Uncompetitive inhibition

Uncompetitive inhibition occurs when the inhibitor binds only to the enzyme-substrate complex, not to the free enzyme, the EIS complex is catalytically inactive. This mode of inhibition is rare and causes a decrease in both V_{max} and the K_m value.

Mixed inhibition

Mixed inhibitors can bind to both the enzyme and the ES complex. It has the properties of both competitive and uncompetitive inhibition.

Both a decrease in V_{max} and an increase in the K_m value are seen in mixed inhibition.

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Enzymes: Kinetics

In 1913, Leonor Michaelis and Maud Menten proposed a quantitative theory of enzyme kinetics, which is referred to as Michaelis-Menten kinetics. Their work was further developed by G. E. Briggs and J. B. S. Haldane, who derived numerous kinetic equations that are still widely used today.

Enzymes can perform up to several million catalytic reactions per second; to determine the maximum speed of an enzymatic reaction, the substrate concentration is increased until a constant rate of product formation is achieved. This is the maximum velocity (V_{max}) of the enzyme. In this state, all enzyme active sites are saturated with substrate. However, V_{max} is only one kinetic parameter that biochemists are interested in. The amount of substrate needed to achieve a given rate of reaction is also of interest. This can be expressed by the Michaelis-Menten constant (K_m), which is the substrate concentration required for an enzyme to reach one half its maximum velocity. Each enzyme has a characteristic K_m for a given substrate.

The efficiency of an enzyme can be expressed in terms of k_{cat}/K_m. The quantity k_{cat}, also called the turnover number, incorporates the rate constants for all steps in the reaction, and is the quotient of V_{max} and the total enzyme concentration. k_{cat}/K_m is a useful quantity for comparing different enzymes against each other, or the same enzyme with different substrates, because it takes both affinity and catalytic ability into consideration. The theoretical maximum for k_{cat}/K_m, called the diffusion limit, is about 10^8 to 10^9 (M^{-1} s^{-1}). At this point, every collision of the enzyme with its substrate will result in catalysis and the rate of product formation is not limited by the reaction rate but by the diffusion rate. Enzymes that reach this k_{cat}/K_m value are called *catalytically perfect* or *kinetically perfect*. Example of such enzymes are triose-phosphate isomerase, carbonic anhydrase, acetylcholinesterase, catalase, fumarase, beta-lactamase, and superoxide dismutase.

Some enzymes operate with kinetics which are faster than diffusion rates, which would seem to be impossible. Several mechanisms have been invoked to explain this phenomenon. Some proteins are believed to accelerate catalysis by drawing their substrate in and preorienting them by using dipolar electric fields. Some invoke a quantum-mechanical tunneling explanation whereby a proton or an electron can tunnel through activation barriers, although for protons tunneling remains somewhat controversial.

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Enzymes: Metabolic pathways and allosteric enzymes

Several enzymes can work together in a specific order, creating metabolic pathways. In a metabolic pathway, one enzyme takes the product of another enzyme as a substrate. After the catalytic reaction, the product is then passed on to another enzyme. The end product(s) of such a pathway are often inhibitors for one of the first enzymes of the pathway (usually the first irreversible step, called *committed step*), thus regulating the amount of end product made by the pathways. Such a regulatory mechanism is called a negative feedback mechanism, because the amount of the end product produced is regulated by its own concentration. Negative feedback mechanism can effectively adjust the rate of synthesis of intermediate metabolites according to the demands of the cells. This helps with effective allocations of materials and energy economy, and it prevents the excess manufacture of end products. Like other homeostatic devices, the control of enzymatic action helps to maintain a stable internal environment in living organisms.

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Enzymes: Enzyme-naming conventions

By common convention, an enzyme's name consists of a description of what it does, with the word ending in *-ase*. Examples are alcohol dehydrogenase and DNA polymerase. Kinases are enzymes that transfer phosphate groups. This results in different enzymes with the same function having the same basic name; they are therefore distinguished by other characteristics, such as their optimal pH (alkaline phosphatase) or their location (membrane ATPase). Furthermore, the reversibility of chemical reactions means that the normal physiological direction of an enzyme's function may not be that observed under laboratory conditions. This can result in the same enzyme being identified with two different names: one stemming from the formal laboratory identification as described above, the other representing its behavior in the cell. For instance the enzyme formally known as *xylitol:NAD+ 2-oxidoreductase (D-xylulose-forming)* is more commonly referred to in the cellular physiological sense as *D-xylulose reductase*, reflecting the fact that the function of the enzyme in the cell is actually the reverse of what is often seen under *in vitro* conditions.

The International Union of Biochemistry and Molecular Biology has developed a nomenclature for enzymes, the EC numbers; each enzyme is described by a sequence of four numbers, preceded by "EC". The first number broadly classifies the enzyme based on its mechanism:

The toplevel classification is

- EC 1 *Oxidoreductases*: catalyze oxidation/reduction reactions

- EC 2 *Transferases*: transfer a functional group (e.g. a methyl or phosphate group)

- EC 3 *Hydrolases*: catalyze the hydrolysis of various bonds

- EC 4 *Lyases*: cleave various bonds by means other than hydrolysis and oxidation

- EC 5 *Isomerases*: catalyze isomerization changes within a single molecule

-EC 6 *Ligases*: join two molecules with covalent bonds

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Enzymes: Thermodynamics

As with all catalysts, all reactions catalyzed by enzymes must be "spontaneous" (containing a net negative Gibbs free energy). With the enzyme, they run in the same direction as they would without the enzyme, just more quickly. However, the uncatalyzed, "spontaneous" reaction might lead to different products than the catalyzed reaction. Furthermore, enzymes can couple two or more reactions, so that a thermodynamically favorable reaction can be used to "drive" a thermodynamically unfavorable one. For example, the cleavage of the high-energy compound ATP is often used to drive other, energetically unfavorable chemical reactions.

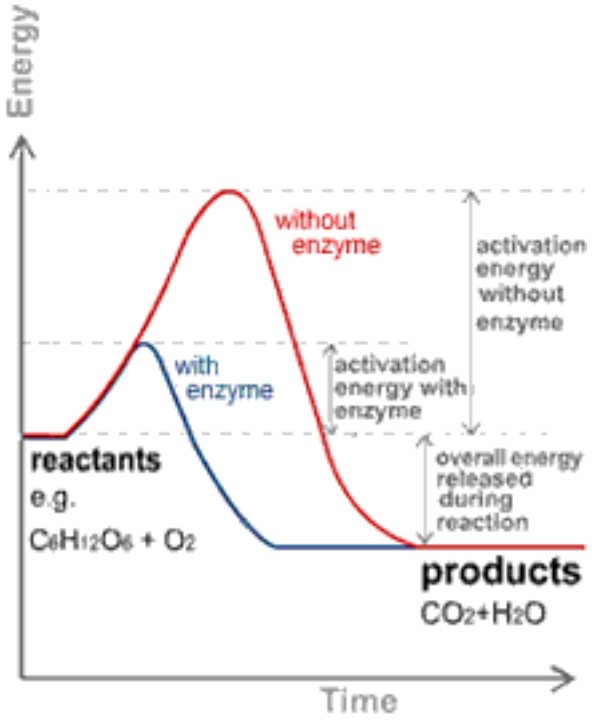

Diagram of a catalytic reaction, showing the energy niveau at each stage of the reaction. The substrates usually need a large amount of energy to reach the transition state, which then reacts to form the end product. The enzyme stabilizes the transition state, reducing the energy of the transition state and thus the energy required to get over this barrier.

Enzymes catalyze the forward and backward reactions equally. They do not alter the equilibrium itself, but only the speed at which it is reached. Carbonic anhydrase catalyzes its reaction in either direction depending on the conditions. $CO_2 + H_2O \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3$ (in tissues - high CO_2 concentration)

$H_2CO_3 \xrightarrow{\text{Carbonic anhydrase}} CO_2 + H_2O$ (in lungs - low CO_2 concentration)

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Enzymes: 3D Structure

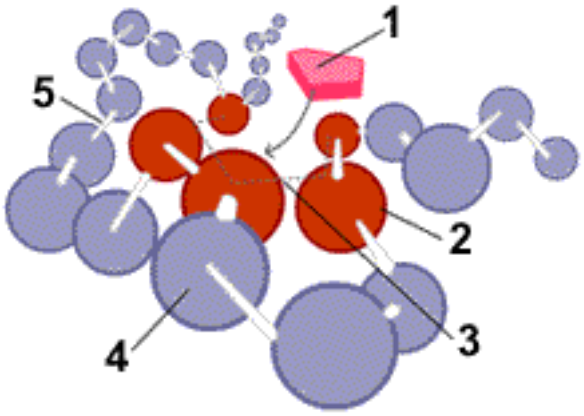
In enzymes, as with other proteins, function is determined by structure. An enzyme can be:

- A monomeric protein, *i.e.*, containing only one polypeptide chain, typically one hundred or more amino acids; or

- an oligomeric protein consisting of several polypeptide chains, different or identical, that act together as a unit.

As with any protein, each monomer is actually produced as a long, linear chain of amino acids, which folds in a particular fashion to produce a three-dimensional product. Individual monomers may then combine via non-covalent interactions to form a multimeric protein. Many enzymes can be unfolded or inactivated by heating, which destroys the three-dimensional structure of the protein.

A polypetide chain folded into a three-dimensional enzyme molecule



1. substrate molecule bound to the active site of the enzyme molecule
2. amino acid molecule involved in active site formation
3. active site
4. amino acid molecule
5. peptide bond

Most enzymes are larger than the substrates they act on and only a very small portion of the enzyme, around 10 amino acids, come into direct contact with the substrate(s). This region, where binding of the substrate(s) and then the reaction occurs, is known as the active site of the enzyme. Some enzymes contain sites that bind cofactors, which are needed for catalysis. Certain enzymes have binding sites for small molecules, which are often direct or indirect products or substrates of the reaction catalyzed. This binding can serve to increase or decrease the enzyme's activity (depending on the molecule and enzyme), providing a means for feedback regulation.

Modifications

Many enzymes contain not only a protein part but need additionally various modifications. These modifications are made *posttranslational*, *i.e.*, after the polypeptide chain is synthesized. Additional groups can be synthesized onto the polypeptide chain, *e.g.*, phosphorylation or glycosylation of the enzyme.

Another kind of posttranslational modification is the cleavage and splicing of the polypeptide chain. Chymotrypsin, a digestive protease, is produced in inactive form as chymotrypsinogen in the pancreas and transported in this form to the stomach where it is activated. This prevents the enzyme from harmful digestion of the pancreas or other tissue. This type of inactive precursor to an enzyme is known as a zymogen.

Enzyme cofactors

Some enzymes do not need any additional components to exhibit full activity. However, others require non-protein molecules to be bound for activity. Cofactors can be either inorganic (*e.g.*, metal ions and Iron-sulfur clusters) or organic compounds, which are also known as coenzymes.

Enzymes that require a cofactor, but do not have one bound are called apoenzymes. An apoenzyme together with its cofactor(s) constitutes a holoenzyme (*i.e*, the active form). Most cofactors are not covalently bound to an enzyme, but are closely associated. However, some cofactors known as prosthetic groups are covalently bound (*e.g.*, thiamine pyrophosphate in certain enzymes).

Most cofactors are either regenerated or chemically unchanged at the end of the reactions. Many cofactors are vitamin-derivatives and serve as carriers to transfer electrons, atoms, or functional groups from an enzyme to a substrate. Common examples are NAD and NADP, which are involved in electron transfer and coenzyme A, which is involved in the transfer of acetyl groups.

Allosteric modulation

Allosteric enzymes change their structure in response to binding of effectors. Modulation can be direct, where effectors bind directly to binding sites in the enzyme, or indirect, where the effector binds to other proteins or protein subunits that interact with the allosteric enzyme and thus influence catalytic activity.

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Ubiquitin

Ubiquitin is a small regulatory protein that is *ubiquitous* in eukaryotes. **Ubiquitination** (or **Ubiquitylation**) refers to the Post-translational modification of a protein by the covalent attachment (via an isopeptide bond) of one or more ubiquitin monomers. Ubiquitin (originally, **Ubiquitous Immunopoeitic Polypeptide**) was first identified in 1975 as an 8.5 kDa protein of unknown function expressed universally in living cells. The basic functions of ubiquitin and the components of the ubiquitination pathway were elucidated in the early 1980s in groundbreaking work performed by Aaron Ciechanover, Avram Hershko and Irwin Rose for which the Nobel Prize in Chemistry was awarded in 2004.

The ubiquitylation system was initially characterised as an ATP-dependent proteolytic system present in cellular extracts. A heat-stable polypeptide present in these extracts, ATP-dependent proteolysis factor 1 (APF-1), was found to become covalently attached to the model protein substrate lysozyme in an ATP and Mg^{2+}-dependent process. Multiple APF-1 molecules were linked to a single substrate molecule by an isopeptide linkage and conjugates were found to be rapidly degraded with the release of free APF-1. Soon after APF-1-protein conjugation was characterised, APF-1 was identified as ubiquitin. The carboxyl group of the C-terminal glycine residue of ubiquitin (Gly76) was identified as the moiety conjugated to substrate lysine residues.

The protein

Ubiquitin properties (human)

Number of residues: 76

Molecular mass: 8564.47 Da

Isoelectric point (pI): 6.79

Gene names: RPS27A (UBA80, UBCEP1), UBA52 (UBCEP2), UBB, UBC

Ubiquitin is a small protein that occurs in all eukaryotic cells. Its main function is to mark other proteins for destruction, known as proteolysis. Several ubiquitin molecules attach to the condemned protein (polyubiquitination), and it then moves to a proteasome, a barrel-shaped structure where the proteolysis occurs. Ubiquitin can also mark transmembrane proteins (for example, receptors) for removal from membranes and fulfill several signalling roles within the cell.

Ubiquitin consists of 76 amino acids and has a molecular mass of about 8500 Da. It is highly conserved among eukaryotic species: Human and yeast ubiquitin share 96% sequence identity. The human ubiquitin sequence is:

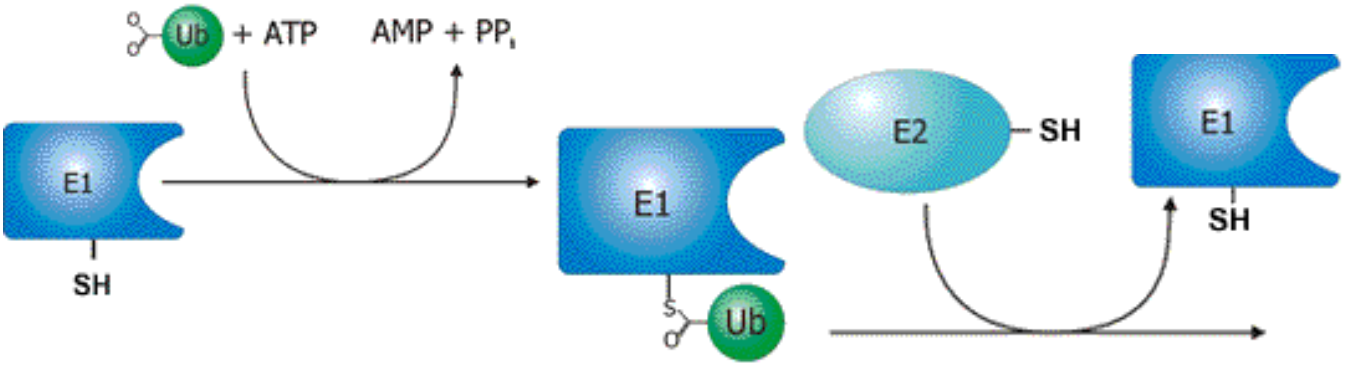
```
MQIFVKTLTGKTITLEVEPSDTIENVKAKIQDKEGIPPDQQRLIFAGKQLEDGRTLSDYNIQKESTLHLVLRLRGG
```

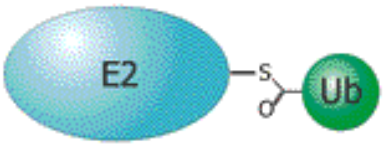
Ubiquitylation

The process of marking a protein with ubiquitin (ubiquitylation or ubiquitination) consists of a series of steps:

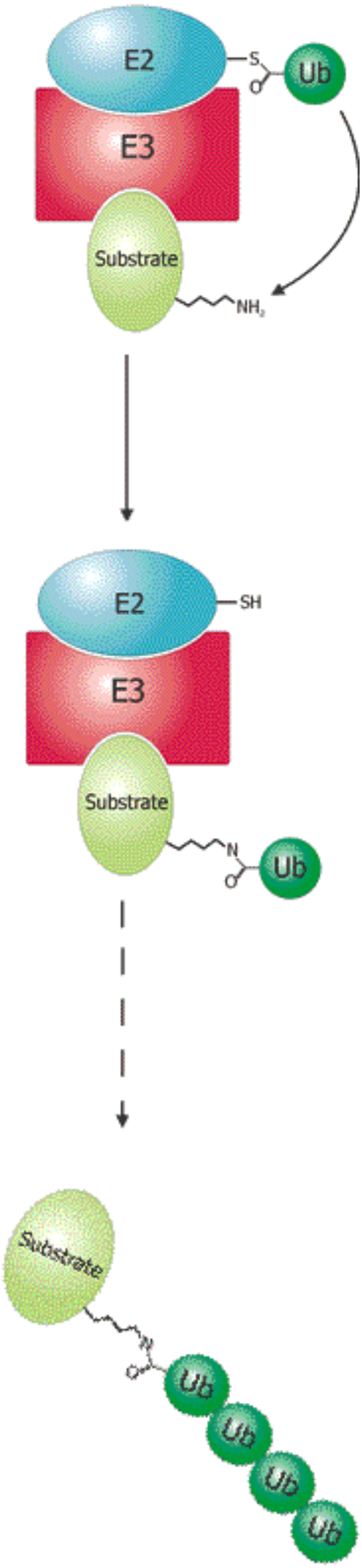
- Activation of ubiquitin - Ubiquitin is activated in a two-step reaction by an E1 ubiquitin-activating enzyme in a process requiring ATP as an energy source. The initial step involves production of an ubiquitin-adenylate intermediate. The second step transfers ubiquitin to the E1 active site cysteine residue, with release of AMP. This step results in a thioester linkage between the C-terminal carboxyl group of ubiquitin and the E1 cysteine sulfhydryl group.
- Transfer of ubiquitin from E1 to the active site cysteine of an ubiquitin-conjugating enzyme E2 via a trans(thio) esterification reaction.
- The final step of the ubiquitylation cascade generally requires the activity of an E3 ubiquitin-protein ligase (often termed simply ubiquitin ligase). E3 enzymes function as the substrate recognition modules of the system and are capable of interaction with both E2 and substrate. E3 enzymes possess one of two domains: - The **HECT** (Homologous to the E6-AP Carboxyl Terminus) domain
- The **RING** domain (or the closely related **U-box** domain)

Transfer can occur in two ways: - Directly from E2, catalysed by RING domain E3s.
- Via an E3 enzyme, catalysed by HECT domain E3s. In this case, a covalent E3-ubiquitin intermediate is formed prior to transfer of ubiquitin to the substrate protein.





Ubiquitin


E2
S
O
Ub
E3
Substrate
NH2
E2
SH
E3
Substrate
N
O
Ub
Substrate
N
O
Ub
Ub
Ub
Ub

In many cases, ubiquitin molecules are further added on to previously-conjugated ubiquitin molecules to forms a polyubiquitin chain. If the chain is longer than 3 ubiquitin molecules, the tagged protein is rapidly degraded by the 26S-proteasome into small peptides (usually 3-24 amino acid residues in length). Ubiquitin moieties are cleaved off the protein by deubiquitinating enzymes and are recycled for further use.

Cell-surface transmembrane molecules that are tagged with ubiquitin are often mono-ubiquitinated, and this modification alters the subcellular localization of the protein, often targeting the protein for destruction in lysosomes.

The ubiquitin pathway is thought to be the method of cellular egress for a number of retroviruses, including HIV and Ebola, but the exact mechanism by which this occurs has yet to be deduced.

The Anaphase-promoting complex (APC) and the SCF complex (for Skp1-Cullin-F-box protein complex) are two examples of multi-subunit E3s involved in recognition and ubiquitination of specific target proteins for degradation by the proteasome.

Disease association

Genetic disorders

- The gene whose disruption causes Angelman syndrome, *UBE3A*, encodes an ubiquitin ligase (E3) enzyme termed E6-AP.
- The gene disrupted in Von Hippel-Lindau syndrome encodes an ubiquitin E3 ligase termed the VHL tumor suppressor or VHL gene.

Immunohistochemistry

Antibodies to ubiquitin are used in histology to identify abnormal accumulations of protein inside cells that are markers of disease. These accumulations are called inclusion bodies. Examples of such abnormal inclusions in cells are

- Neurofibrillary tangles in Alzheimer's disease
- Lewy body in Parkinson's disease
- Pick bodies in Pick's disease
- Inclusions in motor neuron disease
- Mallory's Hyalin in alcoholic liver disease
- Rosenthal fibres in astrocytes

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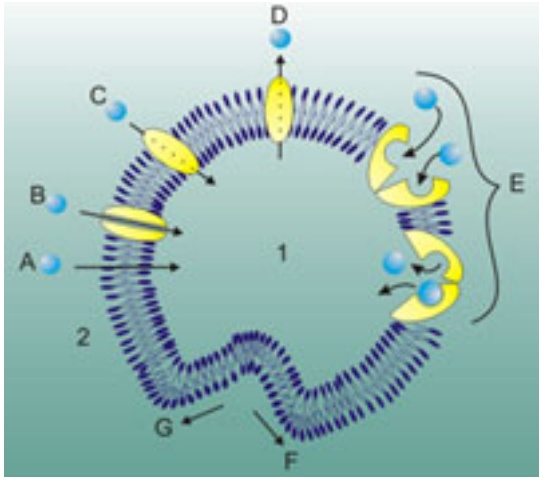
Active transport

Types | Primary | Secondary | Counter-transport | Co-transport



A. Diffusion; B. Ion Channel; C and D. Facilitated Diffusion; **E. Active Transport (Pump)**

Active transport is the mediated transport of biochemicals, and other atomic/molecular substances, across membranes. Unlike passive transport, this process requires chemical energy. In this form of transport, molecules move against either an electrical or concentration gradient (collectively termed an electrochemical gradient). This is achieved by either altering the affinity of the binding site or altering the rate at which the protein changes conformations.

Types

There are two main types: *primary* and *secondary*. In primary transport, energy is directly coupled to the movement of a desired substance across a membrane independent of any other species. Secondary transport concerns the diffusion of one species across a membrane to drive the transport of another.

Primary

Primary active transport directly uses energy to transport molecules across a membrane. Most of the enzymes that perform this type of transport are transmembrane ATPases. A primary ATPase universal to all cellular life is the sodium-potassium pump, which helps maintain the cell potential.

Secondary

In secondary active transport, there is however no direct coupling of ATP; instead, the electrochemical potential difference created by pumping ions out of cells is used. The two main forms of this are counter-transport (antiport) and co-transport (symport).

Counter-transport

In counter-transport two species of an ion or other solutes are pumped in opposite directions across a membrane. One of these species is allowed to flow from high to low concentration which yields the entropic energy to drive the transport of the other solute from a low concentration region to a high one. An example is the sodium-calcium exchanger or antiporter, which allows three sodium ions into the cell to transport one calcium out.

Many cells also possess a calcium ATPase, which can operate at lower intracellular concentrations of calcium and sets the normal or resting concentration of this important second messenger. But the ATPase exports calcium ions more slowly: only 30 per second versus 2000 per second by the exchanger. The exchanger comes into service when the calcium concentration rises steeply or "spikes" and enables rapid recovery. This shows that a single type of ion can be transported by several enzymes, which need not be active all the time (constitutively), but may exist to meet specific, intermittent needs.

Co-transport

Co-transport also uses the flow of one solute species from high to low concentration to move another molecule against its preferred direction of flow. An example is the glucose symporter, which co-transports two sodium ions for every molecule of glucose it imports into the cell.

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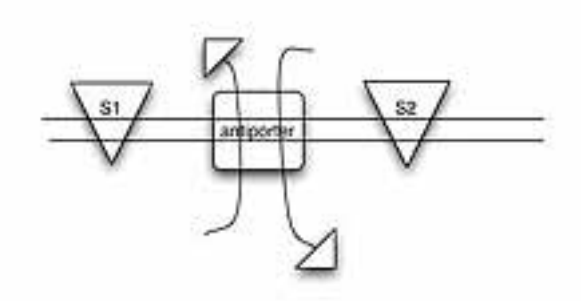
Antiporter

An **antiporter** is an integral membrane protein that is involved in secondary active transport.

It works by binding to one molecule of solute outside the membrane, and one molecule on the inside. By using S2's gradient, we are able to transport S1 against its gradient.



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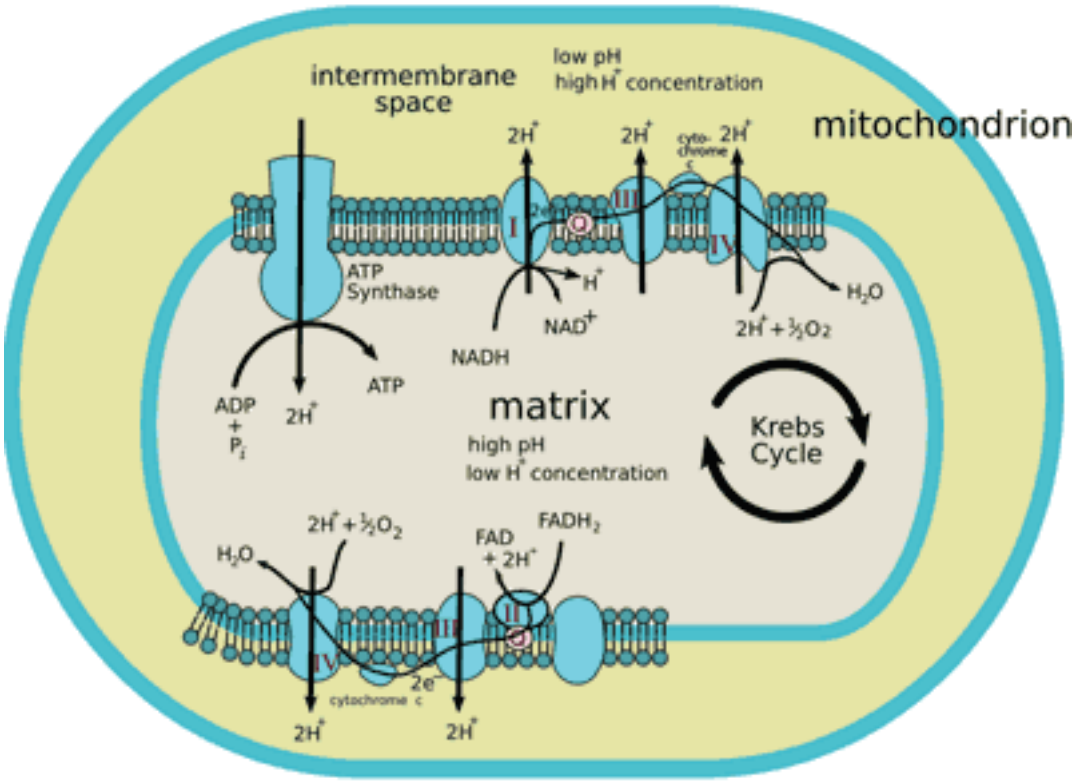
Electron transport

Mitochondrial Electron Transport Chain:



Electron transport chains (also called **electron transfer chains**) are biochemical reactions that produce ATP, which is the energy currency of life. Only two sources of energy are available to living organisms: oxidation-reduction (redox) reactions and sunlight (photosynthesis). Organisms that use redox reactions to produce ATP are called *chemotrophs*. Organisms that use sunlight are called *phototrophs*. Both chemotrophs and phototrophs use electron transport chains to convert energy into ATP.

Background

ATP is made by an enzyme called ATP synthase. The structure of this enzyme and its underlying genetic code is remarkably similar in all known forms of life.

ATP synthase is powered by a transmembrane electrochemical potential gradient, usually in the form of a proton gradient. The function of the electron transport chain is to produce this gradient. In all living organisms, a series of redox reactions is used to produce a transmembrane electrochemical potential

gradient.

Redox reactions are chemical reactions in which electrons are transferred from a donor molecule to an acceptor molecule. The underlying force driving these reactions is the Gibbs free energy of the reactants and products. The Gibbs free energy is the energy available ("free") to do work. Any reaction that decreases the overall Gibbs free energy of a system will proceed spontaneously.

The transfer of electrons from a high-energy molecule (the donor) to a lower-energy molecule (the acceptor) can be spatially separated into a series of intermediate redox reactions. This is an electron transport chain.

The fact that a reaction is thermodynamically possible does not mean that it will actually occur. A mixture of hydrogen gas and oxygen gas does not spontaneously ignite. It is necessary either to supply an activation energy, or to lower the intrinsic activation energy of the system, in order to make most biochemical reactions proceed at a useful rate. Living systems use complex macromolecular structures (enzymes) to lower the activation energies of biochemical reactions.

It is possible to couple a thermodynamically favorable reaction (a transition from a high-energy state to a lower-energy state) to a thermodynamically unfavorable reaction (such as a separation of charges, or the creation of an osmotic gradient), in such a way that the overall free energy of the system decreases (making it thermodynamically possible), while useful work is done at the same time. Biological macromolecules that catalyze a thermodynamically favorable reaction if and only if a thermodynamically unfavorable reaction occurs simultaneously underlie all known forms of life.

Electron transport chains produce energy in the form of a transmembrane electrochemical potential gradient. This energy is used to do useful work. The gradient can be used to transport molecules across membranes. It can be used to do mechanical work, such as rotating bacterial flagella. It can be used to produce ATP and NADH, high-energy molecules that are necessary for growth.

A small amount of ATP is available from substrate-level phosphorylation (for example, in glycolysis). Some organisms can obtain ATP exclusively by fermentation. In most organisms, however, the majority of ATP is generated by electron transport chains.

Electron transport chains in mitochondria

The cells of all eukaryotes (all animals, plants, fungi, algae – in other words, all living things except bacteria and archaea) contain intracellular organelles called mitochondria that produce ATP. Energy sources such as glucose are initially metabolized in the cytoplasm. The products are imported into mitochondria. Mitochondria continue the process of catabolism using metabolic pathways including the Krebs cycle, fatty acid oxidation and amino acid oxidation.

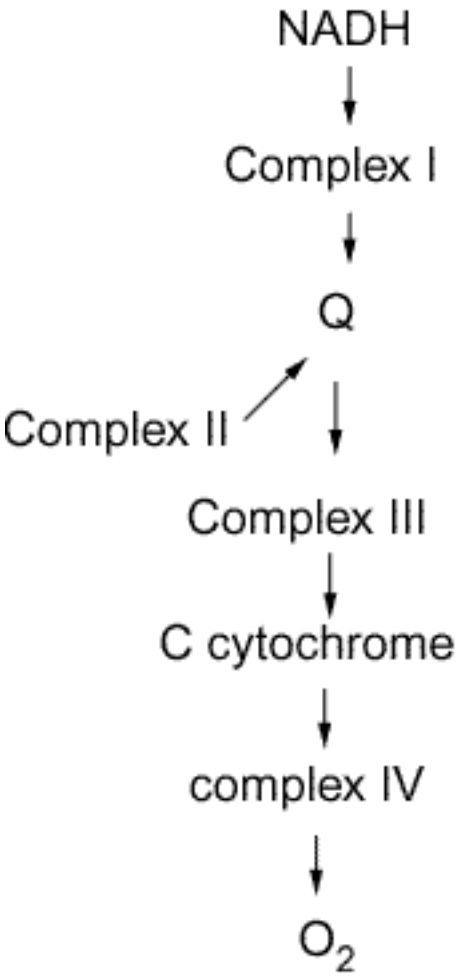
The end result of these pathways is the production of two energy-rich electron donors, NADH and

$FADH_2$. Electrons from these donors are passed through an electron transport chain to oxygen, which is reduced to water. This is a multi-step redox process that occurs on the mitochondrial inner membrane. The enzymes that catalyze these reactions have the remarkable ability to simultaneously create a proton gradient across the membrane, producing a thermodynamically unlikely high-energy state with the potential to do work.

The similarity between intracellular mitochondria and free-living bacteria is striking. The known structural, functional and DNA similarities between mitochondria and bacteria provide strong evidence that mitochondria evolved from intracellular prokaryotic symbionts that took up residence in primitive eukaryotic cells.

Mitochondrial redox carriers

Four membrane-bound complexes have been identified in mitochondria. Each is an extremely complex transmembrane structure that is embedded in the inner membrane. Three of them are proton pumps. The structures are electrically connected by lipid-soluble electron carriers and water-soluble electron carriers. The overall electron transport chain is:



Complex I

Complex I (NADH dehydrogenase) removes two electrons from NADH and transfers them to a lipid-soluble carrier, *ubiquinone* (Q). The reduced product, ubiquinol (QH_2) is free to diffuse within the membrane. At the same time, Complex I moves four protons (H_+) across the membrane, producing a proton gradient.

Complex II

Complex II (succinate dehydrogenase) is not a proton pump. It serves to funnel additional electrons into the quinone pool (Q) by removing electrons from succinate and transferring them (via FAD) to Q. Other electron donors (e.g. fatty acids and glycerol 3-phosphate) also funnel electrons into Q (via FAD), again without producing a proton gradient.

Complex III

Complex III (cytochrome bc_1 complex) removes in a stepwise fashion two electrons from QH2 and transfers them to two molecules of *cytochrome c*, a water-soluble electron carrier located on the outer surface of the membrane. At the same time, it moves four protons across the membrane, producing a proton gradient.

Complex IV

Complex IV (cytochrome c oxidase) removes two electrons from two molecules of cytochrome c and transfers them to molecular oxygen, producing H_2O. At the same time, it moves two protons across the membrane, producing a proton gradient.

Summary

The mitochondrial electron transport chain removes electrons from an electron donor (NADH or $FADH_2$) and passes them to a terminal electron acceptor (O_2) via a series of redox reactions. These reactions are coupled to the creation of a proton gradient across the mitochondrial inner membrane. There are three proton pumps: I, III and IV. The resulting transmembrane proton gradient is used to make ATP via ATP synthase.

The reactions catalyzed by Complex I and Complex III exist roughly at equilibrium. The steady-state concentrations of the reactants and products are approximately equal. This means that these reactions are readily reversible, simply by increasing the concentration of the products relative to the concentration of the reactants (for example, by increasing the proton gradient). ATP synthase is also readily reversible. Thus ATP can be used to make a proton gradient, which in turn can be used to make NADH. This

process of **reverse electron transport** is important in many prokaryotic electron transport chains.

Summary

Electron transport chains are the source of energy for all known forms of life. They are redox reactions that transfer electrons from an electron donor to an electron acceptor. The transfer of electrons is coupled to the translocation of protons across a membrane, producing a proton gradient. The proton gradient is used to produce useful work.

The coupling of thermodynamically favorable to thermodynamically unfavorable biochemical reactions by biological macromolecules is an example of an **emergent property** – a property that could not have been predicted, even given full knowledge of the primitive geochemical systems from which these macromolecules evolved. It is an open question whether such emergent properties evolve only by chance, or whether they necessarily evolve in any large biogeochemical system, given the underlying laws of physics.

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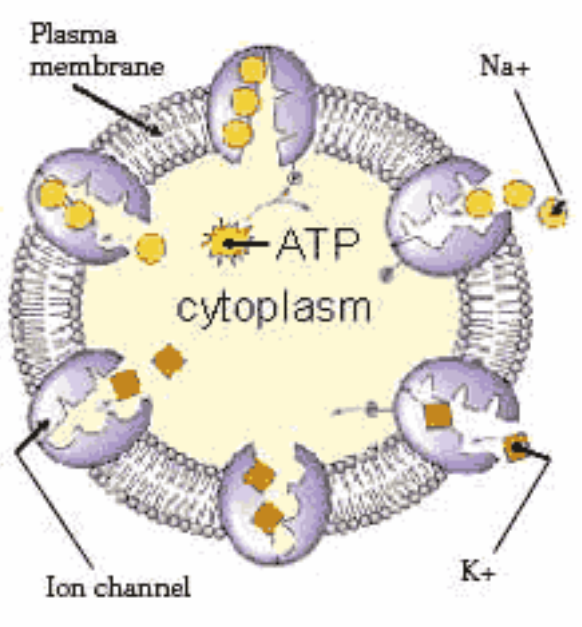
The ATP-Dependent Na/K Pump

Function | Physiology | Pharmacology | Discovery

Na^+/K^+-ATPase (also known as the **Na^+/K^+ pump** or **Na^+/K^+ exchanger**) is an enzyme located in the plasma membrane (specifically an electrogenic transmembrane ATPase). It is found in the plasma membrane of virtually every human cell and is common to all cellular life. It helps maintain cell potential and regulate cellular volume.



Function

In order to maintain the cell potential, cells must keep a low concentration of sodium ions and high levels of potassium ions within the cell (intracellular). Outside cells (extracellular), there are high concentrations of sodium and low concentrations of potassium, so diffusion occurs through ion channels in the plasma membrane. In order to keep the appropriate concentrations, the sodium-potassium pump pumps sodium out and potassium in through active transport.

The mechanism is:

• The pump, with bound ATP, binds 3 intracellular Na^+ ions.
• ATP is hydrolyzed, leading to phosphorylation of the pump at a highly conserved aspartate residue and subsequent release of ADP.
• A conformational change in the pump exposes the Na^+ ions to the outside. The phosphorylated form of the pump has a low affinity for sodium ions, so they are released.
• The pump binds 2 extracellular K^+ ions, leading to the dephosphorylation of the pump.
• ATP binds, and the pump reorients to release potassium ions inside the cell so the pump is ready to go

again.

Physiology

As the plasma membrane is far less permeable to sodium than it is to potassium ions, an electric potential (negative intracellularly) is the eventual result.

The electrical and concentration gradient established by the sodium-potassium ATPase supports not only the cell resting potential but the action potentials of nerves and muscles. Export of sodium from the cell provides the driving force for several facilitated transporters, which import glucose, amino acids and other nutrients into the cell. Translocation of sodium from one side of an epithelium to the other side creates an osmotic gradient that drives the absorption of water.

Another important task of the Na^+-K^+ pump is to provide a Na^+ gradient that is used by certain carrier processes. In the gut, for example, sodium is transported out of the resorbing cell on the blood side via the Na^+-K^+ pump, whereas, on the resorbing side, the Na^+-Glucose symporter uses the created Na^+ gradient as a source of energy to import both Na^+ and Glucose, which is far more efficient than simple diffusion. Similar processes are located in the renal tubular system.

Pharmacology

The Na-K pump found in the membrane of heart cells is an important target of cardiac glycosides (for example digoxin and ouabain), drugs used to improve heart performance by increasing its force of contraction. Contraction of any muscle is dependent on a 100- to 10,000-times higher-than-normal intercellular Ca concentration, which, as soon as it is put back again on its normal level by a carrier enzyme in the plasma membrane, will relax this muscle. Since this carrier enzyme (Na-Ca translocator) uses the Na gradient generated by the Na-K pump to remove Ca from the intercellular space, slowing down the Na-K pump results in a permanently-higher Ca level in the muscle, which will eventually lead to stronger contractions.

Discovery

Na^+/K^+-ATPase was discovered by Jens Christian Skou in 1957. He published his work in Biochimica et Biophysica Acta (vol. 23, pp. 394-401) in a paper entitled "The Influence of some Cations on an Adenosine Triphosphatase from Peripheral Nerves".

In 1997, he received one-half of the Nobel Prize in Chemistry "for the first discovery of an ion-transporting enzyme, Na^+, K^+ -ATPase".

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Proton pump

A **proton pump** is an integral membrane protein that is capable of moving protons across the membrane of a cell, mitochondrion, or other subcellular compartment, thereby creating a difference or gradient in both pH and electrical charge (ignoring differences in buffer capacity) and tending to establish an electrochemical potential.

In bacteria, mitochondria and other ATP-producing organelles, reducing equivalents provided by electron transfer or photosynthesis power this translocation of protons. For example, the translocation of protons by cytochrome c oxidase is powered by reducing equivalents provided by reduced cytochrome c. In the plasma membrane proton ATPase and in the ATPase proton pumps of other cellular membranes, ATP itself powers this transport.

The F_0F_1 ATP synthase of mitochondria and the CF_1 ATP ligase of chloroplasts, in contrast, usually conduct protons from high to low concentration across the membrane while drawing energy from this flow to synthesize ATP.

Bacteriorhodopsin is a photosynthetic pigment used by archaea, most notably halobacteria.

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Symporter

A **symporter**, also known as a **cotransporter**, is an integral membrane protein that is involved in secondary active transport.

It works by binding to two molecules at a time and using the gradient of one solutes concentration to force the other molecule against its gradient.

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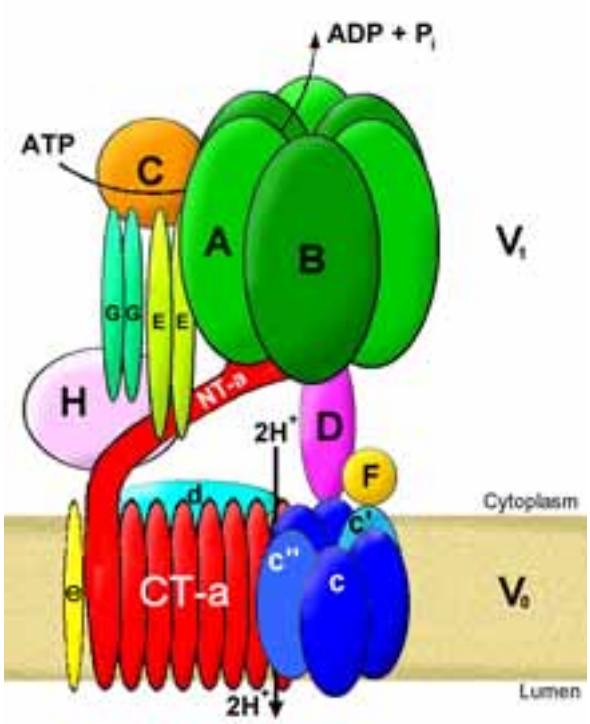
V-ATPase

Vacuolar type H^+-ATPase (V-ATPase) is a highly conserved evolutionarily ancient enzyme with remarkably diverse functions in eukaryotic organisms. V-ATPases acidifiy a wide array of intracellular organelles and pump protons across the plasma membranes of numerous cell types. V-ATPases couple the energy of ATP hydrolysis to proton transport across intracellular and plasma membranes of eukaryotic cells.



V-ATPase schematic

Roles played by V-ATPases

V-ATPases are found within the membranes of many organelles, such as endosomes, lysosomes and secretory vesicles where they play a variety of roles crucial for the function of these organelles. For example, the proton gradient across the yeast vacuolar membrane generated by V-ATPases drives calcium uptake into the vacuole through an H+/Ca++ antiporter system. V-ATPases also play an important role in synaptic transmission in neuronal cells. Norepinephrine enters vesicles in exhange for protons pumped by V-ATPase.

V-ATPases are also found in the plasma membranes of a wide variety of cells such as intercalated cells of the kidney, osteoclasts (bone resorbing cells), macrophages, neutrophils, sperm, midgut cells of

insects and certain tumor cells. Plasma membrane V-ATPases are involved in processes such as pH homeostasis, coupled transport and tumor metastasis. V-ATPases in the acrosomal membrane of sperm acidify the acrosome. This acidification activates proteases required to drill through the plasma membrane of the egg. V-ATPases in the osteoclast plasma membrane pump protons onto the bone surface which is necessary for bone resorption. In the intercalated cells of the kidney, V-ATPases pump protons into the urine, allowing for bicarbonate reabsorption into the blood.

V-ATPase structure

The yeast V-ATPase is the best characterized. There are at least 13 subunits identified to form a functional V-ATPase complex, which consists of two domains. The subunits belong to either the V_o domain (membrane associated subunits, lower case letters on the figure), or the V_1 domain (peripherally associated subunits, upper case letters on the figure).

The V_1 includes 8 subunits, A-H, with three copies of the A and B subunits, one or two copies of E, and two copies of subunit G. The V_1 domain contains tissue specific subunit isoforms including B, C, E, and G. Mutations to the B1 isoform result in the human disease distal renal tubular acidosis and sensorineural deafness.

The V_o domain contains 6 different subunits, a, d, c, c', c'' and e, with possibly four copies of c and one copy of the remaining subunits. The mammalian V_o domain contains tissue specific isoforms for subunits a and d, while yeast V-ATPase contains two organelle specific subunit isoforms of a, Vph1p and Stv1p. Mutations to the a3 isoform result in the human disease infantile malignant osteopetrosis, and mutations to the a4 isoform result in distal renal tubular acidosis, in some cases with sensorineural deafness.

The V_1 domain is responsible for ATP hydrolysis whereas the V_o domain is responsible for proton translocation. ATP hydrolysis at the catalytic nucleotide binding sites on subunit A drives rotation of a central stalk composed of subunits D and F, which in turn drives rotation of a barrel of c subunits relative to the a subunit. The amino-terminal of a (NT-a) along with subunits C, E, G and H compose the peripheral stalk. The carboxy-terminal of subunit a (CT-a) is held fixed relative to the A3B3 head by this peripheral stalk. Movement of the barrel of c subunits past the a subunit is thought to drive proton transport across the membrane. A stoicheometry of two protons translocated for each ATP hydrolyzed has been proposed by (Johnson, 1982).

In addition to the structural subunits of yeast V-ATPase, associated proteins have been identified that are necessary for assembly. These associated proteins are essential for V_o domain assembly and are termed Vma12p, Vma21p and Vma22p. Two of the three proteins, Vma12p and Vma22p form a complex that binds transiently to Vph1p (subunit a) to aid its assembly and maturation. Vma21p coordinates assembly

of the V_o subunits as well as escorting the V_o domain into vesicles for transport to the Golgi.

V-ATPase assembly

Yeast V-ATPases fail to assemble when any of the genes that encode subunits are deleted except for subunits H and c". Without subunit H, the assembled V-ATPase is not active and the loss of the c" subunit results in uncoupling of enzymatic activity.

The precise mechanisms by which V-ATPases assembly are still controversial with evidence suggesting two different possibilities. Mutational analysis and in vitro assays have shown that preassembled V_o and V_1 domains can combine to form one complex in a process called independent assembly. Support for independent assembly includes the findings that the assembled V_o domain can be found at the vacuole in the absence of the V_1 domain, whereas free V_1 domains can be found in the cytoplasm and not at the vacuole. In contrast, in vivo pulse-chase experiments have revealed early interactions between V_o and V_1 subunits, specifically the a and B subunits, suggesting that subunits are added in a step-wise fashion to form a single complex in a concerted assembly process.

Regulation of V-ATPase activity

In vivo regulation of V-ATPase activity is accomplished by reversible dissociation of the V_1 domain from the V_o domain. After inital assembly, both the insect Manduca sexta and yeast V-ATPases can reversibly disassemble into free V_o and V_1 domains after a 2-5 min deprivation of glucose. Reversible disassembly may be a general mechanism of regulating V-ATPase activity since it exists in yeast and insects. Reassembly is proposed to be aided by a complex termed RAVE (regulator of H+-ATPase of vacuolar and endosomal membranes). Interestingly, dissasembly and reassembly of V-ATPases does not require new protein synthesis but does need an intact microtubular network.

Human diseases

Osteopetrosis

Osteopetrosis is generic name that represents a group of heritable conditions in which there is a defect in osteoclastic bone resorption. Both dominant and recessive osteopetroses occur in humans. Autosomal dominant osteopetrosis shows mild symptoms in adults who experience frequent bone fractures due to brittle bones. A form of osteopetrosis that is clinically more severe is termed autosomal recessive infantile malignant osteopetrosis. Three genes have been identified which are responsible for recessive osteopetrosis in humans. Interestingly, they are all directly involved in the proton generation and secretion pathways that are essential for bone resorption. One gene is carbonic anhydrase II (CAII) that

when mutated causes osteopetrosis with renal tubular acidosis. Mutations to the chloride channel ClC7 gene also lead to both dominant and recessive osteopetrosis. Approximately 50% of patients with recessive infantile malignant osteopetrosis have mutations to the a3 subunit isoform of V-ATPase. In humans, 26 mutations have been identified in V-ATPase subunit isoform a3, found in osteoclasts, that result in the bone disease autosomal recessive osteopetrosis.

Distal renal tubular acidosis (dRTA)

The importance of V-ATPase activity in renal proton secretion is highlighted by the inherited disease distal renal tubule acidosis. In all cases, renal tubular acidosis results from a failure of the normal renal mechanisms that regulate systemic pH. There are four types of renal tubular acidosis. Type 1 is Distal renal tubular acidosis and results from a failure of the distal nephron to acidify the urine below pH 5. Some patients with recessive dRTA also have sensorineural hearing loss. Inheritance of this type of RTA results from mutations to either V-ATPase subunit isoforms B1 or a4, or mutations to the AE1 Cl-/HCO3- exchanger. Twelve different mutations to V-ATPase isoform B1 and twenty-four different mutations in a4 lead to dRTA. Reverse transcription polymerase chain reaction studies have shown expression of the a4 subunit in the intercalated cell of the kidney and in the cochlea. dRTA caused by mutations in the a4 subunit gene in some cases can be associated with deafness.

Nomenclature

The term V_o has a lowercase letter "o" (not the number "zero") in subscript. The "o" stands for oligomycin.

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Antigen

Types of antigens | Origin of antigens | Exogenous antigens | Endogenous antigens | Autoantigens | Tumor antigens

An **antigen** is a substance that stimulates an immune response, especially the production of antibodies. Antigens are usually proteins or polysaccharides, but can be any type of molecule, including small molecules (haptens) coupled to a carrier-protein.

Types of antigens

• **Immunogen** - Any substance that provokes the immune response when introduced into the body. An immunogen is always a macromolecule (protein, polysaccharide). Its ability to stimulate the immune reaction depends on its commoness to the host, molecular size, chemical composition and heterogeneity (e.g. simlar to amino acids in a protein).
• **Tolerogen** - An antigen that invokes a specific immune non-responsiveness due to its molecular form. If its molecular form is changed, a tolerogen can become an immunogen.
• **Allergen** - An allergen is a substance that causes the allergic reaction. It can be ingested, inhaled, injected or comes into contact with skin.

Cells present their antigens to the immune system via a histocompatibility molecule. Depending on the antigen presented and the type of the histocompatibility molecule, several types of immune cells can become activated.

Origin of antigens

Antigens can be classified in order of their origins.

Exogenous antigens

Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection. By endocytosis or phagocytosis, these antigens are taken into the antigen-presenting cells (APCs) and processed into fragments. APCs then present the fragments to T helper cells ($CD4^+$) by the use of class II histocompatibility molecules on their surface. Some T cells are specific for the peptide:MHC complex. They become activated and start to secrete cytokines. Cytokines are substances that can activate cytotoxic T lymphocytes (CTL), antibody-secreting B cells, macrophages and other cells.

Endogenous antigens

Endogenous antigens are antigens that have been generated within the cell, as a result of normal cell metabolism, or because of viral or intracellular bacterial infection. The fragments are then presented on the cell surface in the complex with class I histocompatibility molecules. If activated cytotoxic $CD8^+$ T cells recognize them, the T cells begin to secrete different toxins that cause the lysis or apoptosis of the infected cell. In order to keep the cytotoxic cells from killing cells just for presenting self-proteins, self-reactive T cells are deleted from the repertoire as a result of central tolerance (also known as negative selection which occurs in the thymus). Only those CTL that do not react to self-peptides that are presented in the thymus in the context of MHC class I molecules are allowed to enter the bloodstream.

There is an exception to the exogenous/endogenous antigen paradigm, called cross-presentation.

Autoantigens

An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease. These antigens should under normal conditions not be the target of the immune system, but due to mainly genetic and environmental factors the normal immunological tolerance for such an antigen has been lost in these patients.

Tumor antigens

Tumor antigens are those antigens that are presented by the MHC I molecules on the surface of tumor cells. These antigens can sometimes be presented only by tumor cells and never by the normal ones. In this case, they are called **tumor-specific antigens** and typically result from a tumor specific mutation. More common are antigens that are presented by tumor cells and normal cells, and they are called **tumor-associated antigens**. Cytotoxic T lymphocytes that recognized these antigens may be able to destroy the tumor cells before they proliferate or metastasize.

Tumor antigens can also be on the surface of the tumor in the form of, for example, a mutated receptor, in which case they will be recognized by B cells.

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Glycocalix

Glycocalix is the envelope of the surface of an animal cell membrane. The glycocalix consists of oligosaccharides (glycoproteins and glycolipids), covalently bonded with the cell membrane's proteins and lipids.

The glycocalix is always located on the outer side of the lipid bilayer. The elements of the glycocalix (oligosaccharides) are essential in the process of cell identification and integration, which means they are important components of the receptors. For example, the cell identification during the embryogenesis and the cell growth control depends on the glycocalix.

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Glycolipid

Glycolipids are carbohydrate-attached lipids. Their role is to provide energy and also serve as markers for cellular recognition.

They occur where a carbohydrate chain is associated with phospholipids in the cell surface membrane. The carbohydrates are found on the outer surface of all eukaryotic cell membranes.

They extend from the phospholipid bilayer into the aqueous environment outside the cell where it acts as a recognition site for specific chemicals as well as helping to maintain the stability of the membrane and attaching cells to one another to form tissues.

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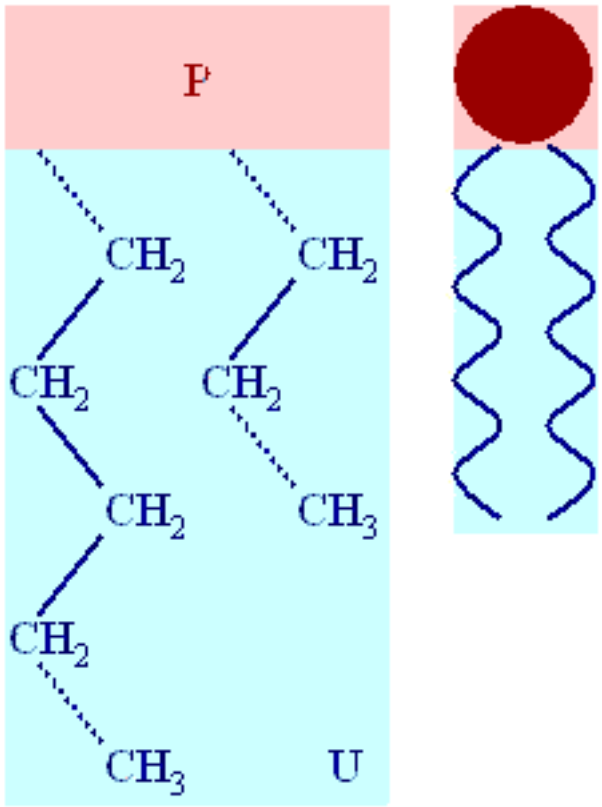
Phospholipid

Phosphoglycerides | Synthesis | Amphipathic character

Phospholipids are a class of lipids formed from four components: fatty acids, a negatively-charged phosphate group, an alcohol and a backbone. Phospholipids with a glycerol backbone are known as glycerophospholipids or **phosphoglycerides**. There is only one type of phospholipid with a sphingosine backbone; sphingomyelin. Phospholipids are a major component of all biological membranes, along with glycolipids and cholesterol.



Two schematic representations of a phospholipid.

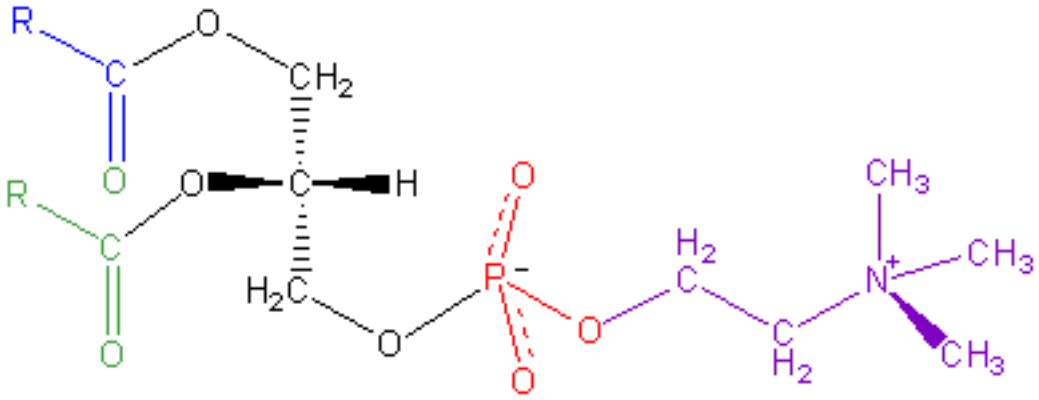
Phosphoglycerides

In phosphoglycerides, the carboxyl group of each fatty acid is esterified to the hydroxyl groups on carbon-1 and carbon-2. The phosphate group is attached to carbon-3 by an ester link. This molecule, known as a phosphatidate, is present in small quantities in membranes, but is also a precursor for the other phosphoglycerides.

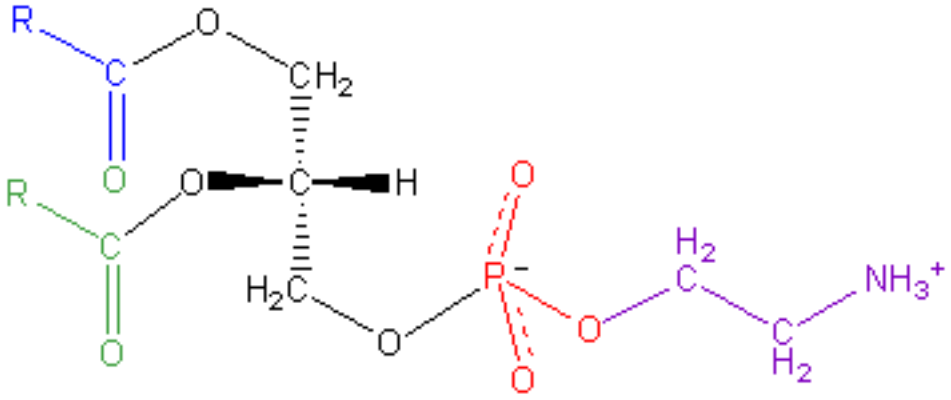
The phosphoglycerides are:

Phosphatidyl choline: major component of lecithin. It is also a source for choline in the synthesis of

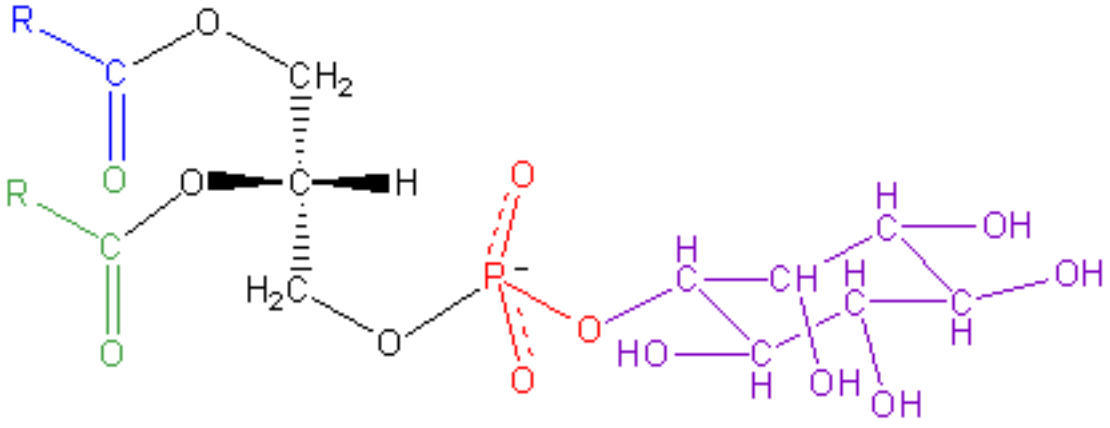
acetylcholine in cholinergic neurons:



Phosphatidyl ethanolamine is the major component of cephalin:

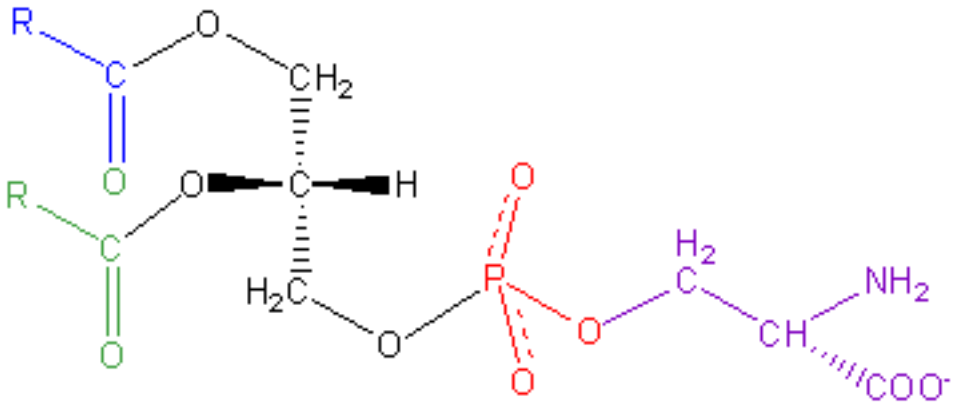


Phosphatidyl inositol:

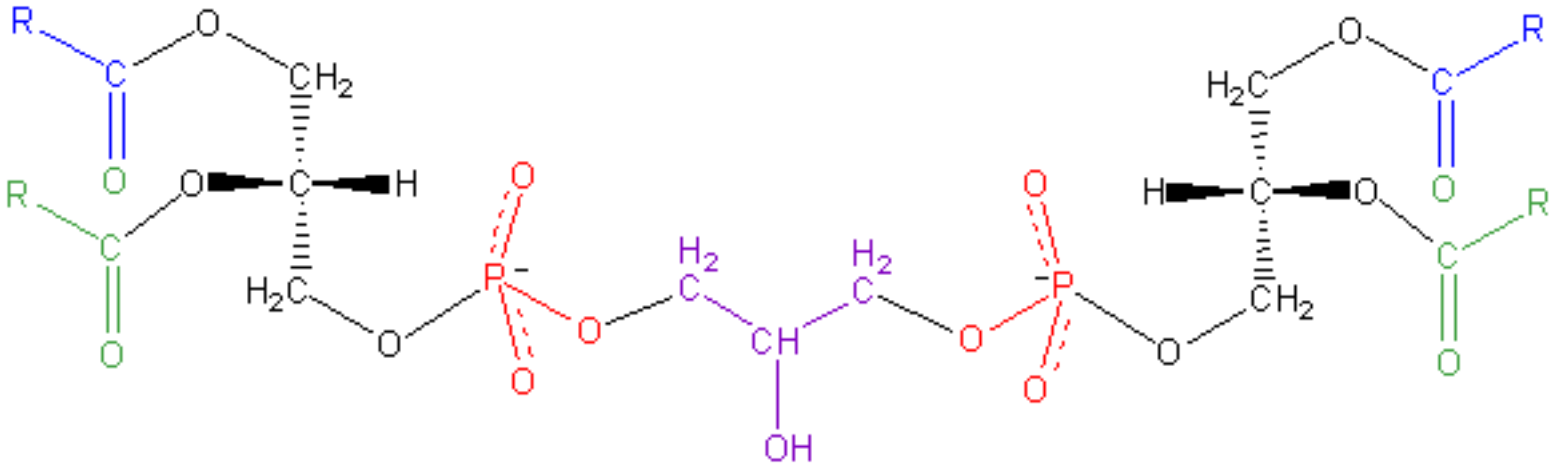


Phosphatidyl serine:

Phospholipid



Diphosphatidyl glycerol:



Synthesis

In phosphoglyceride synthesis, phosphatidates must be activated first. Phospholipids can be formed from an activated diacylglycerol or an activated alcohol. Phosphatidyl serine and phosphatidyl inositol are formed from a phosphoester linkage between the hydroxyl of an alcohol (serine or inositol) and cytidine diphosphodiacylglycerol (CDP-diacylglycerol).

In the synthesis of phospatidyl ethanolamine, the alcohol is phosphorylated by ATP first, and subsequently reacts with cytidine diphosphate (CDP) to form the activated alcohol. The alcohol then reacts with a diacylglycerol to form the final product.

In mammals, phosphatidyl choline can be synthesized via two separate pathways; a series of reactions similar to phosphatidyl ethanolamine synthesis, and the methylation of phosphatidyl ethanolamine, which is catalyzed by phosphatidyl ethanolamine methyltransferase, an enzyme produced in the liver.

Amphipathic character

Due to its polar nature, the head of a phospholipid is hydrophilic (attracted to water); the nonpolar tails

are hydrophobic (not attracted to water). When placed in water, phospholipids form a bilayer, where the hydrophobic tails line up against each other, forming a membrane with hydrophilic heads on both sides extending out into the water. This allows it to form liposomes spontaneously, or small lipid vesicles, which can then be used to transport materials into living organisms and study diffusion rates into or out of a cell membrane. This membrane is partially permeable, very flexible, and has fluid properties, in which embedded proteins and phospholipid molecules are constantly moving laterally across the membrane because of the forces generated by their vibrations. Such movement can be described by the Fluid Mosaic Model, which describes the membrane as a "mosaic" of lipid molecules that act as a solvent for all the substances and proteins within it, so proteins and lipid molecules are then free to diffuse laterally through the lipid matrix and migrate over the membrane.

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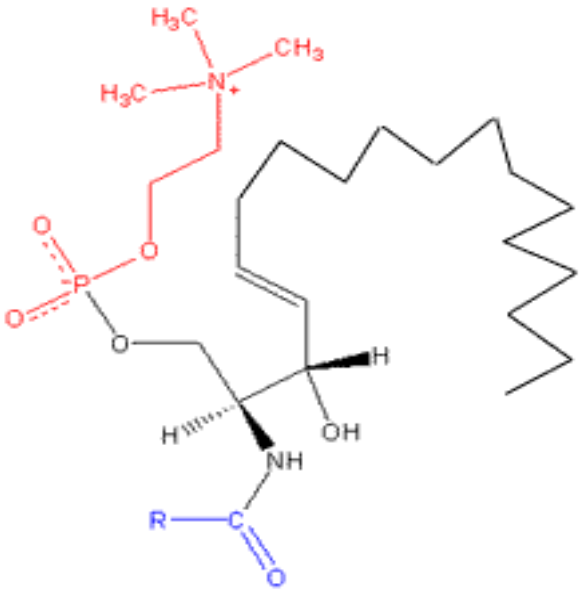
Sphingomyelin

The backbone of sphingomyelin is sphingosine, an amino alcohol formed from palmitate and serine. The amino terminal is acylated with a by a long-chain acyl CoA to yield ceramide. Subsequent substitution of the terminal hydroxyl group by phosphatidyl choline forms sphingomyelin.

Sphingomyelin is present in all eukaryotic cell membranes, and is particularly concentrated in the nervous system because sphingomyelin is a major component of myelin, the fatty insulation wrapped around nerve cells by Schwann cells or oligodendrocytes. Multiple Sclerosis is a disease characterised by deterioration of the myelin sheath, leading to impairment of nervous conduction.



Sphingomyelin (Red:Phosphatidyl choline, Blue:Acyl CoA)

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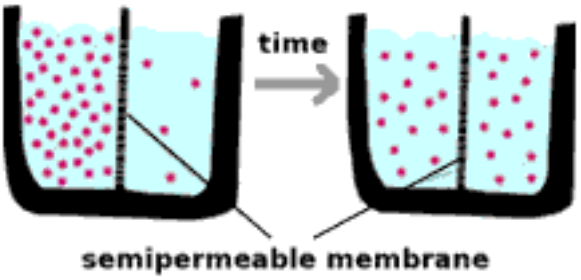
Diffusion



Schematic drawing of the effects of diffusion through a semipermeable membrane.

Diffusion, being the spontaneous spreading of matter (particles), heat, or momentum, is one type of transport phenomena. Diffusion is the movement of particles from higher chemical potential to lower chemical potential (chemical potential can in most cases of diffusion be represented by a change in concentration). It is readily observed for example when dried foodstuff like spaghetti is cooked; water molecules diffuse into the spaghetti strings, making them thicker and more flexible. It is a physical process rather than a chemical reaction, which requires no net energy expenditure. In cell biology, diffusion is often described as a form of passive transport, by which substances cross membranes.

Examples of diffusion

• A balloon filled with helium will deflate a little bit every day, because helium atoms diffuse out of the balloon through its wall.
• When spaghetti is cooked, water molecules diffuse into the spaghetti strings, making them thicker and more flexible. Adding salt to the water reduces diffusion by reducing the osmotic pressure.
• Carbon dioxide bubbles in soft drinks start as small nuclei and grow because of the diffusion of carbon dioxide molecules towards them.
• Heat diffuses through the walls of a mug filled with hot coffee.
• A gas distributes itself over a room by diffusion.
• A sugar cube in a glass of water that is not stirred will dissolve slowly and the sugar molecules will distribute over the water by diffusion.
• Ink in the beaker of water is an example of diffusion. In the end, the ink particles spread evenly throughout the mass of water.

The nature of diffusion

The different forms of diffusion can be modelled quantitatively using the diffusion equation, which goes by different names depending on the physical situation. For instance - steady-state bi-molecular diffusion is governed by Fick's first law, steady-state thermal diffusion is governed by Fourier's law. The diffusion of electrons in an electrical field leads essentially to Ohm's law that is further explained by Einstein relation. The generic diffusion equation is time dependent, and as such applies to non-steady-

state situations as well.

In all cases of diffusion, the net flux of the transported quantity (atoms, energy, or electrons) is equal to a physical property (diffusivity, thermal conductivity, electrical conductivity) multiplied by a gradient (a concentration, thermal, electric field gradient). Noticeable transport occurs only if there is a gradient - for example in thermal diffusion, if the temperature is constant, heat will move as quickly in one direction as in the other, producing no heat transport and change in temperature.

Diffusion occurs as a result of the Second Law of Thermodynamics, which states that the entropy or disorder of any closed system must always increase with time. Because substances diffuse from regions of higher concentration to regions of lower concentration, they are going from a state of higher order to a state of lower order, in accordance with the Second Law of Thermodynamics. Therefore, diffusion is a spontaneous, natural process, and to reverse diffusion would require the expenditure of energy to counteract the higher order of the system and prevent a violation of the laws of entropy.

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Electrochemical gradient

Electrochemical gradients in cellular biology refers to the electrical and chemical properties across a membrane. These are often due to ion gradients, particularly proton gradients, and can represent a type of potential energy available for work in a cell. The useful energy for work accounts for both the concentration gradient of the ions across a cellular membrane and its tendency to move relative to the membrane potential. This can be calculated as a thermodynamic measure termed **electrochemical potential** that combines the concepts of energy stored in the form of chemical potential and electrostatics.

Electrochemical potential is important in electroanalytical chemistry and industrial applications such as batteries and fuel cells. It represents one of the many interchangeable forms of potential energy through which energy may be conserved.

In biological processes the direction an ion will move by diffusion or active transport across membrane is determined by the electrochemical gradient. In mitochondria and chloroplasts, proton gradients are used to generate a **chemiosmotic potential** that is also known as a **proton motive force**. This potential energy is used for the synthesis of ATP by oxidative phosphorylation.

In generic terms, electrochemical potential is the mechanical work done in bringing 1 mole of an ion from a standard state to a specified concentration and electrical potential.

General overview

An electrochemical gradient has two components. First, the electrical component is caused by a charge difference across the lipid membrane. Second, a chemical component is caused by a differential concentration of ions across the membrane. The combination of these two factors determines the thermodynamically favourable direction for an ion's movement across a membrane.

Electrochemical gradients are analogous to hydroelectric dams and equivalent to the water pressure across the dam. Membrane transport proteins such as the sodium-potassium pump within the membrane are equivalent to turbines that convert the waters potential energy to other forms of physical or chemical energy, and the ions that pass through the membrane are equivalent to water that is now found at the bottom of the dam. Alternatively, energy can be used to pump water up into the lake above the dam. Similarly chemical energy in cells can be used to create electrochemical gradients.

Chemistry

The term is typically applied in contexts where a chemical reaction is to take place, such as one involving the transfer of an electron at a battery electrode. In a battery, an electrochemical potential arising from the movement of ions balances the reaction energy of the electrodes. The maximum voltage that a battery reaction can produce is sometimes called the standard electrochemical potential of that reaction. In instances pertaining specifically to the movement of electrically charged solutes, the potential is often expressed in units of volts.

Biological context

In biology too, the term is sometimes used in the context of a chemical reaction, in particular to describe the energy source for the chemical synthesis of ATP. More generally, however, it is used to characterize the inclined tendency of solutes to simply diffuse across a membrane, a process involving no chemical transformation.

Ion gradients

With respect to a cell, organelle, or other subcellular compartments, the inclined tendency of an electrically charged solute, such as a potassium ion, to move across the membrane is decided by the difference in its electrochemical potential on either side of the membrane, which arises from three factors:
• the difference in the concentration of the solute between the two sides of the membrane
• the charge or "valence" of the solute molecule
• the difference in voltage between the two sides of the membrane (i.e. the transmembrane potential).

A solute's electrochemical potential difference is zero at its "reversal potential". The transmembrane voltage to which the solute's net flow across the membrane is also zero. This potential is predicted theoretically either by the Nernst equation (for systems of one permeant ion species) or the Goldman-Hodgkin-Katz equation (for more than one permeant ion species). Electrochemical potential is measured in the laboratory and field using reference electrodes.

Transmembrane ATPases or transmembrane proteins with ATPase domains are often used for making and utilizing ion gradients. The enzyme Na+/K+ ATPase use ATP to make a sodium ion gradient and a potassium ion gradient. The electrochemical potential is used as energy storage, chemiosmotic coupling is one of several ways a thermodynamically unfavorable reaction can be driven by a thermodynamically favorable one. Cotransport of ions by symporters and antiporter carriers are common to actively move ions across biological membranes.

Proton gradients

The proton gradient can be used as an intermediate energy storage for heat production and flagellar rotation. Additionally, it is an interconvertible form of energy in active transport, electron potential generation, NADPH synthesis, and ATP synthesis/hydrolysis.

The electrochemical potential difference between the two sides of the membrane in mitochondria, chloroplasts, bacteria and other membranous compartments that engage in active transport involving proton pumps, is at times called a chemiosmotic potential or proton motive force. In this context, protons are often considered separately using units either of concentration or pH.

Some archaea, most notably halobacteria, make proton gradients by pumping in protons from the environment with the help of the solar driven enzyme bacteriorhodopsin, here it is used for driving the molecular motor enzyme ATP synthase to make the necessary conformational changes required to synthesize ATP.

Proton gradients are also made by bacteria by running ATP synthase in reverse; this is used to drive flagellas.

The F_1F_O ATP synthase is a reversible enzyme. Large enough quantities of ATP cause it to create a transmembrane proton gradient. This is used by fermenting bacteria - which do not have an electron transport chain, and hydrolyze ATP to make a proton gradient - which they use for flagella and the transportation of nutrients into the cell.

In respiring bacteria under physiological conditions, ATP synthase generally runs in the opposite direction creating ATP while using the proton motive force created by the electron transport chain as a source of energy. The overall process of creating energy in this fashion is termed: oxidative phosphorylation. The same process takes place in mitochondria where ATP synthase is located in the inner mitochondrial membrane, so that F_1-part sticks into mitochondrial matrix, where ATP synthesis takes place.

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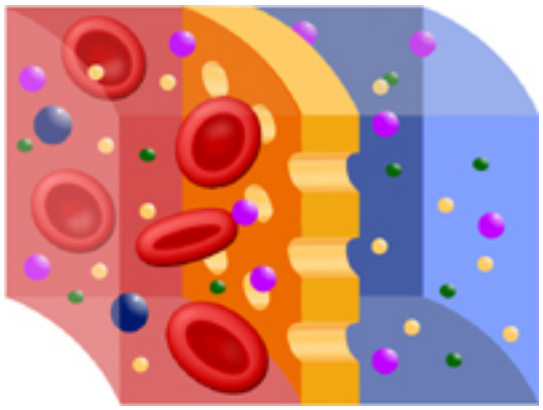
Osmosis

Basic explanation of osmosis | Example of osmosis | Chemical potential | Osmotic pressure | Reverse osmosis



Example of a selectively-permeable membrane

Osmosis is the diffusion of a solvent through a selectively-permeable membrane from a section of high water concentration to a section of low water concentration. The selectively-permeable membrane must be permeable to the solvent, but not to the solute, resulting in a situation across the membrane which drives the diffusion, which permits the presence of osmosis. Osmosis is a natural phenomenon. However, it can be artificially opposed by increasing the pressure in the section of high solute concentration with respect to that in the low solute concentration. The force per unit area required to prevent the passage of water through a selectively-permeable membrane and into a solution of greater concentration is equivalent to the turgor pressure. Osmotic pressure is a colligative property, meaning that the property depends on the concentration of the solute but not on its identity.

Osmosis is an important topic in biology because it provides the primary means by which water is transported into and out of cells.

Basic explanation of osmosis

Consider and focus on a type of permeable membrane that has small enough apertures to allow water molecules to pass through it, however it does not enable larger solvents or solutes to pass through it. An example of this can be visking tubing. First, suppose such a membrane in a volume of pure water. It seems as if there is no flow from one side of the membrane to the other, but at a molecular scale, every time a water molecule hits the membrane, it has a defined likelihood of passing through; water is passing through the membrane, however the circumstances on both sides are equivalent and therefore nothing happens. If there is a solution on the other side, there will be fewer water molecules on that side and thus will collide with the wall less frequently. This will induce a flow of water to the side with the solution. Assuming the membrane does not break, this net flow will slow and finally stop as the pressure on the solution side becomes such that the diffusion in each direction is equal. Like above, if the pressure is

artificially increased within a high solute solution section, with respect to the low solute solution, the pressure from the high solute solution would oppose the natural propensities of osmosis by 'forcing' the water molecules backwards by means of pressure and would serve as a counterbalance to osmosis: this makes it useful for aspects such as water purification.

Example of osmosis

Many plant cells use osmosis. This is because the osmotic entry of water is opposed and eventually equalled by the pressure exerted by the cell wall, creating a steady state. In fact, osmotic pressure is the main cause of support in plant leaves.

When a plant cell is placed in a hypertonic solution, the water in the cells moves to an area higher in solute concentration, and the cell shrinks and so becomes *flaccid*. (This means the cell has become plasmolysed - the cell membrane has completely left the cell wall due to lack of water pressure on it (the opposite of *turgid*).

Osmosis can also be seen very effectively when potato slices are added to a high concentration of salt solution. The water from inside the potato moves to the salt solution, causing the potato to shrink and to lose its 'turgor pressure'. The more concentrated the salt solution, the bigger the difference in size and weight of the potato chip.

In unusual environments, osmosis can be very harmful to organisms. For example, freshwater and saltwater aquarium fish placed in water with a different salt level (than they are adapted to) will die quickly, and in the case of saltwater fish rather dramatically. Additionally, note the use of table salt to kill leeches and slugs.

Chemical potential

When a solute is dissolved in a solvent, the random mixing of the two substances results in an increase in the entropy of the system, which corresponds to a reduction in the chemical potential. For the case of an ideal solution the reduction in chemical potential corresponds to:

$$RT \ln(1 - x_2) \qquad (1)$$

Where R is the gas constant, T is the temperature and x_2 is the solute concentration in terms of mole fraction. Most real solutions approximate the ideal behavior for low solvent concentrations (At higher concentrations interactions between solute and solute cause deviations from Equation 1). This reduced potential creates a 'driving' force and it is this force which enables diffusion of water through the selectively-permeable membrane.

Osmotic pressure

As mentioned before, osmosis is opposed by increasing the pressure in the region of high solute concentration with respect to that in the low solute concentration region. The force per unit area, or pressure, required to prevent the passage of water through a selectively-permeable membrane and into a solution of greater concentration is equivalent to the osmotic pressure of the solution, or turgor. Osmotic pressure is a colligative property, meaning that the property depends on the concentration of the solute but not on its identity.

Increasing the pressure increases the chemical potential of the system in proportion to the molar volume ($d\mu = dPV$). Therefore, osmosis stops, when the increase in potential due to pressure equals the potential decrease from Equation 1, i.e.:

$$\delta PV = -RT \ln(1 - x_2) \qquad (2)$$

Where δP is the osmotic pressure and V is the molar volume of the solvent.

For the case of very low solute concentrations, $-\ln(1-x_2) \approx x_2$ and Equation 2 can be rearranged into the following expression for osmotic pressure:

$$\delta P = RTx_2/V \qquad (3)$$

Reverse osmosis

The osmosis process can be driven in reverse with solvent moving from a region of high solute concentration to a region of low solute concentration by applying a pressure in excess of the osmotic pressure. This reverse osmosis technique is commonly applied to purify water. Sometimes the term forward osmosis is used for osmosis, particularly when used for rehydrating dried food using contaminated water.

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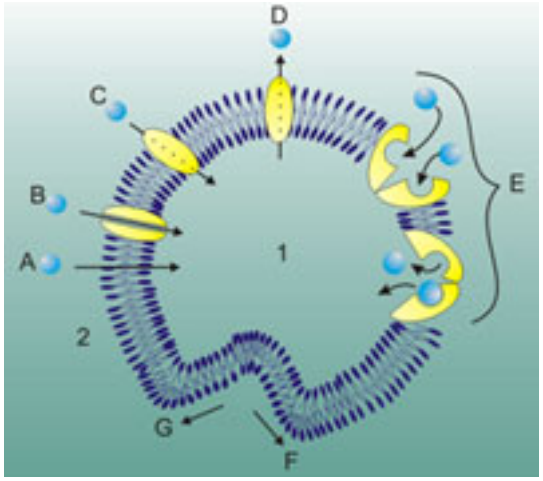
Passive transport

Diffusion | Facilitated diffusion | Filtration | Osmosis



A. Diffusion; B. Ion Channel; C and D. Facilitated Diffusion; E. Active Transport (Pump)

Passive transport is a means of moving biochemicals, and other atomic or molecular substances, across membranes. Unlike active transport, this process does not involve chemical energy. Passive transport is dependent on the permeability of the cell membrane, which, in turn, is dependent on the organization and characteristics of the membrane lipids and proteins. The four main kind of passive transport are diffusion, facilitated diffusion, filtration and osmosis.

Diffusion

Diffusion is the net movement of material from an area of high concentration of that material to an area with lower concentration. The difference of concentration between the two areas is often termed as the concentration gradient, and diffusion will continue until this gradient has been eliminated. Since diffusion moves material from area of higher concentration to the lower, it is described as moving solutes "down the concentration gradient" (compared with active transport, which often moves material from area of low concentration to area of higher concentration, and therefore referred to as moving the material "against the concentration gradient").

If and when the concentration gradient have been eliminated, no net exchange of material occurs. Although material may move forth from one area to the other, it will be balanced by movement of the same amount of material to the opposite direction.

Diffusion is biologically important because it enables the abolishment of concentration gradients in the body. For example, metabolic activity will consume oxygen, which will reduce its concentration in the bloodstream; diffusion of oxygen in the alveoli of the lungs allows it to be replenished.

Facilitated diffusion

Facilitated diffusion is movement of molecules across the cell membrane via special transport proteins that are embedded within the cellular membrane. Many large molecules, such as glucose, are insoluble in lipids and too large to fit through the membrane pores. Therefore, it will bind with its specific carrier proteins, and the complex will then be bonded to a receptor site and moved through the cellular membrane. Bear in mind, however, that facilitated diffusion is a passive process, and the solutes still move down the concentration gradient. The alveoli are tiny grapelike sacs located atthe end of the bronchial tubes. This is where oxygen diffuses into the alveoli and is exchanged for carbon dioxide.

Filtration

Filtration is movement of water and solute molecules across the cell membrane due to hydrostatic pressure generated by the cardiovascular system. Depending on the size of the membrane pores, only solutes of a certain size may pass through it. For example, the membrane pores of the Bowman's capsule in the kidneys are very small, and only albumin, the smallest of the proteins, have any chance of being filtered through. On the other hand, the membrane pores of liver cells are extremely large, to allow a variety of solutes to pass through and be metabolized.

Osmosis

Osmosis is the diffusion of a solvent across a membrane to a region of higher solute concentration. (In biological processes then, it usually is diffusion of water molecules) Most cell membranes are permeable to water, and since the diffusion of water plays such an important role in the biological functioning of any living being, a special term has been coined for it -- osmosis.

Water molecules "stick" together via weak hydrogen bond.

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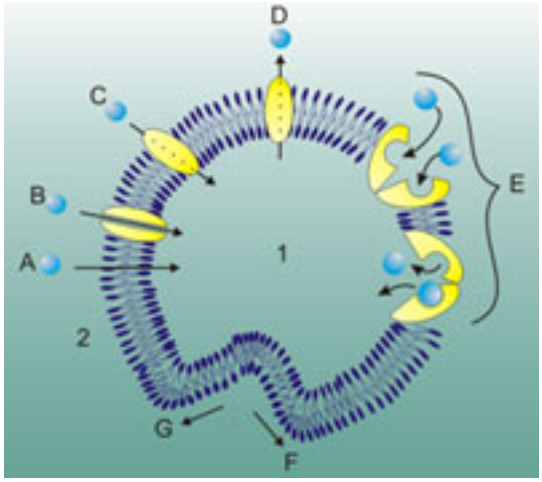
Facilitated diffusion



A. Diffusion; B. Ion Channel; **C and D. Facilitated Diffusion**; E. Active Transport (Pump)

Facilitated diffusion (**facilitated transport**) is a process of diffusion, a form of passive transport, via which molecules diffuse across membranes, with the assistance of transport proteins.

Small uncharged molecules can easily diffuse across cell membranes. However, due to the hydrophobic nature of the lipids that make up cell membranes, water-soluble molecules and ions cannot do so; instead, they are helped across by transport proteins. The transport protein involved is intrinsic, that is, it completely spans the membrane. It also has a binding site for the specific molecule such as glucose, or ion to be transported. After binding to the molecule, the protein changes shape and carries the molecule across the membrane, where it is released. The protein then returns to its original shape, to wait for more molecules to transport.

In contrast to active transport, facilitated diffusion does not require energy and carries molecules or ions down a concentration gradient.

Facilitated diffusion can take place in pores and gated channels. Pores never close, but gated channels open and close in response to stimuli.

The transport proteins participating in facilitated diffusion resemble enzymes. Just as enzymes are substrate specific and only catalyze certain substrates, transport proteins are solute specific and only transport certain solutes. Transport proteins also have a limit of how many solutes they can transport that they cannot exceed. Finally, molecules can inhibit the protein in a way similar to competitive inhibition in enzymes.

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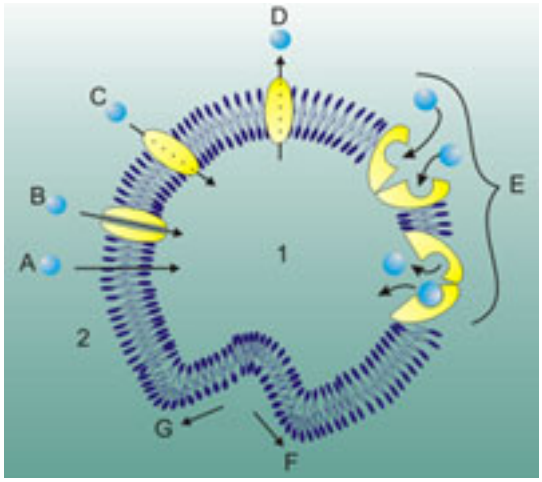
Ion channel



A. Diffusion; **B. Ion Channel**; C and D. Facilitated Diffusion; E. Active Transport (Pump)

Ion channels are pore-forming proteins that help establish the small voltage gradient that exists across the membrane of all living cells, by allowing the flow of ions down their electrochemical gradient. They are present in the membranes that surround all biological cells.

Basic features

An ion channel is an integral membrane protein or more typically an assembly of several proteins. Such "multi-subunit" assemblies usually involve a circular arrangement of identical or related proteins closely packed around a water-filled pore through the plane of the membrane or lipid bilayer. While large-pore channels permit the passage of ions more or less indiscriminately, the archetypal channel pore is just one or two atoms wide at its narrowest point. It conducts a specific species of ion, such as sodium or potassium, and conveys them through the membrane single file--nearly as quickly as the ions move through free fluid. In some ion channels, access to the pore is governed by a "gate," which may be opened or closed by chemical or electrical signals, temperature, or mechanical force, depending on the variety of channel.

Biological role

Because "voltage-gated" channels underlie the nerve impulse and because "transmitter-gated" channels mediate conduction across the synapses, channels are especially prominent components of the nervous system. Indeed, most of the offensive and defensive toxins that organisms have evolved for shutting down the nervous systems of predators and prey (e.g., the venoms produced by spiders, scorpions, snakes, fish, bees, sea snails and others) work by plugging ion channel pores. But ion channels figure in

a wide variety of biological processes that involve rapid changes in cells. In the search for new drugs, ion channels are a favorite target.

Diversity and activation

• Voltage-gated channels open or close, depending on the transmembrane potential. Examples include the sodium and potassium voltage-gated channels of nerve and muscle, that are involved in the propagation of the action potential, and the voltage-gated calcium channels that control neurotransmitter release in pre-synaptic endings.
• Ligand-gated channels open in response to a specific ligand molecule on the external face of the membrane in which the channel resides. Examples include the "nicotinic" Acetylcholine receptor, AMPA receptor and other neurotransmitter-gated channels.
• Cyclic nucleotide-gated channels, Calcium-activated channels and others open in response to internal solutes and mediate cellular responses to second messengers.
• Stretch-activated channels open or close in response to mechanical forces that arise from local stretching or compression of the membrane around them; for example when their cells swell or shrink. Such channels are believed to underlie touch sensation and the transduction of acoustic vibrations into the sensation of sound.
• G-protein-gated channels open in response to G protein-activation via its receptor.
• Inward-rectifier K channels allow potassium to flow into the cell in an inwardly rectifying manner, i.e, potassium flows into the cell but not out of the cell. They are involved in important physiological processes such as the pacemaker activity in the heart, insulin release, and potassium uptake in glial cells.
• Light-gated channels like channelrhodopsin are directly opened by the action of light.
• Resting channels remain open at all times.

Certain channels respond to multiple influences. For instance, the NMDA receptor is partially activated by interaction with its ligand, glutamate, but is also voltage-sensitive and conducts only when the membrane is depolarized. Some calcium-sensitive potassium channels respond to both calcium and depolarization, with an excess of one apparently being sufficient to overcome an absence of the other.

Detailed structure

Channels differ with respect to the ion they let pass (for example, Na^+, K^+, Cl^-), the ways in which they may be regulated, the number of subunits of which they are composed and other aspects of structure. Channels belonging to the largest class, which includes the voltage-gated channels that underlie the nerve impulse, consists of four subunits with six transmembrane helices each. On activation, these helices move about and open the pore. Two of these six helices are separated by a loop that lines the pore and is the primary determinant of ion selectivity and conductance in this channel class and some others. The channel subunits of one such other class, for example, consist of just this "P" loop and two transmembrane helices. The determination of their molecular structure by Roderick MacKinnon using X-ray crystallography won a share of the 2003 Nobel Prize in Chemistry.

Because of their small size and the difficulty of crystallizing integral membrane proteins for X-ray analysis, it is only very recently that scientists have been able to directly examine what channels "look like." Particularly in cases where the crystallography required removing channels from their membranes with detergent, many researchers regard images that have been obtained as tentative. An example is the long-awaited crystal structure of a voltage-gated potassium channel, which was reported in May 2003. One inevitable ambiguity about these structures relates to the strong evidence that channels change conformation as they operate (they open and close, for example), such that the structure in the crystal could represent any one of these operational states. Most of what researchers have deduced about channel operation so far they have established through electrophysiology, biochemistry, gene sequence comparison and mutagenesis.

Diseases of Ion Channels

There are a number of chemicals and genetic disorders which disrupt normal functioning of ion channels and have disastrous consequences for the organism.

Chemicals

• Tetrodotoxin (TTX), used by puffer fish and some types of newts for defense. It is a sodium channel blocker.
• Saxitoxin, produced by a dinoflagellate also known as red tide. It blocks voltage dependent sodium channels.
• Conotoxin, which is used by cone snails to hunt prey.
• Lidocaine and Novocaine belong to a class of local anesthetics which block sodium ion channels.
• Dendrotoxin produced by mamba snakes blocks potassium channels.

Genetic

• Shaker gene mutations cause a defect in the volatage gated ion channels, slowing down the repolarization of the cell.
• Equine hyperkalaemic periodic paralysis as well as Human hyperkalaemic periodic paralysis (HyperPP) are caused by a defect in voltage dependent sodium channels.
• Paramyotonia congenital (PC) and potassium aggravated myotonias (PAM)
• Generalized epilepsy with febrile seizures (GEFS)
• Episodic Ataxia Type-1 (EA1)
• Familial hemiplegic migraine (FHM)

History

The existence of ion channels was hypothesized by the British biophysicists Alan Hodgkin and Andrew Huxley as part of their Nobel Prize-winning theory of the nerve impulse, published in 1952. The existence of ion channels was confirmed in the 1970s with an electrical recording technique known as

the "patch clamp," which led to a Nobel Prize to Erwin Neher and Bert Sakmann, the technique's inventors. Hundreds if not thousands of researchers continue to pursue a more detailed understanding of how these proteins work. In recent years the development of automated patch clamp devices helped to increase the throughput in ion channel screening significantly.

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Detailed structure of cell membrane

Phospholipid molecules in the cell membrane are "fluid," in the sense of free to diffuse and exhibit rapid lateral diffusion. Lipid rafts and caveolae are examples of cholesterol-enriched microdomains in the cell membrane. Many proteins are not free to diffuse. The cytoskeleton undergirds the cell membrane and provides anchoring points for integral membrane proteins. Anchoring restricts them to a particular cell face or surface – for example, the "apical" surface of epithelial cells that line the vertebrate gut – and limits how far they may diffuse within the bilayer. Rather than presenting always a formless and fluid contour, the plasma membrane surface of cells may show structure. Returning to the example of epithelial cells in the gut, the apical surfaces of many such cells are dense with involutions, all similar in size. The finger-like projections, called **microvilli**, increase cell surface area and facilitate the absorption of molecules from the outside. Synapses are another example of highly-structured membrane.

New material is incorporated into the membrane, or deleted from it, by a variety of mechanisms.
(i) Fusion of intracellular vesicles with the membrane not only excretes the contents of the vesicle, but also incorporates the vesicle membrane's components into the cell membrane. The membrane may form blebs that pinch off to become vesicles.
(ii) If a membrane is continuous with a tubular structure made of membrane material, then material from the tube can be drawn into the membrane continuously.
(iii) Although the concentration of membrane components in the aqueous phase is low (stable membrane components have low solubility in water), exchange of molecules with this small reservoir is possible. In all cases, the mechanical tension in the membrane has an effect on the rate of exchange. In some cells, usually having a smooth shape, the membrane tension and area are interrelated by elastic and dynamical mechanical properties, and the time-dependent interrelation is sometimes called homeostasis, area regulation or tension regulation.

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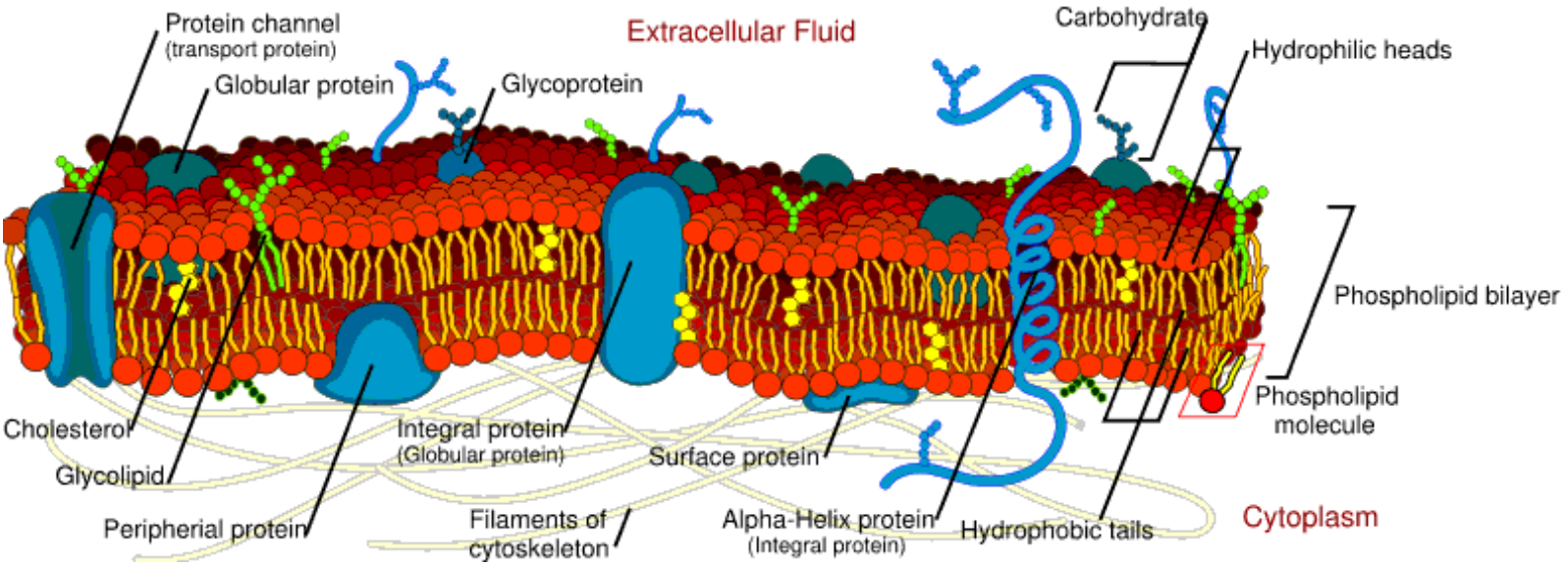
A fluid mosaic

The basic composition and structure of the plasma membrane is the same as that of the membranes that surround organelles and other subcellular compartments. The foundation is a phospholipid bilayer, and the membrane as a whole is often described as a *fluid mosaic* – a two-dimensional fluid of freely diffusing lipids, dotted or embedded with proteins, which may function as channels or transporters across the membrane, or as receptors. The model was first proposed by S.J. Singer (1971) as a lipid protein model and extended to include the fluid character in a publication with G.L. Nicolson in "Science" (1972).



Some of these proteins simply adhere to the membrane (*extrinsic* or *peripheral* proteins), whereas others might be said to reside within it or to span it (*intrinsic* proteins – more at integral membrane protein). *Glycoproteins* have carbohydrates attached to their extracellular domains. Cells may vary the variety and the relative amounts of different lipids to maintain the fluidity of their membranes despite changes in temperature. Cholesterol molecules (in case of eukaryotes) or hopanoids (in case of prokaryotes) in the bilayer assist in regulating fluidity.

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Triglyceride

Chemical structure | Metabolism | Role in disease | Industrial uses | Staining

Triglycerides (also known as **triacylglycerols** or **triacylglycerides**) are glycerides in which the glycerol is esterified with three fatty acids. They are the main constituent of vegetable oil and animal fats.

Chemical structure

C$\mathbf{H_2}$COOR-**CH**COOR'-**C**$\mathbf{H_2}$-COOR"

where R, R', and R" are long alkyl chains; the three **fatty acids** RCOOH, R'COOH and R"COOH can be all different, all the same, or only two the same.

Chain lengths of the fatty acids in naturally occurring triglycerides can be from 3 to 22 carbon atoms, but 16 and 18 are most common. Shorter chain lengths may be found in some substances (butyric acid in butter). Typically, plants and animals have natural fatty acids that comprise only of even numbers of carbon atoms due to the way they are bio-synthesised from acetyl CoA, however bacteria possess the ability to synthesise odd- and branched-chain fatty acids. Consequently, ruminant animal fat contains significant proportions of branched-chain fatty acids, due to the action of bacteria in the rumen.

Most natural fats contain a complex mixture of individual triglycerides; because of this, they melt over a broad range of temperatures. Cocoa butter is unusual in that it is comprises only of a few triglycerides, one of which contains palmitic, oleic and stearic acids in that order. This gives rise to a fairly sharp melting point, causing chocolate to melt in the mouth without feeling greasy.

Metabolism

Triglycerides play an important role in metabolism as energy sources. They contain more than twice as much energy (9 kcal/g) as carbohydrates and proteins. In the intestine, triglycerides are split into glycerol and fatty acids (this process is called lipolysis) (with the help of lipases and bile secretions), which can then move into blood vessels. The triglycerides are rebuilt in the blood from their fragments and become constituents of lipoproteins, which deliver the fatty acids to and from fat cells among other functions. Various tissues can release the free fatty acids and take them up as a source of energy. Fat cells can synthesize and store triglycerides. When the body requires fatty acids as an energy source, the hormone glucagon signals the breakdown of the triglycerides by hormone-sensitive lipase to release free fatty acids. As the brain can not utilize fatty acids as an energy source, the glycerol component of triglycerides can be converted into glycogen for brain fuel when it is broken down. Fat cells may also be broken down for that reason, if the brain's needs ever outweigh the body's.

Role in disease

In the human body, high levels of triglycerides in the bloodstream have been linked to atherosclerosis, and, by extension, the risk of heart disease and stroke. However, the negative impact of raised levels of triglycerides is lower than that of LDL:HDL ratios. The risk can be partly accounted for a strong inverse relationship between triglyceride level and HDL-cholesterol level.

Other diseases caused by high triglycerides include pancreatitis.

Guidelines

The American Heart Association has set guidelines for triglyceride levels:

Levelmg/dL <150 **Level**mmol/L (<1.69mmol/L) **Interpretation** Normal range, lowest risk

Levelmg/dL 150-199 **Level**mmol/L (1.70-2.25mmol/L) **Interpretation** Borderline high

Levelmg/dL 200-498 **Level**mmol/L (2.25-5.63mmol/L) **Interpretation** High

Levelmg/dL >500 **Level**mmol/L (>5.65 mmol/L) **Interpretation** Very high, increased risk

Please note that this information is relevant to triglyceride levels as tested after fasting. Triglyceride levels remain temporarily higher for a period of time after eating.

Reducing triglyceride levels

Cardiovascular exercise and low-moderate carbohydrate diets containing essential fatty acid are recommended for reducing triglyceride levels. When these fail, fibrate drugs, niacin, and some statins are registered for reducing triglyceride levels. Prior alcohol intake can cause elevated levels of triglycerides.

Industrial uses

Triglycerides are also split into their components via transesterification during the manufacture of biodiesel. The fatty acid monoalkyl ester can be used as fuel in diesel engines. The glycerin can be used for food and in pharmaceutical production, among others.

Staining

Staining for fatty acids, triglycerides, lipoproteins, and other lipids is done through the use of lysochromes (fat-soluble dyes). These dyes can allow the qualification of a certain fat of interest by staining the material a specific color. Some examples: Sudan IV, Oil Red O, and Sudan Black B.

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Insulin

Structure and production | Actions on cellular and metabolic level | Signal transduction

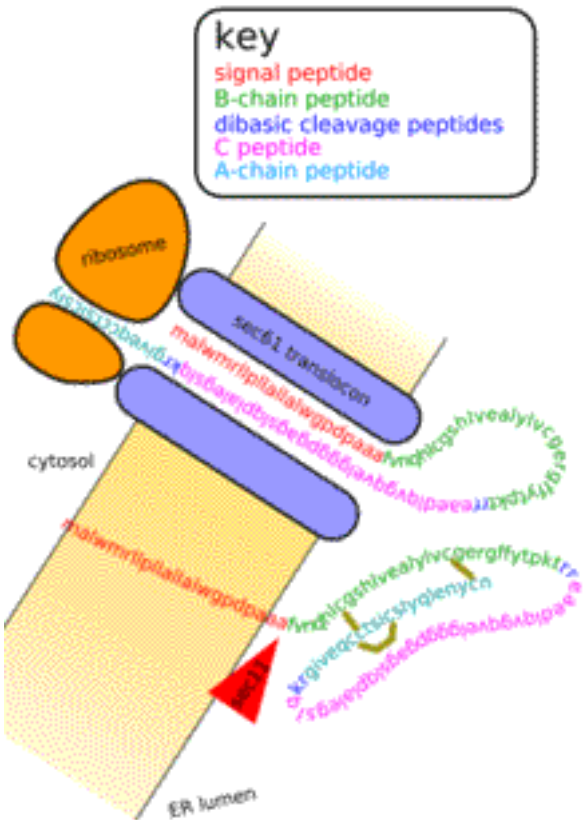
Insulin (from Latin *insula*, "island", as it is produced in the Islets of Langerhans in the pancreas) is a polypeptide hormone that regulates carbohydrate metabolism. Apart from being the primary effector in carbohydrate homeostasis, it has effects on fat metabolism. It can change the liver's ability to release fat stores. Insulin's concentration (more or less, presence or absence) has extremely widespread effects throughout the body.

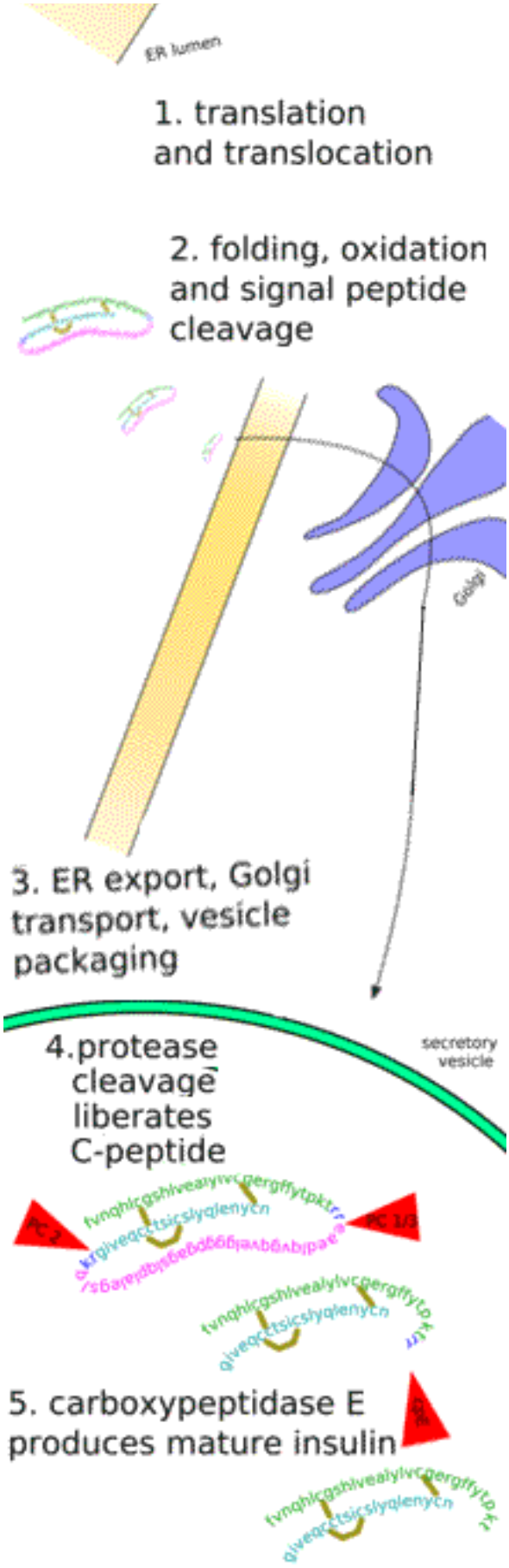
Insulin is used medically in some forms of diabetes mellitus. Patients with type 1 diabetes mellitus depend on exogenous insulin (injected subcutaneously) for their survival because of an absolute deficiency of the hormone; patients with type 2 diabetes mellitus have either relatively low insulin production or insulin resistance or both, and a non-trivial fraction of type 2 diabetics eventually require insulin administration when other medications become inadequate in controlling blood glucose levels.

Insulin has a molecular weight of 5.8 kDa.

Insulin structure varies slightly between species of animal. Its carbohydrate metabolism regulatory function strength in humans also varies. Porcine (pig) insulin is particularly close to humans'.

Structure and production





Insulin undergoes extensive posttranslational modification along the secretory pathway. Cell components and proteins in this image are not to scale.

Insulin is synthesized in humans and other mammals within the beta cells (β-cells) of the islets of Langerhans in the pancreas. One to three million islets of Langerhans (pancreatic islets) form the endocrine part of the pancreas, which is primarily an exocrine gland. The endocrine part accounts for only 2% of the total mass of the pancreas. Within the islets of Langerhans, beta cells constitute 60-80% of all the cells.

In beta cells, insulin is synthesized from the proinsulin precursor molecule by the action of proteolytic enzymes known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E. These modifications liberate the center portion of the molecule, or C-peptide, from the C- and N- terminal ends of the proinsulin. The two remaining polypeptides, the B- and A- chains, are held together by disulfide bonds and together constitute 51 amino acids. Confusingly, the primary sequence of insulin goes in the order "B-C-A", since B and A chains were identified on the basis of mass, and the C peptide was discovered after the others.

Amongst vertebrates, insulin is highly conserved. Bovine insulin differs from human insulin in three amino acid residues, and porcine insulin in one residue. Even insulin from some species of fish is also close enough to human insulin to be effective in humans.

Actions on cellular and metabolic level

The actions of insulin on the global human metabolism level include:

- Control of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about 2/3 of body cells).
- Increase of DNA replication and protein synthesis via control of amino acid uptake.
- Modification of the activity of numerous enzymes (allosteric effect).

The actions of insulin on cells include:

- Increased glycogen synthesis - insulin forces storage of glucose in liver (and muscle) cells in the form of glycogen; lowered levels of insulin cause liver cells to convert glycogen to glucose and excrete it into the blood. This is the clinical action of insulin which is useful in reducing high blood glucose levels as in diabetes.
- Increased fatty acid synthesis - insulin forces fat cells to take in glucose which is converted to triglycerides; lack of insulin causes the reverse.
- Increased esterification of fatty acids - forces adipose tissue to make fats (ie, triglycerides) from fatty acid esters; lack of insulin causes the reverse.
- Decreased proteinolysis - forces reduction of protein degradation; lack of insulin increases protein degradation.
- Decreased lipolysis - forces reduction in conversion of fat cell lipid stores into blood fatty acids; lack of insulin causes the reverse.

- Decreased gluconeogenesis - decreases production of glucose from various substrates in liver; lack of insulin causes glucose production from assorted substrates in the liver and elsewhere.
- Increased amino acid uptake - forces cells to absorb circulating amino acids; lack of insulin inhibits absorption.
- Increased potassium uptake - forces cells to absorb serum potassium; lack of insulin inhibits absorption.
- Arterial muscle tone - forces arterial wall muscle to relax, increasing blood flow, especially in micro arteries; lack of insulin reduces flow by allowing these muscles to contract.

Signal transduction

There are special transport channels in cell membranes through which glucose from the blood can enter a cell. These channels are, indirectly, under insulin control in certain body cell types. A lack of circulating insulin will prevent glucose from entering those cells (eg, in untreated Type 1 diabetes). However, more commonly there is a decrease in the sensitivity of cells to insulin (e.g. the reduced insulin sensitivity characteristic of Type 2 diabetes), resulting in decreased glucose absorption. In either case, there is 'cell starvation', weight loss, sometimes extreme. In a few cases, there is a defect in the release of insulin from the pancreas. Either way, the effect is the same: elevated blood glucose levels.

Activation of insulin receptors leads to internal cellular mechanisms which directly affect glucose uptake by regulating the number and operation of protein molecules in the cell membrane which transport glucose into the cell.

Two types of tissues are most strongly influenced by insulin as far as the stimulation of glucose uptake is concerned: muscle cells (myocytes) and fat cells (adipocytes). The former are important because of their central role in movement, breathing, circulation, etc, and the latter because they accumulate excess food energy against future needs. Together, they account for about 2/3 of all cells in a typical human body.

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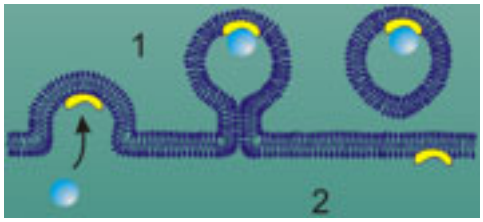
Endocytosis



1=inside, 2=outside the cell

Endocytosis is a process whereby cells absorb material (molecules such as proteins) from outside by engulfing it with their cell membrane. It is used by all cells of the body because most substances important to them are polar and consist of big molecules, and thus cannot pass through the hydrophobic plasma membrane. Endocytosis is the opposite of exocytosis, and always involves the formation of a vesicle from part of the cell membrane.

The absorption of material from the outside environment of the cell is commonly divided into two processes, phagocytosis and pinocytosis.
1. Phagocytosis (literally, cell-eating) is the process by which cells ingest large objects, such as cells which have turned into apoptosis or bacteria and virusses. The membrane folds around the object, and the object is sealed off into a large vacuole known as phagosome. Phagocytosis is not considered to be an endocytic process.
2. Pinocytosis (literally, cell-drinking) is a synonym for endocytosis. This process is concerned with the uptake of solutes and single molecules such as proteins.

Endocytosis pathways

There are three types of endocytosis namely macropinocytosis, clathrin-mediated endocytosis and caveolar endocytosis.
• Macropinocytosis is the invagination of the cell membrane to form a pocket (vesicle) filled with extracellular fluid (and molecules within it). The filling of the pocket occurs in non-specific manner. The vesicle then travels into the cytosol and fuses with other vesicles such as endosomes and lysosomes.
• Clathrin-mediated endocytosis is the specific uptake of large extracellular molecules such as proteins, membrane localized receptors and ion-channels. Uptake of extracellular proteins is prompted after the binding of the protein to a receptor on the cell membrane. These receptors are associated with the cytosolic protein clathrin which initiates the formation of a vesicle by forming a crystaline coat on the membrane of the vesicle.
• Caveolae consist of the protein caveolin-1, cholesterol and glycosphingolipids. Caveolae form flask shaped pits into the membrane that resemble the shape of a cave (hence the name caveolae). Uptake of extracellurar particles is also specifically mediated via receptors present in caveolae.

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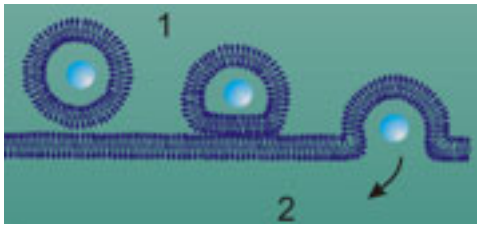
Exocytosis



1=inside, 2=outside the cell

Exocytosis is the process by which a cell releases large biomolecules through its membrane. While in protozoa (monocellular organisms) exocytosis may serve the function of eliminating waste products, in multicellular organisms exocytosis has a signalling or regulatory function. In multicellular organisms there are two types of exocytosis (i) Ca++ triggered non-constitutive and (ii) non Ca++ triggered constitutive one. Exocytosis in neuronal chemical synapses is Ca++ triggered and serves interneuronal signalling. Constitutive exocytosis is performed by all cells and serves the release of components of the extracellular matrix, or just delivery of newly-synthesized membrane proteins that are incorporated in the plasma membrane after the fusion of the transport vesicle.

Several steps are involved in exocytosis - vesicle trafficking, vesicle tethering, vesicle docking, vesicle priming and vesicle fusion.

Vesicle trafficking. Certain vesicle-trafficking steps require the translocation of a vesicle over a significant distance. For example, vesicles that carry proteins from the Golgi apparatus to the cell surface are likely to use motor proteins and a cytoskeletal track to get close to their target before tethering would be appropriate. Both the actin- and the microtubule-based cytoskeletons are implicated in these processes, along with several motor proteins. Once the vesicles reach their targets, they come into contact with tethering factors that can restrain them.

Vesicle tethering. It is useful to distinguish between the initial, loose tethering of vesicles with their targets from the more stable, docking interactions. Tethering involves links over distances of more than about half the diameter of a vesicle from a given membrane surface (>25 nm). Tethering interactions are likely to be involved in concentrating synaptic vesicles at the synapse.

Vesicle docking. The term docking refers to the holding of two membranes within a bilayer's distance of one another (<5-10 nm). Stable docking probably represents several distinct, molecular states: the molecular interactions underlying the close and tight association of a vesicle with its target may include the molecular rearrangements needed to trigger bilayer fusion. A common feature of many proteins that function in vesicle tethering and docking is their propensity to form highly extended, coiled-coil structures. Tethering and docking of a transport vesicle at the target membrane precedes the formation of a tight core SNARE complex.

Vesicle priming. In neuronal exocytosis, the term priming has been used to include all of the molecular rearrangements and ATP-dependent protein and lipid modifications that take place after initial docking of a synaptic vesicle but before exocytosis, such that the influx of calcium ions is all that is needed to trigger nearly instantaneous neurotransmitter release. In other cell types, whose secretion is constitutive (i.e. continuous, calcium ion independent, non-triggered) there is no priming.

Vesicle fusion. The vesicle fusion is driven by SNARE proteins process of merging the vesicle membrane with the target one resulting in release of large biomolecules in the extracellular space (or in case of neurons in the synaptic cleft).

The merging of the donor and the acceptor membranes accomplishes three tasks:
* The surface of the plasma membrane increases (by the surface of the fused vesicle). This is important for the regulation of cell size, e.g., during cell growth.
* The substances within the vesicle are released into the exterior. These might be waste products or toxins, or signalling molecules like hormones or neurotransmitters during synaptic transmission.
* Proteins embedded in the vesicle membrane are now part of the plasma membrane. The side of the protein that was facing the inside of the vesicle now facesthe outside of the cell. This mechanism is important for the regulation of transmembrane receptors and transporters.

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Membrane permeability

The lipid bilayer of cell membrane is semi-permeable, which means that some molecules can pass through the membrane through diffusion. The rate of diffusion varies depending on the molecule size, polarity, charge and concentration on the inside of the membrane versus the concentration on the outside of the membrane. Below are some molecules permeabilities through a lipid bylayer in the absence of all transmembrane proteins. In other words, this is permeability through the lipid bylayer itself without any help from pumps or ion channels:

Hydrophobic Molecules - highly permeable

- O_2 - Oxygen
- N_2 - Nitrogen

Small uncharged Polar Molecules - less permeable

- H_2O - Water
- urea
- glycerol

Large Uncharged Polar Molecules - even less permeable

- Glucose
- Sucrose

Ions - non-permeable

- H^+ - Hydrogen ion
- Na^+ - Sodium ion
- K^+ - Potassium ion
- Ca^{2+} - Calcium ion
- Cl^- - Chloride ion

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Cellular respiration

Cellular respiration is the process in which the chemical bonds of energy-rich molecules such as glucose are converted into energy usable for life processes. Oxidation of organic material-in a bonfire, for example-is an exothermic reaction that releases a large amount of energy rather quickly. The equation for the oxidation of glucose is:

$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$ + Energy released (2830kJ mol^{-1})

In a fire there is a massive uncontrolled release of energy as light and heat. Cellular respiration is the same process but it occurs in gradual steps that result in the conversion of the energy stored in glucose to usable chemical energy in the form of ATP. Waste products ($CO_2 + 6H_2O$) are released through exhaled air, sweat and urine.

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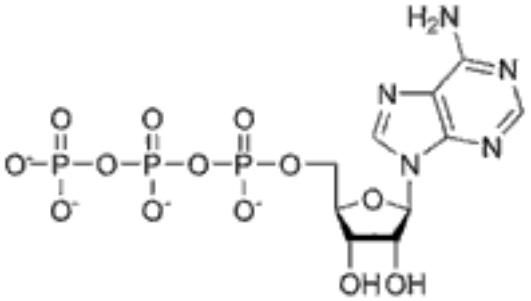
Adenosine triphosphate



Adenosine 5'-triphosphate (**ATP**) is a multifunctional nucleotide primarily known in biochemistry as the "molecular currency" of intracellular energy transfer. In this role ATP transports chemical energy within cells. It is produced as an energy source during the processes of photosynthesis and cellular respiration. ATP is also one of four monomers required for the synthesis of ribonucleic acids. Furthermore, in signal transduction pathways, ATP is used to provide the phosphate for protein-kinase reactions.

Chemical properties

ATP consists of adenosine and three phosphate groups (triphosphate). The phosphoryl groups, starting with that on AMP, are referred to as the alpha (α), beta (β), and gamma (γ) phosphates. ATP is extremely rich in chemical energy, in particular between the second and third phosphate groups. The net change in energy of the decomposition of ATP into ADP and an inorganic phosphate is -12 kCal / mole *in vivo* (inside of a living cell) and -7.3 kCal / mole *in vitro* (in laboratory conditions). This massive release in energy makes the decomposition of ATP extremely exergonic, and hence useful as a means for chemically storing energy.

Synthesis

ATP can be produced by various cellular processes: Under aerobic conditions, the majority of the synthesis occurs in mitochondria during oxidative phosphorylation and is catalyzed by ATP synthase and, to a lesser degree, under anaerobic conditions by fermentation.

The main fuels for ATP synthesis are glucose and triglycerides. The fuels that result from the breakdown of triglycerides are glycerol and fatty acids.

First, glucose and glycerol are metabolised to pyruvate in the cytosol using the glycolyitic pathway. This generates some ATP through substrate phosphorylation catalyzed by two

enzymes: PGK and Pyruvate kinase. Pyruvate is then oxidised further in the mitochondrion.

In the mitochondrion, pyruvate is oxidised by pyruvate dehydrogenase to acetyl-CoA, which is fully oxidised to carbon dioxide by the Krebs cycle. Fatty acids are also broken down to acetyl CoA by beta-oxidation and metabolised by the Krebs cycle. Every turn of the Krebs cycle produces an ATP equivalent (GTP) through substrate phosphorylation catalyzed by Succinyl-CoA synthetase as well as reducing power as NADH. The electrons from NADH are used by the electron transport chain to generate a large amount of ATP by oxidative phosphorylation coupled with ATP synthase.

The whole process of oxidising glucose to carbon dioxide is known as cellular respiration and is more than 40% efficient at transferring the chemical energy in glucose to the more useful form of ATP.

ATP is also synthesized through several so-called "replenishment" reactions catalyzed by the enzyme families of NDKs (nucleoside diphosphate kinases), which use other nucleoside triphosphates as a high-energy phosphate donor, and the ATP:guanido-phosphotransferase family, which uses creatine.

ADP + GTP --> ATP + GDP

In plants, ATP is synthesized in chloroplasts during the light reactions of photosynthesis. Some of this ATP is then used to power the Calvin cycle, which synthesizes triose sugars.

If a clot causes a decrease in oxygen delivery to the cell, the amount of **ATP** produced in the mitochondria will decrease.

Function

ATP energy is released when hydrolysis of the phosphate-phosphate bonds is carried out. This energy can be used by a variety of enzymes, motor proteins, and transport proteins to carry out the work of the cell. Also, the hydrolysis yields free inorganic P_i and ADP, which can be broken down further to another P_i and AMP. ATP can also be broken down to AMP directly, with the formation of PP_i. This last reaction has the advantage of being an effectively irreversible process in aqueous solution.

A few examples of the use of ATP include the active transport of molecules across cell membranes, the synthesis of macromolecules (Eg. proteins), muscle contractions, endocytosis, and exocytosis.

ATP in the human body

The total quantity of ATP in the human body is about 0.1 mole. The energy used by human cells requires the hydrolysis of 200 to 300 moles of ATP daily. This means that each ATP molecule is recycled 2000 to 3000 times during a single day. ATP cannot be stored, hence its consumption must closely follow its synthesis. On a per-hour basis, 1 kilogram of ATP is created, processed and then recycled in the body.

Other uses

There is talk of using ATP as a power source for nanotechnology and implants. Artificial pacemakers could become independent of batteries. ATP is also present as a neurotransmitter independent from its energy-containing function. Receptors that utilise ATP as their ligand are known as purinoceptors.

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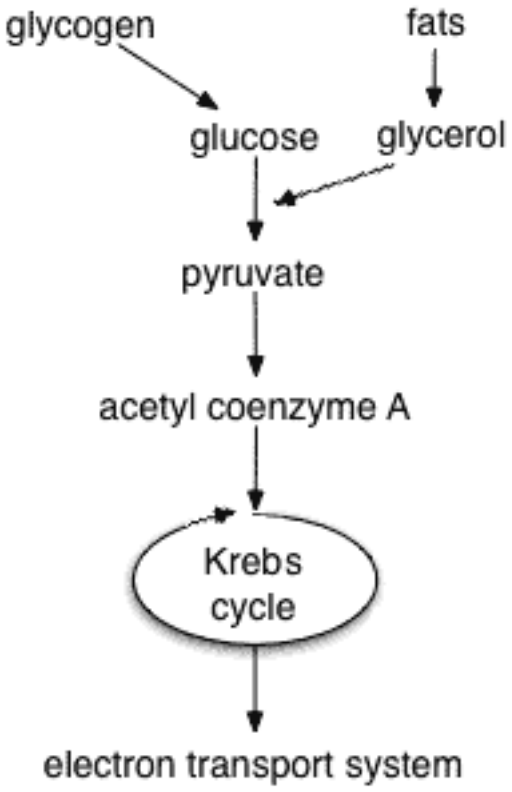
Aerobic respiration

Aerobic respiration requires oxygen in order to generate energy. It is the preferred method of pyruvate breakdown from glycolysis and requires that pyruvate enter the mitochondrion to be fully oxidized by the Krebs cycle. The product of this process is energy in the form of ATP (Adenosine Triphosphate), by substrate-level phosphorylation, NADH and FADH2. The reducing potential of NADH and FADH2 is converted to more ATP via an electron transport chain with oxygen as the "terminal electron acceptor". Most of the ATP produced by cellular respiration is by oxidative phosphorylation, ATP molecules are made due to the chemiosmotic potential driving ATP synthase. Respiration is the process by which cells obtain energy when oxygen is present in the cell.

Theoretically, 36 ATP molecules can be made per glucose during cellular respiration, however, such conditions are generally not realized due to such losses as the cost of moving pyruvate into mitochondria. Aerobic metabolism is rather more efficient than anaerobic metabolism. They share the initial pathway of glycolysis but aerobic metabolism continues with the Krebs cycle and oxidative phosphorylation. The post glycolytic reactions take place in the mitochondria in eukaryotic cells, and at the cell membrane in prokaryotic cells.



Glycolysis

Glycolysis is a metabolic pathway that is found in the cytoplasm of cells in all living organisms and does not require oxygen. The process converts one molecule of glucose into two molecules of pyruvate, and

makes energy in the form of two net molecules of ATP. Four molecules of ATP per glucose are actually produced but two are consumed for the preparatory phase. The initial phosphorylation of glucose is required to destabilize the molecule for cleavage into two triose sugars. During the pay-off phase of glycolysis four phosphate groups are transferred to ADP by substrate-level phosphorylation to make four ATP and two NADH are produced when the triose sugars are oxidized. Glycolysis takes place in the cytoplasm of the cell. The overall reaction can be expressed this way:

$$\text{Glucose} + 2\ \text{ATP} + 2\ \text{NAD}^+ + 2\ \text{P}_i + 4\ \text{ADP} \rightarrow 2\ \text{pyruvate} + 2\ \text{ADP} + 2\ \text{NADH} + 4\ \text{ATP} + 2\ \text{H}_2\text{O} + 4\ \text{H}^+$$

Oxidative decarboxylation

Produces acetyl-CoA from pyruvate inside the mitochondrial matrix. This oxidation reaction also releases carbon dioxide as a product. In the process one molecule of NADH is formed per pyruvate oxidized.

Krebs cycle/Citric Acid cycle

When oxygen is present, acetyl-CoA enters the citric acid cycle inside the mitochondrial matrix, and gets oxidised to CO2 while at the same time reducing NAD to NADH. NADH can be used by the electron transport chain to create further ATP as part of oxidative phosphorylation. To fully oxidise the equivalent of one glucose molecule two acetyl-CoA must be metabolised by the Krebs cycle. Two waste products, H_2O and CO_2 are created during this cycle.

Oxidative phosphorylation

In eukaryotes, oxidative phosphorylation occurs in the mitochondrial cristae. It comprises of the electron transport chain that establishes a proton gradient (chemiosmotic potential) across the inner membrane by oxidising the NADH produced from the Krebs cycle. ATP is synthesised by the ATP synthase enzyme when the chemiosmotic gradient is used to drive the phosphorylation of ADP.

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Anaerobic respiration

In the absence of oxygen, pyruvate is not metabolized by cellular respiration but undergoes a process of fermentation.

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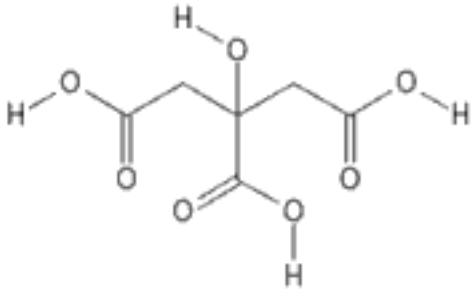
Citrate

A **citrate** is an ionic form of citric acid, such as $C_3H_5O(COO)_3^{3-}$, that is, citric acid minus three hydrogen ions.



Chemical strucutre of citric acid.

Citrates are compounds containing this group, either ionic compounds, the salts, or analogous covalent compounds, esters. An example of a salt is sodium citrate and an ester is trimethyl citrate. See category for a bigger list.

Since citric acid is a multifunctional acid, intermediate ions exist, **hydrogen citrate** ion, $HC_6H_5O_7^{2-}$ and **dihydrogen citrate** ion, $H_2C_6H_5O_7^-$. These may form salts as well, called acid salts.

Salts of the hydrogen citrate ions are weakly acidic, while salts of the citrate ion itself (with an inert cation such as sodium ion) are weakly basic.

Citrate is a key component in the commonly used SSC 20X hybridization buffer. There exists authoritative literature (Maniatis) that incorrectly instructs the preparation of this buffer to include 3M NaCl and 0.3M Sodium Citrate, to be titrated up with NaOH to a pH of 7. When the two components are actually mixed together, the pH is slightly basic. Therefore, the pH of the solution should instead be titrated down to 7 with either citric acid or HCl.

Citrate is also an intermediate in the TCA (Krebs) Cycle. After pyruvate dehydrogenase forms acetyl CoA (from pyruvate using five cofactors: TPP, lipoamide, FAD, NAD+, and CoA), Citrate Synthase catalyzes the condensation of OAA with Acetyl CoA to form citrate. The rest of the cycle entails subsequent conversion into isocitrate, alpha-keto glutarate, succinyl-CoA, succinate, fumarate, malate, and back to OAA. These reactions are catalyzed by isocitrate dehydrogenase, alpha-keto glutarate dehydrogenase, succinyl-CoA synthetase, succinate dehydrogenase, fumarase, and malate dehydrogenase, respectively.

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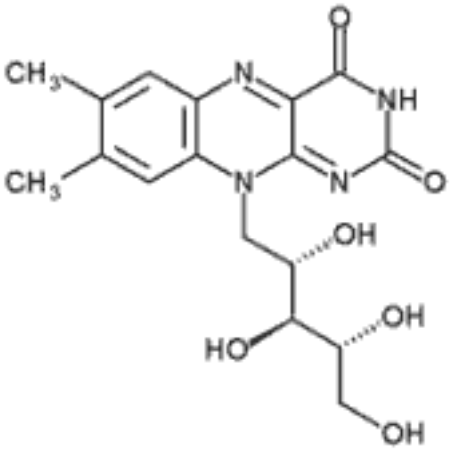
Flavin

Flavin is a tricyclic heteronuclear organic ring based on pteridine whose biochemical source is the vitamin riboflavin. The flavin moiety is often attached with an adenosine diphosphate to form **flavin adenine dinucleotide** (**FAD**), and in other circumstances, is found as **flavin mononucleotide** (or **FMN**), a phosphorylated form of riboflavin. The flavin group is capable of undergoing oxidation-reduction reactions, and can accept either one electron in a two step process or can accept two electrons at once. In the form of $FADH_2$, it is one of the cofactors that can transfer electrons to the electron transfer chain.



Riboflavin

FAD

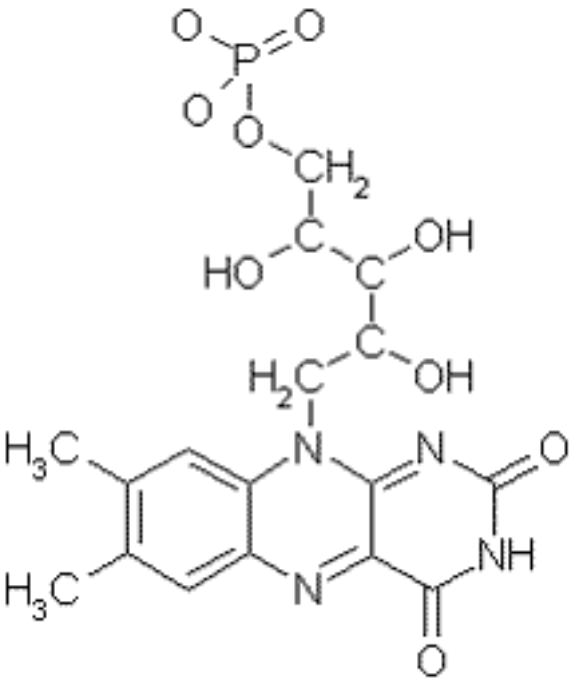
Flavin adenine dinucleotide is a cofactor in the enzymes monoamine oxidase, D-amino acid oxidase, glucose oxidase, and xanthine oxidase.

$FADH / FADH_2$

FADH and $FADH_2$ are reduced forms of FAD. $FADH_2$ is produced in the citric acid cycle. In oxidative phosphorylation, one molecule of $FADH_2$ yields approximately 1.5 ATP

FMN

Flavin mononucleotide is a prosthetic group found in NADH dehydrogenase.



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Nicotinamide adenine dinucleotide

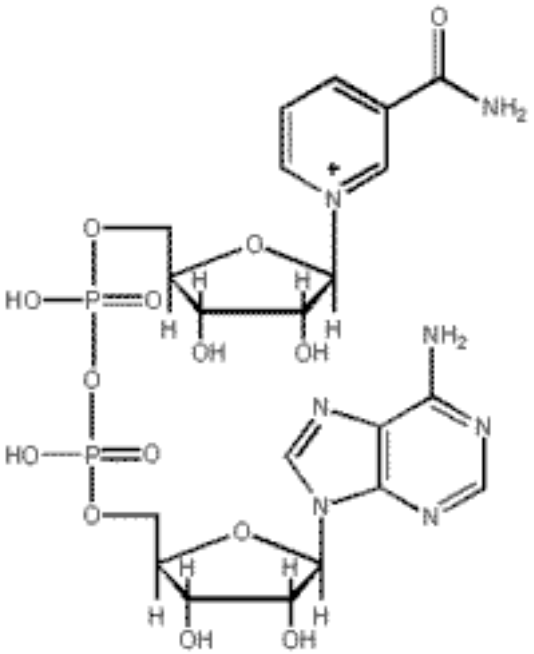
Nicotinamide adenine dinucleotide (**NAD**) and **nicotinamide adenine dinucleotide phosphate** (**NADP**) are two important coenzymes found in cells. NADH is the reduced form of NAD, and NAD^+ is the oxidized form of NAD. It forms NADP with the addition of a phosphate group to the 2' position of the adenosyl nucleotide through an ester linkage.

NAD is used extensively in glycolysis and the citric acid cycle of cellular respiration. The reducing potential stored in NADH can be converted to ATP through the electron transport chain or used for anabolic metabolism. ATP "energy" is necessary for an organism to live. Green plants obtain ATP through photosynthesis, while other organisms obtain it by cellular respiration.

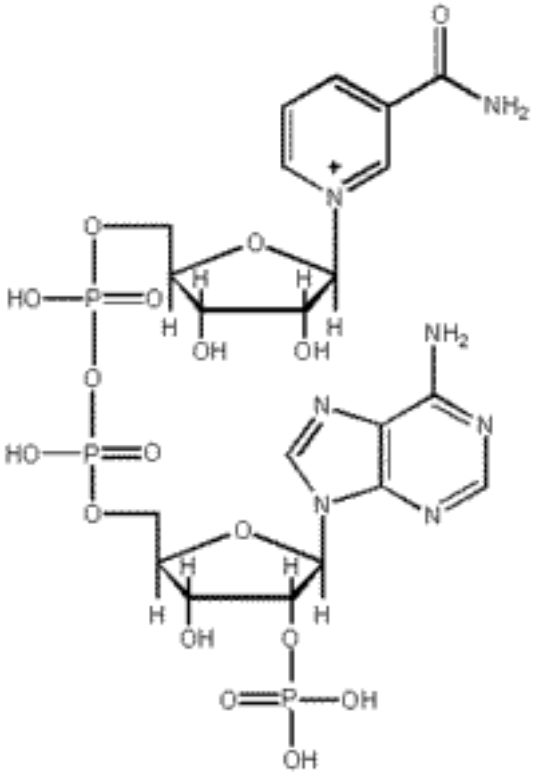
NADP is used in anabolic reactions, such as fat acid and nucleic acid synthesis, that require NADPH as a reducing agent. In chloroplasts, NADP is an oxidising agent important in the preliminary reactions of photosynthesis. The NADPH produced by photosynthesis is then used as reducing power for the biosynthetic reactions in the Calvin cycle of photosynthesis.

$MH_2 + NAD^+ \rightarrow NADH + H^+ + M:$ + energy, where M is a metabolite.

Two hydrogen ions (a hydride ion and an H^+ ion) are transferred from the metabolite. One electron is transferred to the positively-charged nitrogen, and one hydrogen attaches to the carbon atom opposite to the nitrogen.



Nicotinamide adenine dinucleotide (NAD^+)



Nicotinamide adenine dinucleotide phosphate ($NADP^+$)

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Oxalate

An **oxalate** (also **ethanedioate**) is a salt or ester of oxalic acid. The oxalate ion is $(COO)_2^{2-}$ and is oxalic acid without the two hydrogen ions.

Consumption of oxalates (for example, the grazing of animals on oxalate-containing plants such as greasewood) may result in kidney disease or even death due to oxalate poisoning.

Much of its other properties resemble oxalic acid.

Examples

- sodium oxalate - $Na_2C_2O_4$
- calcium oxalate - CaC_2O_4
- dimethyl oxalate - $(CH_3)_2C_2O_4$
- phenyl oxalate ester - $(C_6H_5)_2C_2O_4$

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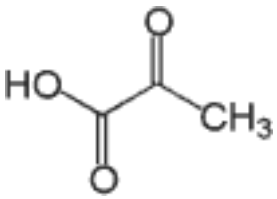
Pyruvic acid

Chemistry | Biochemical role | Pyruvic acid's role in the origin of life

Pyruvic acid (CH_3COCO_2H) is an alpha-keto acid which plays an important role in biochemical processes. The carboxylate anion of pyruvic acid is known as **pyruvate**.



Chemistry

Pyruvic acid is a colorless liquid with a smell similar to acetic acid. It is miscible with water, and soluble in ethanol and diethyl ether. In the laboratory, pyruvic acid may be prepared by heating a mixture of tartaric acid and potassium hydrogen sulfate, or by the hydrolysis of acetyl cyanide, formed by reaction of acetyl chloride with potassium cyanide:

$CH_3COCl + KCN \rightarrow CH_3COCN$

$CH_3COCN \rightarrow CH_3COCOOH$

Biochemical role

Pyruvate is an important chemical compound in biochemistry. It is the output of the metabolism of glucose known as glycolysis. One molecule of glucose breaks down into two molecules of pyruvic acid, which are then used to provide further energy, in one of two ways. Provided that sufficient oxygen is available, pyruvic acid is converted into acetyl-coenzyme A, which is the main input for a series of reactions known as the Krebs cycle. Pyruvate is also converted to oxaloacetate by an anaplerotic reaction and then further broken down to carbon dioxide. These reactions are named after Hans Adolf Krebs, the biochemist awarded the 1953 Nobel Prize for physiology, jointly with Fritz Lipmann, for research into metabolic processes. The cycle is also called the citric acid cycle, because citric acid is one of the intermediate compounds formed during the reactions.

If insufficient oxygen is available, the acid is broken down anaerobically, creating lactic acid in animals and ethanol in plants. Pyruvate from glycolysis is converted by anaerobic respiration to lactate using the enzyme lactate dehydrogenase and the coenzyme NADH in lactate

fermentation, or to acetaldehyde and then to ethanol in alcoholic fermentation.

Pyruvic acid is a key intersection in the network of metabolic pathways. Pyruvic acid can be converted to carbohydrates via gluconeogenesis, to fatty acids or energy through acetyl-CoA, to the amino acid alanine and to ethanol. Therefore it unites several key metabolic processes.

Pyruvic acid's role in the origin of life

Current evolutionary theory on the origin of life posits that the first organisms were anaerobic because the atmosphere of prebiotic Earth was almost devoid of oxygen. As such, requisite biochemical materials must have preceded life and recent experiments indicate that pyruvate can be synthesized abiotically. In vitro, iron sulfide at sufficient pressure and temperature catalyzes the formation of pyruvic acid. Thus, argues Günter Wächtershäuser, the mixing of iron-rich crust with hydrothermal vent fluid is suspected of providing the fertile basis for the formation of life.

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Theoretical yields

The yields in the table below are for one glucose and molecule being fully oxidised to carbon dioxide. It is assumed that all the reduced coenzymes are oxidised by the electron transport chain and used for oxidative phosphorylation.

Step 1: Glycolysis preparatory phase | **coenzyme yield:** None **| ATP yield:** -2 | **Source of ATP:** Phosphorylation of glucose and fructose 6-phosphate uses two ATP from the cytoplasm.

Step 2.1: Glycolysis pay-off phase | **coenzyme yield:** None **| ATP yield:** 4 | **Source of ATP:** Substrate-level phosphorylation

Step 2.2: Glycolysis pay-off phase | **coenzyme yield:** 2 NADH **| ATP yield:** 4 | **Source of ATP:** Oxidative phosphorylation. Only 2 ATP per NADH since the coenzyme must feed into the electron transport chain from the cytoplasm rather than the mitochondrial matrix.

Step 3: Oxidative carboxylation | **coenzyme yield:** 2 NADH **| ATP yield:** 6 | **Source of ATP:** Oxidative phosphorylation.

Step 4.1: Krebs cycle | **coenzyme yield:** None **| ATP yield:** 2 | **Source of ATP:** Substrate-level phosphorylation.

Step 4.2: Krebs cycle | **coenzyme yield:** 6 NADH **| ATP yield:** 18 | **Source of ATP:** Oxidative phosphorylation.

Step 4.3: Krebs cycle | **coenzyme yield:** 2 $FADH_2$ **| ATP yield:** 4 | **Source of ATP:** Oxidative phosphorylation.

Total yield: 36 **Source of ATP:** From the complete oxidation of one glucose molecule to carbon dioxide and oxidation of all the reduced coenzymes.

Although there's a theoretical yield 36 ATP molecules per glucose during cellular respiration, such conditions are generally not realized due to losses such as the cost of moving pyruvate (from glycolysis), phosphate and ADP (substrates for ATP syhthesis) into the mitochondria. All are actively transported using carriers that utilise the stored energy in the proton electrochemical gradient.

- The **pyruvate carrier** is a symporter and the driving force for moving pyruvate into the mitochondria is the movement of protons from the intermembrane space to the matrix.
- The **phosphate carrier** is an antiporter and the driving force for moving phosphate ions into the mitochondria is the movement of hydroxyls ions from the matrix to the intermembrane space.

- The **adenine nucleotide carrier** is an antiporter and exchanges ADP and ATP across the inner membrane. The driving force is due to the ATP (-4) having a more negative charge than the ADP (-3) and thus it dissipates some of the electrical component of the proton electrochemical gradient.

The outcome of these transport processes using the proton electrochemical gradient is that more than 3 H^+ are needed to make 1 ATP. Obviously this reduces the theoretical efficiency of the whole process. Other factors may also dissipate the proton gradient creating an apparently leaky mitochondria. An uncoupling protein known as thermogenin is expressed in some cell types and is a channel that can transport protons. When this protein is active in the inner membrane it short circuits the coupling between the electron transport chain and ATP synthesis. The potential energy from the proton gradient is not used to make ATP but generates heat. This is particularly important in a babies brown fat, for thermogenesis, and hibernating animals.

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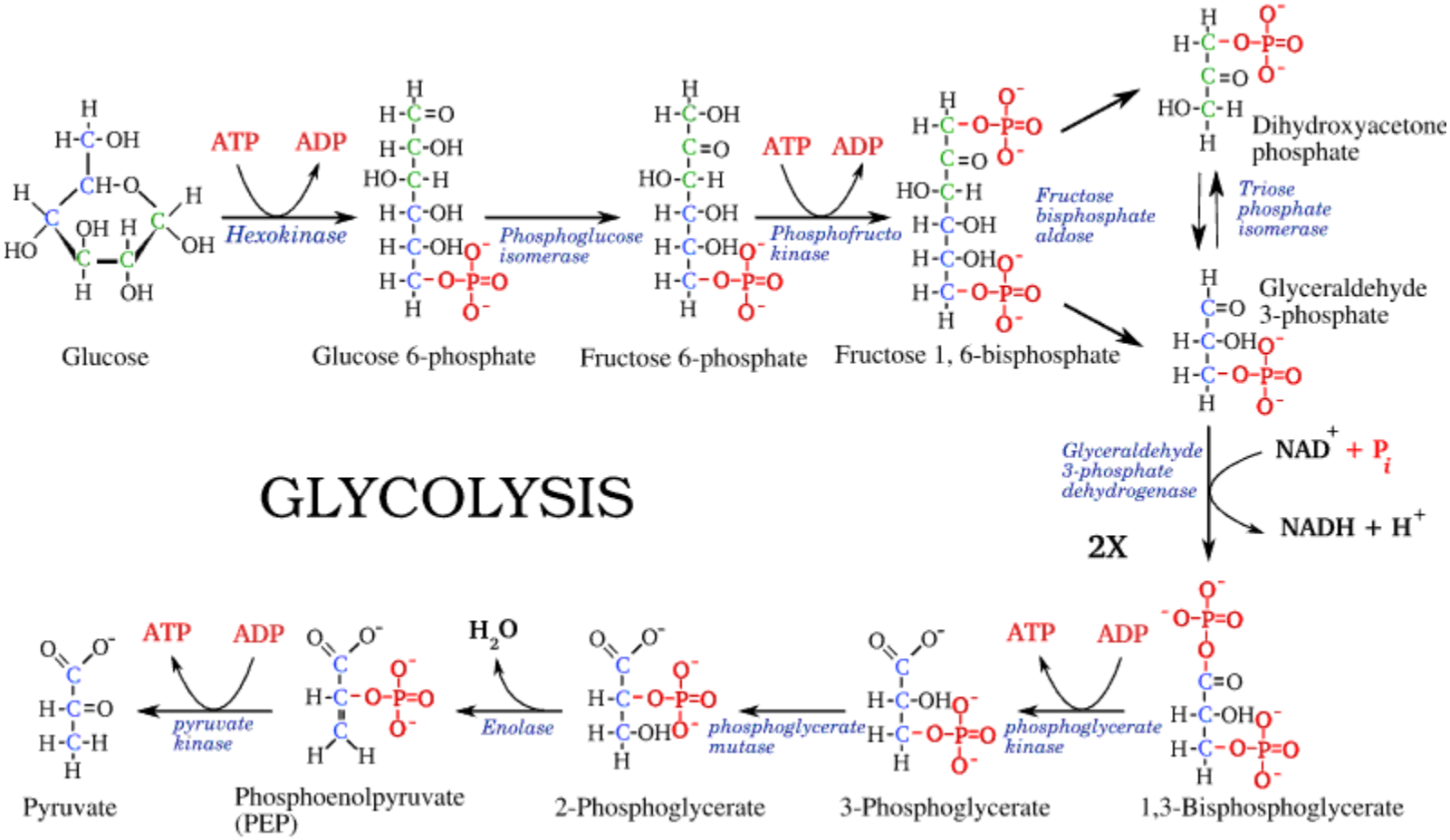
Glycolysis

Glycolysis is a series of biochemical reactions by which a molecule of glucose (Glc) is oxidized to two molecules of pyruvic acid (Pyr).



The word glycolysis is from Greek *glyk* (meaning sweet) and *lysis* (meaning dissolving). It is the initial process of many pathways of carbohydrate catabolism, and serves two principal functions: generation of high-energy molecules (ATP and NADH), and production of a variety of six- or three-carbon intermediate metabolites, which may be removed at various steps in the process for other intracellular purposes (such as nucleotide biosynthesis).

Glycolysis is one of the most universal metabolic processes known, and occurs (with variations) in many types of cells in nearly all types of organisms. Glycolysis alone produces less energy per glucose molecule than complete aerobic oxidation, and so flux through the pathway is greater in anaerobic conditions (i.e., in the absence of oxygen).

The most common and well-known type of glycolysis is the Embden-Meyerhof pathway, initially elucidated by Gustav Embden and Otto Meyerhof. The term can be taken to include alternative pathways, such as the Entner-Doudoroff Pathway. However, **glycolysis** will be used here as a synonym for the Embden-Meyerhof pathway.

Overview

The overall reaction of glycolysis is:

$$Glc + 2NAD^+ + 2ADP + 2P_i \rightarrow 2NADH + 2Pyr + 2ATP + 2H_2O + 2H^+$$

So, for simple fermentations, the metabolism of 1 molecule of glucose has a net yield of 2 molecules of ATP. Cells performing respiration synthesize much more ATP, but this is not considered part of glycolysis proper, although these aerobic reactions do use the product of glycolysis. Eukaryotic aerobic respiration produces an additional 34 molecules (approximately) of ATP for each glucose molecule oxidized. Unlike most of the molecules of ATP produced via aerobic respiration, those of glycolysis are produced by substrate-level phosphorylation.

In eukaryotes, glycolysis takes place within the cytosol of the cell. Some of the glycolytic reactions are conserved in the Calvin cycle that functions inside the chloroplast. This is consistent with the fact that glycolysis is highly conserved in evolution, being common to nearly all living organisms. This suggests great antiquity; it may have originated with the first prokaryotes, 3.5 billion years ago or more.

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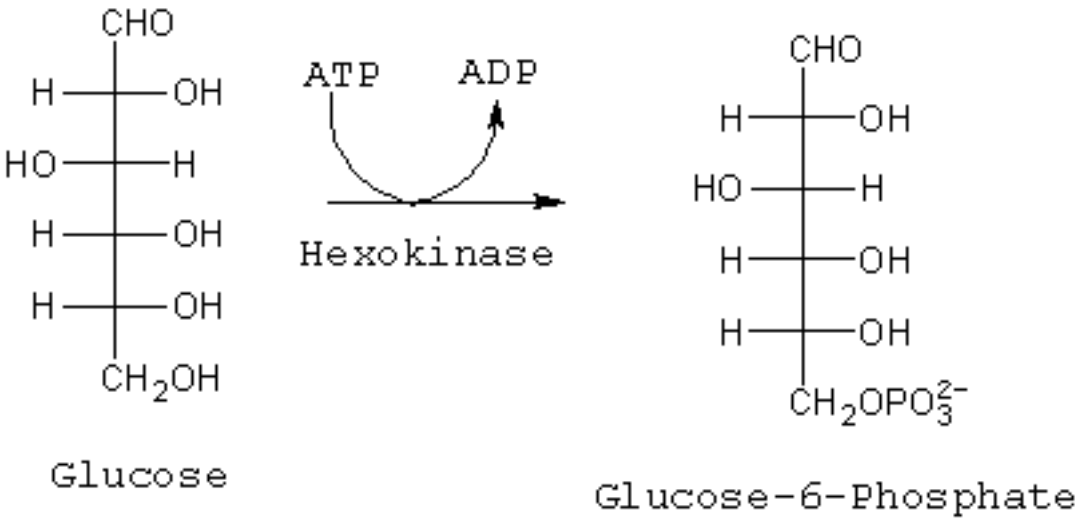
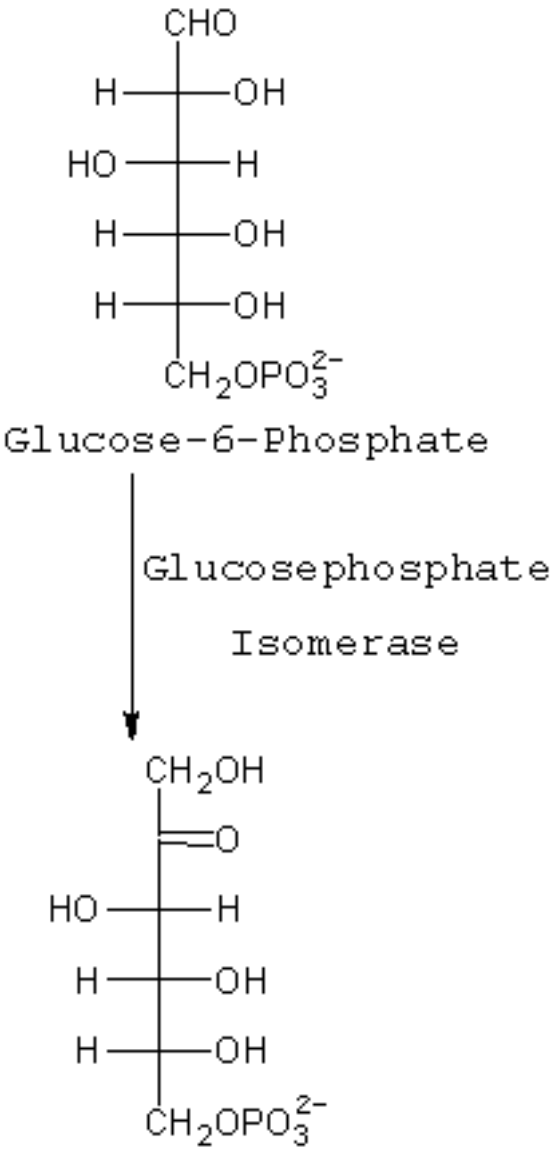
Glycolysis: Preparatory phase

The first five steps are regarded as a preparatory phase since they actually consume energy as the glucose is converted to two three-carbon sugars phosphates (G3P). The bold abbreviations in the two tables correspond to the nomenclature used in the diagram.

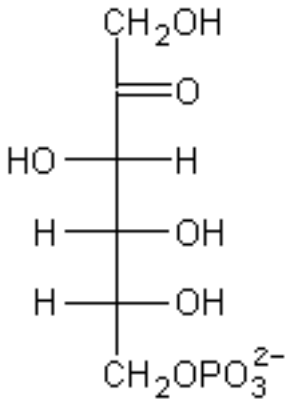
Step 1 | Substrate: glucose Glc **| Enzyme:** hexokinase HK **| Enzyme class:** transferase **| Comment:** ATP used at this step. Glucose is usually from the hydrolysis of starch or glycogen. This reaction has a highly negative change in free energy, and is thus, irreversible.



Step 2 | Substrate: glucose-6-phosphate G6P **| Enzyme:** phosphoglucose isomerase PGI **| Enzyme class:** isomerase **| Comment:** The change in structure is observed through a redox reaction, in which the aldehyde has been reduced to an alcohol, and the adjacent carbon has been oxidized to form a ketone. While this reaction is not normally favorable, it is driven by a low concentration of F6P, which is constantly consumed during the next step of glycolysis. (This phenomenon can be explained through Le Chatelier's Principle.)

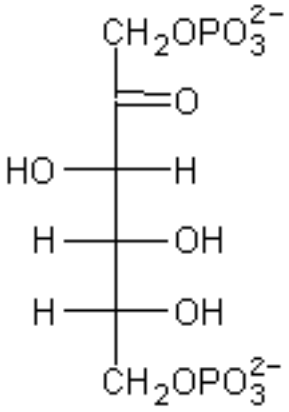


Step 3 | Substrate: fructose 6-phosphate F6P **| Enzyme:** phosphofructokinase PFK-1 **| Enzyme class:** transferase **| Comment:** The energy expenditure of another ATP in this step is justified in 2 ways: the glycolytic process (up to this step) is now irreversible, and the energy supplied destablises the molecule.



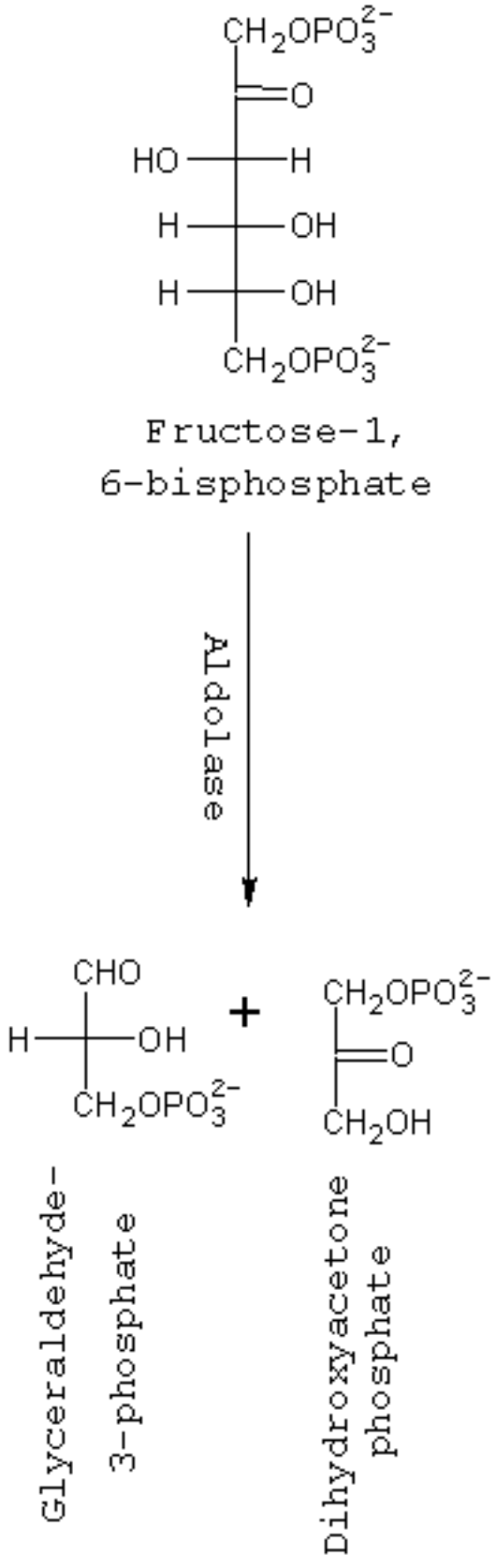
Fructose-6-Phosphate

Phosphofructokinase

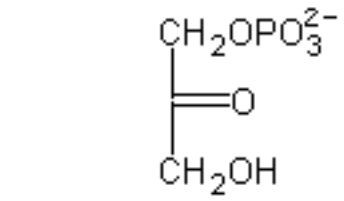


Fructose-1,
6-bisphosphate

Step 4 | Substrate: fructose 1,6-bisphosphate F1,6BP **| Enzyme:** aldolase ALDO **| Enzyme class:** lyase **| Comment:** Destablising the molecule in the previous reaction allows the hexose ring to be split by ALDO into two triose sugars, DHAP and GADP.

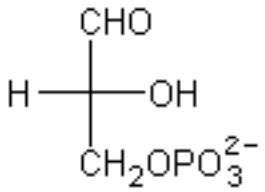


Step 5 | Substrate: dihydroxyacetone phosphate **DHAP | Enzyme:** triose phosphate isomerase TPI | **Enzyme class:** isomerase | **Comment:** TPI rapidly interconverts DHAP with glyceraldehyde 3-phosphate (**GADP**) that proceeds further into glycolysis.



Dihydroxyacetone Phosphate

triosephosphate isomerase



Glyceraldehyde-3-phosphate

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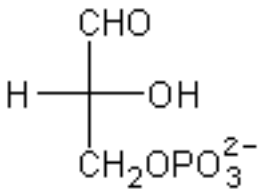
Glycolysis: Pay-off phase

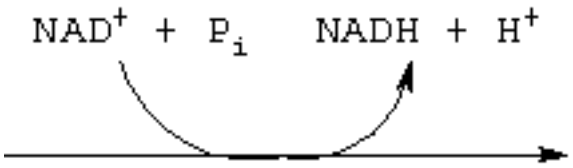
The second half of glycolysis is known as the pay-off phase, characterised by a net gain of the energy-rich molecules ATP and NADH. Since glucose leads to two triose sugars in the preparatory phase, each reaction in the pay-off phase occurs twice per glucose molecule. This yields 2 NADH molecules and 4 ATP molecules, leading to a net gain of 2 NADH molecules and 2 ATP molecules from the gylcolytic pathway per glucose.

Step 6 | Substrate: glyceraldehyde 3-phosphate GADP **| Enzyme:** glyceraldehyde 3-phosphate dehydrogenase GAP **| Enzyme class:** oxidoreductase **| Comment:** Triose sugars are dehydrogenated and inorganic phosphate is added to them. The hydrogen is used to reduce two molecules of NAD, a hydrogen carrier, to give $NADH+H^+$.



Glyceraldehyde-

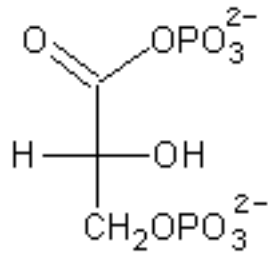
3-phosphate



glyceraldehyde-

3-phosphate

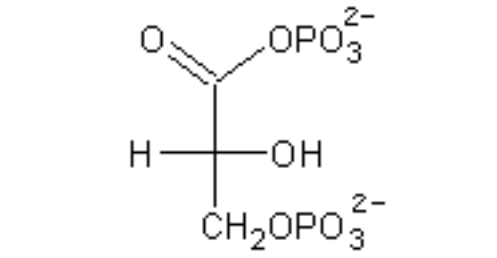
dehydrogenase



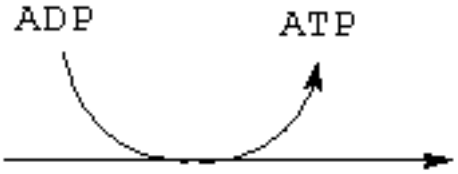
1,3-

bisphosphoglycerate

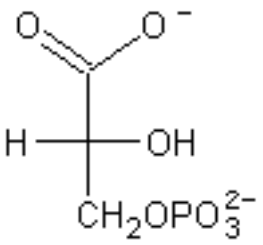
Step 7 | Substrate: 1,3-bisphosphoglycerate 1,3BPG **| Enzyme:** phosphoglycerate kinase PGK **| Enzyme class:** transferase **| Comment:** A reaction that converts ADP to ATP by an enzymatic transfer of a phosphate to ADP; is an example of substrate-level phosphorylation.



1,3-
bisphosphoglycerate

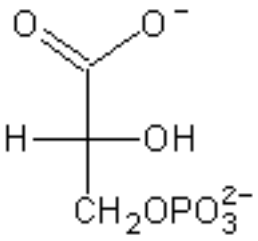


phosphoglycerate
kinase

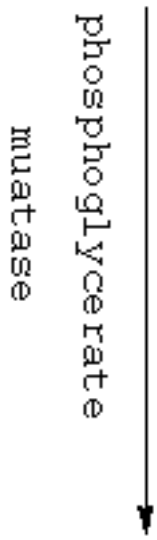


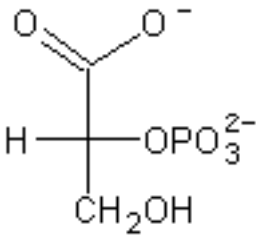
3-phosphoglycerate

Step 8 | Substrate: 3-phosphoglycerate 3PG **| Enzyme:** phosphoglyceromutase PGAM **| Enzyme class:** mutase **| Comment:** Notice that this enzyme is a mutase and not an isomerase. While an isomerase changes the oxidation state of the carbons being reacted, a mutase does not.



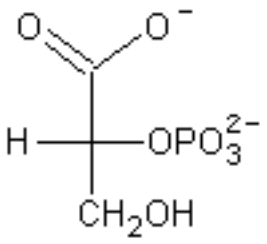
3-phosphoglycerate



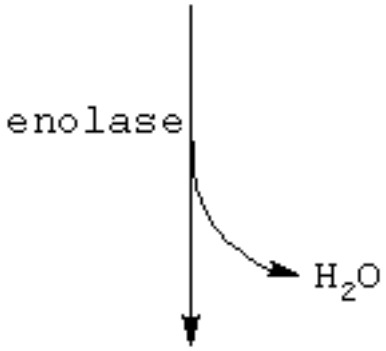


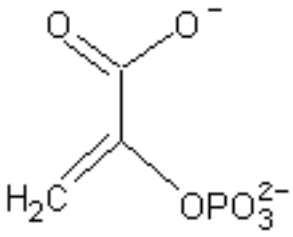
2-phosphoglycerate

Step 9 | Substrate:2-phosphoglycerate 2PG **| Enzyme:** enolase ENO **| Enzyme class:** lyase **| Comment:** none



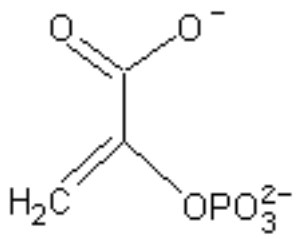
2-phosphoglycerate



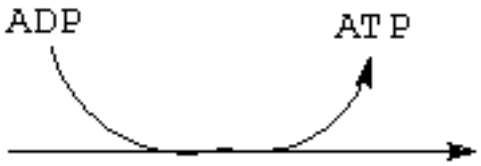


Phosphoenolpyruvate

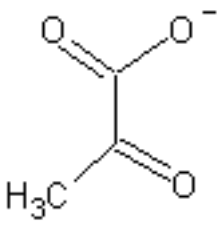
Step 10 | Substrate: phosphoenolpyruvate PEP **| Enzyme:** pyruvate kinase PK **| Enzyme class:** transferase **| Comment:** Another example of substrate-level phosphorylation that converts ADP to ATP, forming pyruvate (**Pyr**).



Phosphoenolpyruvate



pyruvate kinase



Pyruvate

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Glycolysis: Entry of sugars

The first step in glycolysis is phosphorylation of Glc by a family of enzymes called HKs to form G6P. In the liver, an isozyme of hexokinase called GCK is used, which differs primarily in regulatory properties. This reaction consumes 1 ATP, but the energy is well-spent - it keeps $[Glc]_i$ low as to allow continuous entry of Glc through its plasma membrane transporters; prevents Glc leakage out - the cell lacks such transporters for G6P; activates Glc preparing it for the next metabolic changes.

G6P is then rearranged into F6P by GPI. Fru can also enter the glycolytic pathway via phosphorylation at this point.

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Glycolysis: Control of flux

The flux through the glycolytic pathway must be adjusted in response to conditions both inside and outside the cell. The rate is regulated to meet two major cellular needs: (1) the production of ATP, and (2) the provision of building blocks for biosynthetic reactions. In glycolysis, the reactions catalyzed by hexokinase, phosphofructokinase, and pyruvate kinase are effectively irreversible. In metabolic pathways, such enzymes are potential sites of control, and all these three enzymes serve this purpose in glycolysis.

There are several different ways to regulate the activity of an enzyme. An immediate form of control is feedback via allosteric effectors or by covalent modification. A slower form of control is transcriptional regulation that controls the amounts of these important enzymes.

Hexokinase

Hexokinase is inhibited by glucose-6-phosphate (G6P), the product it forms through the ATP driven phosphorylation. This is necessary to prevent an accumulation of G6P in the cell when flux through the glycolytic pathway is low. Glucose will enter the cell but since the hexokinase is not active it can readily diffuse back to the blood through the glucose transporter in the plasma membrane. If hexokinase remained active during low glycolytic flux the G6P would accumulate and the extra solute would cause the cells to enlarge due to osmosis.

In liver cells, the extra G6P is stored as glycogen. In these cells hexokinase is not expressed, instead glucokinase catalyses the phosphorylation of glucose to G6P. This enzyme is not inhibited by high levels of G6P and glucose can still be converted to G6P and then be stored as glycogen. This is important when blood glucose levels are high. During hypoglycemia the glycogen can be converted back to G6P and then converted to glucose by a liver specific enzyme glucose 6-phosphatase. This reverse reaction is an important role of liver cells to maintain blood sugars levels during fasting. This is critical for neuron function since they can only use glucose as an energy source.

Phosphofructokinase-1

Phosphofructokinase is an important control point in the glycolytic pathway since it is immediately downstream of the entry points for hexose sugars.

High levels of ATP inhibit the PFK enzyme by lowering its affinity for F6P. ATP causes this control by binding to a specific regulatory site that is distinct from the catalytic site. This is a good example of allosteric control. AMP can reverse the inhibitory effect of ATP. A consequence is that PFK is tightly controlled by the ratio of ATP/AMP in the cell. This makes sense since these molecules are direct indicators of the energy charge in the cell.

Since glycolysis is also a source of carbon skeletons for biosynthesis, a negative feedback control to glycolysis from the carbon skeleton pool is useful. Citrate is an example of a metabolite that regulates phosphofructokinase by enhancing the inhibitory effect of ATP. Citrate is an early intermediate in the citric acid cycle, and a high level means that biosynthetic precursors are abundant.

Low pH also inhibits phosphofructokinase activity and prevents the excessive rise of lactic acid during anaerobic conditions that could otherwise cause a drop in blood pH (acidosis).

Fructose 2,6-bisphosphate (F2,6BP) is a potent activator of phosphofructokinase (PFK-1) that is synthesised when F6P is phosphorylated by a second phosphofructokinase (PFK2). This second enzyme is inactive when cAMP is high, and links the regulation of glycolysis to hormone activity in the body. Both glucagon and adrenalin cause high levels of cAMP in the liver. The result is lower levels of liver fructose 2,6-bisphosphate such that gluconeogenesis (glycolysis in reverse) is favored. This is consistent with the role of the liver in such situations since the response of the liver to these hormones is to releases glucose to the blood.

Pyruvate kinase

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Glycolysis: Energy pay-off

Each molecule of GADP is then oxidized by a molecule of NAD^+ in the presence of GAP, forming 1,3-bisphosphoglycerate. In the next step, PGK generates a molecule of ATP while forming 3-phosphoglycerate. At this step, glycolysis has reached the break-even point: 2 molecules of ATP were consumed, and 2 new molecules have been synthesized. This step, one of the two substrate-level phosphorylation steps, requires ADP; thus, when the cell has plenty of ATP (and little ADP) this reaction does not occur. Because ATP decays relatively quickly when it is not metabolized, this is an important regulatory point in the glycolytic pathway. PGAM then forms 2-phosphoglycerate; ENO then forms phosphoenolpyruvate; and another substrate-level phosphorylation then forms a molecule of Pyr and a molecule of ATP by means of the enzyme PK. This serves as an additional regulatory step.

After the formation of F1,6bP, many of the reactions are energetically unfavorable. The only reactions that are favorable are the 2 substrate-level phosphorylation steps that result in the formation of ATP. These two reactions pull the glycolytic pathway to completion.

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Glycolysis: Follow-up

The ultimate fate of pyruvate and NADH produced in glycolysis depends upon the organism and the conditions, most notably the presence or absence of oxygen and other external electron acceptors.

In aerobic organisms, pyruvate typically enters the mitochondria where it is fully oxidized to carbon dioxide and water by pyruvate decarboxylase and the set of enzymes of the citric acid cycle (also known as the TCA or Krebs cycle). The products of pyruvate are sequentially dehydrogenated as they pass through the cycle conserving the hydrogen equivalents via the reduction of NAD^+ to NADH. NADH is ultimately oxidized by an electron transport chain using oxygen as final electron acceptor to produce a large amount of ATP via the action of the ATP synthase complex, a process known as oxidative phosphorylation. A small amount of ATP is also produced by substrate-level phosphorylation during the TCA cycle.

Although human metabolism is primarily aerobic, under hypoxic (or partially anaerobic) conditions, for example in overworked muscles that are starved of oxygen or in infarcted heart muscle cells, pyruvate is converted to the waste product lactate. This and similar reactions are known as fermentation, and they are a solution to maintaining the metabolic flux through glycolysis in response to an anaerobic or severely hypoxic environment.

Although fermentation does not produce much energy, it is critical for an anaerobic or hypoxic cell, since it regenerates NAD^+ that is required for glycolysis to proceed. This is important for normal cellular function, as glycolysis is the only source of ATP in anaerobic or severely hypoxic conditions.

There are several types of fermentation wherein pyruvate and NADH are anaerobically metabolized to yield any of a variety of products with an organic molecule acting as the final hydrogen acceptor. For example, the bacteria involved in making yogurt simply reduce pyruvate to lactic acid, whereas yeast produces ethanol and carbon dioxide. Anaerobic bacteria are capable of using a wide variety of compounds, other than oxygen, as terminal electron acceptors in respiration: nitrogenous compounds (such as nitrates and nitrites), sulphur compounds (such as sulphates, sulphites, sulphur dioxide, and elemental sulphur), carbon dioxide, iron compounds, manganese compounds, cobalt compounds, and uranium compounds.

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Glycolysis: Intermediates for other pathways

This article concentrates on the catabolic role of glycolysis with regard to converting potential chemical energy to usable chemical energy during the oxidation of glucose to pyruvate. Many of the metabolites in the glycolytic pathway are also used by anabolic pathways, and, as a consequence, flux through the pathway is critical to maintain a supply of carbon skeletons for biosynthesis.

From an energy perspective, NADH is either recycled to NAD+ during anaerobic conditions, to maintain the flux through the glycolytic pathway, or used during aerobic conditions to produce more ATP by oxidative phosphorylation. From an anabolic metabolism perspective, the NADH has a role to drive synthetic reactions, doing so by directly or indirectly reducing the pool of NADP+ in the cell to NADPH, which is another important reducing agent for biosynthetic pathways in a cell.

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Glycolysis: High aerobic glycolysis

During anaerobic conditions, glycolysis is the cellular mechanism to obtain ATP, by fermentation. However, in mammalian cells, glycolysis is coupled with aerobic respiration. In the presence of oxygen, mitochondria take up pyruvate, the end-product of glycolysis, and further oxidize it into CO_2 and water.

As a result, the flux through the glycolytic pathway is lower during aerobic conditions since the full oxidation of one molecule of pyruvate (equivalent to one-half molecule of glucose) can lead to 18 times more ATP. Malignant rapidly-growing tumor cells, however, have glycolytic rates that are up to 200 times higher than that of their normal tissues of origin, despite the ample availability of oxygen. A classical explanation holds that the local depletion of oxygen within the tumor is the cause of the high glycolytic rate in tumor cells. Nevertheless, there is also strong experimental evidence that attributes these high aerobic glycolytic rates to an overexpressed form of mitochondrially-bound hexokinase responsible for driving the high glycolytic activity when oxygen is not necessarily depleted. This phenomenon was first described in 1930 by Otto Warburg, and hence it is referred to as the Warburg Effect. This has a current important medical application, as aerobic glycolysis by malignant tumors is utilized clinically to diagnose and monitor treatment responses of cancers by imaging uptake of 2-18F-2-deoxyglucose (a radioactive modified hexokinase substrate) with positron emission tomography (PET)

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Glycolysis: Alternative nomenclature

Some of the metabolites in glycolysis have alternative names and nomenclature. In part, this is because some of them are common to other pathways, such as the Calvin cycle.

1. glucose **Glc | Alternative name:** dextrose | **Alternative nomenclature:** none

2. glucose 6-phosphate **G6P | Alternative name:** none | **Alternative nomenclature:** none

3. fructose 6-phosphate **F6P | Alternative name:** none | **Alternative nomenclature:** none

4. fructose 1,6-bisphosphate **F1,6BP | Alternative name:** fructose 1,6-diphosphate | **Alternative nomenclature: FBP, FDP, F1,6DP**

5. dihydroxyacetone phosphate **DHAP | Alternative name:** none | **Alternative nomenclature:** none

6. glyceraldehyde 3-phosphate **GADP | Alternative names:** 3-phosphoglyceraldehyde, **GAP** | **Alternative nomenclature: PGAL, G3P, GALP**

7. 1,3-bisphosphoglycerate **1,3BPG | Alternative names:** glycerate 1,3-bisphosphate, glycerate 1,3-diphosphate, 1,3-diphosphoglycerate | **Alternative nomenclature: PGAP, BPG, DPG**

8. 3-phosphoglycerate **3PG | Alternative name:** glycerate 3-phosphate | **Alternative nomenclature: PGA, GP**

9. 2-phosphoglycerate **2PG | Alternative name:** glycerate 2-phosph | **Alternative nomenclature:** none

10. phosphoenolpyruvate **PEP | Alternative name:** none | **Alternative nomenclature:** none

11. pyruvate **Pyr | Alternative name:** none | **Alternative nomenclature:** none

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Oxidative decarboxylation

Enzyme activity | Setting | Other

Oxidative decarboxylation is the name given to the preparation of pyruvate, a product of glycolysis, for entrance into the citric acid cycle (a.k.a. Krebs cycle). Oxidative decarboxylation is sometimes referred to as "the transition reaction". In this reaction, pyruvate breaks down into carbon dioxide and acetaldehyde, reducing NAD^+ to NADH. Then, the acetaldehyde binds to a sulfur molecule attached to Coenzyme A, forming Acetyl CoA inside the mitochondrion. Coenzyme A is released during the citric acid cycle, allowing oxidative decarboxylation to recur indefinitely under aerobic respiration.

Enzyme activity

Pyruvate dehydrogenase catalyzes this reaction. Its inhibitors have the overall effect of slowing this reaction when there is either little oxygen, or when the cell has a lot of energy (as characterized by the ratios ATP/ADP, NADH/NAD^+ and acetyl-CoA/CoASH). An alternate name for this reaction, the "pyruvate dehydrogenase reaction", is derived from the name of this enzyme.

Setting

Oxidative decarboxylation occurs only inside the mitochondria. The pyruvate enters from the cytosol via a transport protein, consuming energy. It cannot diffuse across the membrane because it is a polar molecule. The acetyl-CoA molecule is very large and cannot leave the mitochondrion. Under normal circumstances, the acetyl-CoA is consumed by the citric acid cycle and the Coenzyme A is regenerated, allowing oxidative decarboxylation to occur again. The carbon dioxide is nonpolar and small, so it can diffuse out of the mitochondria and out of the cell. Note that since oxidative decarboxylation occurs in the mitochondria or their prokaryotic infolding analogs, most prokaryotes do not undergo this process.

Under aerobic conditions, NADH may be oxidized by the electron transport chain into NAD^+, renewing this reactant for use in oxidative decarboxylation. Note that this requires oxygen. In anaerobic conditions, NAD^+ can be regenerated by fermentation; however, the reaction quotient of reactants and products is not large enough that the reaction will proceed, because since the citric acid cycle does not run, product is not consumed.

Other

There is some disagreement as to whether oxidative decarboxylation should be considered a part of the citric acid cycle or not. This is irrelevant to the understanding of the process, but should be noted.

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Oxidative phosphorylation

Oxidative phosphorylation is a biochemical process in cells. It is the final metabolic pathway of cellular respiration, after glycolysis and the citric acid cycle.

The process takes place at a biological membrane. In prokaryotes this is the plasma membrane, and in eukaryotes it is the inner of the two mitochondrial membranes.

NADH and $FADH_2$, electron carrier molecules that were "loaded" during the citric acid cycle, are used in an electron transfer chain (involving NADH-Q reductase, succinate dehydrogenase, cytochrome reductase and cytochrome c oxidase) to pump H^+ across the membrane against a proton gradient.

A large protein complex called ATP synthase is embedded in that membrane and enables protons to pass through in both directions; it generates ATP from ADP and a phosphate when the proton moves with (down) the gradient, and it costs ATP to pump a proton against (up) the gradient. Because protons have already been pumped into the intermembrane space against the gradient, they now can flow back into the mitochondrial matrix via the ATP synthase, generating ATP in the process. The reaction is:

$ADP^{3-} + H^+ + P_i$ <-->$ATP^{4-} + H_2O$

The synthase functions almost as a mechanical motor, with each NADH molecule contributing enough proton motive force to generate 2.5 ATP. Each $FADH_2$ molecule is worth 1.5 ATP. All together, the 8 NADH and 2 $FADH_2$ molecules contributed through oxidation of glucose (glycolysis, conversion of pyruvate to acetyl-CoA, and the Krebs cycle) account for 23 of the 30 total ATP energy carrier molecules. It is worth noting that these ATP values are maximum values and in reality proton leaks across the membrane cause somewhat lower values.

Photophosphorylation, which occurs when plants synthesize glucose during photosynthesis, also uses ATP synthase and a proton gradient to generate ATP. The process occurs across the thylakoid membrane when chlorophyll is energized by light and donates an excited electron to an electron transport chain.

Inhibitors

There are a few well-known toxins that affect the process of oxidative phosphorylation and can lead to breakdown of the chain:

- Cyanide interrupts the electron transport chain in the inner membrane of the mitochondrion because it

binds more strongly than oxygen to the Fe^{3+} (ferric iron ion) in cytochrome a_3, preventing this cytochrome from combining electrons with oxygen.
- Oligomycin functions by inhibiting the ATP synthase protein and preventing it from generating ATP from the proton gradient.
- CCCP (m-chloro-carbonylcyanide-phenylhydrazine) destroys the proton gradient by allowing the protons to flow out of the membrane. Without the gradient, the ATP synthase cannot function and ATP synthesis breaks down.
- A detergent, or substance that destroys cellular membranes by breaking apart their lipid bilayers, will destroy the membrane used in the process and prevent a proton gradient.
- Rotenone prevents the transfer of electrons from Fe-S centers in Complex I (most notably) to ubiquinone. The electrons entering into Complex I are those derived from NADH, and provide the bulk of the reducing potential to the electron transport chain.

For each of these toxins, a backup will cause everything before it to break down as well. For example, if oligomycin is added, protons cannot pass through. As a result, the H^+ pumps are unable to pass protons through because the gradient becomes too strong for them to overcome. NADH and $FADH_2$ are then not oxidized and the citric acid cycle ceases to operate because there are no NAD^+ and FAD coenzymes to be reduced.

Reactive oxygen species

Several highly reactive, transient oxygen derivatives can be formed during this process:

- Hydrogen peroxide
- Superoxide anion
- Hydroxyl radical

A unique feature of the cytochrome c oxidase, complex IV, is its ability to maintain steric control over the reactive oxygen species created as it reduces oxygen to H_2O.

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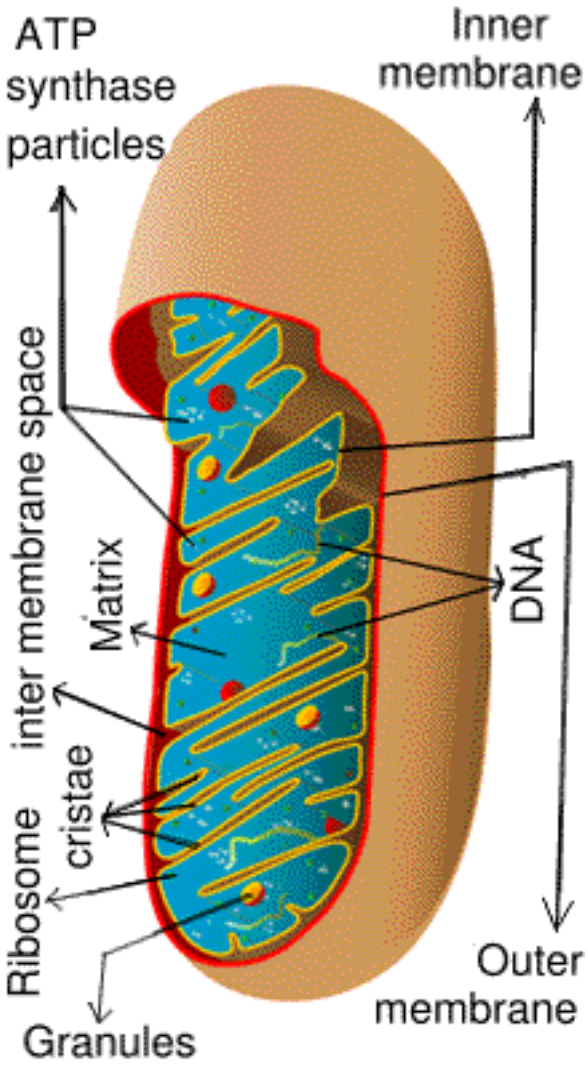
Mitochondrion

Mitochondrion structure | The mitochondrial matrix

A**mitochondrion** (plural **mitochondria**) (from Greek *mitos* thread + *khondrion* granule) is an organelle, variants of which are found in most eukaryotic cells. Mitochondria are sometimes described as "cellular power plants," because their primary function is to convert organic materials into energy in the form of ATP via the process of oxidative phosphorylation. Usually a cell has hundreds or thousands of mitochondria, which can occupy up to 25% of the cell's cytoplasm. Mitochondria usually have their own DNA, and, according to the generally accepted Endosymbiotic theory, they were originally derived from external organisms.

Mitochondrion structure



A mitochondrion contains outer and inner membranes composed of phospholipid bilayers studded with

proteins, much like a typical cell membrane. The two membranes, however, have very different properties.

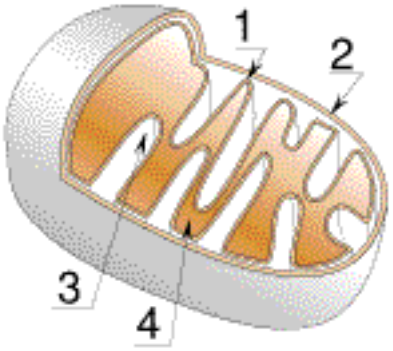
The outer mitochondrial membrane, which encloses the entire organelle, contains numerous integral proteins called *porins*, which contain a relatively large internal channel (about 2-3 nm) that is permeable to all molecules of 5000 daltons or less. Larger molecules can only tranverse the outer membrane by active transport. The outer mitochondrial membrane is composed of about 50% phospholipids by weight and contains a variety of enzymes involved in such diverse activities as the elongation of fatty acids, oxidation of epinephrine (adrenaline), and the degradation of tryptophan.

The inner membrane contains proteins with three types of functions:

- those that carry out the oxidation reactions of the respiratory chain
- ATP synthase, which makes ATP in the matrix
- specific transport proteins that regulate the passage of metabolites into and out of the matrix.

It contains more than 100 different polypeptides, and has a very high protein-to-phospholipid ratio (more than 3:1 by weight, which is about 1 protein for 15 phospholipids). Additionally, the inner membrane is rich in an unusual phospholipid, cardiolipin, which is usually characteristic of bacterial plasma membranes. Unlike the outer membrane, the inner membrane does not contain porins, and is highly-impermeable; almost all ions and molecules require special membrane transporters to enter or exit the matrix.

The mitochondrial matrix



Mitochondria structure :
1) Inner membrane
2) Outer membrane
3) Crista
4) Matrix

The matrix is the space enclosed by the inner membrane. The matrix contains a highly concentrated mixture of hundreds of enzymes, in addition to the special mitochondrial ribosomes, tRNA, and several

copies of the mitochondrial DNA genome. Of the enzymes, the major functions include oxidation of pyruvate and fatty acids, and the citric acid cycle.

Thus, mitochondria possess their own genetic material, and the machinery to manufacture their own RNAs and proteins.This nonchromosomal DNA encodes a small number of mitochondrial peptides (13 in humans) that are integrated into the inner mitochondrial membrane, along with polypeptides encoded by genes that reside in the host cell's nucleus.

The inner mitochondrial membrane is folded into numerous cristae (see diagram above), which expand the surface area of the inner mitochondrial membrane, enhancing its ability to generate ATP. In typical liver mitochondria, for example, the surface area, including cristae, is about five times that of the outer membrane. Mitochondria of cells which have greater demand for ATP, such as muscle cells, contain even more cristae than typical liver mitochondria.

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Mitochondrial functions

Although the primary function of mitochondria is to convert organic materials into cellular energy in the form of ATP, mitochondria play an important role in many metabolic tasks, such as:

- Apoptosis-Programmed cell death
- Glutamate-mediated excitotoxic neuronal injury
- Cellular proliferation
- Regulation of the cellular redox state
- Heme synthesis
- Steroid synthesis
- Heat production (enabling the organism to stay warm).

Some mitochondrial functions are performed only in specific types of cells. For example, mitochondria in liver cells contain enzymes that allow them to detoxify ammonia, a waste product of protein metabolism. A mutation in the genes regulating any of these functions can result in a variety of mitochondrial diseases.

Energy conversion

As stated above, the primary function of the mitochondria is the production of ATP. This is done by metabolizing the major products of glycolysis: pyruvate and NADH (glycolysis is performed outside the mitochondria, in the host cell's cytosol). This metabolism can be performed in two very different ways, depending on the type of cell and the presence or absence of oxygen.

Pyruvate: the citric acid cycle

Each pyruvate molecule produced by glycolysis is actively transported across the inner mitochondrial membrane, and into the matrix where it is combined with coenzyme A to form acetyl CoA. Once formed, acetyl CoA is fed into the *citric acid cycle* , also known as the *tricarboxylic acid (TCA) cycle* or *Krebs cycle*. This process creates 3 molecules of NADH and 1 molecule of $FADH_2$, which go on to participate in the *electron transport chain*.

With the exception of succinate dehydrogenase, which is bound to the inner mitochondrial membrane, all of the enzymes of the citric acid cycle are dissolved in the mitochondrial matrix.

NADH and $FADH_2$: the electron transport chain

This energy from NADH and $FADH_2$ is transferred to oxygen (O_2) in several steps via the electron

transfer chain. The protein complexes in the inner membrane (NADH dehydrogenase, cytochrome c reductase, cytochrome c oxidase) that perform the transfer use the released energy to pump protons (H^+) against a gradient (the concentration of protons in the intermembrane space is higher than that in the matrix).

As the proton concentration increases in the intermembrane space, a strong *concentration gradient* is built up. The main exit for these protons is through the *ATP synthase* complex. By transporting protons from the intermembrane space back into the matrix, the ATP synthase complex can make ATP from ADP and inorganic phosphate (P_i). This process is called chemiosmosis and is an example of facilitated diffusion. Peter Mitchell was awarded the 1978 Nobel Prize in Chemistry for his work on chemiosmosis. Later, part of the 1997 Nobel Prize in Chemistry was awarded to Paul D. Boyer and John E. Walker for their clarification of the working mechanism of ATP synthase.

Under certain conditions, protons may be allowed to re-enter the mitochondial matrix without contributing to ATP synthesis. This process, known as *proton leak* or *mitochondrial uncoupling*, results in the unharnessed energy being released as heat. This mechanism for the metabolic generation of heat is employed primarily in specialized tissues, such as the "brown fat" of newborn or hibernating mammals.

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Mitochondrion: Origin

As mitochondria contain ribosomes and DNA, and are only formed by the division of other mitochondria, it is generally accepted that they were originally derived from endosymbiotic prokaryotes. Studies of mitochondrial DNA, which is often circular and employs a variant genetic code, show their ancestor, the so-called proto-mitochondrion, was a member of the Proteobacteria [Futuyma 2005]. In particular, the pre-mitochondrion was probably related to the rickettsias, although the exact position of the ancestor of mitochondria among the alpha-proteobacteria remains controversial. The endosymbiotic hypothesis suggests that mitochondria descended from specialized bacteria (probably purple nonsulfur bacteria) that somehow survived endocytosis by another species of prokaryote or some other cell type, and became incorporated into the cytoplasm. The ability of symbiont bacteria to conduct cellular respiration in host cells that had relied on glycolysis and fermentation would have provided a considerable evolutionary advantage. Similarly, host cells with symbiotic bacteria capable of photosynthesis would also have an advantage. In both cases, the number of environments in which the cells could survive would have been greatly expanded.

This happened at least 2000 million years ago and mitochondria still show some signs of their ancient origin. Mitochondrial ribosomes are the 70S (bacterial) type, in contrast to the 80S ribosomes found elsewhere in the cell. As in prokaryotes, there is a very high proportion of coding DNA, and an absence of repeats. Mitochondrial genes are transcribed as multigenic transcripts which are cleaved and polyadenylated to yield mature mRNAs. Unlike their nuclear cousins, mitochondrial genes are small, generally lacking introns, and many chromosomes are circular, conforming to the bacterial pattern.

A few groups of unicellular eukaryotes lack mitochondria: the symbiotic microsporidians, metamonads, and entamoebids, and the free-living pelobionts. On rRNA trees these groups appeared as the most primitive eukaryotes, suggesting they appeared before the origin of mitochondrion, but this is now known to be an artifact of long branch attraction - they are apparently derived groups and retain genes or organelles derived from mitochondria. Thus it appears that there are no primitively amitochondriate eukaryotes, and so the origin of mitochondria may have played a critical part in the development of eukaryotic cells.

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Mitochondrion: Reproduction and gene inheritance

Mitochondria replicate their DNA and divide mainly in response to the energy needs of the cell; in other words their growth and division is not linked to the cell cycle. When the energy needs of a cell are high, mitochondria grow and divide. When the energy use is low, mitochondria are destroyed or become inactive. At cell division, mitochondria are distributed to the daughter cells more or less randomly during the division of the cytoplasm. Mitochondria divide by binary fission similar to bacterial cell division. Unlike bacteria, however, mitochondria can also fuse with other mitochondria. Sometimes new mitochondria are synthesized in centers that are rich in proteins and polyribosomes needed for their synthesis.

Mitochondrial genes are not inherited by the same mechanism as nuclear genes. At fertilization of an egg by a sperm, the egg nucleus and sperm nucleus each contribute equally to the genetic makeup of the zygote nucleus. In contrast, the mitochondria, and therefore the mitochondrial DNA, usually comes from the egg only. At fertilization of an egg, a single sperm enters the egg along with the mitochondria that it uses to provide the energy needed for its swimming behavior. However, the mitochondria provided by the sperm are targeted for destruction very soon after entry into the egg. The egg itself contains relatively few mitochondria, but it is these mitochondria that survive and divide to populate the cells of the adult organism. This means that mitochondria are usually inherited purely down the female line.

This maternal inheritance of mitochondrial DNA is seen in most organisms, including all animals. However, mitochondria in some species can sometimes be inherited through the father. This is the norm amongst certain coniferous plants (although not in pines and yew trees). It has been suggested to occur at a very low level in humans.

Uniparental inheritance means that there is little opportunity for genetic recombination between different lineages of mitochondria. For this reason, mitochondrial DNA is usually thought of as reproducing clonally. However, there are several claims of recombination in mitochondrial DNA, most controversially in humans. If recombination does not occur, the whole mitochondrial DNA sequence represents a single haplotype, which makes it useful for studying the evolutionary history of populations.

Mitochondrial genomes have many fewer genes than do the related eubacteria from which they are thought to be descended. Although some have been lost altogether, many seem to have been transferred to the nucleus. This is thought to be relatively common over evolutionary time. A few organisms, such as *Cryptosporidium*, actually have mitochondria which lack any DNA, presumably because all their genes have either been lost or transferred.

The uniparental inheritance of mitochondria is thought to result in intragenomic conflict, such as seen in the petite mutant mitochondria of some yeast species. It is possible that the evolution of separate male and female sexes is a mechanism to resolve this organelle conflict.

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Mitochondrion: Use in population genetic studies

The near-absence of genetic recombination in mitochondrial DNA makes it a useful source of information for scientists involved in population genetics and evolutionary biology. Because all the mitochondrial DNA is inherited as a single unit, or haplotype, the relationships between mitochondrial DNA from different individuals can be represented as a gene tree. Patterns in these gene trees can be used to infer the evolutionary history of populations. The classic example of this is in human evolutionary genetics, where the molecular clock can be used to provide a recent date for mitochondrial Eve. This is often interpreted as strong support for a recent modern human expansion out of Africa. Another human example is the sequencing of mitochondrial DNA from Neanderthal bones. The relatively large evolutionary distance between the mitochondrial DNA sequences of Neanderthals and living humans has been interpreted as evidence for lack of interbreeding between Neanderthals and anatomically modern humans.

However, mitochondrial DNA only reflects the history of females in a population, and so may not give a representative picture of the history of the population as a whole. For example, if dispersal is primarily undertaken by males, this will not be picked up by mitochondrial studies. This can be partially overcome by the use of patrilineal genetic sequences, if they are available (in mammals the non-recombining region of the Y-chromosome provides such a source). More broadly, only studies that also include nuclear DNA can provide a comprehensive evolutionary history of a population; unfortunately, genetic recombination means that these studies can be difficult to analyse.

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Fermentation

Fermentation typically refers to the conversion or changing of sugar to alcohol using yeast. The process is often used to produce wine and beer, but fermentation is also employed in preservation to create lactic acid in sour foods such as pickled cucumbers, kimchi and yogurt. The science of fermentation is known as zymology.

In its strictest sense, **fermentation** (formerly called **zymosis**) is the anaerobic metabolic breakdown of a nutrient molecule, such as glucose, without net oxidation. Fermentation does not release all the available energy in a molecule; it merely allows glycolysis (a process that yields two ATP per glucose) to continue by replenishing reduced coenzymes. Depending on which organism it is taking place in, fermentation may yield lactate, acetic acid, ethanol, or other reduced metabolites. Yeast produces ethanol and CO_2; human muscle (under anaerobic conditions) produces lactic acid.

Fermentation is also used much more broadly to refer to the bulk growth of microorganisms on a growth medium. No distinction is made between aerobic and anaerobic metabolism when the word is used in this sense.

Fermentation usually implies that the action of the microorganisms is desirable. Occasionally wines are enhanced through the process of cofermentation. When fermentation stops prior to complete conversion of sugar to alcohol, a stuck fermentation is said to have occurred.

Reaction

The reaction differs according to the sugar being used in the process of anaerobic respiration, below, the sugar will be glucose ($C_6H_{12}O_6$) the simplest sugar.

Symbol Equation

$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2 + \text{Energy Released } (118kJ\ mol^{-1})$

Word Equation

Sugar (glucose) --> Alcohol + Carbon Dioxide + Energy

History

Since fruits ferment naturally, fermentation precedes human history. Since prehistoric times, however, humans have been taking control of the fermentation process. There is strong evidence that people were fermenting beverages in Babylon circa 5000 BC, ancient Egypt circa 3000 BC, pre-Hispanic Mexico circa 2000 BC, and Sudan circa 1500 BC. There is also evidence of leavened bread in ancient Egypt circa 1500 BC and of milk fermentation in Babylon circa 3000 BC. The Chinese were probably the first to develop vegetable fermentation.

Biochemistry

Fermentation is a process that is important in anaerobic conditions when there is no oxidative phosphorylation to maintain the production of ATP (Adenosine triphosphate) by glycolysis. During fermentation pyruvate is metabolised to various different compounds. Homolactic fermentation is the production of lactic acid from pyruvate; alcoholic fermentation is the conversion of pyruvate into ethanol and carbon dioxide; and heterolactic fermentation is the production of lactic acid as well as other acids and alcohols.

Textbook examples of fermentation products are ethanol (drinkable alcohol), lactic acid, and hydrogen. However, more exotic compounds can be produced by fermentation, such as butyric acid and acetone.

Although the final step of fermentation (conversion of pyruvate to fermentation end-products) does not produce energy, it is critical for an anaerobic cell since it regenerates nicotinamide adenine dinucleotide (NAD^+), which is required for glycolysis. This is important for normal cellular function, as glycolysis is the only source of ATP in anaerobic conditions.

Fermentation products contain chemical energy (they are not fully oxidized) but are considered waste products since they cannot be metabolised further without the use of oxygen (or other more highly-oxidized electron acceptors). A consequence is that the production of ATP by fermentation is less efficient than oxidative phosphorylation, where pyruvate is fully oxidised to carbon dioxide. Fermentation produces two ATP molecules per molecule of glucose compared to approximately 36 by aerobic respiration. Even in vertebrates, however, it is used as an effective means of energy production during short, intense periods of exertion, where the transport of oxygen to the muscles is insufficient to maintain aerobic metabolism. While fermentation is helpful during short, intense periods of exertion, it is not sustained over extended periods in complex aerobic organisms. In humans, for example, lactic acid fermentation provides energy for a period ranging from 30 seconds to 2 minutes. The speed at which ATP is produced is about 100 times that of oxidative phosphorylation. The pH in the cytoplasm quickly drops when lactic acid accumulates in the muscle, eventually inhibiting enzymes involved in glycolysis.

Products

Products produced by fermentation are actually waste products produced during the reduction of pyruvate to regenerate NAD+ in the absence of oxygen.

When yeast ferments, it breaks down the sugar($C_6H_{12}O_6$) into exactly two molecules of ethanol (C_2H_6O) and two molecules of carbon dioxide (CO_2).

- Ethanol fermentation (done by yeast and some types of bacteria) breaks the pyruvate down into ethanol and carbon dioxide. It is important in bread-making, brewing, and wine-making. When the ferment has a high concentration of pectin, minute quantities of methanol can be produced. Usually only one of the products is desired; in bread the alcohol is baked out, and in alcohol production the carbon dioxide is released into the atmosphere.
- Lactic acid fermentation breaks down the pyruvate into lactic acid. It occurs in the muscles of animals when they need energy faster than the blood can supply oxygen. It also occurs in some bacteria and some fungi. It is this type of bacteria that convert lactose into lactic acid in yogurt, giving it its sour taste.

The burning sensation in muscles during hard exercise used to be attributed to the production of lactic acid during a shift to **anaerobic glycolosis**, as oxygen is converted to carbon dioxide by aerobic glycolysis faster than the body can replenish it; but muscle soreness and stiffness after hard exercise is actually due to microtrauma of the muscle fibres. The body falls back on this less-efficient but faster method of producing ATP under low-oxygen conditions. This is thought to have been the primary means of energy production in earlier organisms before oxygen was at high concentration in the atmosphere and thus would represent a more ancient form of energy production in cells. The liver later gets rid of this excess lactate by transforming it back into an important glycolysis intermediate called pyruvate. Aerobic glycolysis is a method employed by muscle cells for the production of lower-intensity energy over a longer period of time.

Bacteria generally produce acids. Vinegar (acetic acid) is the direct result of bacterial metabolism (Bacteria need oxygen to convert the alcohol to acetic acid). In milk, the acid coagulates the casein, producing curds. In pickling, the acid preserves the food from pathogenic and putrefactive bacteria.

Uses

The primary benefit of fermentation is the conversion, e.g., converting juice into wine, grains into beer, and carbohydrates into carbon dioxide to leaven bread.

According to Steinkraus (1995), food fermentation serves five main purposes:

- Enrichment of the diet through development of a diversity of flavors, aromas, and textures in food substrates
- Preservation of substantial amounts of food through lactic acid, alcoholic, acetic acid, and alkaline fermentations
- Biological enrichment of food substrates with protein, essential amino acids, essential fatty acids, and vitamins

- Detoxification during food-fermentation processing
- A decrease in cooking times and fuel requirements

Fermentation has some benefits exclusive to foods. Fermentation can produce important nutrients or eliminate antinutrients. Food can be preserved by fermentation, since fermentation uses up food energy and can make conditions unsuitable for undesirable microorganisms. For example, in pickling the acid produced by the dominant bacteria inhibit the growth of all other microorganisms. Depending on the type of fermentation, some products (e.g., fusel alcohol) can be harmful to people's health.

In alchemy, fermentation is often the same as putrefaction, meaning to allow the substance to naturally rot or decompose.

Fermented foods, by region

- Worldwide: alcohol, wine, vinegar, olives, yogurt
- Asia - East and Southeast Asia: asinan, bai-ming, belacan, burong mangga, dalok, doenjang, jeruk, fish sauce, kimchi, leppet-so, miang, nata de coco, nata de pina, natto, naw-mai-dong, pak-siam-dong, paw-tsaynob in snow, prahok, sake, seokbakji, soy sauce, stinky tofu, szechwan cabbage, tai-tan tsoi, takuan, tempeh, totkal kimchi, yen tsai, zha cai
- Central Asia: kumis (mare milk), kefir, shubat (camel milk)
- India: achar, gundruk, mixed pickle, idli
- Africa: garri, hibiscus seed, hot pepper sauce, injera, lamoun makbouss, mauoloh, msir, mslalla, oilseed, ogili, ogiri
- Americas: cheese, pickling (pickled vegetables), sauerkraut, lupin seed, oilseed, chocolate, vanilla, fermented fish, fish heads, walrus, seal oil, birds (in Inuit cooking)
- Middle East: kushuk, lamoun makbouss, mekhalel, torshi, tursu, boza
- Europe: cheese, sauerkraut, soured milk products such as quark, kefir and filmjolk, fermented Baltic herring, sausages

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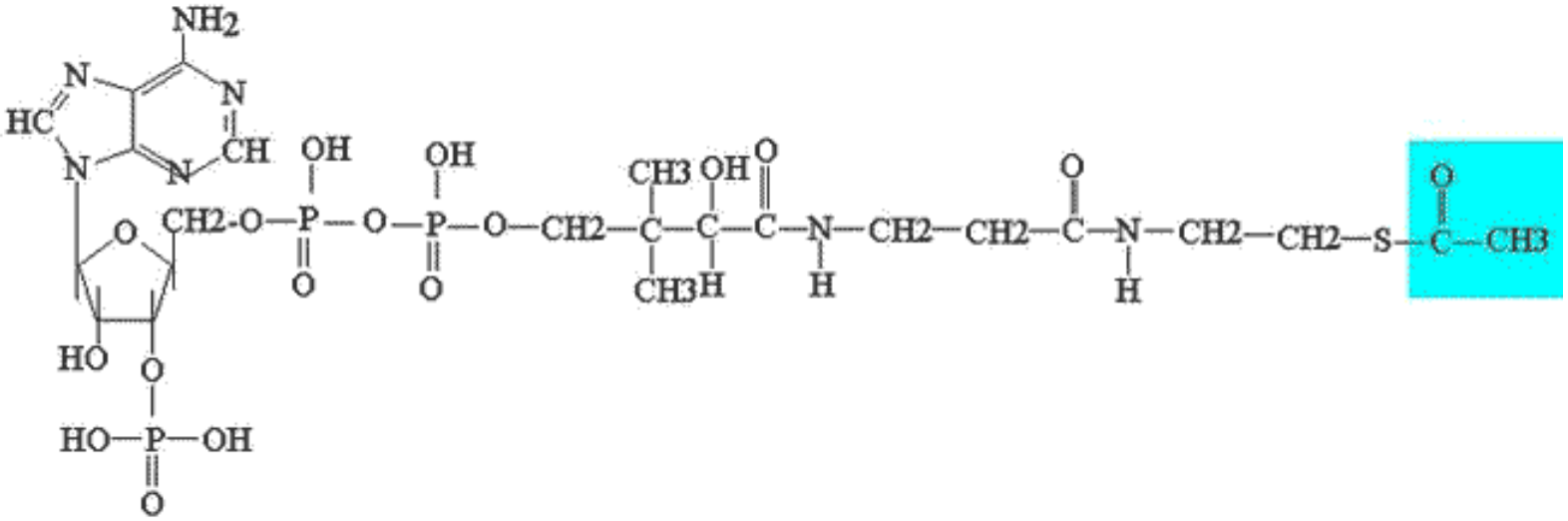
Coenzyme A



Coenzyme A (**CoA**, **CoASH**, or **HSCoA**) is adapted from beta-mercaptoethylamine, panthothenate and adenosine triphosphate and used in metabolism in areas such as fatty acid oxidization and the citric acid cycle. Its main function is to carry acyl groups such as acetyl or thioesters. A molecule of coenzyme A carrying an acetyl group is also referred to as **acetyl-CoA**. It is sometimes referred to as 'CoASH' or 'HSCoA' because when it's not attached to a molecule such as an acetyl group, it is attached to a thiol group, -SH.

Acetyl-CoA is an important molecule itself. It is the precursor to HMG CoA, which is a vital component in cholesterol and ketone synthesis. Furthermore, it contributes an acetyl group to choline to produce acetylcholine, in a reaction catalysed by choline acetyltransferase. Its main task is conveying the carbon atoms within the acetyl group to the citric acid cycle to be oxidized for energy production.

The conversion of pyruvate into Acetyl-CoA is referred to as the Pyruvate Dehydrogenase Reaction. It is catalyzed by an enzyme-complex called pyruvate dehydrogenase. The enzyme consists of 60 subunits: 24 pyruvate dehydrogenase, 24 dihydrolipoyl transacetylase, and 12 dihydrolipoyl dehydrogenase (commonly denoted E1, E2, and E3). 24 pyruvate dehydrogenase has the coenzyme TPP (thiamin pyrophosphate) incorporated into it, 24 dihydrolipoyl transacetylase has lipoate and coenzyme A, and 12 dihydrolipoyl dehydrogenase has the coenzymes FAD and NAD^+. Through a complex reaction, pyruvate is decarboxylated and turned into acetaldehyde, then attached to coenzyme A while NAD^+ is subsequently reduced to NADH and H^+.

Coenzyme A is very central to the balance between carbohydrate metabolism and fat metabolism. Carbohydrate metabolism needs some CoA for the citric acid cycle to continue, and fat metabolism needs a larger amount of CoA for breaking down fatty acid chains during beta-oxidation. Fats can only supply energy by being broken down into small units, and our cells have only one way of doing this: breaking fats down into acetyl-CoA molecules, each of which needs a CoA molecule for its production.

Carbohydrate metabolism recycles CoA in the citric acid cycle; in fat metabolism, which does not involve the citric acid cycle, all of the CoA is trapped in the form of acetyl-CoA. The only way to release enough CoA is to combine acetyl-CoA with each other to create ketone bodies and detach a CoA. (This is why excess ketone bodies are produced in diabetes and during starvation or low-carbohydrate diets.)

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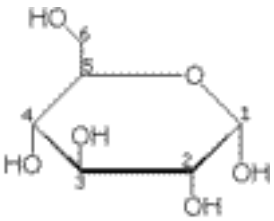
Ethanol fermentation

The need for Fermentation | The chemical process of fermentation | Uses of Ethanol respiration

Ethanol fermentation is a form of anaerobic respiration used primarily by yeasts when oxygen is not present in sufficient quantity for normal cellular respiration, the cellular energy-producing system, to continue.

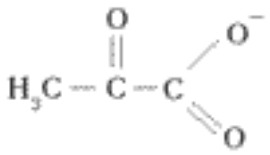
The need for Fermentation

In aerobic respiration (the branch of respiration 'normal' for most organisms), a molecule of Glucose ($C_6H_{12}O_6$, shown left) is broken down through the process of glycolysis into pyruvate ($C_3H_3O_3$, shown right).



Glucose

In the first half of glycolysis, two Adenosine triphosphate (ATP) molecules cause glucose to break into two molecules Glyceraldehyde-3-phosphate (G3P). In the next step, a Nicotinamide adenine dinucleotide (NAD^+) molecule removes a hydrogen atom from a G3P, converting G3P to 3-Biphosphoglycerate and NAD^+ to NADH.

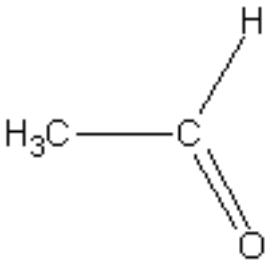


Pyruvate

When oxygen is present, NADH carries its hydrogen elsewhere. Eventually, oxygen reacts with the hydrogen carried by NADH to make water (H_2O). When oxygen is not present in sufficient quantity, NADH cannot give up its hydrogen to oxygen, and so much of the cell's supply of NAD^+ is converted to NADH that G3P can no longer be converted to 3-Biphosphoglycerate, and the generation of ATP by the cell ceases, unless another substance can be used to remove the hydrogen from NADH.

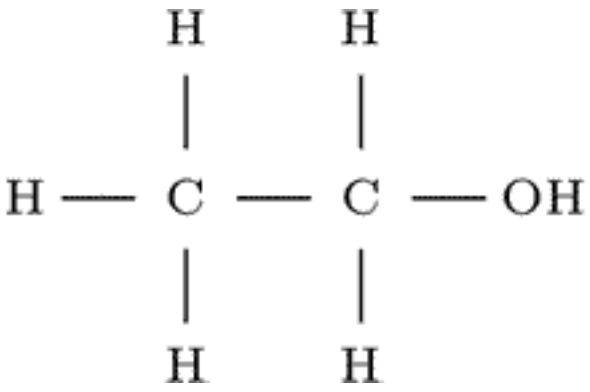
The chemical process of fermentation

Fermentation is a chemical pathway that provides such a substance. In the ethanol fermentation used by yeasts and other organisms, the ionised carboxyl group (COO^-) is removed from the pyruvate to generate a molecule of carbon dioxide, which is released by the yeast into its surroundings. The resulting molecule, acetaldehyde (C_2H_4O, see below), takes the place of oxygen as the chemical that accepts hydrogen from NADH. This hydrogen, together with an H^+ ion released during an earlier stage of glycolysis, is added to the acetaldehyde, making ethanol (C_2H_6O, see below).



Acetaldehyde

Ethanol respiration can be summed up in this chemical equation: $C_6H_{12}O_6$ --> 2 C_2H_5OH + 2 CO_2 + 2ATP



Ethanol

Uses of Ethanol respiration

Ethanol respiration is the form of fermentation used to make alcohol and bread. Yeast cells in the dough of a bread will be cut off from their sources of oxygen, and will generate alcohol (which is boiled away due to the heat) and carbon dioxide (which form bubbles that cause bread to rise). It is also used to mass-produce alcoholic beverages. The yeasts, cut off from oxygen, will ferment a starchy grain or vegetable (such as wheat, corn, potatoes, rye).

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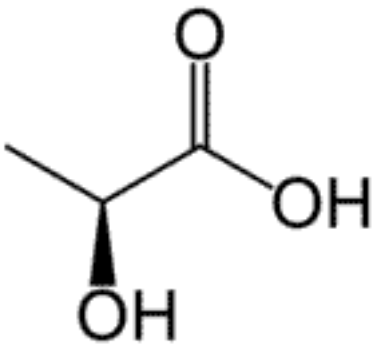
Lactic acid

Exercise and lactate | Cosmetic uses | Lactic acid in food | Lactic acid as a polymer precursor

Lactic acid, also known as milk acid or 2-hydroxypropanoic acid, is a chemical compound that plays a role in several biochemical processes. Lactic acid is a carboxylic acid with a chemical formula of $C_3H_6O_3$. It has a hydroxyl group adjacent to the carboxylic acid, making it an alpha hydroxy acid (AHA). In solution, it can lose a proton from the acidic group, producing the **lactate** ion $CH_3CH(OH)COO^-$.



Lactic acid is chiral and has two optical isomers. One is known as L-(+)-lactic acid or (*S*)-lactic acid and the other, its mirror image, is D-(-)-lactic acid or (*R*)-lactic acid. L-(+)-Lactic acid is the biologically important isomer.

L-Lactate is produced from pyruvate via the enzyme lactate dehydrogenase (LDH) in a process of fermentation. Lactate is constantly produced during normal metabolism and exercise but does not increase in concentration until the rate of lactate production exceeds the rate of lactate removal. The rate of removal is governed by a number of factors including: monocarboxylate transporters, concentration and isoform of LDH and oxidative capacity of tissues. The concentration of blood lactate is usually 1-2 mmol/L at rest, but can rise to over 20 mmol/L during intense exertion.

Increases in lactate concentration typically occur under conditions where the rate of energy demand by tissues cannot be met by aerobic respiration i.e. tissues cannot get or process oxygen and substrates quickly enough. Under these conditions pyruvate dehydrogenase cannot convert pyruvate to acetyl-CoA quickly enough and pyruvate begins to build up. This would normally inhibt glycolysis and reduce ATP production, if not for lactate dehydrogenase reducing pyruvate to form lactate via the reaction:

pyruvate + NADH + H^+ --> lactate + NAD^+.

The purpose of lactate production is to regenerate nicotinamide adenine dinucleotide (NAD^+) needed for

glycolysis and thus allow adenosine triphosphate (ATP) production to continue.

The increased lactate produced can be removed in a number of ways including: oxidation to pyruvate by well-oxygenated muscle cells which is then directly used to fuel the citric acid cycle and conversion to glucose via the Cori cycle in the liver through the process of gluconeogenesis.

Lactic acid fermentation is also performed by *Lactobacillus* bacteria. These bacteria can operate in the mouth; the acid they produce is responsible for the tooth decay known as caries.

In medicine, lactate is one of the main components of Ringer's lactate or lactated Ringer's solution. This intravenous fluid consists of sodium, chloride, potassium, and lactate in solution with distilled water in concentration so as to be isotonic compared to human blood. It is most commonly used for fluid resuscitation after blood loss due to trauma, surgery or a burn injury.

Exercise and lactate

During intense exercise, such as sprinting type activities, when the rate of demand for energy is high, lactate is produced faster than the ability of the tissues to remove it and lactate concentration begins to rise. This is a beneficial process since the regeneration of NAD^+ ensures that energy production is maintained and exercise can continue. Contrary to popular belief, this increased concentration of lactate does not directly cause acidosis, nor is it responsible for muscle pain or "burning". This is because lactate itself is not capable of releasing a proton, and secondly, the acidic form of lactate (lactic acid) cannot be formed under normal circumstances in human tissues. Analysis of the glycolytic pathway in humans indicates that there are not enough hydrogen ions present in the glycolytic intermediates to produce lactic or any other acid.

The acidosis that is associated with increases in lactate concentration during heavy exercise arises from a completely separate reaction. When ATP is hydrolysed, a hydrogen ion is released. ATP-derived hydrogen ions are primarily responsible for the decrease in pH. During intense exercise, oxidative metabolism (aerobic) cannot produce ATP quick enough to supply the demands of the muscle. As a result, glycolysis (i.e. anaerobic metabolism) becomes the dominant energy producing pathway as it can form ATP at high rates. Due to the large amounts of ATP being produced and hydrolysed in a short period of time, the buffering systems of the tissues are overcome, causing pH to fall and creating a state of acidosis. This may be one factor, among many, that contributes to the acute muscular discomfort experienced shortly after intense exercise.

Although it is not firmly established, it is possible that lactate may contribute to an acidotic effect via the strong ion difference, however this has not been well investigated in exercise physiology research and so its contribution is still uncertain.

Cosmetic uses

Lactic acid is popularly known as an AHA in the cosmetics industry. It is widely used as a milder alternative to glycolic acid. It is primarily used as an anti-aging chemical claimed to soften lines, reduce photodamage from the sun, improve skin texture and tone and improve overall appearance.

Several precautions should be taken when using lactic acid as a cosmetic agent because it can increase UV sensitivity to the sun.

Lactic acid in food

Lactic acid is used in a variety of food stuffs to act as an acidity regulator. Although it can be fermented from lactose (milk sugar), most commercially used lactic acid is derived from bacteria such as *Bascillus acidilacti*, *Lactobascillus delbueckii* or *L. bulgaricuswhey* to ferment carbohydrates from sources such as cornstarch, potatoes or molasses. Thus, although it is commonly known as "milk acid", products claiming to be vegan do sometimes feature lactic acid as an ingredient.

Lactic acid as a polymer precursor

Two molecules of lactic acid can be dehydrated to lactide, a cyclic lactone. A variety of catalysts can polymerise lactide to either heterotactic or syndiotactic Polylactide, which as biodegradable polyesters with valuable (*inter alia*) medical properties are currently attracting much attention.

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Photosynthesis

Photosynthesis is an important biochemical process in which plants, algae, and some bacteria convert the energy of sunlight to chemical energy. The chemical energy is used to drive synthetic reactions such as the formaton of sugars or the fixation of nitrogen into amino acids, the building blocks for protein synthesis. Ultimately, nearly all living things depend on energy produced from photosynthesis for their nourishment, making it vital to life on Earth. It is also responsible for producing the oxygen that makes up a large portion of the Earth's atmosphere. Organisms that produce energy through photosynthesis are called photoautotrophs. Plants are the most visible representatives of photoautotrophs, but it should be emphasized that bacteria and algae also contribute to the conversion of free energy into usable energy.

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Photosynthesis in algae and bacteria

Algae is a range from multicellular forms like kelp to microscopic, single-celled organisms. Although they are not as complex as land plants, photosynthesis takes place biochemically the same way. Very much like plants, algae have chloroplasts and chlorophyll, but various accessory pigments are present in some algae such as phycoerythrin in red algae (rhodophytes) , resulting in a wide variety of colours. All algae produce oxygen, and many are autotrophic. However, some are heterotrophic, relying on materials produced by other organisms.

Photosynthetic bacteria do not have chloroplasts (or any membrane-bound organelles), instead, photosynthesis takes place directly within the cell. Cyanobacteria contain thylakoid membranes very similar to those in chloroplasts and are the only prokaryotes that perform oxygen-generating photosynthesis, in fact chloroplasts are now considered to have evolved from an endosymbiotic bacterium, which was also an ancestor of and later gave rise to cyanobacterium. The other photosynthetic bacteria have a variety of different pigments, called bacteriochlorophylls, and do not produce oxygen. Some bacteria such as *Chromatium*, oxidize hydrogen sulfide instead of water for photosynthesis, producing sulfur as waste.

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Bioenergetics of photosynthesis

Photosynthesis is a physiological phenomenon that converts solar energy into photochemical energy. This physiological phenomenon may be described thermodynamically in terms of changes in energy, entropy and free energy. The energetics of photosynthesis, driven by light, causes a change in entropy that in turn yields a usable source of energy for the plant.

The following chemical equation summarizes the products and reactants of carbon reduction in the typical green photosynthesizing plant:

$CO_2 + H_2O \dashrightarrow O_2 + (CH_2O) + 112$ kcal/mol CO_2

On earth, there are two sources of free energy: light energy from the sun, and terrestrial sources, including volcanoes, hot springs and radioactivity of certain elements. The biochemical value of electromagnetic radiation has led plants to use the free energy from the sun in particular. Visible light, which is used specifically by green plants to photosynthesize, may result in the formation of electronically excited states of certain substances called pigments. For example, **Chlorophyll a** is a pigment which acts as a catalyst, converting solar energy into photochemical energy that is necessary for photosynthesis.

With the presence of solar energy, the plant has a usable source of energy, which is termed the free energy (G) of the system. However, thermal energy is not completely interconvertible, which means that the character of the solar energy may lead to the limited convertibility of it into forms that may be used by the plant. This relates back to the work of Josiah Willard Gibbs: the change in free energy ($\Delta_r G$) is related to both the change in entropy ($\Delta_r S$) and the change in enthalpy ($\Delta_r H$) of the system (Rabinowitch).

Gibbs free energy equation: $\Delta_r G = \Delta_r H - T\Delta_r S$... where ΔH is enthalpy, ΔS is entropy, and T is temperature.

Past experiments have shown that the total energy produced by photosynthesis is 112 kcal/mol. However in the experiment, the free energy due to light was 120 kcal/mol. An overall loss of 8 kcal/mol was due to entropy, as described by Gibbs equation (Govindjee). In other words, since the usable energy of the system is related directly to the entropy and temperature of the system, a smaller amount of thermal energy is available for conversion into usable forms of energy (including mechanical and chemical) when entropy is great (Rabinowitch). This concept relates back to the second law of thermodynamics in that an increase in entropy is needed to convert light energy into energy suitable for the plant.

Overall, in conjunction with the oxidation-reduction reaction nature of the photosynthesis equation, and

the interrelationships between entropy and enthalpy, energy in a usable form will be produced by the photosynthesizing green plant.

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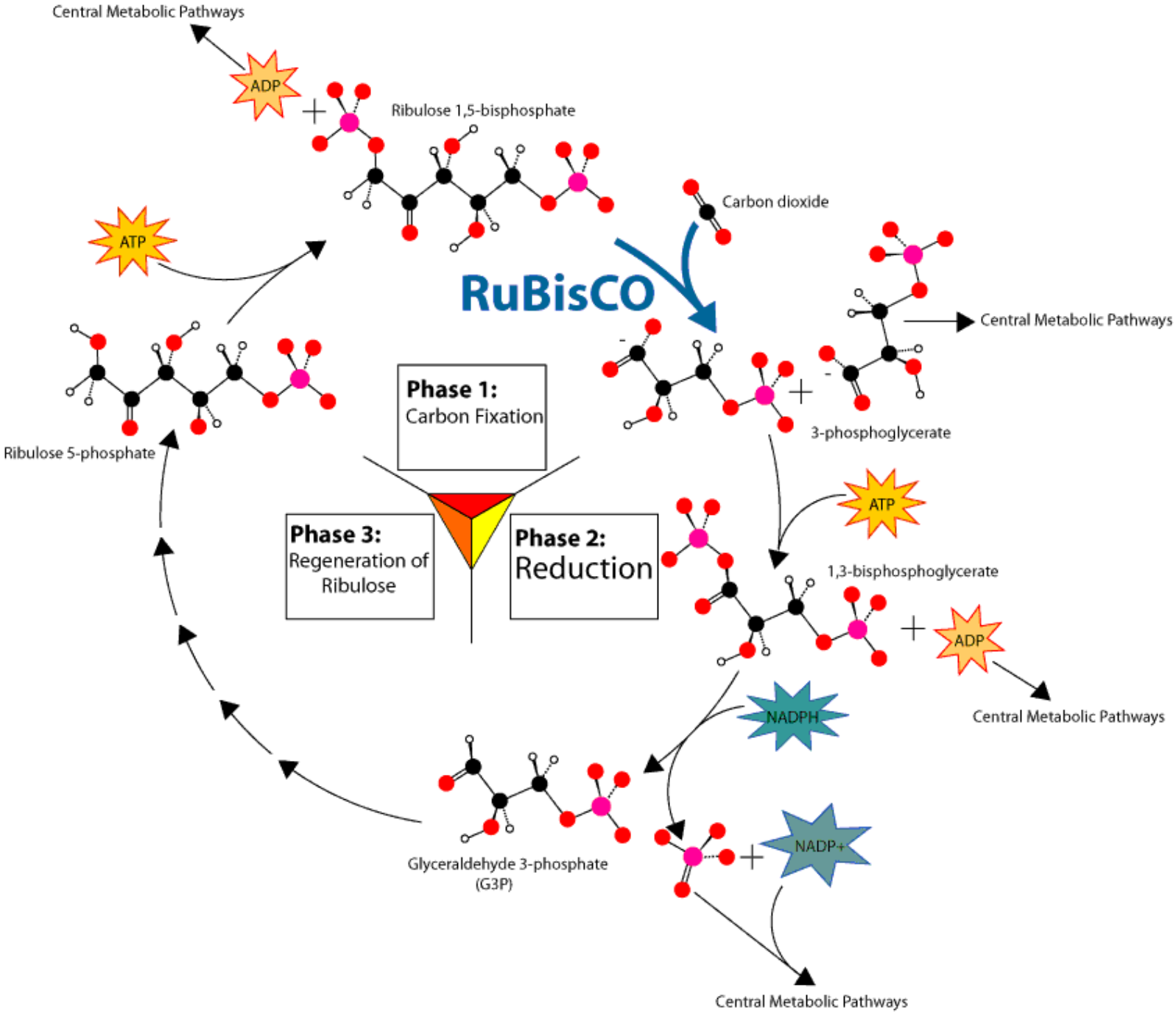
Calvin cycle

The **Calvin cycle** (or **Calvin-Benson cycle** or carbon fixation) is a series of biochemical reactions that takes place in the stroma of chloroplasts in photosynthetic organisms. It was discovered by Melvin Calvin and Andrew Benson at the University of California, Berkeley. James Bassham also made important contributions to elucidating this pathway. It is one of the light-independent reactions.

Overview

Overview of the Calvin cycle and carbon fixation:



During photosynthesis, light energy is used to generate chemical free energy, stored in ATP and NADPH. The light-independent Calvin cycle, also (misleadingly) known as the "dark reaction" or "dark stage", uses the energy from short-lived electronically-excited carriers to convert carbon dioxide and water into organic compounds that can be used by the organism (and by animals which feed on it). This set of reactions is also called *carbon fixation*. The key enzyme of the cycle is called RuBisCO. In the following equations, the

chemical species (phosphates and carboxylic acids) exist in equilibria among their various ionized states as governed by the pH.

The enzymes in the Calvin cycle are functionally equivalent to many enzymes used in other metabolic pathways such as glycolysis and gluconeogenesis, but they are to be found in the chlorophlast stroma instead of the cell cytoplasm, separating the reactions. They are activated in the light (which is why the name "dark reaction" is misleading), and also by products of the light-dependent reaction. These regulatory functions prevent the Calvin cycle from operating in reverse to respiration, which would create a continuous cycle of carbon dioxide being reduced to carbohydrates, and carbohydrates being respired to carbon dioxide. Energy (in the form of ATP) would be wasted in carrying out these reactions that have no net productivity.

The sum of reactions in the Calvin cycle is the following:

$6\ CO_2 + 12\ NADPH + 12\ H^+ + 18\ ATP \rightarrow C_6H_{12}O_6 + 6\ H_2O + 12\ NADP^+ + 18\ ADP + 18\ P_i$

Steps of the Calvin cycle

- The enzyme RuBisCO catalyses the carboxylation of Ribulose-1,5-bisphosphate, a 5 carbon compound, by carbon dioxide (a total of 6 carbons). Two molecules of glycerate-3-phosphate, a 3-carbon compound, are created. (also: 3-phosphoglycerate, 3-phosphoglyceric acid, 3PGA)
- The enzyme phosphoglycerate kinase catalyses the phosphorylation of 3PGA by ATP (which was produced in the light-dependent stage). 1,3-bisphosphoglycerate (glycerate-1,3-bisphosphate) and ADP are the products. (However, note that two PGAs are produced for every CO_2 that enters the cycle, so this step happens twice.)
- The enzyme G3P dehydrogenase catalyses the reduction of 1,3BPGA by NADPH (which was another product of the light-dependent stage). Glyceraldehyde-3-phosphate (also G3P, GP) is produced, and the NADPH itself was oxidised and hence becomes $NADP^+$.

(Simplified versions of the Calvin cycle integrate the remaining steps, except for the last one, into one general step - the regeneration of RuBP - also, one G3P would exit here.)

- Triosephosphate isomerase converts some G3P reversibly into dihydroxyacetone phosphate (DHAP), also a 3-carbon molecule.
- Aldolase and F1,6BPase convert some of these two into fructose-6-phosphate (6C). A phosphate ion is lost to ADP.

Up to this point, as per the overall equation given above, 6 carbon dioxide molecules would have been converted, with the use of 6 RuBP, 12 ATP and 12 NADPH, to 12 G3P molecules. One F6P, (= 2 G3P) then exits the cycle, while 10 of these G3P molecules continue, giving a ratio of 1:5 G3P. Obviously, the ratio of carbon dioxide entering the cycle to RuBP already present is also 1:5.

- F6P is then combined with another G3P (total 9C) and then cleaved into xylulose-5-phosphate (X5P) and erythrose-4-phosphate by transketolase.
- E4P and DHAP are converted into sedoheptulose-7-phosphate (7C) by S1,7BPase. A phosphate ion is lost to ADP.
- S7P is then combined with another G3P (total 10C) and then cleaved into another X5P and ribose-5-phosphate (R5P) again by transketolase.
- X5P is converted into ribulose-5-phosphate (Ru5P, RuP) by epimerase. R5P is also converted into RuP by ribose isomerase.
- Finally, phosphoribulokinase phosphorylates RuP into RuBP, ribulose-1,5-bisphosphate, completing the Calvin *cycle*. This requires the input of one ATP.

All the G3P produced earlier is converted into RuBP (5C), so 10 G3Ps (30C, 10 phosphates) were needed to produce 6 RuBPs (30C, 6 phosphates). 6 ATPs were also needed in the last step, giving a total of 18 ATPs used up per 6 CO_2s. However, four phosphate ions are lost and these also form ATP. The energy in those ATPs is used to drive some of the reactions.

At high temperatures, RuBisCO will react with O_2 instead of CO_2 in *photorespiration*. This turns RuBP into 3PGA and 2-phosphoglycolate, a 2-carbon molecule which can be converted into 3PGA, some of which will exit the Calvin cycle. However, if this continues the RuBP will eventually be depleted, which slows down the cycle

if electrons are entering from the light-dependent reaction too quickly.

Products of the Calvin cycle

The two G3P molecules (or one F6P molecule) which have exited the cycle are used to make carbohydrates. In simplified versions of the Calvin cycle they may be converted to F6P after exit, but this conversion is also part of the cycle. Hexose isomerase converts about half of the F6P molecules into glucose-6-phosphate. These are dephosphorylated and the glucose can be used to form starch, which is stored in, for example, potatoes, or cellulose used to build up cell walls. Other glucose, with fructose, forms sucrose, the plant sugar.

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Photosynthesis Discovery

Although some of the steps in photosynthesis are still not completely understood, the overall photosynthetic equation has been known since the 1800s.

Jan van Helmont began the research of the process in the mid-1600s when he carefully measured the mass of the soil used by a plant and the mass of the plant as it grew. After noticing that the soil mass changed very little, he hypothesized that the mass of the growing plant must come from the water, the only substance he added to the potted plant. This was a partially accurate hypothesis - much of the gained mass also comes from carbon dioxide as well as water. However, this was a signalling point to the idea that the bulk of a plant's biomass comes from the inputs of photosynthesis, not the soil itself.

Joseph Priestley, a chemist and minister, discovered that when he isolated a volume of air under an inverted jar, and burned a candle in it, the candle would burn out very quickly, much before it ran out of wax. He further discovered that a mouse could similarly "injure" air. He then showed that the air that had been "injured" by the candle and the mouse could be restored by a plant.

In 1778, Jan Ingenhousz, court physician to the Austrian Empress, repeated Priestley's experiments. He discovered that it was the influence of sun and light on the plant that could cause it to rescue a mouse in a matter of hours.

In 1796, Jean Senebier, a French pastor, showed that CO_2 was the "fixed" or "injured" air and that it was taken up by plants in photosynthesis. Soon afterwards, Nicolas-Théodore de Saussure showed that the increase in mass of the plant as it grows could not be due only to uptake of CO_2, but also to the incorporation of water. Thus the basic reaction by which photosynthesis is used to produce food (such as glucose) was outlined.

Modern scientists built on the foundation of knowledge from those scientists centuries ago and were able to discover many things.

Cornelis Van Niel made key discoveries explaining the chemistry of photosynthesis. By studying purple sulfur bacteria and green bacteria he was the first scientist to demonstrate that photosynthesis is a light-dependent redox reaction, in which hydrogen reduces carbon dioxide.

Further experiments to prove that the oxygen developed during the photosynthesis of green plants came from water, were performed by Robert Hill in 1937 and 1939. He showed that isolated chloroplasts give off oxygen in the presence of unnatural reducing agents like iron oxalate, ferricyanide or benzoquinone after exposure to light. The Hill reaction is as follows:

$2\ H_2O + 2\ A + (\text{light, chloroplasts}) \rightarrow 2\ AH_2 + O_2$

where A is the electron acceptor. Therefore, in light the electron acceptor is reduced and oxygen is evolved.

Samuel Ruben and Martin Kamen used radioactive isotopes to determine that the oxygen liberated in photosynthesis came from the water.

Melvin Calvin and Andrew Benson, along with James Bassham, elucidated the path of carbon assimilation (the photosynthetic carbon reduction cycle) in plants. The carbon reduction cycle is known as the Calvin cycle, which inappropriately ignores the contribution of Bassham and Benson. Many scientists refer to the cycle as the Calvin-Benson Cycle, Benson-Calvin, and some even call it the Calvin-Benson-Bassham (or CBB) Cycle.

A Nobel Prize winning scientist, Rudolph A. Marcus, was able to discover the function and significance of the electron transport chain.

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Factors affecting photosynthesis

There are three main factors affecting photosynthesis and several corollary factors. The three main are:

- Light irradiance and wavelength
- Carbon dioxide concentration
- Temperature

Light intensity (Irradiance), wavelength and temperature

In the early 1900s Frederick Frost Blackman along with Gabrielle Matthaei investigated the effects of light intensity (irradiance) and temperature on the rate of carbon assimilation.

- At constant temperature, the rate of carbon assimilation varies with irradiance, initially increasing as the irradiance increases. However at higher irradiance this relationship no longer holds and the rate of carbon assimilation reaches a plateau.
- At constant irradiance, the rate of carbon assimilation increases as the temperature is increased over a limited range. This effect is only seen at high irradiance levels. At low irradiance, increasing the temperature has little influence on the rate of carbon assimilation.

These two experiments illustrate vital points: firstly, from research it is known that photochemical reactions are not generally affected by temperature. However, these experiments clearly show that temperature affects the rate of carbon assimilation, so there must be two sets of reactions in the full process of carbon assimilation. These are of course the light-dependent 'photochemical' stage and the light-independent, temperature-dependent stage. Secondly, Blackman's experiments illustrate the concept of limiting factors. Another limiting factor is the wavelength of light. Cyanobacteria which reside several meters underwater cannot receive the correct wavelengths required to cause photoinduced charge separation in conventional photosynthetic pigments. To combat this problem a series of proteins with different pigments surround the reaction center. This unit is called a phycobilisome.

Carbon dioxide

As carbon dioxide concentrations rise, the rate at which sugars are made by the light-independent reactions increases until limited by other factors. One reason for this is that RuBisCO, the enzyme fixing the carbon dioxide in the light-dependent reactions, has a binding affinity for both carbon dioxide and oxygen. Thus, an increase in the concentration of carbon dioxide increases the probability of RuBisCO fixing carbon dioxide instead of oxygen.

A reduced RuBisCO oxygenase activity is advantageous to plants for several reasons.

- One product of oxygenase activity is phosphoglycolate (2 carbon) instead of 3-phosphoglycerate (3

carbon). Phosphoglycolate cannot be metabolized by the Calvin-Benson cycle and represents carbon lost from the cycle. A high oxygenase activity, therefore, drains the sugars that are required to recycle ribulose 5-bisphosphate and for the continuation of the Calvin-Benson cycle.
- Phosphoglycolate is quickly metabolized to glycolate that is toxic to a plant at a high concentration; it inhibits photosynthesis.
- Salvaging glycolate is an energetically expensive process that uses the glycolate pathway and only 75% of the carbon is returned to the Calvin-Benson cycle as 3-phosphoglycerate.
A highly simplified summary is: 2 glycolate + ATP --> 3-phophoglycerate + carbon dioxide + ADP $+NH_3$

The salvaging pathway for the products of RuBisCO oxygenase activity is more commonly known as photorespiration since it is characterized by light dependent oxygen consumption and the release of carbon dioxide.

Corollary factors

- Amount of water
- Leaf morphology
- Leaf nitrogen content
- Molecular carriers such as NADP and FAD

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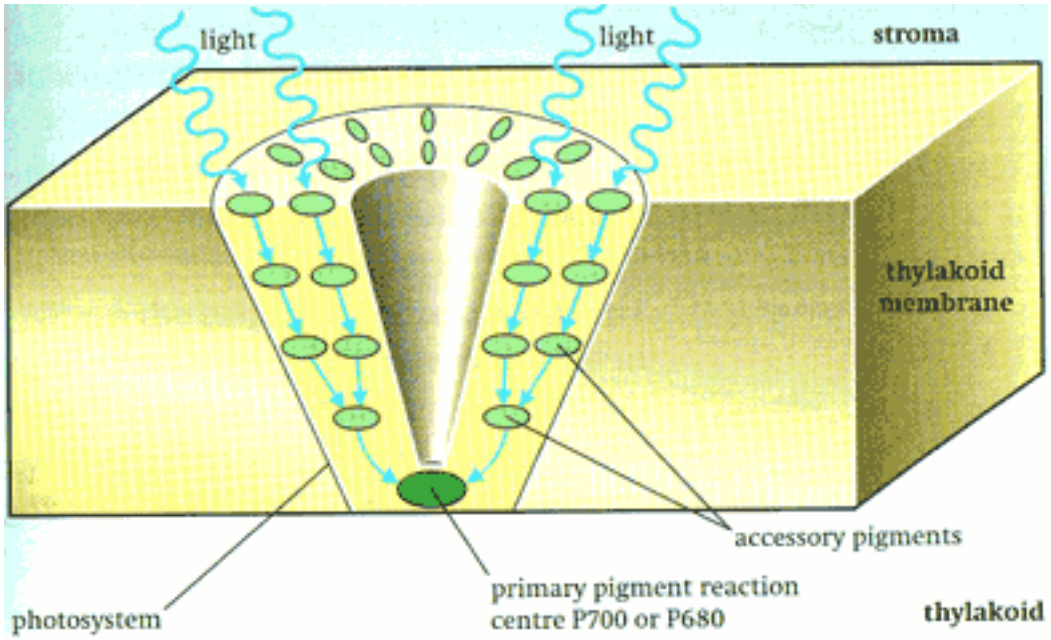
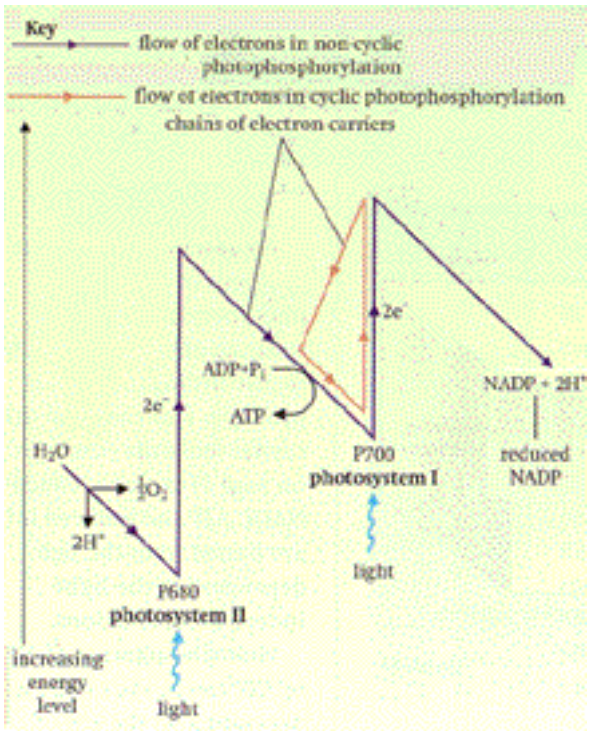
Molecular production



A photosystem: a **light-harvesting** cluster of photosynthetic pigments in a chloroplast thylakoid membrane.

The light energy is converted to chemical energy using the light-dependent reactions. The products of the light dependent reactions are ATP from photophosphorylation and NADPH from photoreduction. Both are then utilized as an energy source for the light-independent reactions.



The 'Z-scheme' of electron flow in light-dependent reactions.

Z scheme

In plants, the **light-dependent reactions** occur in the thylakoid membranes of the chloroplasts and use light energy to synthesize ATP and NADPH. The light dependent reaction has two forms; cyclic and non cylcic reaction. In the non cyclic reaction, The photons are captured in the light-harvesting antenna complexes of [[Photosystem|photosystem II by chlorophyll and other accessory pigments. When a chlorophyll molecule at the core of the photosystem II reaction center obtains sufficient excitation energy from the adjacent antenna pigments, an electron is transferred to the primary electron-acceptor molecule, Phaephytin, through a process called Photoinduced charge separation. These electrons are shuttled through an electron transport chain, the so called ***Z-scheme*** shown in the diagram, that initially functions to generate a chemiosmotic potential across the membrane. An ATP synthase enzyme uses the chemiosmotic potential to make ATP during photophosphorylation while NADPH is a product of the terminal redox reaction in the *Z-scheme*. The electron enters the Photosystem I molecule. The electron is emitted due to the light absorbed by the photosystem. A second electron carrier accepts the electron, which again is passed down lowering energies of electron acceptors. The energy created by the electron acceptors is used to move hydogen ions across the thylakiod membrane into the lumen. The electron is used to reduce the co-enzyme NADH, which has functions in the light independant reaction. The cyclic reaction is similar to that of the non cyclic, but differs in the form that it only generates ATP and no reduced NADP (NADPH) is created. The cyclic reaction takes place only at photosystem I. Once the electron is displaced from the photosystem, the electron is passed down the electron acceptor molecules and returns back to photosystem I, from where is was emitted. Hence the name - cyclic reaction.

Water photolysis

The NADPH is the main reducing agent in chloroplasts, providing a source of energetic electrons to other reactions. Its production leaves chlorophyll with a deficit of electrons (oxidized), which must be obtained from some other reducing agent. The excited electrons lost from chlorophyll in photosystem I are replaced from the electron transport chain by plastocyanin. However, since photosystem II includes the first steps of the *Z-scheme*, an external source of electrons is required to reduce its oxidized **chlorophyll *a*** molecules. The source of electrons in green-plant and cyanobacterial photosynthesis is water. Each water molecule is oxidized by four successive charge-separation reactions by photosystem II to yield a molecule of diatomic oxygen and four hydrogen ions; the electron yielded in each step is transferred to a redox-active tyrosine residue that then reduces the photooxidized paired-chlorophyll *a* species called P680 that serves as the primary (light-driven) electron donor in the photosystem II reaction center. The oxidation of water is catalyzed in photosystem II by a redox-active structure that contains four manganese ions; this oxygen-evolving complex binds two water molecules and stores the four oxidizing equivalents that are required to drive the water-oxidizing reaction. Photosystem II is the only known biological enzyme that carries out this oxidation of water. The hydrogen ions contribute to the transmembrane chemiosmotic potential that leads to ATP synthesis. Oxygen is a waste product of light-independent reactions, but the majority of organisms on Earth use oxygen for cellular respiration, including photosynthetic organisms.

Oxygen and photosynthesis

With respect to oxygen and photosynthesis, there are two important concepts.

- Plant and cyanobacterial (blue-green algal) cells *also use oxygen* for cellular respiration, although they have a net output of oxygen since much more is produced during photosynthesis.
- Oxygen is a *product of the light-driven water-oxidation reaction catalyzed by photosystem II;* it is not generated by the fixation of carbon dioxide. Consequently, the source of oxygen during photosynthesis is water, not carbon dioxide.

Bacterial variations

The concept that oxygen production is not directly associated with the fixation of carbon dioxide was first proposed by Cornelis Van Niel in the 1930s, who studied photosynthetic bacteria. Aside from the cyanobacteria, bacteria only have one photosystem and use reducing agents other than water. They get electrons from a variety of different inorganic chemicals including sulfide or hydrogen, so for most of these bacteria oxygen is not produced.

Others, such as the halophiles (an Archeae) produced so called purple membranes where the bacteriorhodopsin could harvest light and produce energy. The purple membranes was one of the first to be used to demonstrate the chemiosmotic theory: light hit the membranes and the pH of the solution that contained the purple membranes dropped as protons were pumping out of the membrane.

Carbon fixation

The fixation or reduction of carbon dioxide is a light-independent process in which carbon dioxide combines with a five-carbon sugar, ribulose 1,5-bisphosphate (RuBP), to give two molecules of a three-carbon compound, glycerate 3-phosphate (GP). This compound is also sometimes known as 3-phosphoglycerate (PGA). GP, in the presence of ATP and NADPH from the light-dependent stages, is reduced to glyceraldehyde 3-phosphate (G3P). This product is also referred to as 3-phosphoglyceraldehyde (PGAL) or even as triose phosphate (a three-carbon sugar). This is the point at which carbohydrates are produced during photosynthesis. Some of the triose phosphates condense to form hexose phosphates, sucrose, starch and cellulose or are converted to acetyl-coenzyme A to make amino acids and lipids. Others go on to regenerate RuBP so the process can continue.

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Plant photosynthesis

Most plants are photoautotrophs, which means that they are able to synthesize food directly from inorganic compounds using light energy -for example the sun, instead of eating other organisms or relying on nutrients derived from them. This is distinct from chemoautotrophs that do *not* depend on light energy, but use energy from inorganic compounds.

The energy for photosynthesis ultimately comes from absorbed photons and involves a reducing agent, which is water in the case of plants, releasing oxygen as a waste product. The light energy is converted to chemical energy, in the form of ATP and NADPH, which is used for synthetic reactions in photoautotrophs. Most notably plants use the chemical energy to fix carbon dioxide into carbohydrates and other organic compounds through light-independent reactions. The overall equation for carbon fixation (sometimes referred to as carbon reduction) in green plants is

$$n\ CO_2 + 2n\ H_2O + ATP + NADPH \rightarrow (CH_2O)_n + n\ O_2 + n\ H_2O,$$

where n is defined according to the structure of the resulting carbohydrate. However, hexose sugars and starch are the primary products, so the following generalised equation is often used to represent carbon reduction.

$$6\ CO_2 + 12\ H_2O + ATP + NADPH \rightarrow C_6H_{12}O_6 + 6\ O_2 + 6\ H_2O$$

More specifically, carbon fixation produces an intermediate product, which is then converted to the final hexose carbohydrate products. These carbohydrate products are then variously used to form other organic compounds, such as the building material cellulose, as precursors for lipid and amino acid biosynthesis or as a fuel in cellular respiration. The latter not only occurs in plants, but also in animals when the energy from plants get passed through a food chain. Organisms dependent on photosynthetic and chemosynthetic organisms are called heterotrophs. In general outline, cellular respiration is the opposite of photosynthesis: glucose and other compounds are oxidised to produce carbon dioxide, water, and chemical energy. However, both processes actually take place through a different sequence of reactions and in different cellular compartments.

Plants capture light primarily using the pigment chlorophyll, which is the reason that most plants have a green color. The function of chlorophyll is often supported by other accessory pigments such as carotenes and xanthophylls. Both chlorophyll and accessory pigments are contained in organelles (compartments within the cell) called chloroplasts. Although all cells in the green parts of a plant have chloroplasts, most of the energy is captured in the leaves. The cells in the interior tissues of a leaf, called the mesophyll, contain about half a million chloroplasts for every square millimeter of leaf. The surface of the leaf is uniformly coated with a water-resistant, waxy cuticle, that protects the leaf from excessive evaporation of water as well as decreasing the absorption of ultraviolet or blue light to reduce heating.

The transparent, colourless epidermis layer allows light to pass through to the palisade mesophyll cells where most of the photosynthesis takes place.

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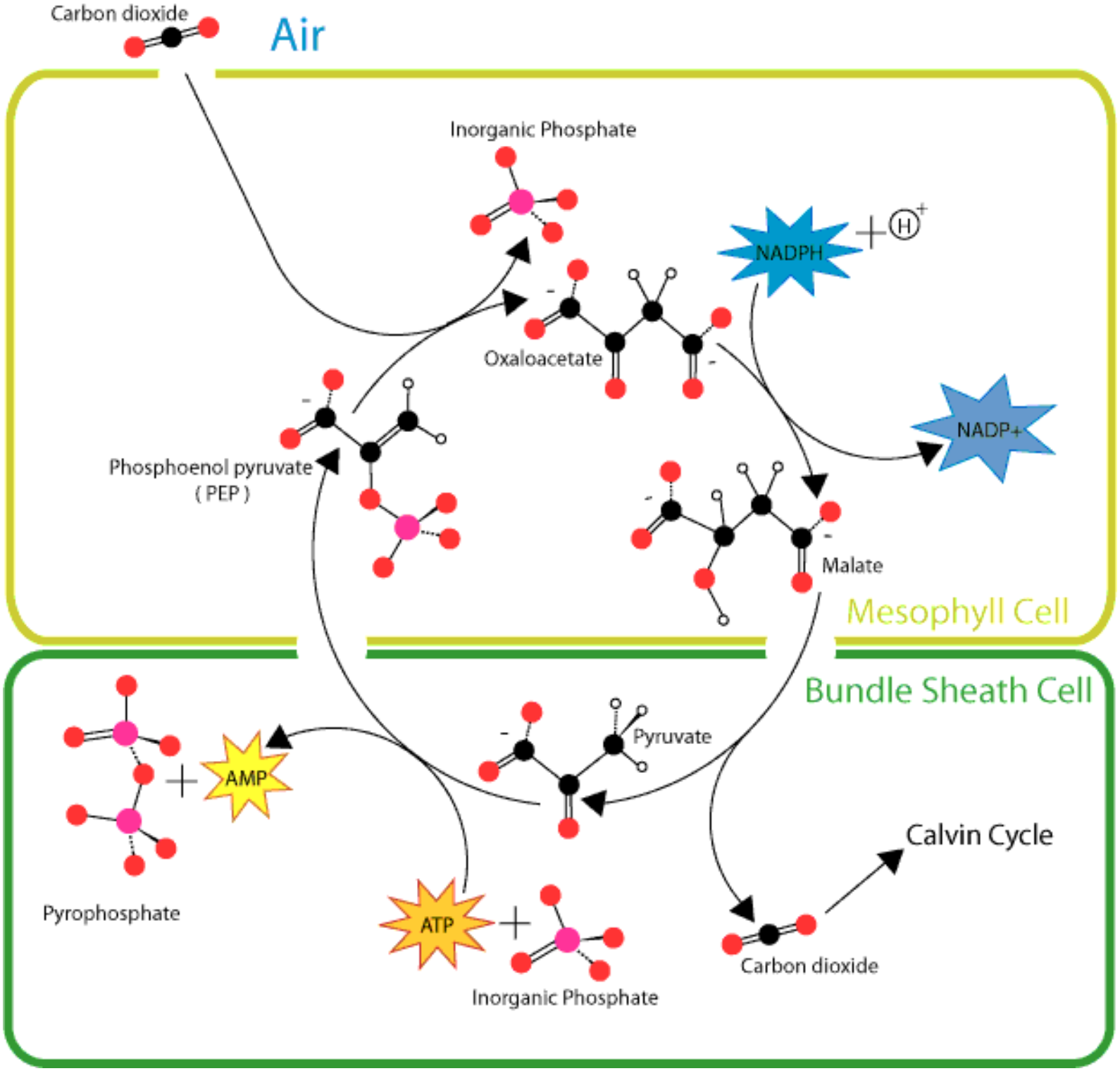
Carbon fixation

The carbon fixation reaction is the first step of the light-independent reactions. Carbon from carbon dioxide is "fixed" into a larger carbohydrate. Three pathways to occur: C3 carbon fixation (the most common), C4 carbon fixation, and CAM (Crassulacean Acid Metabolism). C3 fixation occurs as the first step of the Calvin-Benson cycle in all plants. C4 plants first fix carbon dioxide into malate, which is then used to supply carbon dioxide in the middle of the night to the Calvin-Benson cycle. CAM plants perform a similar process.

Overview of C4 carbon fixation:



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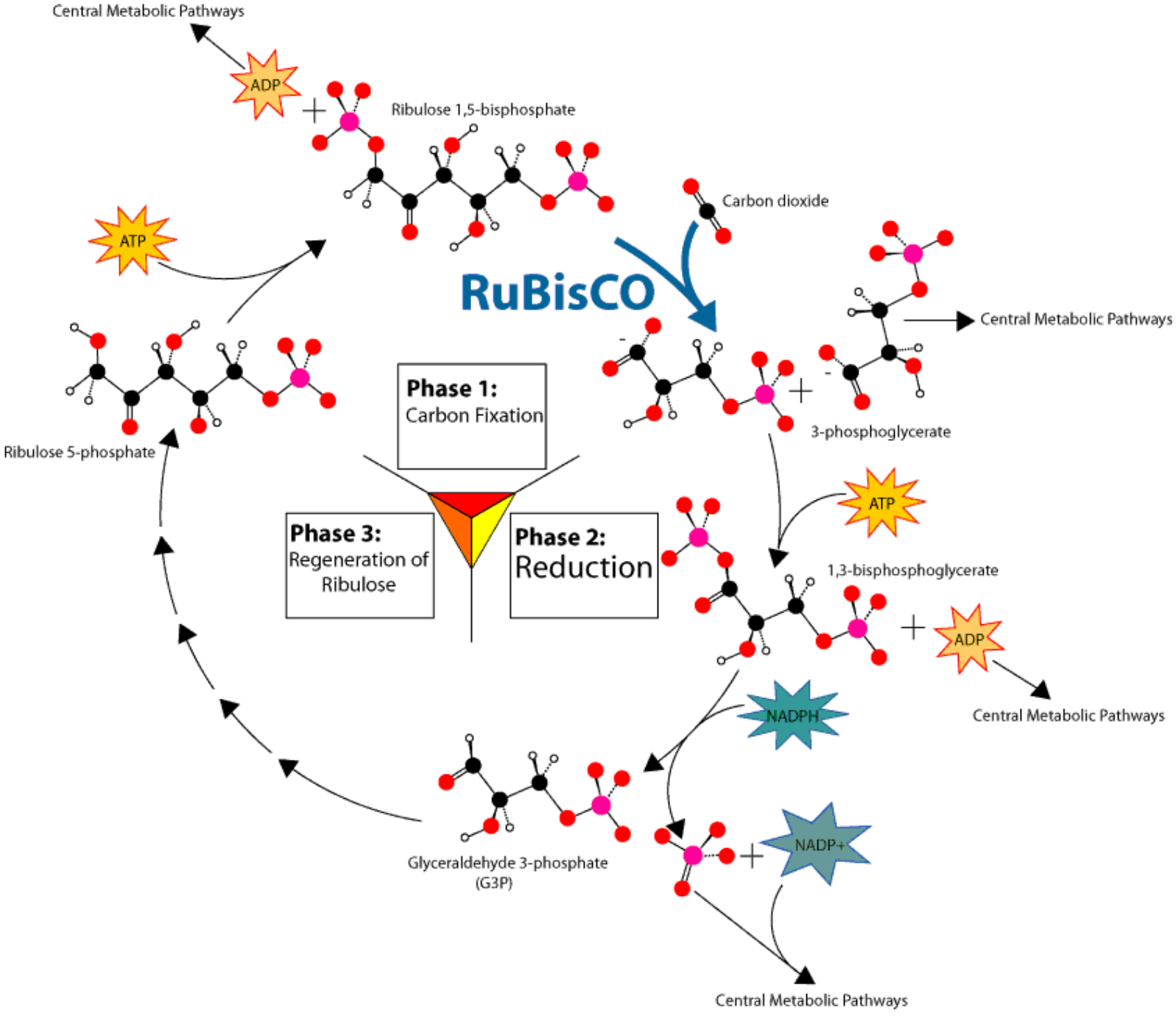
Light-independent reaction overview

In photosynthesis, the **light-independent reactions**, also somewhat misleadingly called the **dark reactions**, are chemical reactions that convert carbon dioxide and other compounds into glucose. These reactions, unlike the light-dependent reactions, do not need light to occur; hence the term *dark reactions*. These reactions take the products of the light-dependent reactions and perform further chemical processes on them. The light-independent reactions are two: carbon fixation and the Calvin-Benson cycle.

In CAM plants, carbon fixation actually *does* take place at night.

Note that regeneration of the substrate for this reaction requires light. Thus it is not that correct to call this reaction as light-independent reaction.

Overview of the Calvin cycle and carbon fixation:



Carbon fixation

The carbon fixation reaction is the first step of the light-independent reactions. Carbon from carbon dioxide is "fixed" into a larger carbohydrate. Three pathways to occur: C3 carbon fixation (the most common), C4 carbon fixation, and CAM (Crassulacean Acid Metabolism). C3 fixation occurs as the first step of the Calvin-Benson cycle in all plants. C4 plants first fix carbon dioxide into malate, which is then used to supply carbon dioxide in the middle of the night to the Calvin-Benson cycle. CAM plants perform a similar process.

Calvin cycle

The Calvin-Benson cycle takes carbon dioxide and converts it to glucose, which the plant uses for energy.

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Light-dependent reaction

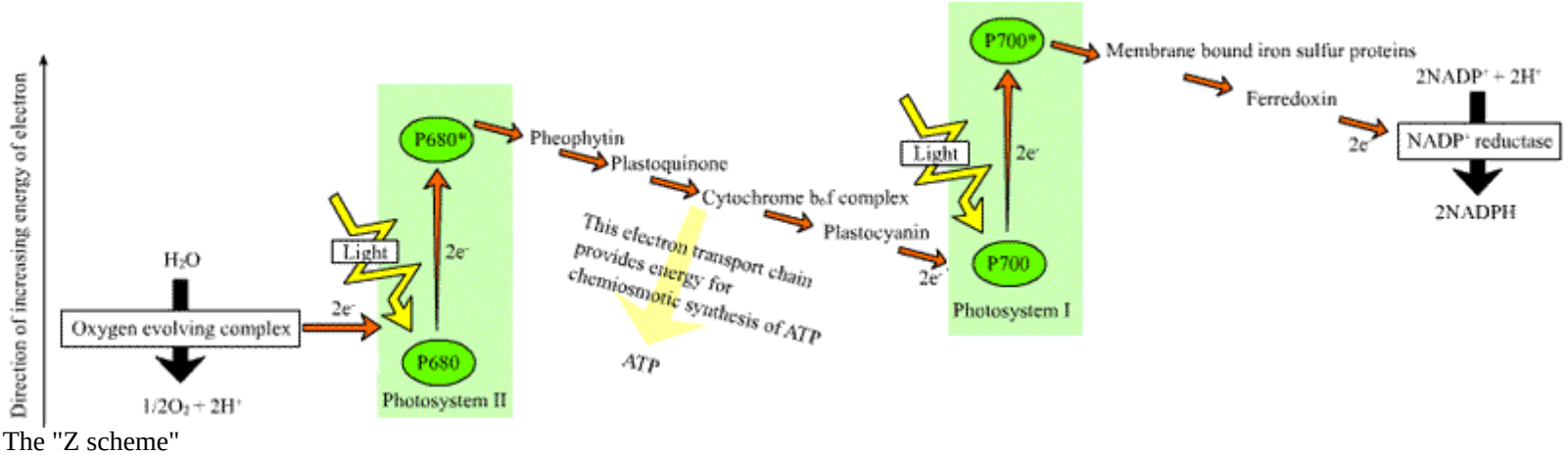
The first stage of the photosynthetic system is the **light-dependent reaction**, which converts solar energy into chemical energy.

Overview

Light absorbed by chlorophyll or other photosynthetic pigments such as carotene is used to drive a transfer of electrons and hydrogen from water (or some other donor molecule) to an acceptor called $NADP^+$, reducing it to the form of NADPH by adding a pair of electrons and a single proton (hydrogen nucleus). The water or some other donor molecule is split in the process; it is the light reaction which produces waste oxygen.

The light reaction also generates ATP by powering the addition of a phosphate group to ADP, a process called photophosphorylation. ATP is a versatile source of chemical energy used in most biological processes. Note, however, that the light reaction produces no carbohydrates such as sugars. The light reaction occurs in the stacked membranes of the grana in the thylakoid membrane. Oxygen is a byproduct.

Electron transport



The "Z scheme"

The process of synthesizing ATP and NADPH are accomplished via the mechanism of an electron transport chain. This is a series of proteins embedded in a biological membrane that transfers high-energy electrons from one to another, accomplishing various activities along the way as the electron drops in energy level. When sunlight strikes a chlorophyll complex (cluster of chlorophyll), the molecule is excited, and an electron is transferred to a higher energy level of the molecule. The excitation is transferred as 'excitation energy' (also called an 'exciton') from one antenna chlorophyll to another until it is captured by a primary reaction center. It can be transferred from one molecule to another of the same kind of pigment, or from a carotenoid to chlorophyll, but not from chlorophyll to a carotenoid, because excitation of carotenoids carries more energy than that of chlorophyll. Only chlorophyll of the reaction center is capable of transferring an electron to an electron acceptor (an intermediate, e.g., pheophytin in photosystem II and another chlorophyll molecule in Photosystem I). Because the energy in light corresponds to its wavelength, the difference in excitation energy also allows the carotenoids to absorb light at wavelengths that chlorophyll does not absorb well. The P680 (photosystem II) and P700 (photosystem I) refer to reaction center molecules of the two photosystems that receive 'excitation energy' from other chlorophyll and accessory pigment molecules; each number 680 or 700 refers to the preferred wavelength of light absorbed, in the red region of the spectrum, by the chlorophyll pigments at the respective reaction centers. These P680 and P700 molecules are in very low concentrations (1 molecule each per about 600 other chlorophyll molecules).

The rate of this stage of the light-dependent reactions can be monitored with the dye DPIP, or ferricyanide or methyl viologen, which accepts some of the electrons that would normally go to NADPH and changes color as a result.

The chlorophyll's electron can follow either of two different pathways, cyclic or non-cyclic.

Cyclic photophosphorylation

In **cyclic electron flow**, the electron begins in a pigment complex called photosystem I, passes from the primary acceptor to ferredoxin, then to a complex of two cytochromes (similar to those found in mitochondria), and then to plastocyanin before returning to chlorophyll. This transport chain produces a proton-motive force, pumping H^+ ions across the membrane; this produces a concentration gradient which can be used to power ATP synthase during chemiosmosis. This pathway is known as cyclic photophosphorylation, and it produces neither O_2 nor NADPH. In bacterial photosynthesis, a single photosystem is used, and therefore is involved in cyclic photophosporylation.

Noncyclic photophosphorylation

The other pathway, noncyclic photophosphorylation, is a two-stage process involving two different chlorophyll photosystems. First, a photon is absorbed by the chlorophyll core of photosystem II, exciting two electrons which are transferred to the primary acceptor . The deficit of electrons is replenished by taking electrons from a molecule of water, splitting it into O_2 and H^+ (hydrogen ions). The electrons transfer from the primary acceptor to plastoquinone, then to plastocyanin, producing proton-motive force as with cyclic electron flow and driving ATP synthesis.

Since the photosystem II complex replaced its lost electrons from an external source, however, these electrons are not returned to photosystem II as they would in the analogous cyclic pathway. Instead, the still-excited electrons are transferred to a photosystem I complex, which boosts their energy level to a higher level using a second solar photon. The highly excited electrons are transferred to the primary acceptor protein, but this time are passed on to ferredoxin, and then to an enzyme called Ferredoxin- $NADP^+$ reductase, for short FNR, which uses them to drive the reaction (as shown):

$NADP^+ + H^+ + 2e^- \rightarrow NADPH$

This consumes the H^+ ions produced by the splitting of water, leading to a net production of O_2, ATP, and NADPH with the consumption of solar photons and water.

Steps

It is important to note that both photosystems are almost simultaneously excited; thus, both photosystems begin functioning at almost the same time.

- Light strikes photosystem II and the energy is absorbed and passed along until it reaches P680 chlorophyll.
- The excited electron is passed to the primary electron acceptor. Photolysis in the thylakoid takes the electrons from water replaces the P680 electrons that were passed to the primary electron acceptor. (O_2 is released as a waste product)
- The electrons are passed to photosystem I via the electron transport chain (ETC) and in the process used to pump protons across the thylakoid membrane into the lumen.
- The stored energy in the proton gradient is used to produce ATP which is used later in the Calvin-Benson Cycle.
- P700 chlorophyll then uses light to excite the electron to its a second primary acceptor.
- The electron is sent down another ETC and used to reduce $NADP^+$ to NADPH.
- The NADPH is then used later in the Calvin-Benson Cycle.

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Pigment

In biology, **pigment** is any material resulting in color in plant or animal cells which is the result of selective absorption. Some biological material has so-called structural color, which is the result of selective reflection or iridescence, usually done with multilayer structures. Unlike structural color, pigment color is the same for all viewing angles. Many biological structures, such as skin, eyes, fur and hair contain pigments (such as melanin) in specialised cells called chromatophores. Butterfly wings typically contain structural color, although many of them contain pigment as well. Creatures that have deficient pigmentation are called albinos.

In the coloring of paint, ink, plastic, fabric and other material, a **pigment** is a dry colorant, usually an insoluble powder. There are both natural and synthetic pigments, both organic and inorganic ones. Pigments work by selectively absorbing some parts of the visible spectrum whilst reflecting others.

A distinction is usually made between a pigment, which is insoluble, and a dye, which is either a liquid, or is soluble. There is a well-defined dividing line between pigments and dyes: a pigment is not soluble in the vehicle (or matrix) while a dye *is*. From this follows that a certain colorant can be both a pigment and a dye depending on in which vehicle it is used. In some cases, a pigment will be made by precipitating a soluble dye with a metallic salt. The resulting pigment is called a "*lake*". Fugitive pigments are non-permanent pigments.

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Bacteriorhodopsin

Bacteriorhodopsin is the photosynthetic pigment used by archaea, most notably halobacteria. It acts as a proton pump, i.e. it captures light energy and uses it to move protons across the membrane out of the cell. The resulting proton gradient is subsequently converted into chemical energy.

Bacteriorhodopsin is an integral membrane protein usually found in two-dimensional crystalline patches known as "purple membrane", which can occupy up to nearly 50% of the surface area of the archaeal cell. The repeating element of the hexagonal lattice is composed of three identical protein chains, each rotated by 120 degrees relative to the others. Each chain has seven transmembrane alpha helices and contains one molecule of retinal buried deep within. It is the retinal molecule that changes its conformation when absorbing a photon, resulting in a conformational change of the surrounding protein and the proton pumping action.

The bacteriorhodopsin molecule is purple and is most efficient at absorbing green light (wavelength 500-650 nm, with the absorption maximum at 568 nm).

The three-dimensional tertiary structure of bacteriorhodopsin resembles that of vertebrate rhodopsins, the pigments that sense light in the retina. Rhodopsins also contain retinal, however the functions of rhodopsin and bacteriorhodopsin are different and there is no homology of their amino acid sequences. Both rhodopsin and bacteriorhodopsin belong to the 7TM receptor family of proteins, but rhodopsin is a G protein coupled receptor and bacteriorhodopsin is not. In the first use of electron crystallography to obtain an atomic-level protein structure, the structure of bacteriorhodopsin was resolved in 1990. It was then used as a template to build models of other G protein-coupled receptors before crystallographic structures were also available for these proteins.

Many molecules have homology to bacteriorhodopsin, including some directly light-activated channels like channelrhodopsin.

All other photosynthetic systems in bacteria, algae and plants use chlorophylls or bacteriochlorophylls rather than bacteriorhodopsin. These also produce a proton gradient, but in a quite different and more indirect way involving an electron transfer chain consisting of several other proteins. Furthermore, chlorophylls are aided in capturing light energy by other pigments known as "antennas"; these are not present in bacteriorhodopsin based systems. Lastly, chlorophyll-based photosynthesis is coupled to carbon fixation (the incorporation of carbon dioxide into larger organic molecules); this is not true for bacteriorhodopsin-based system. It is thus likely that photosynthesis independently evolved at least twice, once in bacteria and once in archaea.

Bacteriorhodopsin

Carotenoid

Properties | Physiological effects | Aroma chemicals

Carotenoids are organic pigments that are naturally occurring in plants and some other photosynthetic organisms like algae, some types of fungus and some bacteria. There are over 600 known carotenoids; they are split into two classes, xanthophylls and carotenes.

Properties

Carotenoids are characterized by a large (35-40 carbon atoms) polyene chain, sometimes terminated by rings. Carotenoids where some of the double bonds have been oxidized such as lutein and zeaxanthin, are known as **xanthophylls**; the un-oxidized carotenoids such as alpha-carotene, beta-carotene and lycopene are known as **carotenes**. Probably the most well-known carotenoid is the one that gives this group its name, carotene, found in carrots and responsible for their bright orange colour.

Their color, ranging from pale yellow through bright orange to deep red, is directly linked to their structure. The double carbon-carbon bonds interact with each other in a process called conjugation. As the number of double bonds increases, the wavelength of the absorbed light increases, giving the compound an increasingly red appearance.

Physiological effects

In photosynthetic organisms, carotenoids play a vital role in the photosynthetic reaction centre. They either participate in the energy-transfer process, or protect the reaction center from auto-oxidation. In non-photosynthetic organisms, carotenoids have been linked to oxidation-preventing mechanisms.

Carotenoids have many physiological functions. Given their structure (above) carotenoids are efficient free-radical scavengers, and they enhance the vertebrate immune system. Consequently, epidemiological studies have shown that people with high beta-carotene intake and high plasma levels of beta-carotene have a significantly reduced risk of lung cancer. But studies of supplementation with large doses of beta-carotene in smokers have shown an increase in cancer risk (possibly because excessive beta-carotene results in breakdown products that reduce plasma Vitamin A and worsen the lung cell proliferation induced by smoke). Similar results have been found in other animals.

Animals are incapable of synthesizing carotenoids, and must obtain them through their diet, yet they are common and often in ornamental features. For example, the pink colour of flamingos and salmon, and the red colouring of lobsters are caused by carotenoids. Carotenoids are used in ornamental traits because, given their physioloigcal and chemical properties, they can be used as honest indicators of individual health, and hence they can be used by animals when selecting potential mates.

Aroma chemicals

Products of carotenoid degradation such as ionones, damascones, and damascenones are also important fragrance chemicals that are used extensively in the perfumes and fragrance industry. Both beta-Damascenone and beta-Ionone although low in concentration in rose distillates are the key odor contributing compounds to flowers. In fact, the sweet floral smells present in black tea, aged tobacco, grape, and many fruits are due to the aromatics compounds resulting from carotenoid breakdown.

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Chlorophyll

Chlorophyll and photosynthesis | Special pair | Chemical structure | Evidence for chlorophyll

Chlorophyll is a green photosynthetic pigment found in plants, algae, and cyanobacteria. Its name is derived from ancient Greek: *chloros* = green and *phyllon* = leaf. Chlorophyll absorbs mostly in the blue and to a lesser extent red portions of the electromagnetic spectrum, hence its intense green color.

Chlorophyll and photosynthesis

In plant photosynthesis, incoming light is absorbed by chlorophyll and other accessory pigments in the antenna complexes of photosystem I and photosystem II. The antenna pigments are predominantly **chlorophyll *a***, **chlorophyll *b*** and carotenoids; their absorption spectra are non-overlapping, this serves to broaden the specific bandwidths of light these individual compounds absorb during the process of photosynthesis. The carotenoids also play a role as antioxidants, and serve to reduce photo-oxidative damage to chlorophyll molecules.

Each antenna complex has between 250 and 400 pigment molecules, and the energy they absorb is shuttled by resonance energy transfer to a specialized chlorophyll *a* at the reaction center of each photosystem. When either of the two chorophyll *a* molecules at the reaction center absorb energy, an electron is excited and transferred to an electron-acceptor molecule, leaving an electron hole in the donor chlorophyll. In a poorly-understood reaction, electrons from water molecules participate in an oxidation reaction, where the hole from the donor chlorophyll is filled (recombined with another electron), and diatomic oxygen is produced. Resulting chemical energy originating from the initial excited electron is eventually captured in the form of ATP and NADPH, and is then ultimately used to convert carbon dioxide (CO_2) to carbohydrates. This CO_2 fixation process results in the conversion (or an integrated external quantum efficiency) of 3% to 6% of the total incident solar radiation, with a theoretical maximum efficiency of 11%.

Special pair

The photosystem reaction centers consist of a "special pair" of chlorophyll *a* molecules that are characterised by their specific absorption maximum. The special pair in photosystem I are designated **P700**, and those from photosystem II are designated **P680**. The P is short for pigment, and the number is the specific absorption peak in nanometers for the chlorophyll molecules in each reaction center.

Chlorophyll *a* is common to all eukaryotic photosynthetic organisms, and, due to its central role in the reaction center, is essential for photosynthesis. The accessory pigments such as chlorophyll *b* and carotenoids are not essential. Some algae, such as brown algae and diatoms, use **chlorophyll *c*** as a substitute for chlorophyll *b*. Historically, red algae have been assumed to have **chlorophyll *d***, although

it could not be isolated from all species and even different collections of the same species. This puzzle has recently been resolved, since the chlorophyll *d* is actually from an epiphytic cyanobacterium (*Acaryochloris marina*) that lives on the red algae. These cyanobacteria have a ratio of chlorophyll *d*: chlorophyll *a* of approximately 30:1, and represent a rare example of a photosystem with chlorophyll *d* at the reaction center of the photosystem. All other known eukaryotes and cyanobacteria use chlorophyll *a*. There are likely to be many chlorophyll-d containing organisms awaiting discovery, for example a free living form was recently found in the Salton Sea (a salt lake in USA).

Other chemical variations of chlorophyll are found in photosynthetic bacteria, other than cyanobacteria. Purple bacteria use **bacteriochlorophyll**, which absorbs infrared light between 800nm - 1000nm, and the green sulphur bacteria **chlorobium chlorophyll**. All known bacteria with bacteriochlorophyll have a form of photosynthesis which does not involve evolution of oxygen and so are called anoxyphotobacteria. There is a very large number of different bacteriochlorophylls in different anoxyphotobacteria including one species which contains Zinc, rather than the usual Magnesium as the co-ordinated metal.

Chemical structure

Chlorophyll is a chlorin pigment, which is structurally similar to porphyrin pigments such as heme. At the center of the porphyrin ring is a magnesium ion. This has various side chains, usually including a long phytyl chain. There are a few different forms that occur naturally:

Chlorophyll *α*:
Molecular formula: $C_{55}H_{72}O_5N_4Mg$

C3 group: -$CH{=}CH_2$

C7 group: -CH_3

C8 group: -CH_2CH_3

C17 group: -CH_2CH_2COO-*Phytyl*

C17-C18 bond: *Single*
Occurrence: *Universal*

Chlorophyll *b*:
Molecular formula: $C_{55}H_{70}O_6N_4Mg$

C3 group: -$CH{=}CH_2$

C7 group: -*CHO*
C8 group: -CH_2CH_3

C17 group: -CH_2CH_2COO-*Phytyl*

C17-C18 bond: *Single*
Occurrence: *Mostly in land plants*

Chlorophyll *c1:*
Molecular formula: $C_{35}H_{30}O_5N_4Mg$

C3 group: -$CH=CH_2$

C7 group: -CH_3

C8 group: -CH_2CH_3

C17 group: -$CH=CHCOOH$
C17-C18 bond: *Double*
Occurrence: *Various algae*

Chlorophyll *c2*
Molecular formula: $C_{35}H_{28}O_5N_4Mg$

C3 group: -$CH=CH_2$

C7 group: -CH_3

C8 group: -$CH=CH_2$

C17 group: -$CH=CHCOOH$
C17-C18 bond: *Double*
Occurrence: *Various algae*

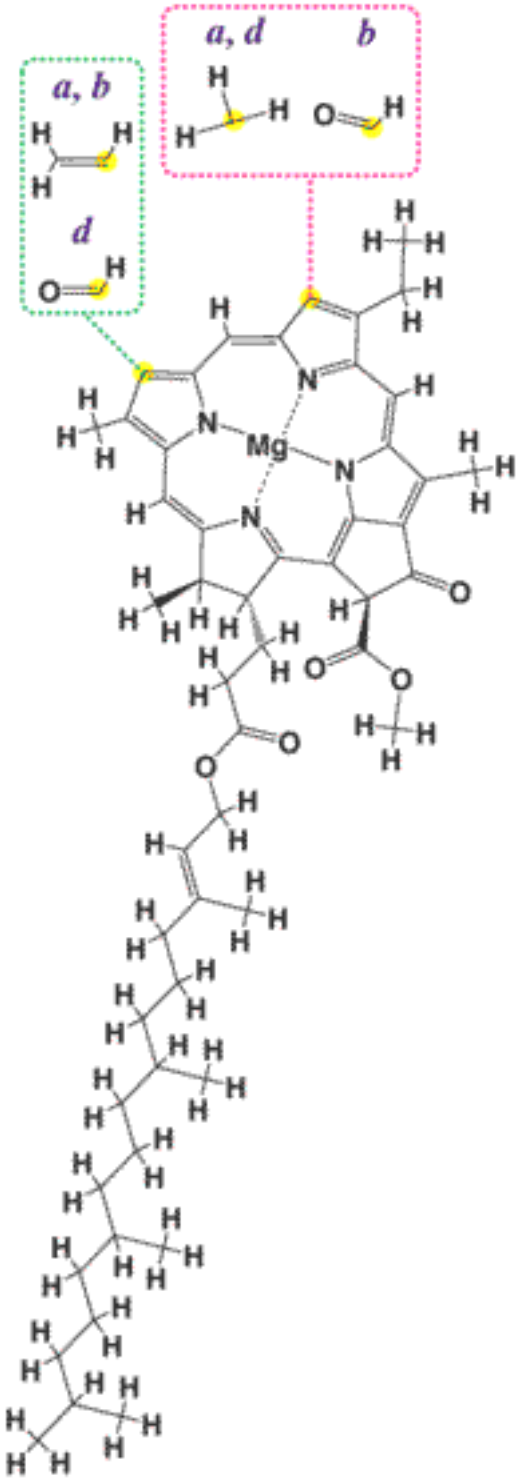
Chlorophyll *d*
Molecular formula: $C_{54}H_{70}O_6N_4Mg$

C3 group: -CHO
C7 group: - CH_3

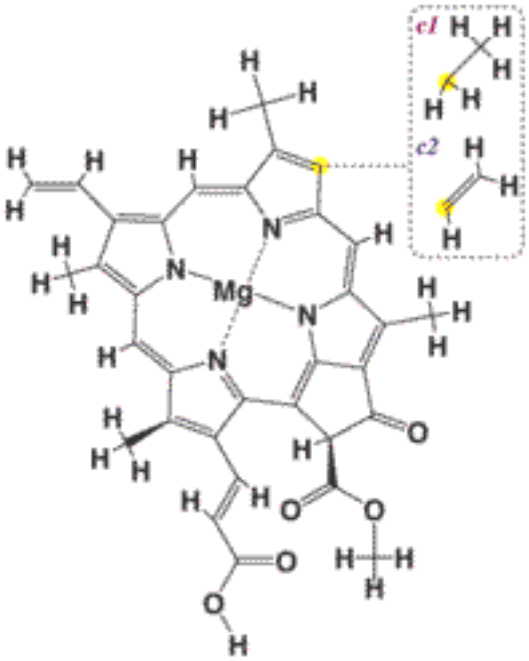
C8 group: -CH_2CH_3

C17 group: -CH_2CH_2COO-*Phytyl*

C17-C18 bond: *Single*
Occurrence: cyanobacteria

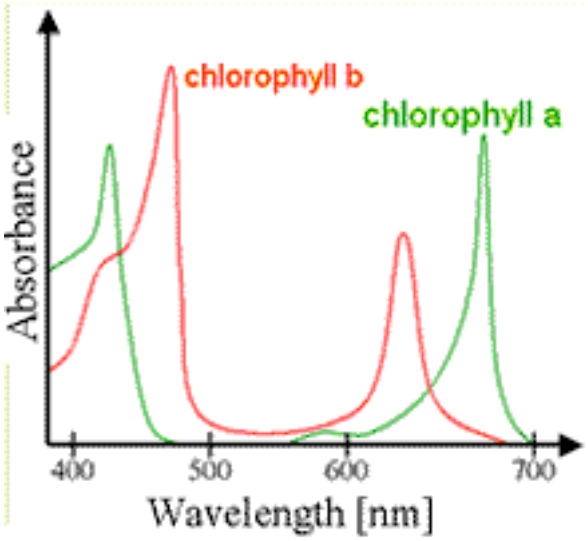


Common structure of chlorophyll *α*, *b* and *d*



Common structure of chlorophyll *c1*, and *c2*

Evidence for chlorophyll



Absorbance spectra of by chlorophyll *α* (green) and *b* (red)

Chlorophyll can be shown to be vital for photosynthesis by destarching a leaf from a variegated plant and exposing it to light for several hours. (Variegated leaves have green areas that contain chlorophyll and white areas that have none.) When tested with iodine solution, a color change revealing the presence of starch occurs only in regions of the leaf that were green and therefore contained chlorophyll. This shows that photosynthesis does not occur in areas where chlorophyll is absent, and constitutes evidence that the presence of chlorophyll is a requirement for photosynthesis.

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Cytochrome

Cytochromes are generally membrane-bound proteins that contain heme groups and carry out electron transport or catalyse reductive/oxidative reactions. They are found in the mitochondrial inner membrane and endoplasmic reticulum of eukaryotes, in the chloroplasts of plants, in photosynthetic microorganisms, and in bacteria.

The heme group is a highly conjugated ring system (which means its electrons are very mobile) surrounding a metal ion, which readily interconverts between the oxidation states. For many cytochromes the metal ion present is that of *iron*, which interconverts between Fe^{2+} (reduced) and Fe^{3+} (oxidized) states (electron-transfer processes) or between Fe^{2+} (reduced) and Fe^{5+} (formal, oxidized) states (oxidative processes). Cytochromes are thus capable of performing oxidation and reduction. Because the cytochromes (as well as other complexes) are held within membranes in an organized way, the redox reactions are carried out in the proper sequence for maximum efficiency.

In the process of oxidative phosphorylation, which is the principal energy-generating process undertaken by organisms which need oxygen to survive, other membrane-bound and soluble complexes and cofactors are involved in the chain of redox reactions, with the additional net effect that protons (H^+) are transported across the mitochondrial inner membrane. The resulting transmembrane proton gradient (protonmotive force) is used to generate ATP, which is the universal chemical energy currency of life. ATP is consumed to drive cellular processes that require energy (such as rotation of flagella, transport of molecules across the membrane, and synthesis of macromolecules).

Several kinds of cytochrome exist and can be distinguished by spectroscopy, exact structure of the heme group, inhibitor sensitivity, and reduction potential:

- Cytochrome *a*
- Cytochrome a_3
- Cytochrome *b*
- Cytochrome *c*
- Cytochrome c_1
- Cytochrome *f*

See the articles on mitochondria and chloroplasts for more information on electron transport and related metabolic pathways. See cytochrome P450 oxidase for more on steroidogenesis and detoxification enzymes.

Cytochrome

Phycobilin

Phycobilins are photosynthetic pigments found in cyanobacteria and in the chloroplasts of red algae, glaucophytes and some cryptomonads (though not in green algae and higher plants). They are unique among the photosynthetic pigments in that they are bonded to certain water-soluble proteins, known as **phycobiliproteins**; phycobilins serve as chromophores (the light-capturing part) of the phycobiliproteins. Phycobiliproteins capture light energy which is then passed on to chlorophylls during photosynthesis.

The phycobilins are especially efficient at absorbing red, orange, yellow and green light, wavelengths which are not well absorbed by chlorophyll *a*. Organisms growing in shallow waters tend to contain phycobilins that can capture yellow/red light, while those at greater depth often contain more of the phycobilins that can capture green light, which is more abundant there.

There are several types of phycobilins: phycourobilin, phycoerythrobilin, cryptoviolin and phycocyanobilin. They can be found in different combinations attached to phycobiliproteins to confer specific spectroscopic properties.

Chemically, phycobilins consist of an open chain of four pyrrole rings (*tetrapyrrole*) and are structurally similar to the bile pigment bilirubin. (Bilirubin's structure is also affected by light, a fact used for the phototherapy of jaundiced newborns.) Phycobilins are also closely related to the chromophores of the light-detecting plant pigment phytochrome which also consist of an open chain of four pyrroles. Chlorophylls are composed of four pyrroles as well, but there they are arranged in a ring and contain a metal atom in the center.

The phycobilins fluoresce at a particular wavelength, and are therefore often used in research as chemical tags, e.g. by binding phycobiliproteins to antibodies in a technique known as immunofluorescence.

The name *phycobilin* comes from the Greek *phyco-* for "algae", and *bilin* referring to bile.

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Xanthophyll

Xanthophylls (originally **phylloxanthins**) are yellow pigments of oxycarotenoid type, from the carotenoid group. They are found in the leaves of most plants and are synthesized within the plastids. They are involved in photosynthesis along with green chlorophyll, which typically covers up the yellow except in autumn, when the chlorophyll decomposes.

In plants, xanthophylls are considered accessory pigments, along with anthocyanins, carotenes, and sometimes phycobilins.

Animals cannot produce xanthophylls, and thus xanthophylls found in animals (e.g. in the eye) come from their food intake. The yellow color of chicken egg yolks also comes from ingested xanthophylls.

Xanthophylls are oxidized derivatives of carotenes. They contain hydroxyl groups and are more polar.

The group of xanthophylls is composed of lutein, zeaxanthin, and α- and β-cryptoxanthin.

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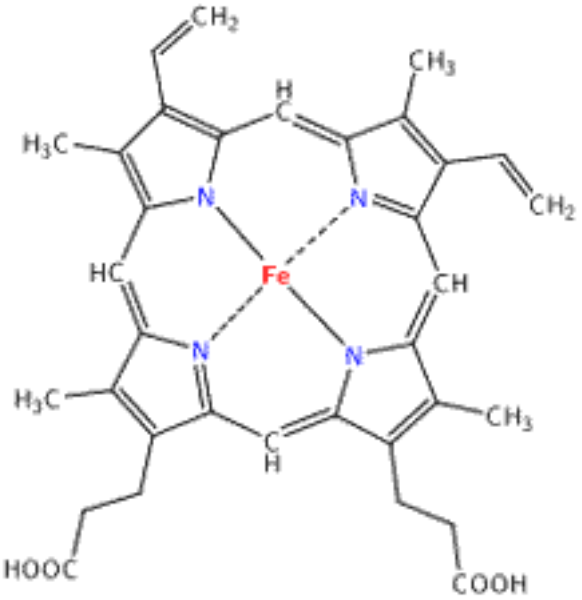
Hemoglobin

Hemoglobin or **haemoglobin** (frequently abbreviated as **Hb**) is the iron-containing oxygen-transport metalloprotein in the red cells of the blood in mammals and other animals. Hemoglobin transports oxygen from the lungs to the rest of the body, such as to the muscles, where it releases the oxygen load.

The name *hemoglobin* is the concatenation of *heme* and *globin*, reflecting the fact that each subunit of hemoglobin is a globular protein with an embedded heme (or haem) group; each heme group contains an iron atom, and this is responsible for the binding of oxygen. The most common types of hemoglobin contains four such subunits, each with one heme group.

Mutations in the gene for the hemoglobin protein result in a group of hereditary diseases termed the *hemoglobinopathies*, the most common members of which are sickle-cell disease and thalassemia.

Structure



Heme group

The Hemoglobin molecule is an assembly of four globular protein subunits. Each subunit is composed of a protein chain tightly associated with a non-protein heme group.

Each individual protein chain arranges in a set of alpha-helix structural segments connected together in a "myoglobin fold" arrangement, so called because this arrangement is the same folding motif used in the heme/globin proteins. This folding pattern contains a pocket which is suitable to strongly bind the heme

group.

A heme group consists of an iron atom held in a heterocyclic ring, known as a *porphyrin*. This iron atom is the site of oxygen binding. The iron atom is bonded equally to all four nitrogens in the center of the ring, which lie in one plane. Two additional bonds perpendicular to the plane on each side can be formed with the iron to form the fifth and sixth positions, one connected strongly to the protein, the other available for binding of oxygen. The iron atom can either be in the Fe^{2+} or Fe^{3+} state, but ferrihaemoglobin (Methaemoglobin) (Fe^{3+}) cannot bind oxygen.

In adult humans, the most common hemoglobin type is a tetramer (which contains 4 subunit proteins) called **hemoglobin A**, consisting of two α and two β subunits non-covalently bound, each made of 141 and 146 amino acid residues, respectively. This is denoted as $\alpha_2\beta_2$. The subunits are structurally similar and about the same size. Each subunit has a molecular weight of about 16,000 daltons, for a total molecular weight of the tetramer of about 64,000 daltons. Haemoglobin A is the most intensively studied of the haemoglobin molecules.

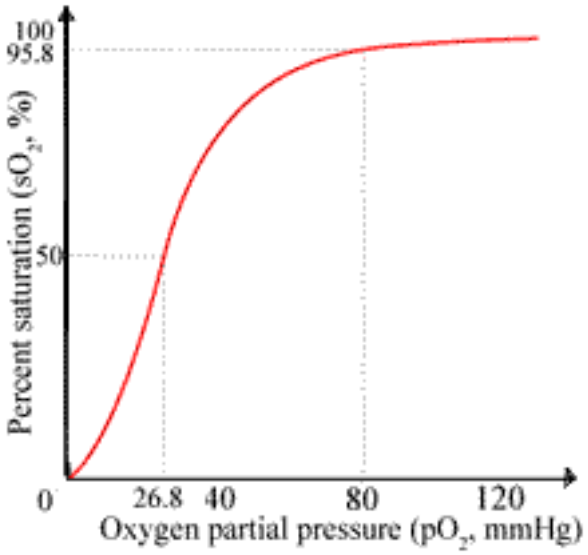
The four polypeptide chains are bound to each other by salt bridges, hydrogen bonds and hydrophobic interaction. There are two kinds of contacts between the α and β chains: $\alpha_1\beta_1$ and $\alpha_1\beta_2$.

Binding of ligands

In the tetrameric form of normal adult hemoglobin, the binding of oxygen is a cooperative process. The binding affinity of hemoglobin for oxygen is increased by the oxygen saturation of the molecule. As a consequence, the oxygen binding curve of hemoglobin is sigmoidal, or *S*-shaped, as opposed to the normal hyperbolic curve associated with noncooperative binding. This positive cooperative binding is achieved through steric conformational changes of the hemoglobin protein complex: When one subunit protein in hemoglobin becomes oxygenated, it induces a conformational or structural change in the whole complex causing the other subunits to gain an increased affinity for oxygen.

Hemoglobin's oxygen-binding capacity is decreased in the presence of carbon monoxide because both gases compete for the same binding sites on hemoglobin, carbon monoxide binding preferentially in place of oxygen. Carbon *di*oxide occupies a different binding site on the hemoglobin. Through the enzyme carbonic anhydrase, carbon dioxide reacts with water to give carbonic acid, which decomposes into bicarbonate and protons:

$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$



The sigmoidal shape of hemoglobin's oxygen-dissociation curve results from cooperative binding of oxygen to hemoglobin.

Hence blood with high carbon dioxide levels is also lower in pH (more acidic). Hemoglobin can bind protons and carbon dioxide which causes a conformational change in the protein and facilitates the release of oxygen. Protons bind at various places along the protein, and carbon dioxide binds at the α-amino group forming carbamate. Conversely, when the carbon dioxide levels in the blood decrease (i.e., in the lung capillaries), carbon dioxide and protons are released from hemoglobin, increasing the oxygen affinity of the protein. This control of hemoglobin's affinity for oxygen by the binding and release of carbon dioxide and acid, is known as the Bohr effect.

The binding of oxygen is affected by molecules such as carbon monoxide (CO) (for example from tobacco smoking, cars and furnaces). CO competes with oxygen at the heme binding site. Hemoglobin binding affinity for CO is 200 times greater than its affinity for oxygen, meaning that small amounts of CO dramatically reduces hemoglobin's ability to transport oxygen. When hemoglobin combines with CO, it forms a very bright red compound called carboxyhemoglobin. When inspired air contains CO levels as low as 0.02%, headache and nausea occur; if the CO concentration is increased to 0.1%, unconsciousness will follow. In heavy smokers, up to 20% of the oxygen-active sites can be blocked by CO.

In similar fashion, hemoglobin also has competitive binding affinity for cyanide (CN^-), sulfur monoxide (SO), nitrogen dioxide (NO_2), and sulfide (S^{2-}), including hydrogen sulfide (H_2S). All of these bind to iron in heme without changing its oxidation state, but they nevertheless inhibit oxygen-binding, causing grave toxicity.

The iron atom in the heme group must be in the Fe^{2+} oxidation state to support oxygen and other gases' binding and transport. Oxidation to Fe^{3+} state converts hemoglobin into hem*i*globin or methemoglobin (pronounced "MET-hemoglobin"), which cannot bind oxygen. Hemoglobin in normal red blood cells is protected by a reduction system to keep this from happening. Nitrogen dioxide and nitrous oxide are

capable of converting a small fraction of hemoglobin to methemoglobin, however this is not usually of medical importance (nitrogen dioxide is poisonous by other mechanisms, and nitrous oxide is routinely used in surgical anesthesia in most people without undue methemoglobin buildup).

In people acclimated to high altitudes, the concentration of 2,3-bisphosphoglycerate (2,3-BPG) in the blood is increased, which allows these individuals to deliver a larger amount of oxygen to tissues under conditions of lower oxygen tension. This phenomenon, where molecule Y affects the binding of molecule X to a transport molecule Z, is called a *heterotropic* allosteric effect.

A variant hemoglobin, called fetal hemoglobin (HbF, $\alpha_2\beta_2$), is found in the developing fetus, and binds oxygen with greater affinity than adult hemoglobin. This means that the oxygen binding curve for fetal hemoglobin is left-shifted (i.e., a higher percentage of hemoglobin has oxygen bound to it at lower oxygen tension), in comparison to that of adult hemoglobin. As a result, fetal blood in the placenta is able to take oxygen from maternal blood.

Degradation of hemoglobin

When red cells reach the end of their life due to aging or defects, they are broken down, and the hemoglobin molecule broken up and the iron recycled. When the porphyrin ring is broken up, the fragments are normally secreted in the bile by the liver. The major final product of heme degradation is bilirubin. Increased levels of this chemical are detected in the blood if red cells are being destroyed more rapidly than usual. Improperly degraded hemoglobin protein or hemoglobin that has been released from the blood cells can clog small blood vessels, especially the delicate blood filtering vessels of the kidneys, causing kidney damage.

Role in disease

Decreased levels of hemoglobin, with or without an absolute decrease of red blood cells, leads to symptoms of anemia. Anemia has many different causes, although iron deficiency and its resultant iron deficiency anemia are the most common causes in the Western world. As absence of iron decreases heme synthesis, red blood cells in iron deficiency anemia are *hypochromic* (lacking the red hemoglobin pigment) and *microcytic* (smaller than normal). Other anemias are rarer. In hemolysis (accelerated breakdown of red blood cells), associated jaundice is caused by the hemoglobin metabolite bilirubin, and the circulating hemoglobin can cause renal failure.

Mutations in the globin chain are associated with the hemoglobinopathies, such as sickle-cell disease and thalassemia.

There is a group of genetic disorders, known as the *porphyrias* that are characterized by errors in metabolic pathways of heme synthesis. King George III of the United Kingdom was probably the most famous porphyria sufferer.

To a small extent, hemoglobin A slowly combines with glucose at a certain location in the molecule. The resulting molecule is often referred to as **Hb A_{1c}**. As the concentration of glucose in the blood increases, the percentage of Hb A that turns into Hb A_{1c} increases. In diabetics whose glucose usually runs high, the percent Hb A_{1c} also runs high. Because of the slow rate of Hb A combination with glucose, the Hb A_{1c} percentage is representative of glucose level in the blood averaged over a longer time (the half-life of red blood cells, which is typically 50-55 days).

Diagnostic use

Hemoglobin levels are amongst the most commonly performed blood tests, usually as part of a full blood count or complete blood count. Results are reported in g/L, g/dL or mol/L. For conversion, 1 g/dL is 0.621 mmol/L. If the hemoglobin level falls below a set point this is called anemia. Anemias are classified by the size of the red blood cells, which are the cells which contain hemoglobin. They can be classified as microcytic (small sized red blood cells), normocytic (normal sized red blood cells) and macrocytic (large sized red blood cells).

Glucose levels in blood can vary widely each hour, so one or only a few samples from a patient analyzed for glucose may not be representative of glucose control in the long run. For this reason a blood sample may be analyzed for Hb A_{1c} level, which is more representative of glucose control averaged over a longer time period (determined by the half-life of the individual's red blood cells, which is typically 50-55 days). People whose Hb A_{1c} runs 6.0% or less show good longer-term glucose control. Hb A_{1c} values which are more than 7.0% are elevated. This test is especially useful for diabetics.

This Hb A_{1c} level is only useful in individuals who have red blood cells (RBCs) with normal survivals (i.e., normal half-life). In individuals with abnormal RBCs, whether due to abnormal hemoglobin molecules (such as Hemoglobin S in Sickle Cell Anemia) or RBC membrane defects - or other problems, the RBC half-life is frequently shortened. In these individuals an alternative test called "fructosamine level" can be used. It measures the degree of glycation (glucose binding) to albumin, the most common blood protein, and reflects average blood glucose levels over the previous 18-21 days, which is the half-life of albumin molecules in the circulation.

Other biological oxygen-binding proteins

Hemoglobin is by no means unique; there are a variety of oxygen transport and binding proteins throughout the animal (and plant) kingdom. Other organisms including bacteria, protozoans and fungi all have hemoglobin-like proteins whose known and predicted roles include the reversible binding of gaseous ligands.

Myoglobin: Found in the muscle tissue of many vertebrates including humans (gives muscle tissue a

distinct red or dark gray color). Is very similar to hemoglobin in structure and sequence, but is not arranged in tetramers, it is a monomer and lacks cooperative binding and is used to store oxygen rather than transport it.

Hemocyanin: Second most common oxygen transporting protein found in nature. Found in the blood of many arthropods and molluscs. Uses copper prosthetic group instead of iron heme groups and is blue in color when oxygenated.

Hemerythrin: Some marine invertebrates and a few species of annelid use this iron containing non-heme protein to carry oxygen in their blood. Appears pink/violet when oxygenated, clear when not.

Chlorocruorin: Found in many annelids, and is very similar to Erythrocruorin, but the heme group is significantly different in structure. Appears green when deoxygenated and red when oxygenated.

Vanabins: Also known as **Vanadium Chromagen** are found in the blood of Sea squirt and are hypothesised to use the rare metal Vanadium as its oxygen binding prosthetic group, but this hypothesis is unconfirmed.

Erythrocruorin: Found in many annelids, including earthworms. Giant free-floating blood protein, contains many dozens even hundreds of Iron heme containing protein subunits bound together into a single protein complex with a molecular masses greater than 3.5 million daltons.

Pinnaglobin: Only seen in the mollusk *Pinna squamosa*. Brown manganese-based porphyrin protein.

Leghemoglobin: In leguminous plants, such as alfalfa or soybeans, the nitrogen fixing bacteria in the roots are protected from oxygen by this iron heme containing, oxygen binding protein.

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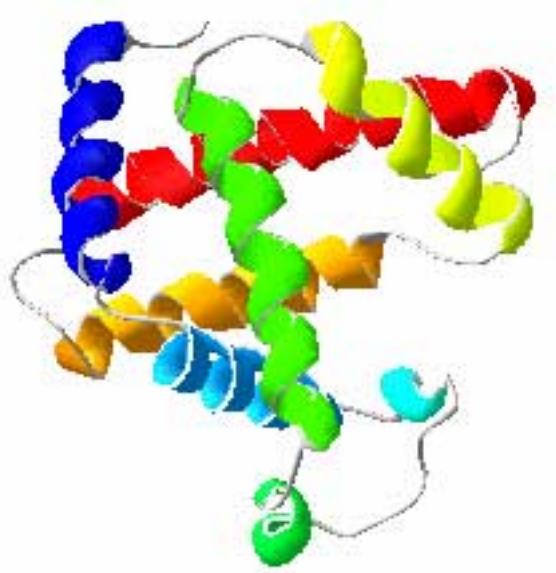
Myoglobin

Myoglobin is a single-chain protein of 153 amino acids, containing a heme (iron-containing porphyrin) group in the center. With a molecular weight of 16,700 Daltons, it is the primary oxygen-carrying pigment of muscle tissues. Unlike the blood-borne hemoglobin, to which it is structurally related, this protein does not exhibit cooperative binding of oxygen. Instead, the binding of oxygen by myoglobin is unaffected by the oxygen pressure in the surrounding tissue. In 1957, John Kendrew and associates successfully determined the structure of myoglobin by high-resolution X-ray crystallography.



3D structure of the Myoglobin protein: alpha helices are shown in colour, and random coil in white, there are no beta sheets in shown. This protein was the first to have its structure solved by X-ray crystallography by Max Perutz and Sir John Cowdery Kendrew in 1958, which led to them receiving a Nobel Prize in Chemistry in 1962.

Role in disease

Myoglobin has been implicated as a cause of acute renal failure following damage to muscle tissue (e.g. rhabdomyolysis, severe crush trauma, malignant hyperthermia, *status epilepticus* and neuroleptic malignant syndrome), due to its toxicity to renal tubular epithelium.

Myoglobin is a sensitive marker for muscle injury, making it a potential marker for myocardial infarction in patients with chest pain. Its specificity and the cost of the analysis has prevented its widespread use.

During muscle death due to infarction, myoglobin is released, which is toxic to the kidneys. If it is misdiagnosed, it can cause much worse conditions, such as cardiac arrest.

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Signal transduction

In biology, signal transduction is any process by which a cell converts one kind of signal or stimulus into another. Processes referred to as signal transduction often involve a sequence of biochemical reactions inside the cell, which are carried out by enzymes and linked through second messengers. Such processes take place in as little time as a millisecond or as long as a few seconds. Slower processes are rarely referred to as signal transduction.

In many transduction processes, an increasing number of enzymes and other molecules become engaged in the events that proceed from the initial stimulus. In such cases the chain of steps is referred to as a "signaling cascade" or a "second messenger pathway" and often results in a small stimulus eliciting a large response.

In bacteria and other one-cell organisms, the variety of signal transduction processes of which the cell is capable influences how many ways it can react and respond to its environment. In a less direct way the same is true of animals and plants. Sensing in all forms of life depends, at the cellular level, on signal transduction.

Stimuli

The environment of a cell may impinge on it in many ways: different kinds of molecules may buffet its surface, its body may be heated or cooled, it may be struck by light of various wavelengths, stretched, sheared or electrified (the nerves and muscles, for example). Signal transduction mediates how cells respond to such stimuli.

Most stimuli impinge from the outside and interact with the cell membrane. Several "signaling molecules", such as the neurotransmitters, allow nerve cells to communicate across synapses, bind to receptor proteins in the membrane and open their ion channels.

Responses

Responses triggered by signal transduction include the activation of a gene, the production of metabolic energy and cell locomotion, for example through remodelling of the cell skeleton.

Gene activation leads to further effects, since genes are expressed as proteins, many of which are enzymes, transcription factors or other regulators of metabolic activity. Because transcription factors can activate still more genes in turn, an initial stimulus can trigger via signal transduction the expression of entire suite of genes and a panoply of physiolgical events. Such mass activations are often referred to as "genetic programs," one example being the sequence of events that take place when an egg is fertilized by a sperm.

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Transmembrane receptors

Hormone recognition by transmembrane receptors | Signal transduction of transmembrane receptors by structural changes | Signal transduction of transmembrane receptors that are ion channels |

Transmembrane receptors are proteins that span the thickness of the plasma membrane of the cell, with one end of the receptor outside (extracellular domain) and one inside (intracellular domain) the cell. When the extracellular domain recognizes the hormone, the whole receptor undergoes a structural shift that affects the intracellular domain, leading to further action. In this case the hormone itself does not pass through the plasma membrane into the cell.

Hormone recognition by transmembrane receptors

The binding of the hormone by the hormone receptor uses the same non-covalent mechanisms, such as hydrogen bonds, electrostatic forces, hydrophobic and Van der Waals forces. The binding affinity of a hormone to its cognate hormone receptor is expressed as a K_d:

$$K_d = \frac{[H] * [R]}{[HR]}$$

[R] is concentration of receptor, [H] is concentration of free hormone, [HR] is concentration of receptor-bound hormone.

The important value for the strength of the signal relayed by the receptor is the concentration of the hormone-receptor complex, which is defined by the affinity of the hormone for the receptor, the concentration of the hormone and, of course, the concentration of the receptor. The concentration of the circulating hormone is the key value for the strength of the signal, since the other two values are constant. For fast reaction, the hormone-producing cells can store prehormones, and quickly modify and release them if necessary. Also, the recipient cell can modify the sensitivity of the receptor, for example by phosphorylation; also, the variation of the number of receptors can vary the total signal strength in the recipient cell.

Signal transduction of transmembrane receptors by structural changes

Signal transduction across the plasma membrane is possible only by many components working together. First, the receptor has to recognize the hormone with the extracellular domain, then activate other proteins within the cytosol with its cytoplasmic domain, which the protein does through a shift in conformation. The activated effector proteins usually stay close to the membrane, or are anchored within the membrane by lipid anchors, a posttranslational modification. Many membrane-associated proteins

can be activated in turn, or come together to form a multi-protein complex that finally sends a signal via a soluble molecule into the cell.

Signal transduction of transmembrane receptors that are ion channels

A ligand-activated ion channel will recognize its ligand, and then undergo a structural change that opens a gap (channel) in the plasma membrane through which ions can pass. These ions will then relay the signal. An example for this mechanism is found in the receiving cell of a synapse.

Signal transduction of transmembrane receptors on change of transmembrane potential

An ion channel can also open when the receptor is activated by a change in cell potential, that is, the difference of the electrical charge on both sides of the membrane. If such a change occurs, the ion channel of the receptor will open and let ions pass through. In neurons, this mechanism underlies the action potential impulses that travel along nerves.

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Types of signals

Intracellular | Intercellular | Hormones

Extracellular

Signal transduction usually involves the binding of extracellular signaling molecules to receptors that face outwards from the membrane and trigger events inside. This takes place via a change in the shape or conformation of the receptor which occurs when the signal molecule "docks" or binds. Receptors typically respond only to the specific molecule or ligand for which they have affinity, and molecules that are even only slightly different tend to have no effect or else to act as inhibitors.

Most extracellular chemical signals are hydrophilic and are unable to penetrate the lipid membrane that surrounds cells. A common kind of extracellular signal is nutrient. In complex organisms this includes the ligands responsible for sensations of smell and taste. Steroids represent an example of extracellular signals that can cross the membrane to permeate cells, which they are able to do because they are lipophilic.

Intracellular

Often, but not always, the intracellular events triggered by the external signal are considered distinct from the event of "transduction" itself, which in the strictest sense refers only to the step that converts the extracellular signal to an intracellular one.

Intracellular signalling molecules in eukaryotic cells include heterotrimeric G protein, small GTPases, cyclic nucleotides, such as cyclic AMP (cAMP) and cyclic GMP (cGMP), calcium ion, phophoinositide derivatives, such as Phosphatidylinositol-triphosphate (PIP3), Diacylglycerol (DAG) and Inositol-triphosphate (IP3), and various protein kinases and phosphatases. Some of these are also called second messengers.

Intercellular

Intercellular communication is accomplished by extracellular signalling and takes place in multicellular organisms. Within endocrinology, which is the study of intercellular signalling in animals, intercellular signalling is subdivided into the following types:
- Endocrine signals are produced by endocrine cells and travel through the blood to reach all parts of the body.
- Paracrine signals target only cells in the vicinity of the emitting cell. Neurotransmitters represent an example.
- Autocrine signals affect only cells that are of the same cell type as the emitting cell. An example for

autocrine signals is found in immune cells.
- Juxtacrine signals are transmitted along cell membranes via protein or lipid components integral to the membrane and are capable of affecting either the emitting cell or cells immediately adjacent.

Hormones

Most of the molecules that enable signalling between the cells or tissues within an individual animal or plant are known as "hormones." Hormone-initiated signal transduction takes the following steps:
1. Biosynthesis of a hormone.
2. Storage and secretion of the hormone.
3. Transport of the hormone to the target cell.
4. Recognition of the hormone by the hormone receptor protein, leading to a conformational change.
5. Relay and amplification of the signal that leads to defined biochemical reactions within the target cell. The reactions of the target cells can, in turn, cause a signal to the hormone-producing cell that leads to the down-regulation of hormone production.
6. Removal of the hormone.

Hormones and other signaling molecules may exit the sending cell by exocytosis or other means of membrane transport. The sending cell is typically of a specialized type. Its recipients may be of one type or several, as in the case of insulin, which triggers diverse and systemic effects.

Hormone signaling is elaborate and hard to dissect. A cell can have several different receptors that recognize the same hormone, but activate different signal transduction pathways; or different hormones and their receptors can invoke the same biochemical pathway. Different tissue types can answer differently to the same hormone stimulus. There are two classes of hormone receptors, "membrane-associated receptors" and intracellular or "cytoplasmic" receptors.

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Calcium as a second messenger

Ca^{2+} acts as a signal molecule within the cell. This works by tightly limiting the time and space when Ca^{2+} is free (and thus active). Therefore, the concentration of free Ca^{2+} within the cell is usually very low; it is stored within organelles, usually the endoplasmic reticulum (sarcoplasmic reticulum in muscle cells), where it is bound to molecules like calreticulin.

Activation of Ca^{2+}

To become active, Ca^{2+} has to be released from the endoplasmic reticulum into the cytosol. There are two combined receptor/ion channel proteins that perform the task of controlled transport of Ca^{2+}:
- The $InsP_3$-receptor will transport Ca^{2+} upon interaction with inositol triphosphate (thus the name) on its cytosolic side. It consists of four identical subunits.
- The ryanodine receptor is named after the plant alkaloid ryanodine. It is similar to the $InsP_3$ receptor and stimulated to transport Ca^{2+} into the cytosol by recognizing Ca^{2+} on its cytosolic side, thus establishing a feedback mechanism; a small amount of Ca^{2+} in the cytosol near the receptor will cause it to release even more Ca^{2+}. It is especially important in neurons and muscle cells. In heart and pancreas cells, another second messenger (cyclic ADP ribose) takes part in the receptor activation.

The localized and time-limited activity of Ca^{2+} in the cytosol is also called a Ca^{2+} wave. The building of the wave is done by:
- the feedback mechanism of the ryanodine receptor and
- the activation of phospholipase C by Ca^{2+}, which leads to the production of inositol triphosphate, which in turn activates the $InsP_3$ receptor.

Function of Ca^{2+}

Ca^{2+} is used in a multitude of processes, among them muscle contraction, release of neurotransmitter from nerve endings, vision in retina cells, proliferation, secretion, cytoskeleton management, cell migration, gene expression and metabolism. The three main pathways that lead to Ca^{2+} activation are :
1. G protein regulated pathways
2. Pathways regulated by receptor-tyrosine kinases
3. Ligand- or current-regulated ion channels

There are two different ways in which Ca^{2+} can regulate proteins:
1. A direct recognition of Ca^{2+} by the protein.
2. Binding of Ca^{2+} in the active site of an enzyme

One of the best studied interactions of Ca^{2+} with a protein is the regulation of calmodulin by Ca^{2+}. Calmodulin itself can regulate other proteins, or be part of a larger protein (for example, phosphorylase kinase). The Ca^{2+}/calmodulin complex plays an important role in proliferation, mitosis and neural signal transduction.

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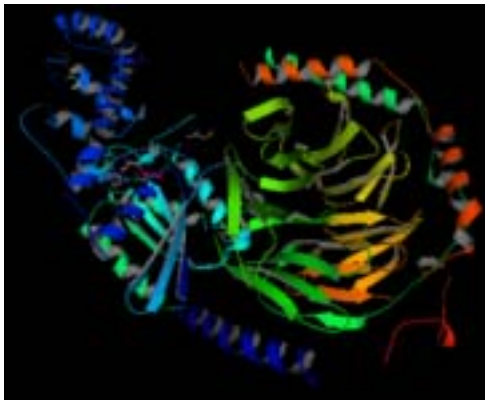
G-protein

G-proteins, short for **guanine nucleotide binding proteins,** are a family of proteins involved in second messenger cascades. They are so called because of their signaling mechanism, which uses the exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP) as a molecular "switch" to allow or inhibit biochemical reactions inside the cell. Alfred Gilman and Martin Rodbell were awarded the Nobel Prize in Physiology or Medicine in 1994 for their discovery and research on G-proteins.


3D structure of a heterotrimeric G-protein

General properties

G-proteins belong to the larger grouping of GTPases. "G-protein" usually refers to the membrane-associated heterotrimeric G-proteins, sometimes referred to as the *"large" G-proteins*. These proteins are activated by G-protein coupled receptors and are made up of alpha (α), beta (β) and gamma (γ) subunits. There are also *"small" G proteins* or small GTPases like ras that are monomeric and not membrane-associated, but also bind GTP and GDP and are involved in signal transduction.

G-proteins are perhaps the most important signal transducing molecules in cells. In fact, diseases such as diabetes and certain forms of pituitary cancer, among many others, are thought to have some root in the malfunction of G-proteins, and thus a fundamental understanding of their function, signaling pathways, and protein interactions may lead to eventual treatments and possibly the creation of various preventive approaches.

Receptor-activated G-proteins

Receptor activated G-proteins are bound to the inside surface of the cell membrane. They consist of the G_{α} and the tightly associated $G_{\beta\gamma}$ subunits. When a ligand activates the G-protein coupled receptor, the G-protein binds to the receptor, releases its bound GDP from the G_{α} subunit, and binds a new molecule

of GTP. This exchange triggers the dissociation of the G_α subunit, the $G_{\beta\gamma}$ dimer, and the receptor. Both, G_α-GTP and $G_{\beta\gamma}$, can then activate different 'signalling cascades' (or 'second messenger pathways') and effector proteins, while the receptor is able to activate the next G-protein. The G_α subunit will eventually hydrolize the attached GTP to GDP by its inherent enzymatic activity, allowing it to reassociate with $G_{\beta\gamma}$ and starting a new cycle.

A well characterized example of a G-protein triggered signalling cascade is the cAMP pathway. The enzyme adenylate cyclase is activated by $G_{\alpha s}$-GTP and synthesizes the second messenger cyclic adenosine monophosphate (cAMP) from ATP. Second messengers then interact with other proteins downstream to cause a change in cell behavior.

Alpha subunits

G_α subunits consist of two domains, the GTPase domain, and the alpha-helical domain. There exist at least 20 different alpha subunits, which are separated into several main families:

* $G_{\alpha s}$ or simply G_s (stimulatory) - activates adenylate cyclase to increase cAMP synthesis
* $G_{\alpha i}$ or simply G_i (inhibitory) - inhibits adenylate cyclase
* G_{olf} (olfactory) - couples to olfactory receptors
* G_t (transducin) - transduces visual signals in conjunction with rhodopsin in the retina
* G_q - stimulates phospholipase C
* The $G_{12/13}$ family - important for regulating the cytoskeleton, cell junctions, and other processes related to movements

Beta-gamma complex

The β and γ subunits are closely bound to one another and are referred to as the *beta-gamma complex*. The $G_{\beta\gamma}$ complex is released from the G_α subunit after its GDP-GTP exchange. The free $G_{\beta\gamma}$ complex can act as a signaling molecule itself, by activating other second messengers or by gating ion channels directly. For example, the $G_{\beta\gamma}$ complex, when bound to histamine receptors, can activate phospholipase A_2. $G_{\beta\gamma}$ complexes bound to muscarinic acetylcholine receptors, on the other hand, directly open G-protein coupled inward rectifying potassium (GIRK) channels.

G-protein Coupled Receptors

G-protein-coupled receptors (GPCRs), also known as seven transmembrane receptors, heptahelical receptors, or 7TM receptors, are a protein family of transmembrane receptors that transduce an extracellular signal (ligand binding) into an intracellular signal (G protein activation). The GPCRs are the largest protein family known, members of which are involved in all types of stimulus-response pathways, from intercellular communication to physiological senses. The diversity of functions is matched by the wide range of ligands recognized by members of the family, from photons (rhodopsin, the archetypal GPCR) to small molecules (in the case of the histamine receptors) to proteins (for example, chemokine receptors). This pervasive involvement in normal biological processes has the consequence of involving GPCRs in many pathological conditions, which has led to GPCRs being the target of 40 to 50% of modern medicinal drugs.

Physiological roles

GPCRs are present in a wide variety of physiological processes. Some examples include:

1. the visual sense: the opsins use a photoisomerization reaction to translate electromagnetic radiation into cellular signals. Rhodopsin, for example, uses the conversion of 11-cis-retinal to all-trans-retinal for this purpose.
2. the sense of smell: receptors of the olfactory epithelium bind odorants (olfactory receptors) and pheromones (vomeronasal receptors)
3. behavioral and mood regulation: receptors in the mammalian brain bind several different neurotransmitters, including serotonin and dopamine
4. regulation of immune system activity and inflammation: chemokine receptors bind ligands that mediate intercellular communication between cells of the immune system; receptors such as histamine receptors bind inflammatory mediators and engage target cell types in the inflammatory response
5. autonomic nervous system transmission: both the sympathetic and parasympathetic nervous systems are regulated by GPCR pathways. These systems are responsible for control of many automatic functions of the body such as blood pressure, heart rate and digestive processes.

There are two types GPCRs viz chemosensory and endo GPCRs.

Receptor structure

GPCRs are integral membrane proteins that possess seven membrane-spanning domains or

transmembrane helices. The extracellular parts of the receptor can be glycosylated. These extracellular loops also contain two highly conserved cysteine residues which build disulfide bonds to stabilize the receptor structure.

Early structural models for GPCRs were based on their weak analogy to bacteriorhodopsin for which a structure had been determined by both electron and X ray-based crystallography. In 2000, the first crystal structure of a mammalian GPCR, that of bovine rhodopsin, was solved. While the main feature, the seven transmembrane helices, is conserved, the structure differs significantly from that of bacteriorhodopsin. Some seven transmembrane helix proteins (such as channelrhodopsin) that resemble GPCRs may contain different functional groups, such as entire ion channels, within their protein.

Ligand binding and signal transduction

While in other types of receptors that have been studied ligands bind externally to the membrane, the ligands of GPCRs typically bind within the transmembrane domain.

The transduction of the signal through the membrane by the receptor is not completely understood. It is known that the inactive G protein is bound to the receptor in its inactive state. Once the ligand is recognized, the receptor shifts conformation and thus mechanically activates the G protein, which detaches from the receptor. The receptor can now either activate another G protein, or switch back to its inactive state. This is an overly simplistic explanation, but suffices to convey the overall set of events.

It is believed that a receptor molecule exists in a conformational equilibrium between active and inactive states. The binding of ligands to the receptor may shift the equilibrium. Three types of ligands exist: agonists are ligands which shift the equilibrium in favour of active states; inverse agonists are ligands which shift the equilibrium in favour of inactive states; and neutral antagonists are ligands which do not affect the equilibrium. It is not yet known how exactly the active and inactive states differ from each other.

If a receptor in an active state encounters a G protein, it may activate it. Some evidence suggests that receptors and G-proteins are actually pre-coupled. For example, binding of G-proteins to receptors affects the receptor's affinity for ligands.

GPCR signaling without G-proteins

In the late 1990s, evidence began accumulating that some GPCRs are able to signal without G-proteins. The ERK2 mitogen-activated protein kinase, a key signal transduction mediator downstream of receptor activation in many pathways, has been shown to be activated in response to cAMP-mediated receptor activation in the slime mold D. discoideum despite the absence of the associated G-protein α- and β-subunits.

In mammalian cells the well-studied β2-adrenoceptor has been demonstrated to activate the ERK2

pathway after arrestin-mediated uncoupling of G-protein mediated signalling. It therefore seems likely that some mechanisms previously believed to be purely related to receptor desensitisation are actually examples of receptors switching their signalling pathway rather than simply being switched off.

Receptor regulation

GPCRs are known to become less sensitive to their ligand when they are exposed to it for a prolonged period of time. The key reaction of this downregulation is the phosphorylation of the intracellular (or cytoplasmic) receptor domain by protein kinases.

Phosphorylation by cAMP-dependent protein kinases

Cyclic AMP-dependent protein kinases (protein kinase A) are activated by the signal chain coming from the G protein (that was activated by the receptor) via adenylate cyclase and cyclic AMP (cAMP). In a feedback mechanism, these activated kinases phosphorylate the receptor. The longer the receptor remains active, the more kinases are activated, the more receptors are phosphorylated.

Phosphorylation by GRKs

The G-protein-coupled receptor kinases (GRKs) are protein kinases that phosphorylate only active GPCRs.

Phosphorylation of the receptor can have two consequences:

1. **Translocation.** The receptor is, along with the part of the membrane it is embedded in, brought to the inside of the cell, where it is dephosphorylated and then brought back. This mechanism is used to regulate long-term exposure, for example, to a hormone.
2. **Arrestin linking.** The phosphorylated receptor can be linked to arrestin molecules that prevent it from binding (and activating) G proteins, effectively switching it off for a short period of time. This mechanism is used, for example, with rhodopsin in retina cells to compensate for exposure to bright light. In many cases, arrestin binding to the receptor is a prerequisite for translocation.

Receptor oligomerization

It is generally accepted that that G-protein-coupled receptors can form homo- and/or hetero-dimers and possibly more complex oligomeric structures. However, it is presently unproven that true hetero-dimers exist. Present bio-chemical and physical techniques lack the resolution to differentiate between distinct homo-dimers assembled into an oligomer or true 1:1 hetero-dimers. It is also unclear what the functional significance of oligomerization is. This is an actively studied area in GPCR research.

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GTPases

GTPases are a large family of enzymes that can bind and hydrolyze GTP. The GTP binding and hydrolysis takes place in the highly conserved *G domain* common to all GTPases. GTPases play an important role in:

* Signal transduction at the intracellular domain of transmembrane receptors, including recognition of taste, smell and light.
* Protein biosynthesis (aka translation) at the ribosome.
* Control and differentiation during cell division.
* Translocation of proteins through membranes.
* Transport of vesicles within the cell. (GTPases control assembly of vesicle coats).

Mechanism of GTP

The hydrolysis of the γ phosphate of GTP supposedly occurs by the S_N2 mechanism via a *pentavalent intermediate state* depending on Mg^{2+}.

Regulatory GTPases

Regulatory GTPases, also called the GTPase superfamily, are GTPases used for regulation of other biochemical processes. Most prominent among the regulatory GTPases are the G proteins.

GTP switch

All regulatory GTPases have a common mechanism that enables them to switch a signal transduction chain on and off. Throwing the switch is performed by the unidirectional change of the GTPase from the *active, GTP-bound form* to the *inactive, GDP-bound form* by hydrolysis of the GTP through intrinsic GTPase-activity, effectively switching the GTPase *off*. This reaction is initiated by GTPase-activating proteins (GAPs), coming from another signal transduction pathway. It can be reverted (switching the GTPase *on* again) by Guanine nucleotide exchange factors (GEFs), which cause the GDP to dissociate from the GTPase, leading to its association with a new GTP. This closes the cycle to the active state of the GTPase; the irreversible hydrolysis of the GTP to GDP forces the cycle to run only in one direction. Only the active state of the GTPase can transduce a signal to a reaction chain.

Switch regulation

The efficiency of the signal transduction via a GTPase depends on the ratio of active to inactive GTPase. That equals:

$$\frac{\mathrm{GTPase} * \mathrm{GTP}}{\mathrm{GTPase} * \mathrm{GDP}} = \frac{k_{\mathrm{diss.GDP}}}{k_{\mathrm{cat.GTP}}}$$

with $k_{diss.GDP}$ being the dissociation constant of GDP, and $k_{cat.GTP}$ the hydrolysis constant of GTP for the specific GTPase. Both constants can be modified by special regulatory proteins.
The amount of active GTPase can be changed in several ways :

1. Acceleration of GDP dissociation by GEFs speeds up the building of active GTPase.

2. Inhibition of GDP dissociation by guanine nucleotide dissociation inhibitors (GDIs) slows down the building of active GTPase.

3.Acceleration of GTP hydrolysis by GAPs reduces the amount of active GTPase.

4. GTP analogues like *γ-S-GTP*, *β,γ-methylene-GTP*, and *β,γ-imino-GTP* that cannot be hydrolized fixate the GTPase in its active state.

Heterotrimeric G proteins

These G proteins are made from three subunits, with the G domain located on the largest one (the *α unit*); together with the two smaller subunits (*β* and *γ units*), they form a tightly associated protein complex. α and γ unit are associated with the membrane by lipid anchors. Heterotrimeric G proteins act as the specific reaction partners of G protein-coupled receptors. The GTPase is normally inactive. Upon receptor activation, the intracellular receptor domain activates the GTPase, which in turn activates other molecules of the signal transduction chain, either via the α unit or the βγ complex. Among the target molecules of the active GTPase are adenylate cyclase and ion channels. The heterotrimeric G proteins can be classified by sequence homology of the α unit into four families:

1. G_s *family.* These G proteins are used in the signal transduction of taste and smell. They always use the activation of adenylate cyclase as the next step in the signal chain. Their function is permanently activated by the cholera toxin, which is the cause of the fatal effects of infection with *Vibrio cholerae*.

2. G_i *family.* The *i* stands for *inhibition* of the adenylate cyclase; another effector molecule for this protein family is *phospholipase C*. Also, G_t and G_g proteins are summarized under this label due to sequence homologies. G_t proteins, aka transducin, is used in the light recognition pathway in retina cells.

G_g protein occurs in the taste recognition for *bitter*. Most G_i protein family members can be inhibited by the pertussis toxin of *Bordetella pertussis*.

3. *G_q family*. These proteins usually have phospholipase C as effector protein.

4. *G_{12} family*. These G proteins can be activated by thromboxan receptors and thrombin receptors. Their effector proteins are unknown.

By combination of different α, β and γ subunits, a great variety (>1000) G proteins can be produced. GDP is not needed for GTP.

Activation cycle of heterotrimeric G proteins

In the basic state, the G_α-GDP-$G_{\beta\gamma}$ complex and the receptor that can activate it are separately associated with the membrane. On receptor activation, the receptor becomes highly affine for the G protein complex. On binding with the complex, GDP dissociates from the complex; the *free* complex has a high affinity for GTP. Upon GTP binding, both G_α-GTP and $G_{\beta\gamma}$ separate from both the receptor and from each other. Depending on the lifetime of the active state of the receptor, it can activate more G proteins this way.
Both G_α-GTP and $G_{\beta\gamma}$ can now activate separate effector molecules and activate them, thus sending the signal further down the signal reaction chain. Once the intrinsic GTPase activity of the α unit has hydrolyzed the GTP to GDP, the two parts can reassociate to the original, inactive state. The speed of the hydrolysis reaction works as an internal clock for the length of the signal.

The Ras GTPase superfamily

These are small monomeric proteins homologous to Ras. They are also called small GTPases. Small GTPases have a molecular weight of about 21 kilo-Dalton and generally serve as molecular swithes for a variety of cellular signaling events. According to their primary amino acid sequences and biochemical properties, the Ras superfamily is further divided into five subfamilies: Ras, Rho, Rab, Arf and Ran.

Translation factor family

These GTPases play an important role in initiation, elongation and termination of protein biosynthesis.

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Eicosanoids

In biochemistry, **eicosanoids** are a class of oxygenated hydrophobic molecules that largely function as autocrine and paracrine mediators. Eicosanoids derive from 20-carbon polyunsaturated essential fatty acids, most commonly arachidonic acid (AA) in humans. The IUPAC and the IUBMB use the equivalent term **Icosanoid**.

Nomenclature

The prefix *eicosa-* (from the Greek for twenty) denotes the number of carbon atoms in arachidonic acid. The term "eicosanoids" is used as a collective name for molecules derived from 20-carbon fatty acids. Current usage limits this to the leukotrienes and prostanoids, but several other classes are technically eicosanoid, including the resolvins, isofurans, isoprostanes, lipoxins, epoxyeicosatrienoic acids (EETs), neuroprotectin D and some endocannabinoids.

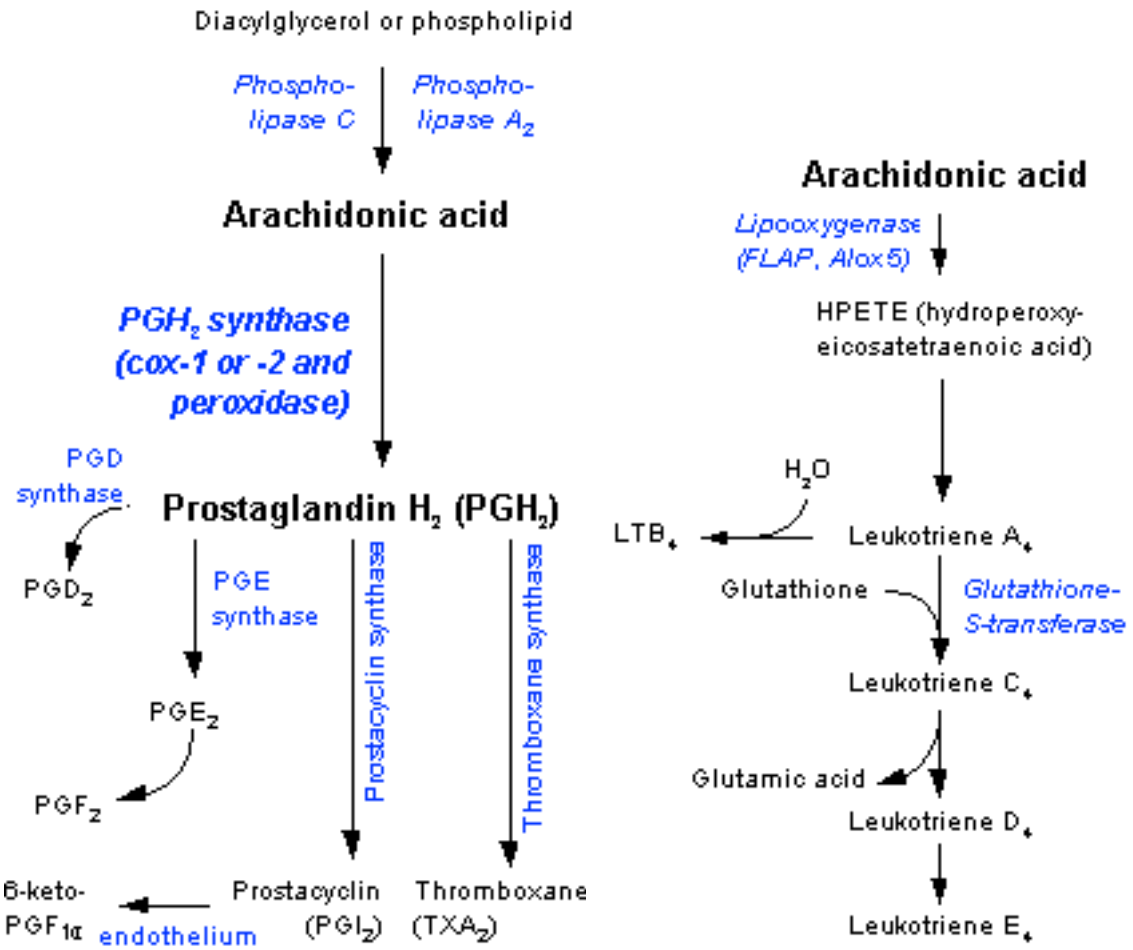
The numbering of eicosanoids is used to denote the number of double bonds. The AA-derived prostanoids have two, while the leukotrienes have four.

Synthesis

The first step of eicosanoid biosynthesis is the release from phospholipids (by phospholipase A_2) or diacylglycerol (by phospholipase C) of a 20-carbon essential fatty acid (EFA) containing three, four, or five double bonds, (the ω-6 GLA, ω-6 AA or ω-3 EPA, respectively). Most human eicosanoids derive from AA. This EFA has two possible eicosanoid fates:

* 5-lipoxygenase pathway: Leukotrienes

* Cyclooxygenase pathway ("prostanoids"): Prostaglandins; Prostacyclin; Thromboxanes



Leukotrienes

5-lipoxygenase uses the nuclear-membrane protein cofactor 5-lipoxygenase-activating protein (FLAP) to sequentially convert arachidonic acid, first into 5-hydroperoxyeicosatetraenoic acid (5-HPETE), and then 5-HPETE into leukotriene A4 (LTA4). LTA4 may be converted into LTB4 by the enzyme leukotriene A4 epoxide hydrolase. Eosinophils, mast cells, and alveolar macrophages use the enzyme leukotriene C4 synthase to conjugate glutathione with LTA4 to make leukotriene C4 (LTC4). LTC4 is transported out of the cell, where a glutamic acid moiety is removed from it to make leukotriene D4 (LTD4). LTD4 is cleaved by dipeptidases to make leukotriene E4 (LTE4).

LTC4, LTD4 and LTE4 all contain cysteine and are collectively known as the cysteinyl leukotrienes.

Prostanoids

All prostanoids originate from prostaglandin H (PGH, as PGH_1, PGH_2, or PGH_3), which is converted by different enzymes into the various compounds. The enzyme PGH2-synthase is in fact a combination of a peroxidase and a cyclooxygenase (*Cox-1* or *Cox-2*). The *Cox* enzymes are the molecular target of the NSAIDs, such as aspirin.

PGH is converted:

* By PGE synthetase into PGE (which in turn is converted into PGF)
* By PGD synthetase into PGD
* By Prostacyclin synthase into prostacyclin (PGI2)
* By Thromboxane synthase into thromboxanes

Receptors

There are specific receptors for all eicosanoids:

* Leukotrienes:
-- CysLT1 (Cysteinyl leukotriene receptor type 1)
-- CysLT2 (Cysteinyl leukotriene receptor type 2)
-- BLT1 (Leukotriene B4 receptor)

* Prostanoids:
--PGD_2: DP-(PGD_2)

--PGE_2:

- EP_1-(PGE_2)

- EP_2-(PGE_2)

- EP_3-(PGE_2)

- EP_4-(PGE_2)

-- $PGF_{2\alpha}$: FP-($PGF_{2\alpha}$)

-- PGI_2 (prostacyclin): IP-(PGI_2)

-- TXA_2 (thromboxane): TP-(TXA_2)

Function and pharmacology

Leukotrienes

Leukotrienes play an important role in inflammation, especially as part of the Slow Reacting Substance of Anaphylaxis, and blocking leukotriene receptors can play a role in the management of inflammatory diseases such as asthma (montelukast, zafirlukast), psoriasis, and rheumatoid arthritis.

Prostanoids

Prostanoids mediate local symptoms of inflammation: vasoconstriction or vasodilation, coagulation,

pain and fever. Inhibition of cyclooxygenase, specifically the inducible COX II isoform, is the hallmark of NSAIDs (non-steroidal anti-inflammatory drugs), such as aspirin. COX II is responsible for pain and inflammation, while COX I is responsible for platelet clotting actions.

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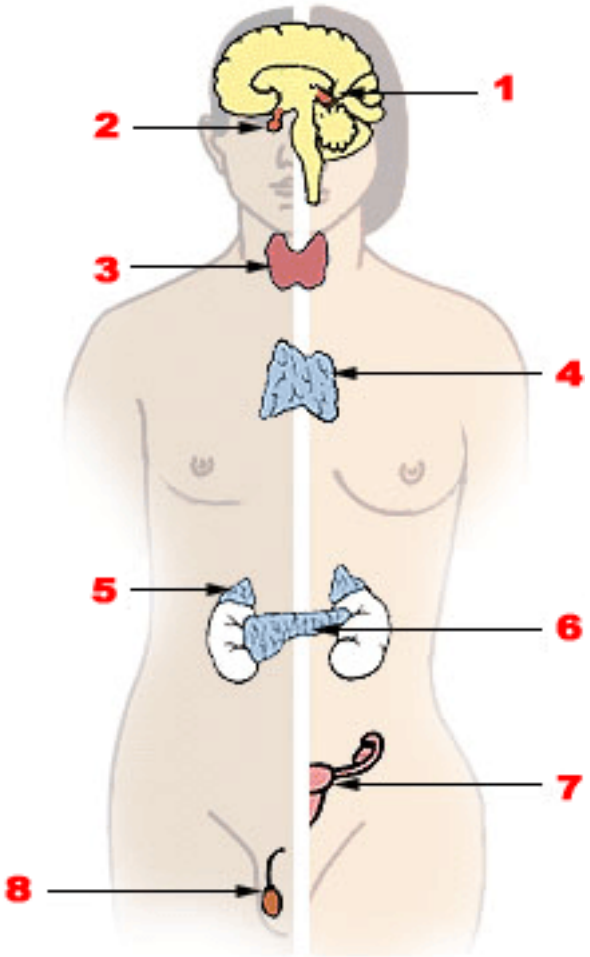
Endocrine System

Physiology | List of endocrine glands and the hormones secreted | Difuse Endocrine System

The endocrine system is a control system of ductless glands that secrete chemical messengers called hormones that circulate within the body via the bloodstream to affect distant organs. Hormones act as "messengers", and are carried by the bloodstream to different cells in the body, which interpret these messages and act on them.



Major endocrine glands. (Male left, female on the right.)
1. Pineal gland
2. Pituitary gland
3. Thyroid gland
4. Thymus
5. Adrenal gland
6. Pancreas
7. Ovary
8. Testis

The endocrine system does not include exocrine glands such as salivary glands, sweat glands and glands within the gastrointestinal tract.

The field of medicine that deals with disorders of endocrine glands is endocrinology, a branch of the wider field of internal medicine.

Physiology

The endocrine system links the brain to the organs that control body metabolism, growth and development, and reproduction.

Signal transduction of some hormones with steroid structure involves nuclear hormone receptor proteins that are a class of ligand activated proteins that, when bound to specific sequences of DNA serve as on-off switches for transcription within the cell nucleus. These switches control the development and differentiation of skin, bone and behavioral centers in the brain, as well as the continual regulation of reproductive tissues.

The endocrine system regulates its hormones through negative feedback. Increases in hormone activity decrease the production of that hormone. The immune system and other factors contribute as control factors also, altogether maintaining constant levels of hormones.

List of endocrine glands and the hormones secreted

In both sexes (starting from the head and going downwards):
Hypothalamus: Thyrotropin-releasing hormone (TRH), Gonadotropin-releasing hormone (GnRH), Growth hormone-releasing hormone (GHRH), Corticotropin-releasing hormone (CRH), Somatostatin, Dopamine.
Pituitary gland>Anterior lobe (adenohypophysis): GH (human growth hormone), PRL (prolactin), ACTH (adrenocorticotropic hormone), TSH (thyroid-stimulating hormone), FSH (follicle-stimulating hormone), LH (luteinizing hormone).
Pituitary gland>Posterior lobe (neurohypophysis): Oxytocin, ADH (antidiuretic hormone)
Pineal gland: Melatonin
Thyroid gland: Thyroxine (T4), a form of thyroid hormone, Triiodothyronine (T3), a form of thyroid hormonem, Calcitonin.
Parathyroid gland: Parathyroid hormone (PTH).
Heart: Atrial-natriuretic peptide (ANP).
Stomach and intestines: Gastrin, Secretin, Cholecystokinin (CCK), Somatostatin, Neuropeptide Y
Liver: Insulin-like growth factor, Angiotensinogen, Thrombopoietin
Islets of Langerhans in the pancreas: Insulin, Glucagon, Somatostatin
Adrenal glands>Adrenal cortex: Glucocorticoids - cortisol, Mineralocorticoids - aldosterone, Androgens (including testosterone)

Adrenal glands>Adrenal medulla: Adrenaline (epinephrine), Noradrenaline (norepinephrine)
Kidney: Renin, Erythropoietin (EPO), Calcitriol
Skin: Calciferol (vitamin D3)
Adipose tissue: Leptin

In males only:
Testes: Androgens (testosterone)

In females only:
Ovarian follicle: Oestrogens, Testosterone
Corpus luteum: Progesterone
Placenta (when pregnant): Progesterone, Human chorionic gonadotrophin (HCG), Human placental lactogen (HPL)

Difuse Endocrine System

Organs aren't the sole way for hormones to be sent into the body; there are a host of specific cells which secrete hormones independently. These are called the "diffuse" endocrine system, and include myocytes in the heart (atria) and epithelial cells in the stomach and small intestines. In fact, if one were to classify any chemical excretions in the term "hormone," every cell in the human body could be considered a part of the endocrine system.

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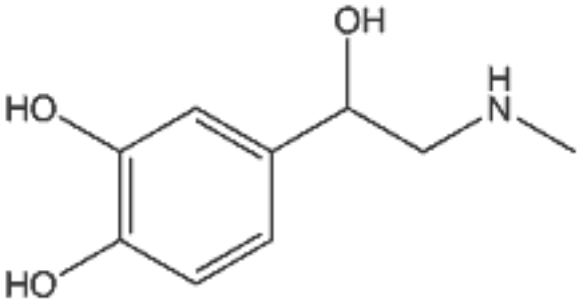
- Induces new root formation by breaking root apical dominance induced by cytokinins

Epinephrine

Actions in the body | Pharmacology

Epinephrine or **adrenaline**, sometimes spelled "epinephrin" or "adrenalin" respectively, is a hormone and a neurotransmitter. Epinephrine is a catecholamine, a sympathomimetic monoamine derived from the amino acids phenylalanine and tyrosine. The Latin roots ad-+renes and the Greek roots *epi-*+*nephros* both literally mean "on/to the kidney" (referring to the adrenal gland, which secretes epinephrine). Epinephrine is sometimes shortened to **epi** in medical jargon.

In May 1886, William Bates reported the discovery of a substance produced by the suprarenal gland in the *New York Medical Journal*. Epinephrine was isolated and identified in 1895 by Napoleon Cybulski, Polish physiologist. The discovery was repeated in 1897 by John Jacob Abel. Jokichi Takamine discovered the same hormone in 1900, without knowing about the previous discovery; but, in later years, counterevidence is shown from the experiment note that Kaminaka leaves that the Takamine team is the discoverer of first adrenaline. It was first artificially synthesized in 1904 by Friedrich Stolz.



The chemical formula of epinephrine, a.k.a. 4-(1-hydroxy- 2-(methylamino)ethyl)benzene-1,2-diol, is $C_9H_{13}NO_3$

Actions in the body

Epinephrine plays a central role in the short-term stress reaction—the physiological response to threatening, exciting or environmental stressor conditions such as high noise levels or bright light. It is secreted by the adrenal medulla. When released into the bloodstream, epinephrine binds to multiple receptors and has numerous effects throughout the body. It increases heart rate and stroke volume, dilates the pupils, and constricts arterioles in the skin and gut while dilating arterioles in leg muscles. It elevates the blood sugar level by increasing hydrolysis of glycogen to glucose in the liver, and at the same time begins the breakdown of lipids in fat cells. Epinephrine has a suppressive effect on the adaptive immune system.

Epinephrine is used as a drug to promote peripheral vascular resistance via alpha-stimulated vasoconstriction in cardiac arrest and other cardiac disrhythmias resulting in diminished or absent cardiac output, such that blood is shunted to the body's core. This beneficial action comes with a

significant negative consequence, increased cardiac irritability, which may lead to additional complications immediately following an otherwise successful resuscitation. Alternatives to this treatment include vasopressin, a powerful antidiuretic which also promotes peripheral vascular resistance leading to blood shunting via vasoconstriction, but without the attendant increase to myocardial irritability.

Because of its suppressive effect on the adaptive immune system, epinephrine is used to treat anaphylaxis and sepsis. Allergy patients undergoing immunotherapy can get an epinephrine rinse before the allergen extract is administered, thus reducing the immune response to the administered allergen. It is also used as a bronchodilator for asthma if specific beta-2-adrenergic agonists are unavailable or ineffective. Adverse reactions to epinephrine include palpitations, tachycardia, anxiety, headache, tremor, hypertension, and acute pulmonary edema.

A pheochromocytoma is a tumor of the adrenal gland (or, rarely, the ganglia of the sympathetic nervous system), which secretes excessive amounts of catecholamines, usually epinephrine.

Pharmacology

Epinephrine's actions are mediated through adrenergic receptors (sometimes referred to as adrenoceptors).

It binds to α1 receptors of liver cells, which activate inositol-phospholipid signaling pathway, signaling the phosphorylation of insulin, leading to reduced ability of insulin to bind to its receptors.

Epinephrine also activates β-adrenergic receptors of the liver and muscle cells, thereby activating the adenylate cyclase signaling pathway, which will in turn increase glycogenolysis. Specifically, β2 receptors exist on many blood vessels. Activation of the adenylate cyclase pathway on this tissue causes inhibition of myosin light chain kinase which, in turn, relaxes the smooth muscle cells of the blood vessel walls to bring about vasodilation.

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Growth factor

Growth factors and cytokines | Types | Uses in medicine

Growth factor is a protein that acts as a signaling molecule between cells (like cytokines and hormones) that attaches to specific receptors on the surface of a target cell and promotes differentiation and maturation of these cells.

Growth factors and cytokines

The term *growth factor* is sometimes used interchangeably among scientitsts with the term *cytokine*. Historically, cytokines were associated with hematopoietic (blood forming) cells and immune system cells (e.g., lymphocytes and tissue cells from spleen, thymus, and lymph nodes). For the circulatory system and bone marrow in which cells can occur in a liquid suspension and not bound up in solid tissue, it makes sense for them to communicate by soluble, circulating protein molecules. However, as different lines of research converged, it became clear that some of the same signaling proteins the hematopoietic and immune systems used were also being used by all sorts of other cells and tissues, during development and in the mature organism.

Growth factor signifies a positive effect on cell growth and cellular differentiation, but *cytokine* is a neutral term in regards to what it is being signaled. In this sense, some cytokines can be growth factors such as G-CSF and GM-CSF as listed below. However some cytokines are actually used as "death" signals, such as the FAS ligand, which causes target lymphocytes to commit a form of suicide known as programmed cell death or *apoptosis*.

Types

Individual growth factor proteins tend to occur as members of larger families of structurally and evolutionarily related proteins. There are dozens and dozens of growth factor families such as TGF-beta (transforming growth factor), BMP (bone morphogenic protein), neurotrophins (NGF, BDNF, and NT3), fibroblast growth factor (FGF), and so on.

Several well known growth factors are:

* granulocyte-colony stimulating factor (G-CSF)
* granulocyte-macrophage colony stimulating factor (GM-CSF)
* nerve growth factor (NGF)
* neurotrophins
* platelet-derived growth factor (PDGF)
* erythropoietin (EPO)

* thrombopoietin (TPO)
* myostatin (GDF-8)
* Growth Differentiation factor-9 (GDF9)
* basic fibroblast growth factor (bFGF or FGF2)

Uses in medicine

For the last two decades, growth factors have been increasingly used in treatment of hematologic and oncologic diseases like:

*neutropenia
* myelodysplastic syndrome (MDS)
* leukemias
* aplastic anaemia
* bone marrow transplantation

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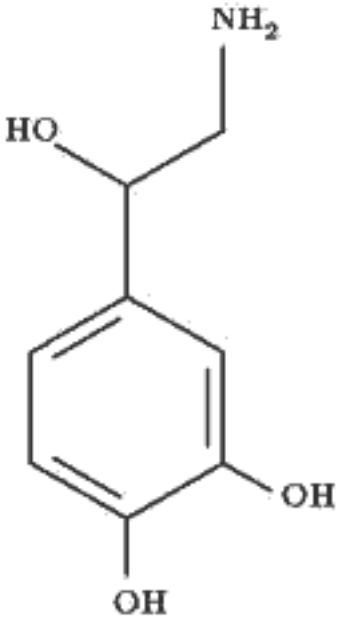
Norepinephrine

Norepinephrine (INN) or **noradrenaline** (BAN) is a catecholamine and a phenethylamine with chemical formula $C_8H_{11}NO_3$. The natural stereoisomer is L-(-)-(R)-norepinephrine. It is released from the adrenal glands as a hormone into the blood, but it is also a neurotransmitter in the nervous system where it is released from noradrenergic neurons during synaptic transmission. As a stress hormone, it affects parts of the human brain where attention and impulsivity are controlled. Along with epinephrine, this compound effects the fight-or-flight response, activating the sympathetic nervous system to directly increase heart rate, release energy from fat, and increase muscle readiness.



The host of physiological changes activated by a stressful event are unleashed in part by activation of a nucleus in the brain stem called the locus ceruleus. This nucleus is the origin of most norepinephrine pathways in the brain. Neurons using norepinephrine as their neurotransmitter project bilaterally from the locus ceruleus along distinct pathways to the cerebral cortex, limbic system, and the spinal cord, among other projections.

At synapses it acts on both alpha and beta adrenoreceptors.

Antidepressants

Changes in the norepinephrine system are implicated in depression. Serotonin-norepinephrine reuptake inhibitors (SNRIs) treat depression by increasing the amount of serotonin and norepinephrine available to postsynaptic cells in the brain. There is some recent evidence showing that the norepinephrine

transporter also normally transports some dopamine as well, implying that SNRIs may also increase dopamine transmission. This is because SNRIs work by preventing the serotonin and norepinephrine transporter from taking their respective neurotransmitters back to their storage vesicles for later use. If the norepinephrine transporter normally recycles some dopamine too, then SNRIs will also enhance dopaminergic transmission. Therefore, the antidepressant effects associated with increasing norepinephrine levels may also be partly or largely due to the concurrent increase in dopamine (particularly in the prefrontal cortex).

Some other antidepressants (for example some tricyclic antidepressants (TCAs)) affect norepinephrine as well, in some cases without affecting other neurotransmitters (at least not directly).

Role in attention

Norepinephrine, along with dopamine, has come to be recognized as playing a large role in attention and focus. In response, Eli Lilly Pharmaceuticals has released Strattera (atomoxetine), a selective norephinephrine reuptake inhibitor, for the treatment of ADHD in adults and children. Strattera is unique in medications specifically indicated for ADHD, as, unlike the psychostimulants (methylphenidate, dextroamphetamine, Adderall (a racemic mixture of amphetamine salts)), it affects norepinephrine, rather than dopamine. As a result, Strattera has a very low abuse potential and can act 24 hours-per-day. (It should be noted that some antidepressants, including SNRIs, have been used off-label for treatment of ADHD.)

Clinical use

Norepinephrine (commonly referred to by the brand name Levophed) is also a powerful medicine used in critically-ill patients as a vasopressor. It is given intravenously and acts on both alpha-1 and beta-1 adrenergic receptors to cause vasoconstriction. Norepinephrine is mainly used to treat patients in septic shock.

Biosynthesis

Norepinephrine is synthesized by a series of enzymatic steps in the adrenal medulla from the amino acid tyrosine. The first reaction is the oxidation into dihydroxyphenylalanine (L-DOPA), followed by decarboxylation into the neurotransmitter dopamine, and the final oxidation into norepinephrine. Norepinephrine can be further methylated by phenylethanolamnine N-methyltransferase to epinephrine (called adrenaline outside the USA).

Noradrenaline metabolites

In mammals noradrenaline is rapidly degraded to various metabolites. The principle metabolites are:
• Normetanephrine (via the enzyme catechol-O-methyl transferase, COMT)

- 3,4-Dihydroxymandelic acid (via monoamine oxidase, MAO)
- 3-Methoxy-4-hydroxymandelic acid (via MAO)
- 3-Methoxy-4-hydroxyphenylglycol (via MAO)

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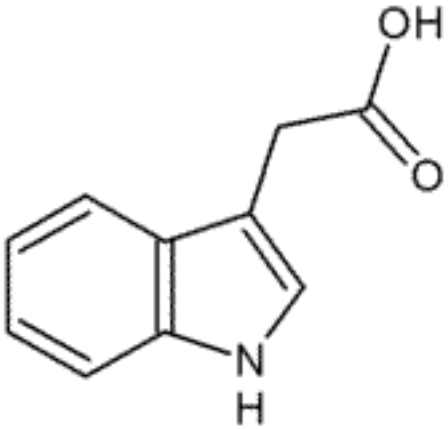
Auxin

Auxins are a class of plant growth substance (often called phytohormones or plant hormones). Auxins play an essential role in coordination of many growth and behavioral processes in the plant life cycle.



IAA appears to be the most active Auxin in plant growth.

Overview

Auxins have been demonstrated to be a basic coordinative signal of plant development. Their pattern of active transport through the plant is complex, and auxins typically act in concert with (or opposition to) other plant hormones. For example, the ratio of auxin to cytokinin in certain plant tissues determines initiation of root versus shoot buds. As a result, a plant can (as a whole) react on external conditions and adjust to them, without requiring a nervous system.

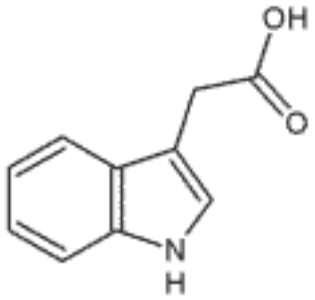
The most important member of the auxin family is **indole-3-acetic acid** (IAA). It generates the majority of auxin effects in intact plants, and is the most potent native auxin. However, molecules of IAA are chemically labile in aqueous solution, so IAA cannot be applied commercially as a plant growth regulator.

- *Naturally-occurring auxins* include 4-chloro-indoleacetic acid, phenylacetic acid (PAA) and indole-3-butyric acid (IBA).
- *Synthetic auxin analogs* include 1-naphthaleneacetic acid (NAA), 2,4-dichlorophenoxyacetic acid (2,4-D), and others.

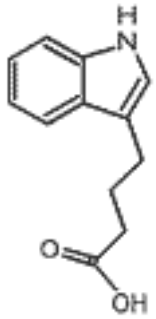
Gallery of native auxins

IAA:

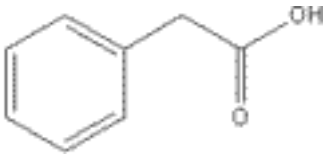
Auxin



IBA:

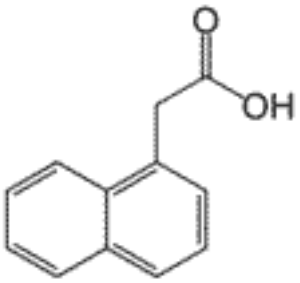


PAA:

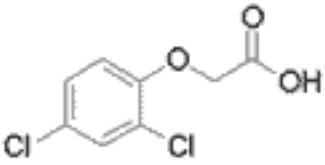


Gallery of synthetic auxins

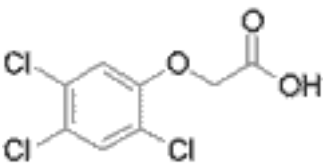
1-NAA:



2,4-D*:*



2,4,5-T:



Auxins are often used to promote initiation of root growth and are the active ingredient of the commercial preparations used in horticulture to root stem cuttings). They can also be used to promote uniform flowering, to promote fruit set, and to prevent premature fruit drop.

Used in high doses, auxin stimulates the production of ethylene. Excess ethylene can inhibit elongation growth, cause leaves to fall (leaf abscission), and even kill the plant. Some synthetic auxins such as 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) can be used as herbicides. Broad-leaf plants (dicots) such as dandelions are much more susceptible to auxins than narrow-leaf plants (monocots) like grass and cereal crops.

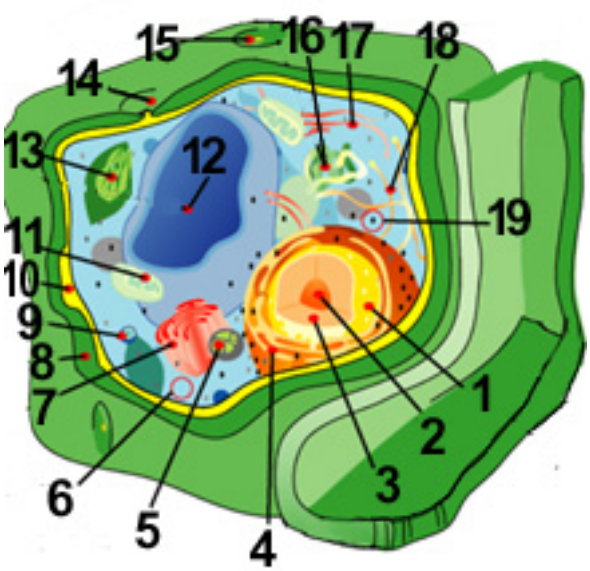
Hormonal activity

Auxins coordinate development at all levels of plants, from the cellular level to organs and ultimately the whole plant.

On a cellular level

On the cellular level, auxins' presence is essential for both cell division and respective cell growth, resulting usually in its axial elongation. Auxins also directly stimulate or inhibit the expression of specific genes. Auxin induces transcription by targeting for degradation members of the Aux/IAA family of transcriptional repressor proteins, The degradation of the Aux/IAAs leads to the derepression of ARF-mediated transcription. Aux/IAAs are targeted for degradation by ubiquitination, catalysed by an SCF-type ubiquitin-protein ligase.

Plant Cell Structure



1. Nuclear envelope
2. Nucleolus
3. Nucleus

4. Rough endoplasmic retuculum
5. Leukoplast
6. Cytoplasm
7. Golgi vesicles (golge apparatus)
8. Cell wall
9. Peroxisome
10. Plasma membrane
11. Mitochodrion (mitochondria)
12. Vacuole
13. Chloroplast
14. Plasmodesmata
15. Plasmodesmata
16. Smooth endoplasmic reticulum
17. Filamentous cytoskeleton
18. Small membranous vesicles
19. Ribosomes

The plant cell wall is made up of cellulose and protein, and, in many cases, lignin. It is very firm and prevents any sudden expansion of cell volume, and, without contribution of auxins, any expansion at all.

According to the "acid growth theory," auxins may directly stimulate cell elongation by causing responsive cells to actively transport hydrogen ions out of the cell, thus lowering the pH around cells. This acidification of the cell wall region activates enzymes known as expansins, which break bonds in the cell wall structure, making the cell wall less rigid. When the cell wall is degraded (not entirely) by the action of auxins, this now-less-rigid wall is expanded by the pressure coming from within the cell, especially by growing vacuoles.

Organ patterns

Growth and division of plant cells result in growth of tissue, and specific tissue growth contributes to the development of plant organs. Growth of cells contributes to the plant's size, but uneven localized growth produces bending, turning and directionalization of organs, for example, stems turning toward light sources (phototropism), growth of roots in response to gravity (gravitropism), and other tropisms.

Organization of the plant

As auxins contribute to organ shaping, they are also fundamentally required for proper development of the plant itself. Without hormonal regulation and organization, plants would be merely proliferating heaps of similar cells. Auxin employment begins in the embryo of the plant, where directional distribution of auxin ushers in subsequent growth and development of primary growth poles, then forms buds of future organs. Throughout the plant's life, auxin helps the plant maintain the polarity of growth and recognize where it has its branches (or any organ) connected.

An important principle of plant organization based upon auxin distribution is **apical dominance**, which means that the auxin produced by the apical bud (or growing tip) diffuses downwards and inhibits the development of ulterior lateral bud growth, which would otherwise compete with the apical tip for light and nutrients. Removing the apical tip and its suppressive hormone allows the lower dormant lateral buds to develop, and the buds between the leaf stalk and stem produce new shoots which compete to become the lead growth. This behavior is used in pruning by horticulturists.

Uneven distribution of auxin: To cause growth in the required domains, it is necessary that auxins be active preferentially in them. Auxins are not synthesized everywhere, but each cell retains the potential ability to do so, and only under specific conditions will auxin synthesis be activated. For that purpose, not only do auxins have to be translocated toward those sites where they are needed but there has to be an established mechanism to detect those sites. Translocation is driven throughout the plant body primarily from peaks of shoots to peaks of roots. For long distances, relocation occurs via the stream of fluid in phloem vessels, but, for short-distance transport, a unique system of coordinated polar transport directly from cell to cell is exploited. This process of polar auxin transport is directional and very strictly regulated. It is based in uneven distribution of auxin efflux carriers on the plasma membrane, which send auxins in the proper direction.

Locations

- Synthesized in shoot (and root) meristematic tissue
- Synthesized in young leaves
- Synthesized in mature leaves in very tiny amounts
- Synthesized in mature root cells in even smaller amounts (speculative)
- Transported throughout the plant more prominently downward from the shoot apices
- Released by meristematic cells when they are in good growing conditions
- Released by all cells when they are experiencing conditions that would normally cause a shoot meristematic cell to produce auxin (speculative)
- Directly or indirectly induced by high levels of ethylene (speculative)
- Peaks during the day

Effects

- Stimulates cell elongation (if gibberellins are also present, the effect is stronger)
- Stimulates cell division (if cytokinins are also present)
- Induces formation and organization of phloem (and xylem)
- Participates in phototropism, gravitropism, tropism toward moisture and other developmental changes
- Induces new root formation by breaking root apical dominance induced by cytokinins
- Induces shoot apical dominance
- Directly stimulates ethylene synthesis (stimulation of ethylene in lateral buds causes inhibition of its growth and potentiation of apical dominance)
- Inhibits (in low amounts) ethylene formation and transport of precursor

- Inhibits abscission prior to formation of abscission layer (inhibits senescence of leaves)
- Induces sugar and mineral accumulation at the site of application
- Stimulates Flower initiation
- Is sex determinator
- Inhibits root hair growth and causes them to die back (speculative)
- Stimulates the rate of metabolism of cells in the root, thus increasing their efficiency of water and mineral uptake(speculative)
- Indicates when cells have more than enough sugar and gases available than are needed for existence at their present size. It is a shoot health indicator and growth signal, and one of its essential missions is to compliment the excess sugar and gases with an excess of root-derived water and minerals. It therefore induces new roots. If Cytokinin is present, this is an indication that the root is healthy and the plant is completely ready to grow. In this case, it simply cooperates with cytokinin to cause cell division and balanced plant growth. (speculative)
- Appears in general to be induced at the site of high concentrations of sugar, but always moving in a direction away from this synthesis. Since Auxin attracts nutrients to the cell where it is, this transport of auxin away from sugar synthesis may partly explain the transport of sugar in the phloem to the roots. The sugar may just be following the auxin. (speculative)

Molecular mechanisms of auxin action

Although auxins and their effects have been known for a long time, mechanisms of action in plants have remained unknown for a long time. In 2005, it was demonstrated that the F-box protein TIR1, which is part of the ubiquitin ligase complex SCFTIR1, is an auxin receptor. This marking process leads to the degradation of the repressors by the proteasome, alleviating repression and leading to specific gene expression in response to auxins.

Another protein called ABP1 (Auxin Binding Protein 1) is a putative receptor, but its role is unclear.

Herbicide manufacture

The defoliant Agent Orange was a mix of 2,4-D and 2,4,5-T. 2,4-D is still in use and is thought to be safe, but 2,4,5-T was more or less banned by the EPA in 1979. The dioxin TCDD is an unavoidable contaminant produced in the manufacture of 2,4,5-T. As a result of the integral dioxin contamination, 2,4,5-T has been implicated in leukaemia, miscarriages, birth defects, liver damage, and other diseases.

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Hormone

History | Physiology of hormones | Types of hormones | Pharmacology

A **hormone** (from Greek *horman* - "to set in motion") is a chemical messenger from one cell (or group of cells) to another. All multicellular organisms (including plants) produce hormones.

The best-known animal (and human) hormones are those produced by endocrine glands of vertebrate animals, but hormones are produced by nearly every organ system and tissue type in a human or animal body. Hormone molecules are secreted (released) directly into the bloodstream; however, some hormones, called ectohormones, are secreted to the outside environment. They move by circulation or diffusion to their target cells, which may be nearby cells (paracrine action) in the same tissue or cells of a distant organ of the body. The function of hormones is to serve as a signal to the target cells; the action of hormones is determined by the pattern of secretion and the signal transduction of the receiving tissue.

Hormone actions vary widely, but can include stimulation or inhibition of growth, induction or suppression of apoptosis (programmed cell death), activation or inhibition of the immune system, regulating metabolism and preparation for a new activity (e.g., fighting, fleeing, mating) or phase of life (e.g., puberty, caring for offspring, menopause). In many cases, one hormone may regulate the production and release of other hormones. Many of the responses to hormone signals can be described as serving to regulate metabolic activity of an organ or tissue. Hormones also control the reproductive cycle of virtually all multicellular organisms.

History

The concept of internal secretion developed in the 19th century; Claude Bernard described it in 1855, but did not specifically address the possibility of secretions of one organ acting as messengers to others. Still, various endocrine conditions were recognised and even treated adequately (e.g., hypothyroidism with extract of thyroid glands).

The major breakthrough was the identification of secretin, the hormone secreted by the duodenum that stimulates pancreatic secretions, by Ernest Starling and William Bayliss in 1902. Previously, the process had been considered (e.g., by Ivan Pavlov) to be regulated by the nervous system. Starling and Bayliss demonstrated that injecting duodenal extract into dogs rapidly increased pancreatic secretions, raising the possibility of a chemical messenger.

Starling is also credited with introducing the term *hormone*, having coined it in a 1905 lecture. Later reports indicate it was suggested to him by the Cambridge physiologist William B. Hardy.

The remainder of the 20th century saw all the major hormones discovered, as well as the cloning of the

relevant genes and the identification of the many interlocking feedback mechanisms that characterise the endocrine system.

Physiology of hormones

Most cells are capable of producing one or more, sometimes many, molecules which signal other cells to alter their growth, function, or metabolism. The classical endocrine glands and their hormone products are specialized to serve regulation on the overall organism level, but can often be used in other ways or only on the tissue level.

The rate of production of a hormone is often regulated by a homeostatic control system, generally by negative feedback. Homeostatic regulation of hormones depends, apart from production, on the metabolism and excretion of hormones.

Hormone secretion can be stimulated and inhibited by:

- Other hormones (*stimulating*- or *releasing*-hormones)
- Plasma concentrations of ions or nutrients, as well as binding globulins
- Neurons and mental activity
- Environmental changes, e.g., of light or temperature

One special group of hormones is trophic hormones that stimulate the hormone production of other endocrine glands. For example: thyroid-stimulating hormone (TSH) causes growth and increased activity of another endocrine gland - the thyroid - hence increasing output of thyroid hormones.

A recently-identified class of hormones is that of the "Hunger Hormones" - ghrelin, orexin and PYY 3-36 - and "Satiety hormones" - e.g., leptin, obestatin.

Types of hormones

Vertebrate hormones fall into four chemical classes:

- Amine-derived hormones are derivatives of the amino acids tyrosine and tryptophan. Examples are catecholamines and thyroxine.
- Peptide hormones consist of chains of amino acids. Examples of small peptide hormones are TRH and vasopressin. Peptides composed of scores or hundreds of amino acids are referred to as proteins. Examples of protein hormones include insulin and growth hormone.
- Steroid hormones are derived from cholesterol. The adrenal cortex and the gonads are primary sources. Examples of steroid hormones are testosterone and cortisol. Sterol hormones such as calcitriol are a homologous system.
- Lipid and phospholipid hormones are derived from lipids such as linoleic acid and phospholipids such

as arachidonic acid. The main class is the eicosanoids, which includes the widely-studied prostaglandins.

Pharmacology

Many hormones are used as medication. The most commonly-prescribed hormones are estrogens and progestagens (in the contraceptive pill and as HRT), thyroxine (as levothyroxine, for hypothyroidism) and steroids (for autoimmune diseases and several respiratory disorders). Insulin is used by many diabetics. Local preparations for use in otolaryngology often contain pharmacologic equivalents of adrenaline, while steroid and vitamin D creams are used extensively in dermatological practice.

A "pharmacologic dose" of a hormone is a medical usage referring to an amount of a hormone far greater than naturally occurs in a healthy body. The effects of pharmacologic doses of hormones may be different from responses to naturally-occurring amounts and may be therapeutically useful. An example is the ability of pharmacologic doses of glucocorticoid to suppress inflammation.

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Integrin

Structure | Function | Attachment of cell to the ECM | Signal transduction

An **integrin**, or **integrin receptor**, is an integral membrane protein in the plasma membrane of cells. It plays a role in the attachment of a cell to the extracellular matrix (ECM) (especially in growth cone axon guidance) and in signal transduction from the ECM to the cell. There are many different types of integrin and many cells have multiple types on their surface. Integrins are of vital importance to most multicellular organisms from humans to sponges.

Mutations in the genes encoding for integrin can be found in certain types of cancer, for instance breast cancer. A failure of integrin to anchor a cell to the ECM can play a role in the metastasis of certain cancer cells.

Other types of protein that play a role in cell-cell/cell-matrix interaction and communication are cadherins, NCAMs and selectins.

Structure

Integrins are obligate heterodimers containing two distinct chains, termed the α (alpha) and β (beta) subunits. About 18 α and 8 β subunits have been characterized. In addition, variants of some of the subunits are formed by differential splicing, for example 4 variants of the beta-1 subunit exist. Through different combinations of these alpha and beta subunits, some 24 unique integrins are generated. Integrin subunits penetrate the plasma membrane, and in general have very short cytoplasmic domains of about 40-70 amino acids, with the exception of the beta-4 subunit which has a cytoplasmic domain of 1088 amino acids. Outside the cell plasma membrane, the chains lie close together along a length of about 23 nm, the final 5 nm of each chain form a ligand-binding region for the ECM. The molecular mass of the integrin subunits can vary from 90 Kda to 160Kda. ß subunits have four cysteine-rich repeated sequences. a subunits bind several divalent cations. X-ray crystal structure has been obtained for the complete extracellular regions of one integrin, and this shows the molecule to be folded into an inverted V-shape which brings the ligand-binding sites close to the cell membrane. The current hypothesis, is that integrin function involves changes in shape to move the ligand binding site into a more accessible position away from the cell surface, and this shape change also triggers intracellular signalling.

Function

Two main functions of integrins are:

- Attachment of the cell to the ECM.
- Signal transduction from the ECM to the cell.

However, they are also involved in a wide range of other biological activities. These include: binding of viruses, including adenovirus, Echo viruses, Hanta viruses, foot and mouth disease viruses, to cells; immune patrolling. Cell migration.

Attachment of cell to the ECM

Integrins couple the ECM outside a cell to the cytoskeleton (in particular the microfilaments) inside the cell. Which ligand in the ECM the integrin can bind to is mainly decided by which α and β subunits the integrin is made of. Among the ligands of integrins are fibronectin, collagen, and laminin. The connection between the cell and the ECM enables the cell to endure pulling forces without being ripped out of the ECM. The ability of a cell to create this kind of bond is also of vital importance in ontogeny.

The connections between integrin and the ligands in the ECM and the microfilaments inside the cell are indirect: they are linked via scaffolding proteins like talin, paxillin and alpha-actinin. These act by regulating kinases like FAK (focal adhesion kinase)and Src kinase family members to phosphorylate substrates such as p130CAS thereby recruiting signaling adaptors such as Crk.

Cell attachment to the ECM is a basic requirement to build a multicellular organism. Integrins are not simply hooks, but give the cell critical signals about the nature of its surroundings. Together with signals arising from receptors for soluble growth factors like VEGF, EGF and many others, they enforce a cellular decision on what biological action to take, be it attachment, movement, death, or differentiation. Thus integrins lie at the heart, both literally and figuratively, of cellular biological processes.

Recent studies have focused on the role of ECM to influence the cellular microenvironment and resulting cellular function. Not only are integrins used, but recent advances in synthetic ECM analogues - such as synthetic peptide nanofiber scaffolds - are allowing well-defined blank scaffolds to serve as the basis for carefully controlled microenvironments for these studies.

Signal transduction

Integrins play an important role in cell signaling. Connection with ECM molecules can cause a signal to be relayed into the cell through protein kinases that are connected with the intracellular end of the integrin molecule.

The signals the cell receives through the integrin can have relation to:

- cell growth
- cell division
- cell survival
- cellular differentiation
- apoptosis (programmed cell death) .

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Peptide hormone

Peptide hormones are a class of peptides that are secreted into the blood stream and have endocrine functions in living animals.

Like other proteins, peptide hormones are synthesized from amino acids according to an mRNA template, which is itself synthesized from a DNA template inside the cell's nucleus. Peptide hormone precursors (pre-prohormones) are then processed in several stages, typically in the endoplasmic reticulum, including removal of the N-terminal signal sequence and sometimes glycosylation, resulting in prohormones. The prohormones are then packaged into membrane-bound secretory vesicles, which can be secreted from the cell by exocytosis in response to specific stimuli.

These prohormones often contain superfluous amino acid residues that were needed to direct folding of the hormone molecule into its active configuration but have no function once the hormone folds. Specific endopeptidases in the cell cleave the prohormone just before it is released into the blood stream, generating the mature hormone form of the molecule. Mature peptide hormones then diffuse through the blood to all of the cells of the body, where they interact with specific receptors on the surface of their target cells.

Notable peptide hormones

Several important peptide hormones are secreted from the pituitary gland. The anterior pituitary secretes luteinizing hormone and follicle stimulating hormone, which act on the gonads, prolactin, which acts on the mammary gland, adrenocorticotrophic hormone (ACTH), which acts on the adrenal cortex to regulate the secretion of glucocorticoids, and growth hormone, which acts on bone, muscle and the liver. The posterior pituitary gland secretes antidiuretic hormone, also called vasopressin, and oxytocin. Peptide hormones are produced by many different organs and tissues, however, including the heart (atrial-natriuretic peptide (ANP) or atrial natriuretic factor (ANF)) and pancreas (insulin and somatostatin), the gastrointestinal tract (cholecystokinin, gastrin), and fat stores (leptin).

Many neurotransmitters are secreted and released in a similar fashion to peptide hormones, and some 'neuropeptides' may be used as neurotransmitters in the nervous system in addition to acting as hormones when released into the blood. When a peptide hormone binds to receptors on the surface of the cell, a second messenger appears in the cytoplasm.

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Steroid hormone

Steroid hormones are steroids which act as hormones. They can be grouped into five groups by the receptors to which they bind: glucocorticoids, mineralocorticoids, androgens, estrogens, and progestagens. Vitamin D derivatives are a sixth closely related hormone system with homologous receptors, though technically sterols rather than steroids.

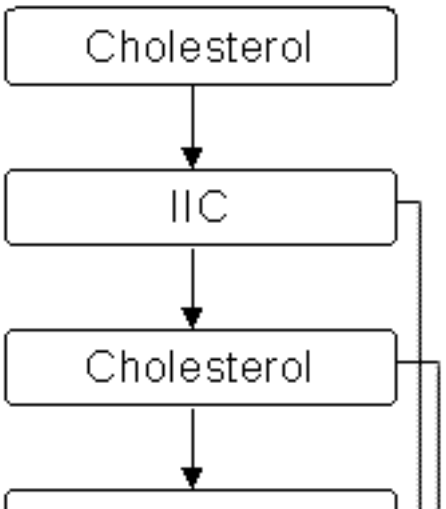
Overview

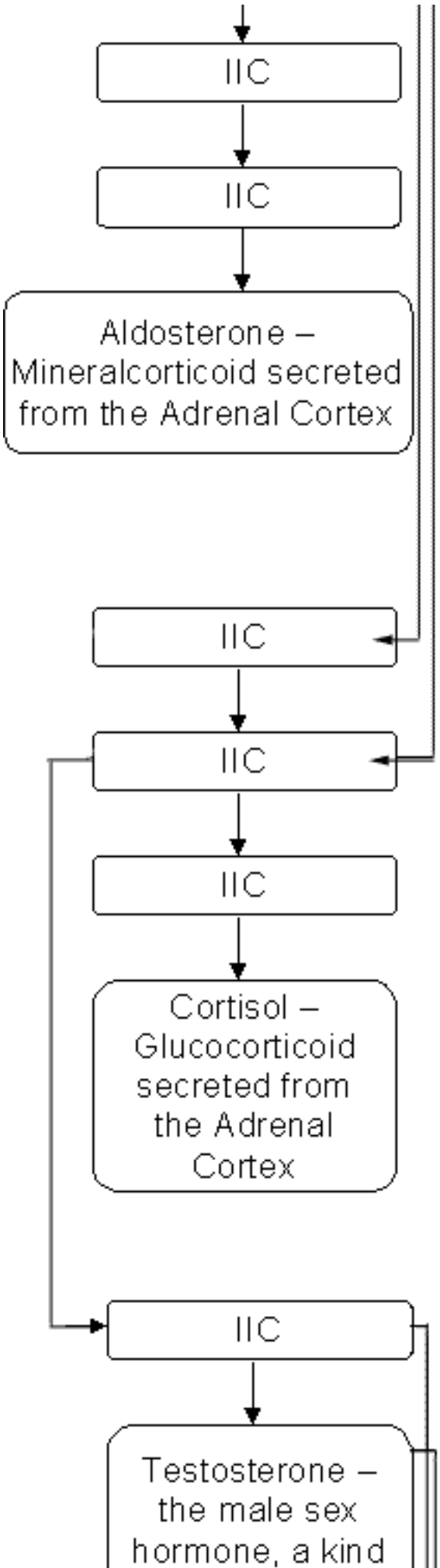
The natural steroid hormones are generally synthesized from cholesterol in the gonads and adrenal glands. Steroid hormones are generally carried in the blood bound to specific carrier proteins such as sex hormone binding globulin or corticosteroid binding globulin. Further conversions and catabolism occurs in the liver, other "peripheral" tissues, and in the target tissues.

Because steroids and sterols are lipid soluble, they can diffuse fairly freely from the blood through the cell membrane and into the cytoplasm of target cells. In the cytoplasm the steroid may or may not undergo an enzyme-mediated alteration such as reduction, hydroxylation, or aromatization. In the cytoplasm, the steroid binds to the specific receptor, a large metalloprotein. Upon steroid binding, many kinds of steroid receptor *dimerizes*, two receptor subunits join together to form one functional DNA-binding unit that can enter the cell nucleus. In some of the hormone systems known, the receptor is associated with a heat shock protein which is released on the binding of the ligand, the hormone. Once in the nucleus, the steroid-receptor ligand complex binds to specific DNA sequences and induces transcription of its target genes.

Synthesis

Steroids made from Cholesterol:




IIC
IIC
Aldosterone – Mineralcorticoid secreted from the Adrenal Cortex
IIC
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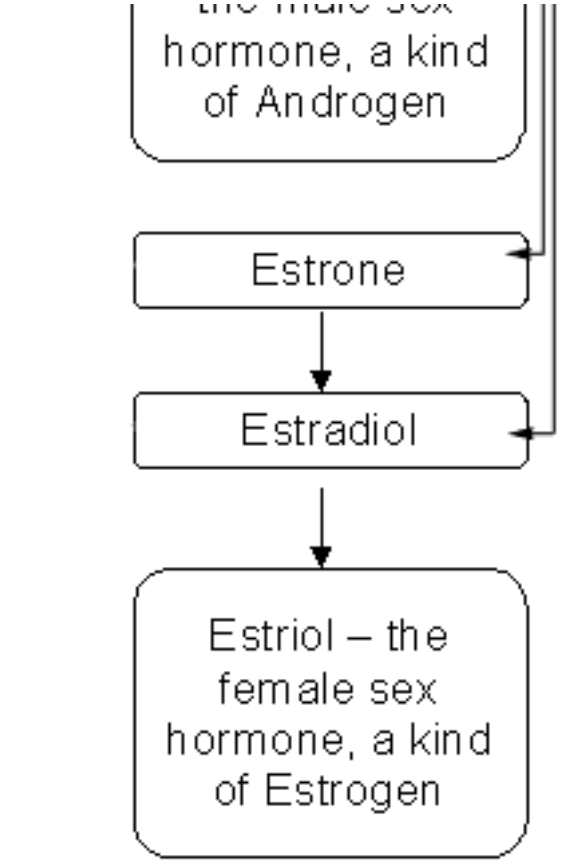
IIC
Cortisol – Glucocorticoid secreted from the Adrenal Cortex
IIC
Testosterone – the male sex hormone, a kind



Principal natural human steroid hormones

- Glucocorticoids - cortisol
- Mineralocorticoids - aldosterone
- Sex steroids - Androgens - testosterone
- dehydroepiandrosterone (DHEA)
- dehydroepiandrosterone sulfate (DHEAS)
- androstenedione
- dihydrotestosterone (DHT)
- Estrogens - estradiol
- estrone
- estriol
- Progestagens - progesterone

The principal sterol hormone:

- Vitamin D derivatives - calcitriol

Synthetic steroids and sterols

A variety of synthetic steroids and sterols have also been contrived. Most are steroids but some non-steroidal molecules can interact with the steroid receptors because of a similarity of shape. Some synthetic steroids are weaker, some much stronger, than the natural steroids whose receptors they activate.

Some examples of synthetic steroid hormones:

- Glucocorticoids: prednisone, dexamethasone, triamcinolone
- Mineralocorticoid: fludrocortisone
- Vitamin D: dihydrotachysterol
- Androgens: oxandrolone, decadurabolin (also known as anabolic steroids)
- Estrogens: diethylstilbestrol (DES)
- Progestins: norethindrone, medroxyprogesterone acetate

Steroidogenic enzymes: Review on structure, function, and role in regulation of steroid hormone biosynthesis

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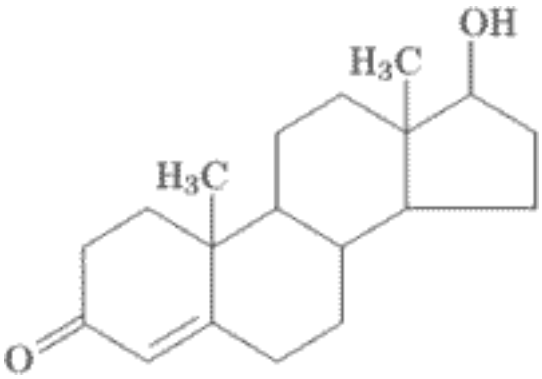
Testosterone

Sources of testosterone | Mechanism of effects | Effects of testosterone on humans

Sources of testosterone | Mechanism of effects | Effects of testosterone on humans

Testosterone is a steroid hormone from the androgen group. Testosterone is secreted in the testes of males and the ovaries of females. It is the principal male sex hormone and the "original" anabolic steroid. In both males and females, it plays key roles in health and well-being. Examples include enhanced libido, energy, immune function, and protection against osteoporosis. On average, the adult male body produces about thirty times the amount of testosterone an adult female's body does.



Sources of testosterone

Like other steroid hormones, testosterone is derived from cholesterol. The largest amounts of testosterone are produced by the testes in men, but it is also synthesized in smaller quantities in women by the theca cells of the ovaries, by the placenta, as well as by the zona reticulosa of the adrenal cortex in both sexes.

In the testes, testosterone is produced by the Leydig cells. The male generative glands also contain Sertoli cells which require testosterone for spermatogenesis. Like most hormones, testosterone is supplied to target tissues in the blood where much of it is transported bound to a specific plasma protein, **sex hormone binding globulin** (SHBG).

Mechanism of effects

The effects of testosterone in humans and other vertebrates occur by way of two main mechanisms: by activation of the androgen receptor (directly or as DHT), and by conversion to estradiol and activation of certain estrogen receptors.

Free testosterone (T) is transported into the cytoplasm of target tissue cells, where it can bind to the androgen receptor, or can be reduced to 5α-dihydrotestosterone (DHT) by the cytoplasmic enzyme 5α-reductase. DHT binds to the same androgen receptor even more strongly than T, so that its androgenic potency is about 2.5 times that of T. The T-receptor or DHT-receptor complex undergoes a structural change that allows it to move into the cell nucleus and bind directly to specific nucleotide sequences of the chromosomal DNA. The areas of binding are called hormone response elements (HREs), and influence transcriptional activity of certain genes, producing the androgen effects.

Androgen receptors occur in many different vertebrate body system tissues, and both males and females respond similarly to similar levels. Greatly differing amounts of testosterone prenatally, at puberty, and throughout life account for a large share of biological differences between males and females.

The bones and the brain are two important tissues in humans where the primary effect of testosterone is by way of aromatization to estradiol. In the bones, estradiol accelerates maturation of cartilage into bone, leading to closure of the epiphyses and conclusion of growth. In the central nervous system, testosterone is aromatized to estradiol. Estradiol rather than testosterone serves as the most important feedback signal to the hypothalamus (especially affecting LH secretion). In many mammals, prenatal or perinatal "masculinization" of the sexually dimorphic areas of the brain by estradiol derived from testosterone programs later male sexual behavior.

Effects of testosterone on humans

In general, androgens promote protein synthesis and growth of those tissues with androgen receptors. Testosterone effects can be classified as *virilizing* and *anabolic* effects, although the distinction is somewhat artificial, as many of the effects can be considered both. Anabolic effects include growth of muscle mass and strength, increased bone density and strength, and stimulation of height growth and bone maturation. Virilizing effects include maturation of the sex organs, particularly the penis and the formation of the scrotum in fetuses, and after birth (usually at puberty) a deepening of the voice, growth of the beard and torso hair. Many of these fall into the category of male secondary sex characteristics. Increased testosterone causes deepening of the voice in both sexes at puberty. To take advantage of its virilizing effects, testosterone is often administered to transmen (female-to-male transsexual and transgender people) as part of the hormone replacement therapy, with a "target level" of the normal male testosterone level. And like-wise, transwomen are sometimes prescribed drugs [anti-androgens] to decrease the level of testosterone in the body and allow for the effects of estrogen to develop. Testosterone is also often used by bodybuilders to enhance muscle build.

Testosterone effects can also be classified by the age of usual occurrence. For postnatal effects in both males and females, these are mostly dependent on the levels and duration of

circulating free testosterone.

Most of the *prenatal androgen effects* occur between 7 and 12 weeks of gestation.

- Genital virilization (midline fusion, phallic urethra, scrotal thinning and rugation, phallic enlargement)
- Development of prostate and seminal vesicles

Early infancy androgen effects are the least understood. In the first weeks of life for male infants, testosterone levels rise. The levels remain in a pubertal range for a few months, but usually reach the barely detectable levels of childhood by 4-6 months of age. The function of this rise in humans is unknown. It has been speculated that "brain masculinization" is occurring since no significant changes have been identified in other parts of the body.

Early postnatal effects are the first visible effects of rising androgen levels in childhood, and occur in both boys and girls in puberty.

- Adult-type body odor
- Increased oiliness of skin and hair, acne
- Pubarche (appearance of pubic hair)
- Axillary hair
- Growth spurt, accelerated bone maturation
- Fine upper lip and sideburn hair

Advanced postnatal effects begin to occur when androgen has been higher than normal adult female levels for months or years. In males these are normal late pubertal effects, and only occur in women after prolonged periods of excessive levels of free testosterone in the blood.

- Phallic enlargement (including clitoromegaly)
- Increased libido and erection frequency
- Pubic hair extends to thighs and up toward umbilicus
- Facial hair (sideburns, beard, mustache)
- Chest hair, periareolar hair, perianal hair
- Subcutaneous fat in face decreases
- Increased muscle strength and mass
- Deepening of voice
- Growth of the adam's apple
- Growth of spermatogenic tissue in testes, male fertility
- Growth of jaw, brow, chin, nose, and remodeling of facial bone contours
- Shoulders widen and rib cage expands
- Completion of bone maturation and termination of growth. This occurs indirectly via estradiol metabolites and hence more gradually in men than women.

"Adult testosterone effects" are important in adult males, and may decline as testosterone levels decline in the later decades of adult life.

- Maintenance of muscle mass and strength
- Maintenance of bone density and strength
- Libido and erection frequency
- Mental and physical energy

Michael Exton, Tillmann Krüger et al. examined the effect of a 3-week period of sexual abstinence on the neuroendocrine response to masturbation-induced orgasm .

"The procedure was conducted for each participant twice, both before and after a 3-week period of sexual abstinence. Plasma was subsequently analysed for concentrations of adrenaline, noradrenaline, cortisol, prolactin, luteinizing hormone and testosterone concentrations. Orgasm increased blood pressure, heart rate, plasma catecholamines and prolactin. These effects were observed both before and after sexual abstinence. In contrast, although plasma testosterone was unaltered by orgasm, higher testosterone concentrations were observed following the period of abstinence. These data demonstrate that acute abstinence does not change the neuroendocrine response to orgasm but does produce elevated levels of testosterone in males."

Another study has shown that serum testosterone levels peak seven days after abstaining from ejaculation.

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Signal amplification

A principle of signal transduction is the signal amplification. The binding of one or a few neurotransmitter molecules can enable the entry of millions of ions. The binding of one or just a few hormone molecules can induce an enzymatic reaction that affect many substrates. The amplification can occur at several points of the signal pathway.

A receptor that has been activated by a hormone can activate many downstream effector proteins. For example, a rhodopsin molecule in the plasma membrane of a retina cell in the eye that was activated by a photon can activate up to 2000 effector molecules (in this case, transducin) per second. The total strength of signal amplification by a receptor is determined by:
- The lifetime of the hormone-receptor-complex. The more stable the hormone-receptor-complex is, the less likely the hormone dissociates from the receptor, the longer the receptor will remain active, thus activate more effector proteins.
- The amount and lifetime of the receptor-effector protein-complex. The more effector protein is available to be activated by the receptor, and the faster the activated effector protein can dissociate from the receptor, the more effector protein will be activates in the same amount of time.
- Deactivation of the activated receptor. A receptor that is engaged in a hormone-receptor-complex can be deactivated, either by covalent modification (for example, phosphorylation), or by internalization.

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Second messenger

Intracellular signal transduction is largely carried out by second messenger molecules, usually low-weight and diffusible. They are synthesized or released by specific enzymatic reactions, usually as a result of an external signal that was received by a transmembrane receptor and pre-processed by other membrane-associated proteins. There are three basic types of second messenger molecules:
- **Hydrophobic** molecules like diacylglycerol, InsP3 and phosphatidylinositols are membrane-associated and diffuse from the plasma membrane into the juxtamembrane space where they can reach and regulate membrane-associated effector proteins.
- **Hydrophilic** molecules are water-soluble molecules, like cAMP, cGMP, and Ca2+, that are located within the cytosol.
- **gases**, nitric oxide (NO) and carbon monoxide (CO), that can diffuse both through cytosol and across cellular membranes.

These intracellular messengers have some properties in common:
- They can be synthesized/released and broken down again in specific reactions by enzymes.
- Some (like Ca2+) can be stored in special organelles and quickly released when needed.
- Their production/release and destruction can be localized, enabling the cell to limit space and time of signal activity.

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Nuclear receptors

Nuclear (or cytoplasmic) receptors are soluble proteins localized within the cytoplasm or the nucleoplasm. The hormone has to pass through the plasma membrane, usually by passive diffusion, to reach the receptor and initiate the signal cascade. The nuclear receptors are ligand-activated transcription activators; on binding with the ligand (the hormone), they will pass through the nuclear membrane into the nucleus and enable the production of a certain gene and, thus, the production of a protein.

The typical ligands for nuclear receptors are lipophilic hormones, with steroid hormones (for example, testosterone, progesterone and cortisol) and derivatives of vitamin A and D among them. These hormones play a key role in the regulation of metabolism, organ function, developmental processes and cell differentiation. The key value for the signal strength is the hormone concentration, which is regulated by :

- Biosynthesis and secretion of hormones in the endocrine tissue. As an example, the hypothalamus receives information, both electrical and chemical. It produces releasing factors that affect the hypophysis and make it produce glandotrope hormones which, in turn, activate endocrine organs so that they finally produce hormones for the target tissues. This hierarchical system allows for the amplification of the original signal that reached the hypothalamus. The released hormones dampen the production of these hormones by feedback inhibition to avoid overproduction.

- Availability of the hormone in the cytosol. Several hormones can be converted into a storage form by the target cell for later use. This reduces the amount of available hormone.

- Modification of the hormone in the target tissue. Some hormones can be modified by the target cell so they no longer trigger the hormone receptor (or at least, not the same one), effectively reducing the amount of available hormone.

The nuclear receptors that were activated by the hormones attach at the DNA at receptor-specific Hormone Responsive Elements (HREs), DNA sequences that are located in the promoter region of the genes that are activated by the hormone-receptor complex. As this enables the transcription of the according gene, these hormones are also called inductors of gene expression. The activation of gene transcription is much slower than signals that directly affect existing proteins. As a consequence, the effects of hormones that use nucleic receptors are usually long-term. Although the signal transduction via these soluble receptors involves only a few proteins, the details of gene regulation are yet not well understood. The nucleic receptors all have a similar, modular structure:

N-AAAABBBBCCCCDDDDEEEEFFFF-C

where CCCC is the DNA-binding domain that contains zinc fingers, and EEEE the ligand-binding domain. The latter is also responsible for dimerization of most nuclearic receptors prior to DNA binding.

As a third function, it contains structural elements that are responsible for transactivation, used for communication with the translational apparatus. The zinc fingers in the DNA-binding domain stabilize DNA binding by holding contact to the phosphate backbone of the DNA. The DNA sequences that match the receptor are usually hexameric repeats, either normal, inverted or everted. The sequences are quite similar, but their orientation and distance are the parameters by which the DNA-binding domains of the receptors can tell them apart.

Steroid receptors

Steroid receptors are a subclass of nuclear receptors, located primarily within the cytosol. In the absence of steroid hormone, the receptors cling together in a complex called aporeceptor complex, which also contains chaperone proteins (also known as heatshock proteins or Hsps). The Hsps are necessary to activate the receptor by assisting the protein to fold in a way such that the signal sequence which enables its passage into the nucleus is accessible.
Steroid receptors can also have a repressive effect on gene expression, when their transactivation domain is hidden so it cannot activate transcription. Furthermore, steroid receptor activity can be enhanced by phosphorylation of serine residues at their N-terminal end, as a result of another signal transduction pathway, for example, a by a growth factor. This behaviour is called crosstalk.

RXR- and orphan-receptors

These nuclear receptors can be activated by:
- a classic endocrine-synthesized hormone that entered the cell by diffusion.
- a hormone that was built within the cell (for example, retinol) from a precursor or prohormone, which can be brought to the cell through the bloodstream.
- a hormone that was completely synthesized within the cell, for example, prostaglandin.

These receptors are located in the nucleus and are not accompanied by chaperone proteins. In the absence of hormone, they bind to their specific DNA sequence, repressing the gene. Upon activation by the hormone, they activate the transcription of the gene they were repressing.

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Protein phosphorylation

Phosphorylation is the addition of a phosphate (PO_4) group to a protein or a small molecule.

In eukaryotes, protein phosphorylation is probably the most important regulatory event. Many enzymes and receptors are switched "on" or "off" by phosphorylation and dephosphorylation. Phosphorylation is catalyzed by various specific **protein kinases**, whereas **phosphatases** *de*phosphorylate.

Adding a phosphoryl (PO_3) to a polar R group of an amino acid might not seem like it would do much to a protein, but it can actually turn a nonpolar hydrophobic protein into a polar and extremely hydrophilic molecule.

An example of the important role that phosphorylation plays is the p53 tumor suppressor gene, which-when active-stimulates transcription of genes that suppress the cell cycle, even to the extent that it undergoes apoptosis. However, this activity should be limited to situations where the cell is damaged or physiology is disturbed. To this end, the p53 protein is extensively regulated. In fact, p53 contains more than 18 different *phosphorylation* sites.

Upon the deactivating signal, the protein becomes dephosphorylated again and stops working. This is the mechanism in many forms of signal transduction, for example the way in which incoming light is processed in the light-sensitive cells of the retina.

Signaling networks

The network underlying phosphorylation can be very complex. In some cellular signalling pathways, a protein A phosphorylates B, and B phosphorylates C, but A also phosphorylates C directly, and B can phosphorylate D, which may in turn phosphorylate A.

Types of phosphorylation

Within a protein, phosphorylation can occur on several amino acids. Phosphorylation on serine is the most common, followed by threonine. Tyrosine phosphorylation is relatively rare. However, since tyrosine phosphorylated proteins are relatively easy to purify using antibodies, tyrosine phosphorylation sites are relatively well understood. Histidine and aspartate phosphorylation occurs in prokaryotes as part of two-component signalling.

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Calmodulin

Calmodulin (CaM) is a Ca^{2+}-binding protein that is a key component of the Ca^{2+} second-messenger system and is involved in controlling many of the biochemical processes of cells.

Calmodulin is a small, acidic protein approximately 148 amino acids long (16706 Dalton) and, as such, is a favorite for testing protein simulation software. It contains four **EF-hand** "motifs" or domains, each of which binds a Ca^{2+} ion. It typically binds 0, 2, or 4 calcium ions, and binds and regulates different proteins in each state. There are over a hundred proteins known to bind calmodulin. It is highly conserved across all eukaryotes, and its expression is essential for biological cells to progress through mitosis.

Calmodulin-stimulated protein phosphatase (EC 3.1.3.16) and calmodulin-dependent kinases are the major calmodulin-binding proteins in the brain.

Calmodulin 3D structure

Other calcium-binding proteins

Calmodulin belongs to one of the two main groups of calcium-binding proteins, called EF hand proteins. The other group, called annexins, bind calcium and phospholipid (e.g., lipocortin). Many other proteins bind calcium, although binding calcium may not be considered their principal function in the cell.

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Protein kinase

A **protein kinase** is an enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). This usually results in a functional change of the target protein (substrate), by changing enzyme activity, cellular location or association with other proteins. Up to 30% of all proteins may be modified by kinase activity, and kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction, the transmission of signals within the cell. The human genome contains about 500 protein kinase genes; they constitute about 2% of all eukaryotic genes.

The chemical activity of a kinase involves removing a phosphate group from ATP and covalently attaching it to one of three amino acids that have a free hydroxyl group. Most kinases act on both Serine and Threonine, others act on Tyrosine, and a number (dual specificity kinases) act on all three.

Because protein kinases have profound effects on a cell, their activity is highly regulated. Kinases are turned on or off by phosphorylation (sometimes by the kinase itself - cis-phosphorylation/ autophosphorylation), by binding of activator proteins or inhibitor proteins, or small molecules, or by controlling their location in the cell relative to their substrates.

Disregulated kinase activity is a frequent cause of disease, particularly cancer, where kinases regulate many aspects that control cell growth, movement and death. Drugs which inhibit specific kinases are being developed to treat several diseases, and some are currently in clinical use, including Gleevec (imatinib) and Iressa (gefitinib).

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Serine/threonine-specific protein kinases

Serine/threonine protein kinases (EC 2.7.1.37) phosphorylate the OH group of serine or threonine (which have similar sidechains). Activity of these protein kinases can be regulated by specific events (e. g. DNA damage), as well as numerous chemical signals, including:

* cAMP/cGMP
* Diacylglycerol
* Ca^{2+}/calmodulin

While serine/threonine kinases all phosphorylate serine or threonine residues in their substrates, they select specific residues to phosphorylate on the basis of residues that flank the phosphoacceptor site, which together comprise the *consensus sequence*. Since the consensus sequence residues of the substrate to be phosphorylated make contact with the catalytic cleft of the kinase at several key amino acids (usually through hydrophobic forces and ionic bonds), a kinase is usually not specific to a single substrate, but instead can phosphorylate a whole "substrate family" having common recognition sequences. While the catalytic domain of these kinases is highly conserved, the sequence variation that is observed in the kinome (the subset of genes in the genome that encode kinases) provides for recognition of distinct substrates. Most kinases are inhibited by a pseudosubstrate that binds to the kinase like a real substrate but lacks the amino acid to be phosphorylated. When the pseudosubstrate is removed, the kinase can perform its normal function.

Many serine/threonine protein kinases do not have their own individual EC numbers and use "2.7.1.37", which is a general EC number for any enzyme that phosphorylates proteins while converting ATP to ADP (i.e. ATP:protein phosphotransferases.) This category is currently being reviewed by the Nomenclature Committee of IUBMB (NC-IUBMB), and it is believed that the various serine/threonine-kinases will get their own EC numbers eventually.

Pelle is a serine/threonine kinase that can phosphorylate itself, and also Tube and Toll.

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Protein kinase A

Protein kinase A (EC 2.7.1.37) consists of two domains, a small domain with several β sheet structures and a larger domain containing several α helices. The binding sites for substrate and ATP are located in the catalytic cleft between the domains (or lobes). When ATP and substrate bind, the two lobes rotate so that the terminal phosphate group of the ATP and the target amino acid of the substrate move into the correct positions for the catalytic reaction to take place.

Regulation

Protein kinase A has several functions in the cell, including regulation of glycogen, sugar, and lipid metabolism. It is controlled by cAMP: in the absence of cAMP, the kinase is a tetramer of two regulatory and two catalytic subunits (R_2C_2), with the regulatory subunits blocking the catalytic center of the catalytic subunits. Binding of cAMP to the regulatory subunit leads to dissociation of active RC dimers. Also, the catalytic subunit itself can be regulated by phosphorylation.

Downregulation of protein kinase A occurs by a feedback mechanism: one of the substrates that is activated by the kinase is a phosphodiesterase, which converts cAMP to AMP, thus reducing the amount of cAMP that can activate protein kinase A.

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Protein kinase C

Protein kinase C ('PKC', EC 2.7.1.37) is actually a family of protein kinases consisting of ~10 isozymes. They are divided into three subfamilies: conventional (or classical), novel, and atypical based on their second messenger requirements. Conventional (c)PKCs contain the isoforms α, β_I, β_{II}, and γ. These require Ca^{2+}, diacylglycerol (DAG), and a phospholipid such as phosphatidylcholine for activation. Novel (n)PKCs include the &Δ;, ε, η, and θ isoforms, and require DAG, but do not require Ca^{2+} for activation. Thus, conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. On the other hand, Atypical (a)PKCs (including ζ and ι / λ isoforms) require neither Ca^{2+} nor diacylglycerol for activation. The term "protein kinase C" usually means the protein kinase Cα enzyme, a conventional PKC.

Structure and regulation

The structure of all PKCs consists of a regulatory domain and a catalytic domain tethered together by a hinge region. The catalytic region is highly homologous among the different isoforms, as well as to a lesser degree the catalytic region of other serine/threonine kinases. The second messenger requirement differences in the isoforms are a result of the regulatory region, which are similar within the classes, but differ among them. Most of the crystal structure of the catalytic region of PKC has not been determined, except for PKC theta and iota. Due to its similarity to other kinases whose crystal structure have been determined, the structure can be strongly predicted.

The regulatory domain or the amino-teminus of the PKCs contains several shared subregions. The C1 domain, present in all of the isoforms of PKC has a binding site for DAG as well as non-hydrolysable analogues called phorbol esters. This domain is functional and capable of binding DAG in both conventional and novel isoforms, however, the C1 domain in atypical PKCs is incapable of binding to DAG or phorbol esters. The C2 domain acts as a Ca2+ sensor and is present in both conventional and novel isoforms, but functional as a Ca2+ sensor only in the conventional. The pseudosubstrate region, which is present in all three classes of PKC, is a small sequence of amino acids that mimic a substrate and bind the substrate-binding cavity in the catalytic domain keeping the enzyme inactive. When Ca2+ and DAG are present in sufficient concentrations, they bind to the C2 and C1 domain, respectively, and recruit PKC to the membrane. This interaction with the membrane results in release of the pseudosubstrate from the catalytic site and activation of the enzyme. In order for these allosteric interactions to occur, however, PKC must first be properly folded and in the correct conformation permissive for catalytic action. This is contingent upon phosphorylation of the catalytic region, discussed below.

The catalytic region or kinase core of the ABC kinases contains approximately 40% amino acid sequence similarity. This similarity increases to ~ 70% across PKCs and even higher when comparing within classes. For example, the two atypical PKC isoforms, ζ and ι/λ, are 84% identical. Of the over 30

protein kinase structures whose crystal structure has been revealed, all of them have the same basic organization. They are a bilobal structure with a β sheet comprising the N-terminal lobe and an α helix constituting the C-terminal lobe. Both the ATP- and substrate-binding sites are located in the cleft formed by these two lobes. This is also where the pseudosubstrate domain of the regulatory region binds. Another feature of the PKC catalytic region that is essential to the viability of the kinase is its phosphorylation. The catalytic and novel PKCs have three phosphorylation sites, termed: the activation loop, the turn motif, and the hydrophobic motif. The atypical PKCs are phosphorylated only on the activation loop and the turn motif. Phosphorylation of the hydrophobic motif is rendered unnecessary by the presence of a glutamic acid in place of a serine, which, as a negative charge, acts similarly to a phosphorylated residue. These phosphorylation events are essential for the activity of the enzyme, and 3-phosphoinositide-dependent protein kinase-1 (PDK1) is the upstream kinase responsible for initiating the process by transphosphorylation of the activation loop.

Upon activation, protein kinase C enzymes are translocated to the plasma membrane by RACK proteins (membrane-bound receptor for activated protein kinase C proteins). The protein kinase C enzymes are known for their long-term activation: they remain activated after the original activation signal or the Ca^{2+}-wave is gone. This is presumably achieved by the production of diacylglycerol from phosphatidylcholine by a phospholipase; fatty acids may also play a role in long-term activation.

Function

The consensus sequence of protein kinase C enzymes is similar to that of protein kinase A, since it contains basic amino acids close to the Ser/Thr to be phosphorylated. Their substrates are MARCKS proteins, MAP kinase, transcription factor inhibitor IκB, the vitamin D_3 receptor VDR, Raf kinase, calpain, and the epidermal growth factor receptor.

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Ca^{2+}/calmodulin-dependent protein kinases

Also called *CaM kinases* (EC 2.7.1.123), these kinases are primarily regulated by the Ca^{2+}/calmodulin complex. These kinases show a memory effect on activation. Two types of CaM kinases are:

- *Specialized CaM kinases*. An example is the myosin light chain kinase (MLCK) that phosphorylates myosin, causing muscles to contract.

- *Multifunctional CaM kinases*. Also collectively called *CaM kinase II*, which play a role in many processes, such as neurotransmitter secretion, transcription factor regulation, and glycogen metabolism. Between 1% and 2% of the proteins in the brain are CaM kinase II.

Structure and autoregulation

The CaM kinases consist of an N-terminal catalytic domain, a regulatory domain, and an association domain. In the absence of Ca^{2+}/calmodulin, the catalytic domain is autoinhibited by the regulatory domain, which contains a pseudosubstrate sequence. Several CaM kinases aggregate into a homooligomer or heterooligomer. Upon activation by Ca^{2+}/calmodulin, the activated CaM kinases autophosphorylate each other in an intermolecular reaction. This has two effects:

1. An increase in affinity for the calmodulin complex, prolonging the time the kinase is active.

2. Continued activation of the phosphorylated kinase complex even after the calmodulin complex has dissociated from the kinase complex, which prolongs the active state even more.

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MAP kinases

Mitogen-activated protein kinases (MAPKs) (EC 2.7.1.37) respond to extracellular stimuli (mitogens) and regulate various cellular activities, such as gene expression, mitosis, differentiation, and cell survival/apoptosis. Extracellular stimuli lead to activation of a MAPK via a signaling cascade composed of MAPK, MAPK kinase (MAPKK), and MAPKK kinase (MAPKKK). A MAPKKK that is activated by extracellular stimuli phosphorylates a MAPKK on its serine and threonine residues, and then this MAPKK activates a MAPK through phosphorylation on its serine and tyrosine residues. This MAPK signaling cascade has been evolutionarily well-conserved from yeast to mammals.

To date, four distinct groups of MAPKs have been characterized in mammals: (1) extracellular signal-regulated kinases (ERKs), (2) c-Jun N-terminal kinases (JNKs), (3) p38 isoforms, and (4) ERK5. The ERKs (also known as classical MAPKs) signaling pathway is preferentially activated in response to growth factors and phorbol ester (a tumor promoter), and regulates cell proliferation and cell differentiation. The JNKs (also known as stress-activated protein kinases; SAPKs) and p38 signaling pathways are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation and apoptosis. And ERK5, which has been found recently, is activated both by growth factors and by stress stimuli, and it participates in cell proliferation.

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Mos/Raf kinases

Mos/Raf kinases form part of the MAPKK Kinase family and are activated by growth factors. The enzyme functions to stimulate growth of cells. Raf inhibition has become the target for new anti-metastatic cancer drugs as they inhibit the MAPK cascade and reduce cell proliferation.

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Tyrosine-specific protein kinases

Tyrosine-specific protein kinases (EC 2.7.1.112) phosphorylate tyrosine amino acid residues, and are, like serine/threonine-specific kinases, used in signal transduction. They act primarily as growth factor receptors and in downstream signaling from growth factors; some examples:

* Platelet-derived growth factor (PDGF) receptor;
* Epidermal growth factor (EGF) receptor;
* Insulin receptor and insulin-like growth factor (IGF1) receptor;
* Stem cell factor (*scf*) receptor (also called *c-kit*).

Receptor tyrosine kinases

These kinases consist of a transmembrane receptor with a tyrosine kinase domain protruding into the cytoplasm. They play an important role in regulating cell division, cellular differentiation, and morphogenesis. More than 50 receptor tyrosine kinases are known in mammals.

Structure

The extracellular domain serves as the ligand receptor. It can be a separate unit that is attached to the rest of the receptor by a disulfide bond. The same mechanism can be used to bind two receptors together to form a homo- or heterodimer. The transmembrane element is a single α helix. The intracellular or cytoplasmic domain is responsible for the (highly conserved) kinase activity, as well as several regulatory functions.

Regulation

Ligand binding causes two reactions:

1. Dimerization of two monomeric receptor kinases or stabilization of a loose dimer. Many ligands of receptor tyrosine kinases are multivalent. Some tyrosine receptor kinases (e.g., the platelet-derived growth factor receptor) can form heterodimers with other similar but not identical kinases of the same subfamily, allowing a highly varied response to the extracellular signal.

2. *Trans*-autophosphorylation (phosphorylation by the other kinase in the dimer) of the kinase.

The autophosphorylation causes the two subdomains of the intrinsic kinase to shift, opening the kinase domain for ATP binding. In the inactive form, the kinase subdomains are aligned so that ATP cannot reach the catalytic center of the kinase. When several amino acids suitable for phosphorylation are present in the kinase domain (e.g., the insulin-like growth factor receptor), the activity of the kinase can

increase with the number of phosphorylated amino acids; in this case, the first phosphorylation is said to be a *cis*-autophosphorylation, switching the kinase from "off" to "standby".

Signal transduction

The active tyrosine kinase phosphorylates specific target proteins, which are often enzymes themselves. An important target is the ras protein signal-transduction chain.

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Histidine-specific protein kinases

Histidine kinases are structurally distinct from most other protein kinases and are found mostly in prokaryotes as part of two-component signal transduction mechanisms. A phosphate group from ATP is first added to a histidine residue within the kinase, and later transferred to an aspartate residue on a 'receiver domain' on a different protein, or sometimes on the kinase itself. The aspartyl phosphate residue is then active in signaling.

Histidine kinases are found widely in prokaryotes, as well as in plants and fungi. The pyruvate dehydrogenase family of kinases in animals is structurally related to histidine kinases, but instead phosphorylate serine residues, and probably do not use a phospho-histidine intermediate.

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Phosphatase

A **phosphatase** is an enzyme that hydrolyses phosphoric acid monoesters into a phosphate ion and a molecule with a free hydroxyl group. This action is directly opposite to that of phosphorylases and kinases, which attach phosphate groups to their substrates by using energetic molecules like ATP. A common phosphatase in the body is alkaline phosphatase.

The presence or absence of the phosphate group on proteins, especially enzymes, is known to play a regulatory role in many biochemical pathways and signal transduction pathways. Hence together, specialized kinases and phosphatases regulate enzymatic activity.

Phosphatases can be categorised into two main categories: metalloenzymes (which are dependent on the presence of two or more metal ions in their active sites for activity), and non-metalloenzymes. These categories can then be divided into further sub-categories.

Best known of the non-metalloenzymes are the protein tyrosine phosphatases, which hydrolyse phospho-tyrosine residues. However, the metalloenzymes by far comprise the greatest bulk of phosphatases, and contain such enzymes as alkaline phosphatase (three metal ions, only two of which are catalytically active), the serine threonine phosphatases and inositol monophosphatase (a key enzyme in manic depression).

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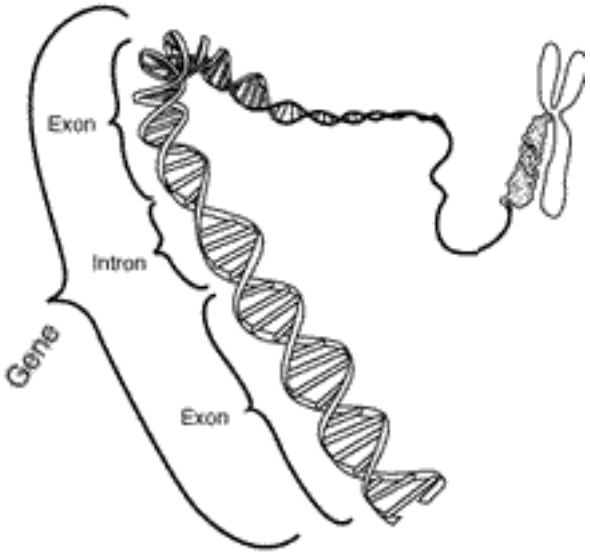
Gene



Genes are the units of heredity in living organisms. They are encoded in the organism's genome, composed of DNA or RNA, and direct the physical development and behavior of the organism. Most genes encode proteins, or biological macromolecules composed of linear chains of amino acids that effect most of the chemical reactions carried out by the cell. Some genes do not encode proteins; these genes produce non-coding RNA molecules that play key roles in protein biosynthesis and gene regulation. Molecules that result from gene expression, whether RNA or protein, are collectively known as gene products.

Most genes contain regions, called non-coding regions, than do not code for the gene products. Much of this non-coding region dictates gene regulation. A critical non-coding region of a gene is the promoter, a short DNA sequence that is required for initiation of gene expression. The genes of eukaryotic organisms often contain non-coding regions called introns which are removed from the messenger RNA in a process known as alternative splicing. The regions that actually encode the gene product, which can be much smaller than the introns, are known as exons.

Basic properties of genes

Definitions

The word "gene" was coined in 1909 by Danish botanist Wilhelm Johannsen for the fundamental physical and functional unit of heredity. The word was derived from Hugo De Vries' term *pangen*, itself a derivative of the word *pangenesis* coined by Darwin (1868).[*citationneeded*] The word pangenesis is made from the Greek words *pan* (a prefix meaning "whole", "encompassing") and *genesis* ("birth") or *genos* ("origin").

Although classical genetics and evolutionary biology use the term "gene" to refer to a conceptual entity or "unit of inheritance", modern molecular genetics typically uses the term to refer to a physical molecule. The Sequence Ontology Project, an effort directed by the larger Gene Ontology system, defines a gene as "*a locatable region of genomic sequence, corresponding to a unit of inheritance, which is associated with regulatory regions, transcribed regions and/or other functional sequence regions*".

The word "gene" is also used in common speech to refer to the inheritance of a trait, as in "a cancer gene" or "the gene for obesity"; however, biologists rarely use the term in this sense because it is highly unlikely that such complex and large-scale phenomena would be attributable to the influence of a single molecular gene.

Molecular properties

In molecular biology, a gene is a region of DNA (or RNA, in the case of some viruses) that determines the amino acid sequence of a protein (the coding sequence) and the surrounding sequence that controls when and where the protein will be produced (the regulatory sequence). The genetic code determines how the coding sequence is converted into a protein sequence. The protein-coding regions of genes are composed of a series of three-nucleotide sequences called codons. Each codon specifies a particular amino acid to be added to the protein chain; thus genes determine the protein's primary structure. Most genes are expressed in a two-stage process: first, the DNA is transcribed by enzymes known as RNA polymerases to produce an RNA molecule known as messenger RNA (mRNA), and second, the mRNA is translated by specialized cellular machinery known as the ribosome into a polypeptide chain that then folds into a functional protein. The genetic code is essentially the same for all known life, from bacteria to humans.

Through the proteins they encode, genes govern the cells in which they reside. In multicellular organisms, they control the development of the individual from the fertilized egg and the day-to-day functions of the cells that make up tissues and organs. The roles of their protein products range from mechanical support of the cell structure to the transportation and manufacture of other molecules and to the regulation of other proteins' activities.

Types of genes

Due to rare, spontaneous errors (e.g. in DNA replication), mutations in the sequence of a gene may arise. Once propagated to the next generation, this mutation may lead to variations within a species' population. Variants of a single gene are known as alleles, and differences in alleles may give rise to

differences in traits, for example eye colour. A gene's most common allele is called the wild type allele, and rare alleles are called mutants. (However, this does not imply that the wild-type allele is the ancestor from which the mutants are descended.)

In most cases, RNA is an intermediate product in the process of manufacturing proteins from genes. However, for some gene sequences, the RNA molecules are the actual functional products. For example, RNAs known as ribozymes are capable of enzymatic function, and small interfering RNAs have a regulatory role. The DNA sequences from which such RNAs are transcribed are known as non-coding RNA, or RNA genes.

Most living organisms carry their genes and transmit them to offspring as DNA, but some viruses carry only RNA. Because they use RNA, their cellular hosts may synthesize their proteins as soon as they are infected and without the delay in waiting for transcription. On the other hand, RNA retroviruses, such as HIV, require the reverse transcription of their genome from RNA into DNA before their proteins can be synthesized.

Human gene nomenclature

For each known human gene the HUGO Gene Nomenclature Committee (HGNC) approve a gene name and symbol (short-form abbreviation). All approved symbols are stored in the HGNC Database. Each symbol is unique and each gene is only given one approved gene symbol. It is necessary to provide a unique symbol for each gene so that people can talk about them. This also facilitates electronic data retrieval from publications. In preference each symbol maintains parallel construction in different members of a gene family and can be used in other species, especially the mouse.

Typical numbers of genes in an organism

The table below gives typical numbers of genes and genome size for some organisms. Estimates of the number of genes in an organism are somewhat controversial because they depend on the discovery of genes, and no techniques currently exist to prove that a DNA sequence contains no gene. (In early genetics, genes could be identified only if there were mutations, or alleles.) Nonetheless, estimates are made based on current knowledge:

Plant: <50,000
Human, mouse or rat: 25,000
Fugu fish: 40,000
Fruit Fly: 13,767
Worm: 19,000
Fungus: 6,000
Bacterium: 500–6,000
Mycoplasma genitalium: 500
DNA virus: 10–900

RNA virus: 1–25
Viroid: 0–1

Chemistry and function of genes

Chemical structure of a gene

Four kinds of sequentially linked nucleotides compose a DNA molecule or strand (more at DNA). These four nucleotides constitute the genetic alphabet. A sequence of three consecutive nucleotides, called a codon, is the protein-coding vocabulary. The sequence of codons in a gene specifies the amino-acid sequence of the protein it encodes.

In most eukaryotic species, very little of the DNA in the genome encodes proteins, and the genes may be separated by vast sequences of so-called junk DNA. Moreover, the genes are often fragmented internally by non-coding sequences called introns, which can be many times longer than the coding sequence. Introns are removed on the heels of transcription by splicing. In the primary molecular sense, they represent parts of a gene, however.

All the genes and intervening DNA together make up the genome of an organism, which in many species is divided among several chromosomes and typically present in two or more copies. The location (or locus) of a gene and the chromosome on which it is situated is in a sense arbitrary. Genes that appear together on the chromosomes of one species, such as humans, may appear on separate chromosomes in another species, such as mice. Two genes positioned near one another on a chromosome may encode proteins that figure in the same cellular process or in completely unrelated processes. As an example of the former, many of the genes involved in spermatogenesis reside together on the Y chromosome.

Many species carry more than one copy of their genome within each of their somatic cells. These organisms are called diploid if they have two copies or polyploid if they have more than two copies. In such organisms, the copies are practically never identical. With respect to each gene, the copies that an individual possesses are liable to be distinct alleles, which may act synergistically or antagonistically to generate a trait or phenotype. The ways that gene copies interact are explained by chemical dominance relationships (more at genetics, allele).

Expression of molecular genes

For various reasons, the relationship between DNA strand and a phenotype trait is not direct. The same DNA strand in two different individuals may result in different traits because of the effect of other DNA strands or the environment.

- The DNA strand is expressed into a trait only if it is transcribed to RNA. Because the transcription starts from a specific base-pair sequence (a promoter) and stops at another (a terminator), our DNA strand needs to be correctly placed between the two. If not, it is considered as junk DNA, and is not

expressed.
- Cells regulate the activity of genes in part by increasing or decreasing their rate of transcription. Over the short term, this regulation occurs through the binding or unbinding of proteins, known as transcription factors, to specific non-coding DNA sequences called regulatory elements. Therefore, to be expressed, our DNA strand needs to be properly regulated by other DNA strands.
- The DNA strand may also be silenced through DNA methylation or by chemical changes to the protein components of chromosomes (see histone). This is a permanent form of regulation of the transcription.
- The RNA is often edited before its translation into a protein. Eukaryotic cells splice the transcripts of a gene, by keeping the exons and removing the introns. Therefore, the DNA strand needs to be in an exon to be expressed. Because of the complexity of the splicing process, one transcribed RNA may be spliced in alternate ways to produce not one but a variety of proteins (alternative splicing) from one pre-mRNA. Prokaryotes produce a similar effect by shifting reading frames during translation.
- The translation of RNA into a protein also starts with a specific start and stop sequence.
- Once produced, the protein interacts with the many other proteins in the cell, according to the cell metabolism. This interaction finally produces the trait.

This complex process helps explain the different meanings of "gene":

- a nucleotide sequence in a DNA strand;
- or the transcribed RNA, prior to splicing;
- or the transcribed RNA after splicing, i.e. without the introns

The latter meaning of gene is the result of more "material entity" than the first one.

Mutations and evolution

Just as there are many factors influencing the expression of a particular DNA strand, there are many ways to have genetic mutations.

For example, natural variations within *regulatory sequences* appear to underlie many of the heritable characteristics seen in organisms. The influence of such variations on the trajectory of evolution through natural selection may be as large as or larger than variation in sequences that encode proteins. Thus, though regulatory elements are often distinguished from genes in molecular biology, in effect they satisfy the shared and historical sense of the word. Indeed, a breeder or geneticist, in following the inheritance pattern of a trait, has no immediate way to know whether this pattern arises from coding sequences or regulatory sequences. Typically, he or she will simply attribute it to variations within a gene.

Errors during DNA replication may lead to the duplication of a gene, which may diverge over time. Though the two sequences may remain the same, or be only slightly altered, they are typically regarded as separate genes (i.e. not as alleles of the same gene). The same is true when duplicate sequences appear in different species. Yet, though the alleles of a gene differ in sequence, nevertheless they are

regarded as a single gene (occupying a single locus).

History

The existence of genes was first suggested by Gregor Mendel, who, in the 1860s, studied inheritance in pea plants and hypothesized a factor that conveys traits from parent to offspring. Although he did not use the term *gene*, he explained his results in terms of inherited characteristics. Mendel was also the first to hypothesize independent assortment, the distinction between dominant and recessive traits, the distinction between a heterozygote and homozygote, and the difference between what would later be described as genotype and phenotype. Mendel's concept was finally named when Wilhelm Johannsen coined the word *gene* in 1909.

In the early 1900s, Mendel's work received renewed attention from scientists. In 1910, Thomas Hunt Morgan showed that genes reside on specific chromosomes. He later showed that genes occupy specific locations on the chromosome. With this knowledge, Morgan and his students began the first chromosomal map of the fruit fly *Drosophila*. In 1928, Frederick Griffith showed that genes could be transferred. In what is now known as Griffith's experiment, injections into a mouse of a deadly strain of bacteria that had been heat-killed transferred genetic information to a safe strain of the same bacteria, killing the mouse.

In 1941, George Wells Beadle and Edward Lawrie Tatum showed that mutations in genes caused errors in certain steps in metabolic pathways. This showed that specific genes code for specific proteins, leading to the "one gene, one enzyme" hypothesis. Oswald Avery, Collin Macleod, and Maclyn McCarty showed in 1944 that DNA holds the gene's information. In 1953, James D. Watson and Francis Crick demonstrated the molecular structure of DNA. Together, these discoveries established the central dogma of molecular biology, which states that proteins are translated from RNA which is transcribed from DNA. This dogma has since been shown to have exceptions, such as reverse transcription in retroviruses.

Richard Roberts and Phillip Sarp discovered in 1977 that genes can be split into segments. This leads to the idea that one gene can make several proteins. Recently (as of 2003-2006), biological results let the notion of gene appear more slippery. In particular, genes do not seem to sit side by side on DNA like discrete beads. Instead, regions of the DNA producing distinct proteins may overlap, so that the idea emerges that "genes are one long continuum". (Pearson, 2006)

Evolutionary concept of gene

George C. Williams first explicitly advocated the gene-centric view of evolution in his book *Adaptation and Natural Selection*. Also, he proposed an evolutionary concept of gene to be used when we are talking about natural selection favoring some gene. The definition is: "that which segregates and recombines with appreciable frequency." According to this definition, even an asexual genome could be considered a gene, insofar it have an appreciable permanency through many generations.

The difference is: the molecular gene *transcribes* as a unit, and the evolutionary gene *inherits* as a unit.

Richard Dawkins' *The Selfish Gene* and *The Extended Phenotype* defended the idea that the gene is the only replicator in living systems. This means that only genes transmit their structure largely intact and are potentially immortal in the form of copies. So, genes should be the unit of selection. In River Out of Eden, Dawkins further refined the idea of gene-centric selection by describing life as a river of compatible genes flowing through geological time. Scoop up a bucket of genes from the river of genes, and we have an organism serving as temporary bodies. A river of genes may fork into two branches representing two non-interbreeding species as a result of geographical separation.

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Exon

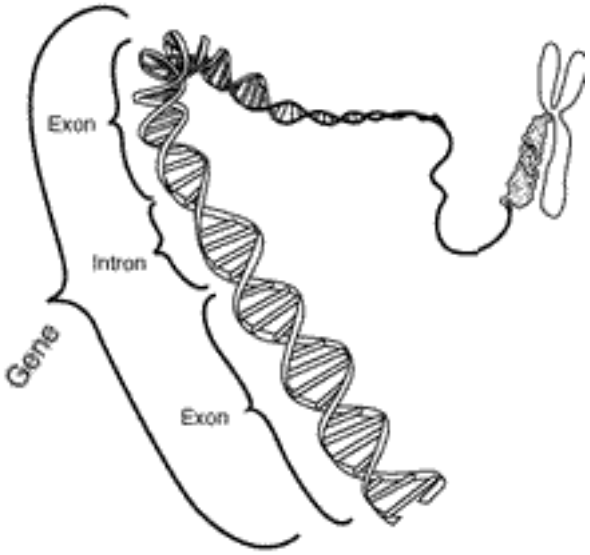

Diagram of the location of introns and exons within a gene.

Exons are the regions of DNA within a gene that are not spliced out from the transcribed RNA and are retained in the final messenger RNA (mRNA) molecule. Exons of many eukaryotic genes are interrupted by segments of non-coding DNA (introns). The term "exon" was coined by Walter Gilbert in 1978.

Function

In many genes, each exon contains part of the open reading frame (ORF) that codes for a specific portion of the complete protein, however, the term exon is often misused to refer only to coding sequences for the final protein. This is not true, since many noncoding exons are known in human genes (Zhang 1998).

Some of the exons will be wholly or part of the 5' untranslated region (5' UTR) or the 3' untranslated region (3' UTR) of each transcript. The untranslated regions are important for efficient translation of the transcript as well as being important for controlling the rate of translation and half life of the transcript. Furthermore, transcripts made from the same gene may not have the same exon structure since parts of the mRNA could be removed by the process of alternative splicing. Some mRNA transcripts have exons with no ORF's and thus are sometimes referred to as non-coding RNA.

Exonization is the creation of a new exon, as result of mutations in intronic sequences.

Polycistronic messages have multiple ORF's in one transcript and also have small regions of untranslated sequence between each ORF.

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Intron

Introduction | Intron evolution

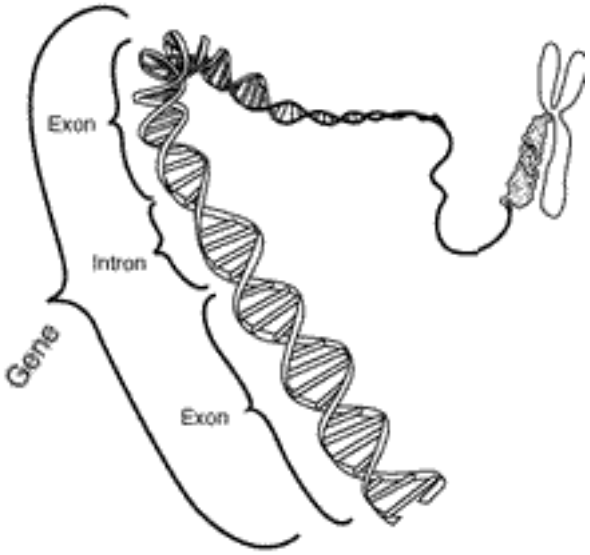
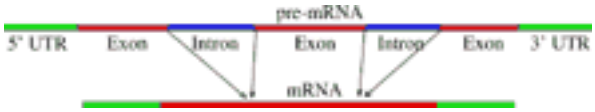


Diagram of the location of introns and exons within a gene.

Introns are sections of DNA that will be spliced out after transcription, but before the RNA is used. Introns are common in eukaryotic RNAs of all types, but are found in prokaryotic tRNA and rRNA genes only. The regions of a gene that remain in spliced mRNA are called exons. The number and length of introns varies widely among species and among genes within the same species. For example, the pufferfish *Takifugu rubripes* has little intronic DNA. Genes in mammals and flowering plants, on the other hand, often have numerous introns, which can be much longer than the nearby exons.

Introduction



Simple illustration of pre-mRNA to mRNA splicing.

Introns sometimes allow for alternative splicing of a gene, so that several different proteins that share some sections in common can be produced from a single gene. The control of mRNA splicing, and hence of which alternative is produced, is performed by a wide variety of signal molecules. Introns also sometimes contain "old code," sections of a gene that were probably once translated into protein but which are now discarded.

While most of the sequence in any given intron is junk DNA with no known function, several short sequences that are important for efficient splicing are known. The exact mechanism for these *intronic splicing enhancers* is not well understood, but it is thought that they serve as binding sites on the

transcript for proteins that stabilize the spliceosome. It is also possible that RNA secondary structure formed by intronic sequences may have an effect on splicing.

The discovery of introns lead to the Nobel Prize in Physiology or Medicine in 1993 for Phillip Allen Sharp and Richard J. Roberts.

Some introns such as Group I and Group II introns are actually ribozymes that are capable of catalyzing their own splicing out of the primary RNA transcript. This self splicing was discovered by Thomas Cech who shared the 1989 Nobel Prize in Chemistry with Sidney Altman for the discovery of the catalytic properties of RNA.

Intron evolution

There are two competing theories as to the evolutionary origin of introns, which is usually studied in a highly conserved family of genes such as the actins. In the introns-early model ancestral genes are believed to have included a large number of introns, some of which have been lost over evolutionary time, leading to the different but similar intron patterns in related genes of different species. The introns-late model suggests instead that introns occur in the same location in variants of a given gene because the location is in some way predisposed to the introduction of an intron, and therefore that a similar intron pattern may arise in two different species by a form of convergent evolution.

Evolutionary "change in intron-exon structure is gradual, clock-like, and largely independent of coding-sequence evolution."

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Proteolysis

Proteasome | Importance of the ubiquitin proteasome system | Structure of the 26S proteasome | An Overview of the Proteosome/Ubiquitin Mechanism

Proteolysis is the directed degradation (digestion) of proteins by cellular enzymes called proteases or by intramolecular digestion.

Proteolysis is used by the cell for several purposes. They include:
- Removal of N-terminal methionine residues after translation.
- Removal of the signal sequence of peptides after their transport through a membrane
- Separation of viral proteins that were translated from a monocistronic mRNA
- Digestion of proteins from foods as a source of amino acids
- Conversion of predecessor-proteins (proenzymes, zymogens, prehormones) into their final structures.
- Degradation of cyclins at different stages of the cell cycle.

Proteasome

Proteasomes are complex structures inside cells that break down proteins. Ubiquitin proteasome system or ubiquitin-26S proteasome system, is a barrel-shaped multi-protein complex that can specifically digest other proteins into short polypeptides and amino acids in an ATP-driven reaction. The Ubiquitin proteasome system is essential for many cellular processes including cell cycle, signal transduction and regulation of gene expression. The importance of proteolytic degradation inside cells and the role of ubiquitin in proteolytic pathways was acknowledged in the awarding of the 2004 Nobel Prize in Chemistry to Aaron Ciechanover, Avram Hershko and Irwin Rose.

Importance of the ubiquitin proteasome system

The ubiquitin-proteasome system is the primary mechanism in eukaryotic cells for degrading unwanted and misfolded proteins. Through the cascade of E1 ubiquitin activating, E2 ubiquitin conjugating, and E3 ubiquitin ligase enzymes, ubiquitin monomers are attached sequentially to target proteins. The polyubiquitinated proteins are then recognized by the 26S proteasome, a large ATP-dependent multicatalytic protease, which removes the ubiquitin chain and degrades the proteins to short peptides. The selection and specific timing of polyubiquitination of the target proteins are conferred by different E3 ubiquitin ligases. In addition to degrading misfolded proteins, the proteasome is involved in destruction of proteins that are regulated temporally (e.g. cell cycle regulators), or by environmental factors (e.g. cholesterol synthesis regulators and several transcription factors). In plants it is also involved in circadian clocks and phytohormones signaling pathways.

Cell cycle progression is controlled by ordered action of cyclin-dependent kinases (CDKs), activated by

defined cyclins, appearing for given periods in the cycle. When the function of a CDK-cyclin complex is accomplished, the associated cyclin partner becomes polyubiquitinated and destroyed by the ubiquitin-26S proteasome system. The irreversible nature of proteolysis is utilized by cells to give the cell cycle directionnality. In the cell cycle, two structurally related multicomponent ubiquitin ligases, the Anaphase-promoting complex (APC) and the Skp1/Cul1/F-box protein (SCF) complexes (SCF complex) have essential and complementary functions by temporally controlled degradation of various cell cycle proteins (See also Ubiquitin ligase). In plants, auxin signaling is mediated by auxin-induced degradation of the Aux/IAA proteins by SCF^{TIR1}, where TIR1 is an auxin receptor.

Structure of the 26S proteasome

The 26S proteasome is used for the digestion of ubiquitin-marked proteins. It is a barrel-shaped multi-protein complex that can specifically digest other proteins into short polypeptides and amino acids in an ATP-driven reaction. The proteasome is hollow, providing an enclosed space for protein digestion, and has openings at the two ends to allow entry of the targeted protein. It is located on both sides of a cell's nuclear membrane and consists of a 20S core protease particle and two 19S regulatory particles. The 20S unit consists of 2 rings of α subunits and 2 rings of β subunits, stacked in the order αββα as a series of heptameric rings. It is about 15 nm long and 11.5 nm wide. The alpha subunits are structural, while three of the beta subunits are catalytic and exert the proteolytic activity: β1, β2 and β5. In mammals, different catalytic subunits can be induced or repressed in response to cytokines such as interferon; the different beta subunits alter the cleavage and length preferences of the proteasome.

Each 19S unit consists of a lid and a base with a 19S regulatory particle is attached to each end of the 20S core particle via its base. Some of the subunits in the base are ATPases.

The core 20S proteasome associates with different caps, including the PA28 complex; these different caps modify the activity of the proteasome. The 20S core particle is also known as the Catalytic Particle (or CP) and can exert its proteolytic activity without ubiquitin/ATP. In many mammalian cells the 20S proteasome is the most represented species and has been shown to degrade target proteins that have been oxidized or unfolded.

An Overview of the Proteosome/Ubiquitin Mechanism

- Recognition: Ubiquinated proteins dock into the 19S cap
- Dissociation: An ATP-dependent process unravels the protein and releses the ubiquitin.
- Translocation: The protein is fed into the shaft where it reaches the inner two rings responsible for proteolysis.
- Destruction: The protein is entirely degraded into 8-11 amino acid oligopeptides which are released.

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Proteolysis

RNA Degradation

After a certain amount of time, the message is degraded into its component nucleotides, usually with the assistance of RNases. The limited longevity of mRNA enables a cell to alter protein synthesis rapidly in response to its changing needs.

Different mRNAs within the same cell have distinct lifetimes. In bacterial cells, individual mRNAs can survive from seconds to more than an hour; in mammalian cells, mRNA lifetimes range from several minutes to days. The greater the stability of an mRNA, the more protein may be produced from that transcript.

Ribonuclease

Ribonuclease, abbreviated commonly as **RNase**, is an nuclease that catalyzes the breakdown of RNA into smaller components. They can be divided into endonucleases and exonucleases, and comprise several sub-classes within the EC 3.1 class of enzymes.

RNases are extremely common, resulting in very short lifespans for any RNA that is not in a protected environment. One mechanism of protection is **ribonuclease inhibitor (RI)**, which comprises a relatively large fraction of cellular protein (~0.1%) and which binds to certain ribonucleases with the highest affinity of any protein-protein interaction; the dissociation constant for the RI-RNase A complex is ~20 fM under physiological conditions. RI is used in most laboratories that study RNA to protect their samples against degradation from environmental RNases.

Perhaps surprisingly, RNases tend to be insensitive to the cleaved sequence. There appear to be no RNase analogs of the restriction enzymes, which cleave highly specific sequences of double-stranded DNA. This deficit may be overcome using RNase H and single-stranded DNA complementary to the desired cleavage sequence.

RNases play a critical role in many biological processes, including angiogenesis and self-incompatibility in flowering plants (angiosperms).

Major types of endoribonucleases

- **RNase A** is an RNase that is commonly used in research. RNase A (e.g., bovine pancreatic ribonuclease A: PDB 2AAS, EC 3.1.27.5) is one of the hardiest enzymes in common laboratory usage; one method of isolating it is to boil a crude cellular extract until all enzymes other than RNase A are denatured. It is sequence specific for single stranded RNAs. It cleaves 3'end of unpaired C and U

residues.
- **RNase P** is a type of ribonuclease and is currently under heavy research. RNase P is unique from other RNases in that it is a ribozyme - a ribonucleic acid that acts as a catalyst in the same way that a protein based enzyme would. Its function is to cleave off an extra, or precursor, sequence of RNA on tRNA molecules. Further RNase P is one of two known multiple turnover ribozymes in nature (the other being the ribosome).
- **RNase H** is a ribonuclease that cleaves the RNA in a DNA/RNA duplex to produce ssDNA. RNase H is a non-specific endonuclease and catalyzes the cleavage of RNA via a hydrolytic mechanism, aided by an enzyme-bound divalent metal ion. In contrast to other ribonucleases, such as RNase V1, RNase H leaves a 3'-phosphorylated product.
- **RNase III** is specific for double-stranded RNA.
- **RNase T1** is sequence specific for single stranded RNAs. It cleaves 3'-end of unpaired G residues.
- **RNase T2** is sequence specific for single stranded RNAs. It cleaves 3'-end of all 4 residues, but preferentially 3'-end of As.
- **RNase U2** is sequence specific for single stranded RNAs. It cleaves 3'-end of unpaired A residues.
- **RNase V1** is non-sequence specific for double stranded RNAs. It cleaves base-paired nucleotide residues.
- **RNase I** cleaves 3'-end of of all 4 residues with no base preference
- **RNase PhyM** is sequence specific for single stranded RNAs. It cleaves 3'-end of unpaired A and U residues.
- **RNase V**

Major types of exoribonucleases

- **Polynucleotide Phosphorylase (PNPase)** functions both as an exonuclease as well as a nucleotidyltransferase.
- **RNase PH** functions both as an exonuclease as well as a nucleotidyltransferase.
- **RNase II** is responsible for the processive 3'-to-5' degradation of single-stranded RNA.
- **RNase R** is a close homolog of RNase II, but it can, unlike RNase II, degrade RNA with secondary structures without help of accessory factors.
- **RNase D** is involved in the 3'-to-5' processing of pre-tRNAs.
- **RNase T** is the major contributor for the 3'-to-5' maturation of many stable RNAs.
- **Oligoribonuclease** degrades short oligonucleotides to mononucleotides.
- **Exoribonuclease I** degrades single-sranded RNA from 5'-to-3', exists only in eukaryotes.
- **Exoribonuclease II** is a close homolog of Exoribonuclease I.

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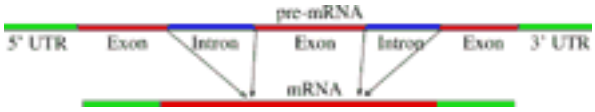
Splicing



Simple illustration of exons and introns in pre-mRNA. The mature mRNA is formed by splicing.

Splicing is a modification of genetic information after transcription, in which introns are removed and exons are joined. Splicing prepares precursor messenger RNA in eukaryotes to produce mature messenger RNA. This mature messenger RNA is then prepared to undergo translation as part of protein synthesis to produce proteins. Splicing occurs by a series of biochemical reactions between RNA nucleotides, which are catalyzed by proteins, RNA, or both.

Splicing pathways

Several methods of RNA splicing occur in nature. The type of splicing depends on the structure of the spliced intron and the catalysts required for splicing to occur. Regardless of which pathway is used, the excised introns are discarded.

Spliceosomal

Spliceosomal introns often reside in eukaryotic protein-coding genes. Within the intron, a 3' splice site, 5' splice site, and branch site are required for splicing. Splicing is catalyzed by the spliceosome which is a large RNA-protein complex composed of five small nuclear ribonucleoproteins (snRNPs, pronounced "snurps"). The RNA components of snRNPs interact with the intron and may be involved in catalysis. Two types of spliceosomes have been identified (the major and minor) which contain different snRNPs.

- Major
The major spliceosome splices introns containing GU at the 5' splice site and AG at the 3' splice site. It is composed of the U1, U2, U4, U5, and U6 snRNPs.

U1- binds 5' splice site U2- binds the branch U4- inhibits U6, lost to activate spliceosome U5 - binds U1 and U2 to create lariat U6 - When, activated, displaces U1 and binds U2. U2-U6 forms active catalytic complex

- Minor
The minor spliceosome is very similar to the major spliceosome, however it splices rare introns with different splice site sequences. Here, the 3' and 5' splice sites are AU and AC, respectively. While the

minor and major spliceosomes contain the same U5 snRNP, the minor spliceosome has different, but functionally analogous snRNPs for U1, U2, U4, and U6, which are respectively called U11, U12, U4atac, and U6atac. - Trans-splicing
Trans-splicing is a form of splicing that joins two exons that are not within the same RNA transcript.

Self-splicing

Self-splicing occurs for rare introns that form a ribozyme, performing the functions of the spliceosome by RNA alone. There are three kinds of self-splicing introns, *Group I*, *II*, and *III*. Group II and III introns perform splicing similar to the spliceosome without requiring any protein. This similarity suggests that Group II and III introns may be evolutionarily related to the spliceosome. Self-splicing may also be very ancient, and may have existed in an RNA world that was present before protein.

tRNA splicing

tRNA (also tRNA-like) splicing is another rare form of splicing that usually occurs in tRNA. The splicing reaction involves a different biochemistry than the spliceomsomal and self-splicing pathways. Ribonucleases cleave the RNA and ligases join the exons together. This form of splicing does also not require any RNA components for catalysis.

Evolution

Splicing occurs in all the kingdoms or domains of life, however, the extent and types of splicing can be very different between the major divisions. Eukaryotes splice many protein-coding messenger RNAs and some non-coding RNAs. Prokaryotes, on the other hand, splice rarely, but mostly non-coding RNAs. Another important difference between these two groups of organisms is that prokaryotes completely lack the spliceosomal pathway.

Because spliceosomal introns are not conserved in all species, there is debate concerning when spliceosomal splicing evolved. Two models have been proposed: the intron late and intron early models.

Biochemical mechanism

Spliceosomal splicing and self-splicing involves a two-step biochemical process. Both steps involve transesterification reactions that occur between RNA nucleotides. tRNA splicing, however, is an exception and does not occur by transesterification.

Spliceosomal and self-splicing transesterification reactions occur in a specific order. First, a specific *branch-point* nucleotide within the intron reacts with the first nucleotide of the intron, forming an *intron lariat*. Second, the last nucleotide of the first exon reacts with the first nucleotide of the second exon, joining the exons and releasing the intron lariat.

Alternative splicing

In many cases, the splicing process can create many unique proteins by variations in the splicing of the same messenger RNA. This phenomenon is called alternative splicing.

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Activator (genetics)

An **activator**, is a DNA-binding protein that regulates one or more genes by increasing the rate of transcription. The activator may increase transcription by virtue of a connected domain which assists in the formation of the RNA polymerase holoenzyme, or may operate through a coactivator. A coactivator binds the DNA-binding activator and contains the domain assisting holoenzyme formation. A particular activator may bind one or more specific coactivators.

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Alternative splicing

Alternative splicing is the process that occurs in eukaryotes in which the splicing process of a pre-mRNA transcribed from one gene can lead to different mature mRNA molecules and therefore to different proteins. Also viruses have adapted to this biochemical process when using the protein biosynthesis apparatus.

When the pre-mRNA has been transcribed from the DNA, it includes several introns and exons. In nematodes, the mean is 4-5 exons and introns; in the fruit fly *Drosophila* there can be more than 100 introns and exons in one transcribed pre-mRNA. But introns and exons are not yet determided at this stage. This decision is made during the splicing process. The regulation and selection of splice sites is done by Serine/Arginine-residue proteins, or SR proteins. The use of alternative splicing factors leads to a modification of the definition of a "gene". Some have proposed that a gene should be considered as a twofold information structure:

- A DNA sequence coding for the pre-mRNA
- An additional DNA code or other regulating process, which regulates the alternative splicing.

There are four known modes of alternative splicing:

- **Alternative selection of promoters**: this is the only method of splicing which can produce an alternative N-terminus domain in proteins. In this case, different sets of promoters can be spliced with certain sets of other exons.
- **Alternative selection of cleavage/polyadenylation sites**: this is the only method of splicing which can produce an alternative C-terminus domain in proteins. In this case, different sets of polyadenylation sites can be spliced with the other exons.
- **Intron retaining mode**: in this case, instead of splicing out an intron, the intron is retained in the mRNA transcript. However, the intron must be properly encoding for amino acids. The intron's code must be properly expressible, otherwise a stop codon or a shift in the reading frame will cause the protein to be non-functional.
- **Exon cassette mode**: in this case, certain exons are spliced out to alter the sequence of amino acids in the expressed protein.

Importance in molecular genetics

Alternative splicing is of great importance to genetics - it invalidates the old theory of one DNA sequence coding for one polypeptide (the "one-gene-one-protein" hypothesis). External information is needed in order to decide which polypeptide is produced, given a DNA sequence and pre-mRNA. (This does not necessarily negate the central dogma of molecular biology which is about the flow of information from genes to proteins). Since the methods of regulation are inherited, the interpretation of a mutation may be changed.

It has been proposed that for eukaryotes it was a very important step towards higher efficiency, because information can be stored much more economically. Several proteins can be encoded in a DNA sequence whose length would only be enough for two proteins in the prokaryote way of coding. Others have noted that it is unnecessary to change the DNA of a gene for the evolution of a new protein. Instead, a new way of regulation could lead to the same effect, but leaving the code for the established proteins unharmed.

Another speculation is that new proteins could be allowed to evolve much faster than in prokaryotes. Furthermore, they are based on hitherto functional amino acid subchains. This may allow for a higher probability for a functional new protein. Therefore the adaptation to new environments can be much faster - with fewer generations - than in prokaryotes. This might have been one very important step for multicellular organisms with a longer life cycle.

A common myth is that alternative splicing is responsible for humans supposedly being the most complex animals, saying that humans perform more alternative splicing than the other animals. However, this is not the case. A study conducted on the subject found that "the amount of alternative splicing is comparable, with no large differences between humans and other animals."

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Coactivator (genetics)

A coactivator is a protein increases gene expression by binding to an activator which contains a DNA binding domain. The coactivator is unable to bind DNA by itself.

The coactivator increases the rate of initiation by stabilising the formation of the RNA polymerase holoenzyme enabling faster clearance of the promoter

The same coactivator will likely be used to increase transcription of many different genes, since it is the actiator the provides the specificity to a particular sequence.

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Enhancer

In genetics, an **enhancer** is a short region of DNA that can be bound with proteins (namely, the trans-acting factors, much like a set of transcription factors) to enhance transcription levels of genes (hence the name) in a gene-cluster. An enhancer does not need to be particularly close to the genes it acts on, and need not be located on the same chromosome. An enhancer does not need to bind close to the transcription initiation site to affect its transcription, as some have been found to bind several hundred thousand base pairs upstream or downstream of the start site. Enhancers can also be found within introns. An enhancer's orientation may even be reversed without affecting its function. Furthermore, an enhancer may be excised and inserted elsewhere in the chromosome, and still affect gene transcription. That is the reason that intron polymorphisms are checked though they are not transcribed and translated.

Currently, there are two different theories on the information processing that occurs on enhancers:

- Enhanceosomes - rely on highly cooperative, coordinated action and can be disabled by single point mutations that move or remove the binding sites of individual proteins
- Flexible billboards - less integrative, multiple proteins independently regulate gene expression and their sum is read in by the basal transcriptional machinery

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Gene expression

Gene expression, also called **protein expression** or often simply **expression** is the process by which a gene's DNA sequence is converted into the structures and functions of a cell.

Gene expression is a multi-step process that begins with transcription of DNA, which genes are made of, into messenger RNA. It is then followed by post transcriptional modification and translation into a gene product, followed by folding, post-translational modification and targeting.

The amount of protein that a cell expresses depends on the tissue, the developmental stage of the organism and the metabolic or physiologic state of the cell.

Measurement

Indirectly, the expression of particular genes may be assessed with DNA microarray technology, which can provide a rough measure of the cellular concentration of different messenger RNAs; often thousands at a time. While the name of this type of assessment is actually a misnomer, it is often referred to as expression profiling. The expression of many genes is known to be regulated after transcription, so an increase in mRNA concentration need not always increase expression. A more sensitive and more accurate method of relative gene expression measurement is real-time polymerase chain reaction. With carefully constructed standard curve it can even produce an absolute measurement such as in number of copies of mRNA per nanolitre of homogenized tissue, or in number of copies of mRNA per total poly-adenosine RNA. Protein expression levels can be measured by fusing the desired protein to another reporter protein, such as the green fluorescent protein or the enzyme beta-galactosidase. The expression level of these reporter proteins can be directly quantitated using standard techniques.

Regulation of gene expression

Regulation of gene expression is the cellular control of the amount and timing of appearance of the functional product of a gene. Any step of gene expression may be modulated, from the DNA-RNA transcription step to post-translational modification of a protein. Gene regulation gives the cell control over structure and function, and is the basis for cellular differentiation, morphogenesis and the versatility and adaptability of any organism.

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Promoter

In genetics, a **promoter** is a DNA sequence that enables a gene to be transcribed. The promoter is recognized by RNA polymerase, which then initiates transcription. In RNA synthesis, promoters are a means to demarcate which genes should be used for messenger RNA creation - and, by extension, control which proteins the cell manufactures.

The perfect promoter is called a canonical sequence.

Promoter elements

- Core promoter - Transcription Start Site (TSS)
- Approximately -35
- A binding site for RNA polymerase - RNA polymerase I: transcribes genes encoding ribosomal RNA
- RNA polymerase II: transcribes genes encoding messenger RNA and certain small nuclear RNAs
- RNA polymerase III: transcribes genes encoding tRNAs and other small RNAs
- General transcription factor binding sites
- Proximal promoter - Approximately -250
- Specific transcription factor binding sites
- Distal promoter - Anything further upstream (but not an enhancer or other regulatory region whose influence is positional/orientation independent)
- Specific transcription factor binding sites

Promoters represent critical elements that can work in concert with other regulatory regions (enhancers, silencer (DNA), boundary elements/insulators) to direct the level of transcription of a given gene.

The usage of canonical sequence for a promoter is problematic, and should be clarified. Canonical implies perfect, in some sense. In the case of a transcription factor binding site, then there may be a single sequence which binds the protein most strongly under specified cellular conditions. This might be called canonical. However, natural selection may favor less energetic binding as a way of regulating transcriptional output. In this case, we may call the most common sequence in a population, the wild-type sequence. It may not even be the most advantageous sequence to have under prevailing conditions. Recent evidence also indicates that several genes (including the proto-oncogene c-myc) have G-quadruplex motifs as potential regulatory signals.

A major question in evolutionary biology is how important tinkering with promoter sequences is to evolutionary change, for example, the changes that have occurred in the human lineage after separating from chimps. Some evolutionary biologists, for example Allan Wilson, have proposed that evolution in promoter or regulatory regions may be more important than changes in coding sequences over such time frames.

Promoter sequences

Prokaryotic promoters

In prokaryotes, the promoter consists of two short sequences at -10 and -35 position *upstream* of the gene, that is, prior to the gene in the direction of transcription. The sequence at -10 is called the Pribnow box and usually consists of the six nucleotides TATAAT. The Pribnow box is absolutely essential to start transcription in prokaryotes. The other sequence at -35 usually consists of the six nucleotides TTGACA. Its presence allows a very high transcription rate.

```
<-- upstream                                                    downstream -->
5'-
XXXXXXXPPPPPXXXXXXPPPPPPXXXXGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGXXXX-
3'
-35       -10       Gene to be transcribed
(note that the optimal spacing between the -35 and -10 sequences is 19 nt)
```

Probability of occurrence of each nucleotide

```
for -10 sequence
T    A    T    A    A    T
77%  76%  60%  61%  56%  82%

for -35 sequence
T    T    G    A    C    A
69%  79%  61%  56%  54%  54%
```

Eukaryotic promoters

Eukaryotic promoters are extremely diverse and are difficult to characterize. They typically lie upstream of the gene and can have regulatory elements several kilobases away from the transcriptional start site. In eukaryotes, the transcriptional complex can cause the DNA to bend back on itself, which allows for placement of regulatory sequences far from the actual site of transcription. Many eukaryotic promoters, but by no means all, contain a TATA box (sequence TATAAA), which in turn binds a TATA binding protein which assists in the formation of the RNA polymerase transcriptional complex. The TATA box typically lies very close to the transcriptional start site (often within 50 bases).

Eukaryotic promoter regulatory sequences typically bind proteins called transcription factors which are involved in the formation of the transcriptional complex. An example is the E-box (sequence CACGTG), which binds transcription factors in the basic-helix-loop-helix (bHLH) family (e.g. BMAL1-Clock, cMyc).

Binding

The binding of a promoter sequence (P) to a sigma factor-RNAP complex (R) is a two step process:

- R+P <-->RP(closed). K = 10E7
- RP(closed) --> RP(open). K = 10E-2

Diseases Associated with Aberrant Promoter Function

Though OMIM is a major resource for gathering information on the relationship between mutations and natural variation in gene sequence and susceptibility to hundreds of diseases, it requires a sophisticated search strategy to extract those diseases that are associated with defects in transcriptional control where the promoter is believed to have direct involvement. This is a list of diseases that evidence suggests have some involvement of promoter malfunction, either through direct mutation of a promoter sequence or mutation in a transcription factor or transcriptional co-activator. Keep in mind that most diseases are heterogeneous in etiology, meaning that one "disease" is often many different diseases at the molecular level, though the symptoms exhibited and the response to treatment might be identical. How diseases respond differently to treatment as a result of differences in the underlying molecular origins is partially addressed by the discipline of pharmacogenomics. Not listed here are the many kinds of cancers that involve aberrant changes in transcriptional regulation owing to the creation of chimeric genes through pathological chromosomal translocation.

- Asthma
- Beta thalassemia
- Rubinstein-Taybi syndrome

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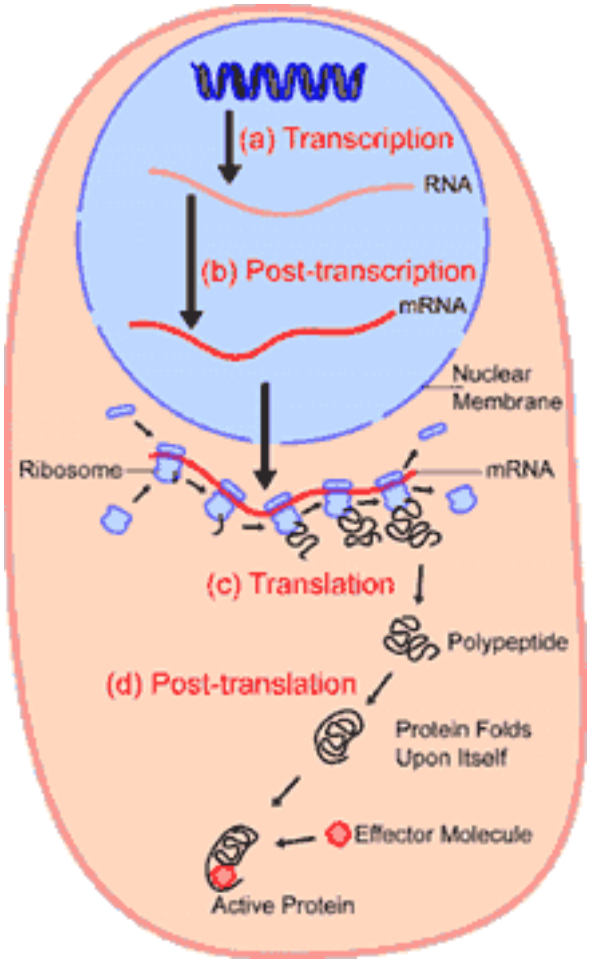
Protein biosynthesis

Transcription | Translation | Events following biosynthesis (Protein Synthesis)

Protein biosynthesis(Synthesis) is the process in which cells build proteins. The term is sometimes used to refer only to protein translation but more often it refers to a multi-step process, beginning with transcription and ending with translation. Protein biosynthesis although very similar, differs between prokaryotes and eukaryotes.



An overview of protein synthesis.
Within the nucleus of the cell (light blue), genes (DNA, dark blue) are transcribed into RNA. This RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA (red) that is then transported out of the nucleus and into the cytoplasm (peach), where it undergoes translation into a protein. mRNA is translated by ribosomes (purple) that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. Newly synthesized proteins (black) are often further modified, such as by binding to an effector molecule (orange), to become fully active.

Transcription

Transcription only requires one strand of the DNA double helix. This is called the template strand. Transcription starts with the process of initiation. RNA polymerase, an enzyme, binds to a specific region on DNA that designates the starting point of transcription. This binding region is called the promoter. As the RNA polymerase binds on to the promoter, the DNA strands are beginning to unwind.

The second process is elongation. RNA polymerase travels along the template (noncoding) strand, synthesizing a ribonucleotide polymer. RNA polymerase does not use the coding strand as a template because a copy of any strand produces a base sequence **complementary** to the strand which is being copied. Therefore DNA from the noncoding strand is used as a template to copy the coding strand.

As the polymerase reaches the termination stage, modifications are required for the newly transcribed mRNA to be able to travel to the other parts of the cell, including cytoplasm and endoplasmic reticulum. A 5′ cap is added to the mRNA to protect it from degradation. A poly-A tail is added on the 3′ end for protection and as a template for further process. In eukaryotes (higher organisms) the vital progess of splicing (genetics) occurs at this stage.

Translation

During translation, mRNA is transcribed from DNA and decoded by specialized cellular structures called ribosomes to make proteins. Protein biosynthesis is divided into initiation, elongation and termination phases.

The ribosome has sites, which allow another specialized RNA molecule, known as tRNA, to bind to the mRNA. Binding of the correct tRNA to the mRNA on the ribosome is accomplished by an "anticodon" that is part of the tRNA. Thus, the correct tRNA, chemically linked to a specific amino acid, is directed to the ribosome to be added to a growing (nascent) polypeptide.

As the ribosome travels down the mRNA one codon at a time, another tRNA is attached to the mRNA at one of the ribosome sites. The first tRNA is released, but the amino acid that is attached to the first tRNA is now moved to the second tRNA, and binds to its amino acid. This translocation continues on, and a long chain of amino acid (protein), is formed.

When the entire unit reaches the end codon on the mRNA, it falls apart and a newly formed protein is released. This is termination. It is important to know that during this process, many enzymes are used to either assist or facilitate the whole procedure.

Events following biosynthesis (Protein Synthesis)

The events following biosynthesis include post-translational modification and protein folding.

During and after synthesis, polypeptide chains often fold to assume, so called, native secondary and tertiary structures. This is known as *protein folding*.

Many proteins undergo *post-translational modification*. This may include the formation of disulfide bridges or attachment of any of a number of biochemical functional groups, such as acetate, phosphate, various lipids and carbohydrates. Enzymes may also remove one or more amino acids from the leading (amino) end of the polypeptide chain, leaving a protein consisting of two polypeptide chains connected by disulfide bonds.

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Transcription factor

In molecular biology, a **transcription factor** is a protein that binds DNA at a specific promoter or enhancer region or site, where it regulates transcription. Transcription factors can be selectively activated or deactivated by other proteins, often as the final step in signal transduction.

Classes

There are three classes of transcription factors:

- General transcription factors are involved in the formation of a preinitiation complex. The most common are abbreviated as TFIIA, TFIIB, TFIID, TFIIE, TFIIF, TFIIH. They are ubiquitous and interact with the core promoter region surrounding the transcription start site(s) of all class II genes.
- Upstream transcription factors are proteins that bind somewhere upstream of the initiation site to stimulate or repress transcription.
- Inducible transcription factors are similar to upstream transcription factors but require activation or inhibition.

Motifs found in transcription factors

- Helix-turn-helix (HTH) bind the major groove of the DNA.
- Zinc fingers function as structural platforms for DNA binding.
- Leucine zippers function in associating the transcription factors with each other.
- Basic-helix-loop-helix (bHLH) bind DNA with two alpha helices containing basic amino acid residues which are linked by a loop and are typically dimeric.
- G-quadruplex Motifs are recently being studied extensively for their role as a TF binding site

Examples of transcription factors

STAT

The Signal Transducers and Activator of Transcription (STAT) protein regulate many aspects of cell growth, survival and differentiation. The transcription factors of this family are activated by the Janus Kinase JAK and dysregulation of this pathway is frequently observed in primary tumors and leads to increased angiogenesis and enhanced survival of tumors. Knockout studies have provided evidence that STAT proteins are involved in the development and function of the immune system and play a role in maintaining immune tolerance and tumor surveillance.

Function of STAT proteins

STAT proteins were originally described as latent cytoplasmic transcription factors that require phosphorylation for nuclear retention. The unphosphorylated STAT proteins shuttle between the cytosol and the nucleus waiting for its activation signal. Once the activated transcription factors reach the nucleus, they bind to a consensus DNA-recognition motif called gamma activated sites (GAS) in the promoter region of cytokine inducible genes and activate transcription of these genes.

Activation of STAT proteins

Extracellular binding of Cytokines induces activation of the intracellular Janus kinase that phosphorylates a specific tyrosine residue in the STAT protein which promotes the dimerization of STAT monomers via their SH2 domain. The phosphorylated dimer is then actively transported in the nucleus via importin a/b and RanGDP complex. Once inside the nucleus the active STAT dimer binds to cytokine inducible promoter regions of genes containing gamma activated site (GAS) motif and activate transcription of this proteins. The STAT protein can be dephosphorylated by nuclear phosphatases which leads to inactivation of STAT and the transcription factor becomes transported out of the nucleus by exportin crm1/RanGTP.gg

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Absorption spectrum

Electromagnetic radiation may be characterised by its wavelength. An **absorption spectrum** is a diagram which shows the wavelengths of electromagnetic radiation absorbed by a material. The material could be a gas, a solute or a solid. An absorption spectrum is, in a sense, the inverse of an emission spectrum.

Atoms and molecules may change states when they absorb specific amounts of energy. Atomic states are defined by the arrangement of electrons in atomic orbitals. An electron in some orbital may be excited to a more energetic orbital by absorbing exactly one photon which has energy equal to the energy difference of the two orbitals.

Molecular states are defined by the molecule's modes of vibration and rotation. These vibrational and rotational modes are quantised, similar to the atomic orbitals, and may be excited by absorbing single photons.

In both the atomic and molecular cases, the excited states do not persist: after some random amount of time, the atoms and molecules revert back to their original, lower energy state. In atoms, the excited electron returns to a lower orbital, emitting a photon. In molecules, the vibrational or rotational mode decays, also emitting a photon.

When this decay occurs, the photon produced is not emitted in the same direction as the original photon. If a cloud of gas (atoms or molecules) comes between a light source and an observer, the observer will see gaps in the spectrum of the light corresponding to the wavelengths of the photons which were absorbed. These gaps occur despite the re-emission of photons because the re-emitted photons do not travel along the original path to the observer. These gaps appear as black lines in an image of the spectrum.

Elements have particular sets of lines at particular wavelengths, corresponding to the energy levels of their atomic orbitals. (Strictly speaking, the lines correspond to the energy differences between the orbitals.) This allows for the identification of elements from absorption spectra. This method is used in deducing the presence of elements in stars and other gaseous objects which cannot be measured directly.

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Action spectrum

An **action spectrum** is the rate of a physiological activity plotted against wavelength of light. It shows which wavelength of light is most effectively used in a specific chemical reaction. Some reactants are able to use specific wavelengths of light more effectively to complete their reactions. For example, chlorophyll is much more efficient at using the red and blue spectrums of light to carry out photosynthesis. Therefore, the action spectrum graph would show spikes above the wavelengths representing the colours red and blue.

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Chromatography

History | Chromatography theory | Retention | Plate theory | Paper chromatography | Thin layer chromatography (TLC) | Column chromatography | Gas-liquid chromatography | Ion exchange chromatography | Immobilized metal ion affinity chromatography | High performance liquid chromatography (HPLC) | Normal phase (NP) liquid chromatography | Reversed phase (RP) liquid chromatography | Gel permeation chromatography | Affinity chromatography

Chromatography is a family of analytical chemistry techniques for the separation of mixtures. It involves passing the sample, a mixture which contains the analyte, in the "mobile phase", often in a stream of solvent, through the "stationary phase." The stationary phase retards the passage of the components of the sample. When components pass through the system at different rates they become separated in time, like runners in a mass-start foot race. Each component has a characteristic time of passage through the system, called a "retention time." Chromatographic separation is achieved when the retention time of the analyte differs from that of other components in the sample.

A **chromatograph** takes a chemical mixture carried by liquid or gas and separates it into its component parts as a result of differential distributions of the solutes as they flow around or over a stationary liquid or solid phase. Various techniques for the separation of complex mixtures rely on the differential affinities of substances for a gas or liquid mobile medium and for a stationary absorbing medium through which they pass; such as paper, gelatin, alumina or silica.

A **chromatogram** is the visual output of the chromatograph. Different peaks or patterns on the chromatograph correspond to different components of the separated mixture.

Analytical chromatography is used to determine the identity and concentration of molecules in a mixture. **Preparative chromatography** is used to purify larger quantities of a molecular species. Most of the following refers to analytical chromatography. This is a method used to divide/separate mixtures.

History

It was the Russian botanist Mikhail Tsvet (Mikhail Semyonovich Tsvet) who invented the first chromatography technique in 1901 during his research on chlorophyll. He used a liquid-adsorption column containing calcium carbonate to separate plant pigments. The method was described on December 30, 1901 at the XI Congress of Naturalists and Doctors in St. Petersburg. The first printed description was in 1903, in the Proceedings of the Warsaw Society of Naturalists, section of biology. He first used the term *chromatography* in print in 1906 in his two papers about chlorophyll in the German botanical journal, *Berichte der Deutschen Botanischen Gesellschaft*. In 1907 he demonstrated his chromatograph for the German Botanical Society. The phenomenon of precipitational separation was observed before Tsvet as well. His contribution was turning the phenomenon into the method of

scientific analysis.

The Greek word *chroma* in *chroma*tography means *colour* in English and refers both to Tsvet's name that is literally translated from Russian as *colour* and to the colour of the plant pigments he was separating at that time.

In 1952 Archer John Porter Martin and Richard Laurence Millington Synge were awarded the Chemistry Nobel Prize for their invention of partition chromatography.

The technology of chromatography advanced rapidly throughout the 20th century. Researchers found that the principles underlying Tsvet's chromatography could be applied in many different ways, giving rise to the different varieties of chromatography described below. Simultaneously, advances continually improved the technical performance of chromatography, allowing increasingly similar molecules to be resolved.

Chromatography theory

Chromatography is a separation method that exploits the differences in partitioning behavior between a **mobile phase** and a **stationary phase** to separate the components in a mixture. Components of a mixture may be interacting with the stationary phase based on charge, relative solubility or adsorption. There are two theories of chromatography, the plate and rate theories.

Retention

The retention is a measure of the speed at which a substance moves in a chromatographic system. In continuous development systems like HPLC or GC, where the compounds are eluted with the eluent, the retention is usually measured as the *retention time* R_t or t_R, the time between injection and detection. In interrupted development systems like TLC the retention is measured as the *retention factor* R_f, the run length of the compound divided by the run length of the eluent front:

$$R_f = \frac{\begin{matrix}distance\\moved\ by\\compound\end{matrix}}{\begin{matrix}distance\\moved\ by\\eluent\end{matrix}}$$

The retention of a compound often differs considerably between experiments and laboratories due to variations of the eluent, the stationary phase, temperature, and the setup. It is therefore important to

compare the retention of the test compound to that of one or more standard compounds under absolutely identical conditions.

Plate theory

The plate theory of chromotography was developed by Archer John Porter Martin and Richard Laurence Millington Synge. The plate theory describes the chromotography system, the mobile and stationary phases, as being in equilibrium. The partition coefficient *K* is based on this equilibrium, and is defined by the following equation:

$$K = \frac{\begin{matrix}Concentration\\ of\ solute\\ in\ stationary\\ phase\end{matrix}}{\begin{matrix}Concentration\\ of\ solute\\ in\ mobile\ phase\end{matrix}}$$

K is assumed to be independent of concentration, and can change if experimental conditions are changed, for example temperature is increased or decreased. As *K* increases, it takes longer for solutes to separate. For a column of fixed length and flow, the retention time (t_R) and retention volume (V_r) can be measured and used to calculate *K*.

Paper chromatography

This is an older technique which involves placing a small spot of sample solution onto a strip of chromatography paper. The paper is placed into a jar containing a shallow layer of solvent and sealed. As the solvent rises through the paper it meets the sample mixture which starts to travel up the paper with the solvent. Different compounds in the sample mixture travel different distances according to how strongly they interact with the paper. This allows the calculation of an R_f value and can be compared to standard compounds to aid in the identification of an unknown substance.

Thin layer chromatography (TLC)

In *thin layer chromatography* or *TLC* the stationary phase consists of a thin layer of adsorbent like silica gel, alumina, or cellulose on a flat carrier like a glass plate, a thick aluminum foil, or a plastic sheet.

The process is similar to paper chromatography with the advantage of faster runs, better separations, and

the choice between different adsorbents. TLC is a standard laboratory method in organic chemistry. Because of its simplicity and speed TLC is often used for monitoring chemical reactions and for the qualitative analysis of reaction products.

TLC plates are made by mixing the adsorbent with a small amount of inert binder like calcium sulfate (gypsum) and water, spreading the thick slurry on the carrier, drying the plate, and activation of the adsorbent by heating in an oven. The thickness of the adsorbent layer is typically around 0.1-0.25mm for analytical purposes and around 1-2mm for preparative TLC.

Several methods exists to make colorless spots visible:

- Often a small amount of a fluorescent dye is added to the adsorbent that allows the visualization of UV absorbing spots under a blacklight ("UV_{254}").
- Iodine vapors are a general unspecific color reagent.
- Specific color reagents exist into which the TLC plate is dipped or which are sprayed onto the plate.

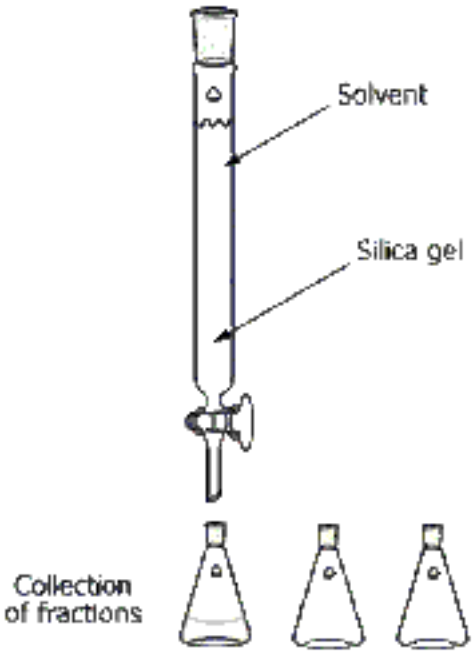
Once visible, the R_f values of the spots can be determined. These values should be the same regardless of the extent of travel of the solvent, and in theory are independent of a single experimental run. They do depend on the solvent used, and the type of TLC plate.

Thin layer chromatography is also used in finding which pigments a plant contains. By taking extract of the plants cellulose and applying the technique, one can adequately find the pigments. It may also be used to detect pesticides or insecticides in food, or in forensics to analyze the dye composition of fibers.

Column chromatography

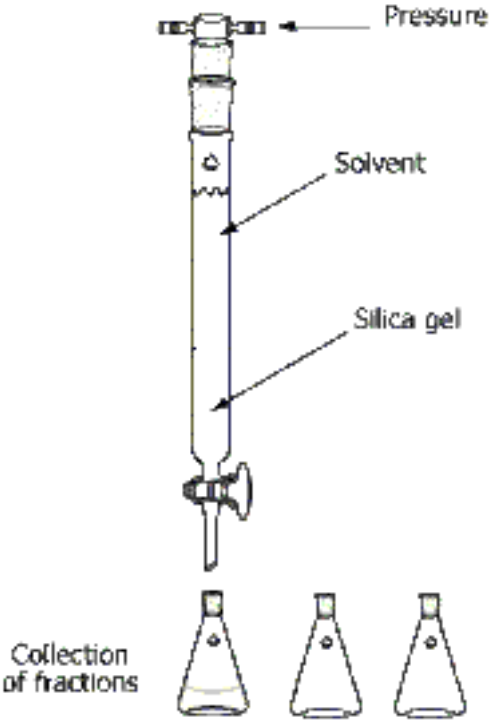
Column chromatography utilizes a vertical glass column filled with some form of solid support with the sample to be separated placed on top of this support. The rest of the column is filled with a solvent which, under the influence of gravity, moves the sample through the column. Similarly to other forms of chromatography, differences in rates of movement through the solid medium are translated to different exit times from the bottom of the column for the various elements of the original sample.

Standard column chromatography



In 1978, W. C. Stills introduced a modified version of column chromatography called **flash column chromatography** ("flash"). The technique is very similar to the traditional column chromatography, except for that the solvent is driven through the column by applying positive pressure.

Flash column chromatography



When applying positive pressure on top of the column, most separations could be performed in less than 20 minutes with improved separations compared to the old method. This makes flash column

chromatography the method of choice for most synthetic organic chemists when purifying organic compounds.

In the modern Flash chromatography systems which can be purchased, the glass columns are replaced with pre-packed plastic cartridges. Solvent is pumped through the cartridge, which is much quicker. Systems may also be linked with detectors and fraction collectors providing automation. The introduction of gradient pumps means quicker separations and less solvent usage.

Gas-liquid chromatography

Gas-liquid chromatography is based on a partition equilibrium of analyte between a liquid stationary phase and a mobile gas. It is useful for a wide range of non-polar analytes, but poor for thermally labile molecules.

Ion exchange chromatography

Ion exchange chromatography is a column chromatography that uses a charged stationary phase. It is used to separate charged compounds including amino acids, peptides, and proteins. The stationary phase is usually an ion exchange resin that carries charged functional groups which interact with oppositely charged groups of the compound to be retained:

- Positively charged ion exchanger (*anion exchanger*) interacts with anions
- Negatively charged ion exchanger (*cation exchanger*) interacts with cations.

Bound compounds can be eluted from the column by gradient elution or isocratic elution with a change in salt concentration or pH. Ion exchange chromatography is commonly used to purify proteins using FPLC.

Immobilized metal ion affinity chromatography

IMAC is a popular and powerful way to purify proteins. It is based on the specific coordinate covalent binding between histidine or other unique amino acids (either naturally present on the surface of the protein or grafted with recombinant DNA techniques) and various immobilized metal ions, such as copper, nickel, zinc, or iron...

Salt concentration is increased to produce later fractions.

High performance liquid chromatography (HPLC)

High performance liquid chromatography, usually referred to simply as **HPLC**, is a form of column chromatography used frequently in biochemistry and Analytical Chemistry. The analyte is forced

through a column (stationary phase) by a liquid (mobile phase) at high pressure, which decreases the time the separated components remain on the stationary phase and thus the time they have to diffuse within the column. Diffusion within the column leads to broad peaks and loss of resolution. Less time on the column then translates to narrower peaks in the resulting chromatogram and thence to better resolution (it's easier to differentiate one peak from another) and sensitivity (tall, narrow peaks can be easier to discriminate from noise than shorter, broader peaks). Another way to decrease time the analyte stays on the column is to use a solvent gradient. A solvent gradient is how the composition of the mobile phase changes over a period of time and can be used to force the analyte off of the column at a faster rate.

Normal phase (NP) liquid chromatography

Normal phase HPLC (NP-HPLC) was the first kind of HPLC setup used. This method uses a polar stationary phase and a nonpolar mobile phase, and is used when the analyte of interest has a polar nature. The polar analyte associates with and is retained by the polar stationary phase. NP-HPLC has fallen out of favor recently with the development of reversed phase HPLC.

Reversed phase (RP) liquid chromatography

Reversed phase HPLC (RP-HPLC) was developed due to the increasing interest in large nonpolar biomolecules. Like the name implies the nature of the stationary phase is reversed. The RP-HPLC consists of a nonpolar stationary phase and a polar mobile phase. One common stationary phase is a *normal* silica which has been treated with RMe_2SiCl, where R is a straight chain alkyl group such as $C_{18}H_{37}$ or C_8H_{17}. It is the case that for a given substance the retention time is longer when the mobile phase is more polar. This is the reverse of the situation which exists when normal silica is used as the stationary phase.

Reversed phase columns are quite difficult to damage when compared with normal silica columns. But they must never be used with strong aqueous bases (alkali) as these will destroy the silica, however they can be used with aqueous acid but the column should not be exposed to the acid for too long. One reason is because the acid will corrode the metal parts of the HPLC equipment. The metal content of HPLC columns must be kept low if the best possible ability to separate substances is to be retained. A good test for the metal content of a column is to inject a sample which is a mixture of 2,2'- and 4,4'- bipyridine. Because the 2,2'-bipy can chelate the metal it is normal that when a metal ion is present on the surface of the silica the shape of the peak for the 2,2'-bipy will be distorted, tailing will be seen on this distorted peak.

Gel permeation chromatography

Gel permeation chromatography (also known as size exclusion chromatography, gel-filtration chromatography or Sephadex gel chromatography) separates molecules on basis of size. Smaller

molecules enter a porous media and take longer to exit the column, whereas larger particles leave the column ealier. The elution volume decreases roughly linearly with the logarithm of the molecular hydrodynamic volume (often assumed to be proportional to molecular weight), although columns need to be calibrated using 4-5 standard samples (e.g., folded proteins of known molecular weight) to determine the void volume and the slope of the logarithmic dependence. These parameters may vary with solution conditions.

Since gel filtration is generally a low resolution chromatography (i.e., does not discern similar species well), it is often reserved for the final, "polishing" step of a purification. GPC is good for determining the quaternary structure of purified proteins, especially since it can be carried out under native solution conditions. GPC can also assay protein tertiary structure; since GPC measures the hydrodynamic volume (not molecular weight!), it can discern folded and unfolded versions of the same protein. For example, the apparent hydrodynamic radius of a typical protein domain might be 14 Γ… and 36 Γ… for the folded and unfolded forms, respectively; the folded form elutes much later, since it is smaller.

Affinity chromatography

Affinity chromatography is based on selective non-covalent interaction between an analyte and specific molecules. It is very specific, but not very robust. It is often used in biochemistry in the purification of proteins (or better: protein constructs). These constructs can be of fusion proteins with a so-called His-tag, biotinylated or possibly antigens. After purification some of these tags are usually removed and the pure protein is obtained

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Electrophoresis

Applications

Electrophoresis is the movement of an electrically charged substance under the influence of an electric field. This movement is due to the Lorentz force, which may be related to fundamental electrical properties of the body under study and the ambient electrical conditions by the equation given below. *F* is the Lorentz force, *q* is the charge carried by the body, *E* is the electric field :

$$\bar{F}_e = q\bar{E}$$.

The resulting electrophoretic migration is countered by forces of friction such that the rate of migration is constant in a constant and homogeneous electric field:

$$F_f = vf$$

Where *v* is the velocity and *f* is the frictional coefficient.

$$q\bar{E} = vf$$

The electrophoretic mobility μ is defined as followed.

$$\mu = \frac{v}{E} = \frac{q}{f}$$

The expression above applied only to ions at a concentration approaching 0 and in a non-conductive solvent. Polyionic molecules are surrounded by a cloud of counterions which alter the effective electric field applied on the ions to be separated. This render the previous expression a poor approximation of what really happens in an electrophoretic aparatus.

The mobility depends on both the particle properties (e.g., surface charge density and size) and solution properties (e.g., ionic strength, electric permittivity, and pH). For high ionic strengths, an approximate expression for the electrophoretic mobility is given by the Smoluchowski equation,

$$\mu_e = \frac{\epsilon\epsilon_0\zeta}{\eta},$$

where ε is the dielectric constant of the liquid, ϵ_0 is the permitivitty of free space, η is the viscosity of the liquid, and ζ is the zeta potential (i.e., surface potential) of the particle.

Applications

Gel electrophoresis is an application of electrophoresis in molecular biology. The content of the buffers (solutions) and gels used to enhance viscosity greatly affects the mobility of micromolecules. This process is used to determine the different size of High density lipoproteins in order to establish a more accurate representation of their effectiveness.

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Fluorescence

Fluorescence is a luminescence that is mostly found as an optical phenomenon in cold bodies, in which the molecular absorption of a photon triggers the emission of a lower-energy photon with a longer wavelength. The energy difference between the absorbed and emitted photons ends up as molecular vibrations or heat. Usually the absorbed photon is in the ultraviolet, and the emitted light is in the visible range, but this depends on the absorbance curve and Stokes shift of the particular fluorophore. Fluorescence is named after the mineral fluorite, composed of calcium fluoride, which exhibits this phenomenon.

Equations

Chemical Process

Fluorescence occurs when a molecule or quantum dot relaxes to its ground state after being electronically excited.

Excitation: $S_0 + hv \rightarrow S_1$

Fluorescence (emission): $S_1 \rightarrow S_0 + hv$

*h*v is a generic term for photon energy where: h = Planck's constant and v = frequency of light. (The specific frequencies of exciting and emitted light are dependent on the particular system.)

State S_0 is called the ground state of the fluorophore (fluorescent molecule) and S_1 is its first (electronically) excited state.

A molecule in its excited state, S_1, can relax by various competing pathways. It can undergo 'non-radiative relaxation' in which the excitation energy is dissipated as heat (vibrations) to the solvent. Excited organic molecules can also relax via conversion to a triplet state which may subsequently relax via phosphorescence or by a secondary non-radiative relaxation step.

Relaxation of an S_1 state can also occur through interaction with a second molecule through

fluorescence quenching. Molecular oxygen (O_2) is an extremely efficient quencher of fluorescence because of its unusual triplet ground state.

Molecules that are excited through light absorption or via a different process (e.g. as the product of a reaction) can transfer energy to a second 'sensitizer' molecule, which is converted to its excited state and can then fluoresce. This process is used in lightsticks.

Fluorescence Quantum Yield

The fluorescence quantum yield gives the efficiency of the fluorescence process. It is defined as the ratio of the number of photons emitted to the number of photons absorbed.

$$\Phi = \frac{\#photons\ emitted}{\#photons\ absorbed}$$

The maximum fluorescence quantum yield is 1.0 (100%); every photon absorbed results in a photon emitted. Compounds with quantum yields of 0.10 are still considered quite fluorescent. Another way to define the quantum yield of fluorescence, is by the rates excited state decay:

$$\frac{k_f}{\sum_i k_i}$$

where k_f is the rate of spontaneous emission of radiation and

$$\sum_i k_i$$

is the sum of all rates of excited state decay. Other rates of excited state decay are caused by mechanisms other than photon emission and are therefore

often called "non-radiative rates", which can include: dynamic collisional quenching, near-field dipole-dipole interaction (or resonance energy transfer), internal conversion and inter-system crossing. Thus, if the rate of any pathway changes, this will affect both the excited state lifetime and the fluorescence quantum yield.

Fluorescence quantum yield are measured by comparison to a standard with known quantum yield; the quinine salt, quinine sulfate, in a sulfuric acid solution is a common fluorescence standard.

Fluorescence Lifetime

The fluorescece lifetime refers to the time the molecule stays in its excited state before emitting a photon. Fluorescence typically follows first-order kinetics:

$$[S_1] = [S_1]_0 \, e^{\frac{-t}{\tau}}$$

S_1 is the remaining concentration of excited state molecules at time = t, $[S_1]_0$ is the initial concentration after excitation. The lifetime is related to the rates of excited state decay as:

$$\tau = \frac{1}{\sum_i k_i}$$

Thus, it is similar to a first-order chemical reaction in which the first-order rate constant is the sum of all of the rates (a parallel kinetic model). Thus, the lifetime is related to the facility of the relaxation pathway. If the rate of spontaneous emission, or any of the other rates are fast the lifetime is short (for commonly used fluorescent compounds typical excited state decay times for fluorescent compounds that emit photons with energies from the UV to near infrared are within the range of 0.5 to 20 nanoseconds). The fluorescence lifetime is an important parameter for practical applications of fluorescence such as Fluorescence resonance energy transfer.

Rules

There are several rules that deal with fluorescence. The *Kasha-Vavilov rule* dictates that the quantum yield of luminescence is independent of the wavelength of exciting radiation.

This is not quite true and is violated severely in many simple molecules. A somewhat more reliable statement, although still with exceptions, would be that the fluorescence spectrum shows very little dependence on the wavelength of exciting radiation.

The *Jablonski diagram* describes most of the relaxation mechanism for excited state molecules.

Applications

There are many natural and synthetic compounds that exhibit fluorescence, and they have a number of applications:

Lighting

The common fluorescent tube relies on fluorescence. Inside the glass tube is a partial vacuum and a small amount of mercury. An electric discharge in the tube causes the mercury atoms to emit light. The emitted light is in the ultraviolet (UV) range and is invisible, and also harmful to living organisms, so the tube is lined with a coating of a fluorescent material, called the *phosphor*, which absorbs the ultraviolet and re-emits visible light. Fluorescent lighting is very energy efficient compared to incandescent technology, but over-illumination and unnatural spectra can lead to adverse health effects.

Recently, "white light-emitting diodes" ("white LEDs") have become available, which work through a similar process. Typically, the actual light-emitting semiconductor produces light in the blue part of the spectrum, which strikes a phosphor compound deposited on a reflector; the phosphor fluoresces in the orange part of the spectrum, the combination of the two colors producing a net effect of apparently white light.

Compact fluorescent lighting (CFL) is the same as any typical fluorescent lamp with advantages. It is self-ballasted and used to replace incandescents in most applications. They are highly efficient with high CRI and good color temp index rating.

The modern mercury vapor streetlight is said to have been evolved from the fluorescent lamp.

Glow sticks oxidise phenyl oxalate ester in order to produce light.

Biochemistry and medicine

There is a wide range of applications for fluorescence in this field. Large biological molecules can have a fluorescent chemical group attached by a chemical reaction, and the fluorescence of the attached tag enables very sensitive detection of the molecule. Examples:

- automated sequencing of DNA by the chain termination method; each of four different chain terminating bases has its own specific fluorescent tag. As the labeled DNA molecules are separated, the fluorescent label is excited by a UV source, and the identity of the base terminating the molecule is identified by the wavelength of the emitted light.
- DNA detection: the compound ethidium bromide, when free to change its conformation in solution, has very little fluorescence. Ethidium bromide's fluorescence is greatly enhanced when it binds to DNA, so this compound is very useful in visualising the location of DNA fragments in agarose gel electrophoresis
- The DNA microarray
- Immunology: An antibody has a fluorescent chemical group attached, and the sites (e.g., on a microscopic specimen) where the antibody has bound can be seen, and even quantified, by the fluorescence.
- FACS (fluorescent-activated cell sorting)
- Fluorescence has been used to study the structure and conformations of DNA and proteins

with techniques such as Fluorescence resonance energy transfer. This is especially important in complexes of multiple biomolecules.
- Aequorin, from the jellyfish *Aequorea victoria*, produces a blue glow in the presence of Ca^{2+} ions (by a chemical reaction). It has been used to image calcium flow in cells in real time. The success with aequorin spurred further investigation of *A. victoria* and led to the discovery of Green Fluorescent Protein (GFP), which has become an extremely important research tool. GFP and related proteins are used as reporters for any number of biological events including such things as sub-cellular localization. Levels of gene expression are sometimes measured by linking a gene for GFP production to another gene.

Also, many biological molecules have an intrinsic fluorescence that can sometimes be used without the need to attach a chemical tag. Sometimes this intrinsic fluorescence changes when the molecule is in a specific environment, so the distribution or binding of the molecule can be measured. Bilirubin, for instance, is highly fluorescent when bound to a specific site on serum albumin. Zinc protoporphyrin, formed in developing red blood cells instead of hemoglobin when iron is unavailable or lead is present, has a bright fluorescence and can be used to detect these problems.

As of 2006, the number of fluorescence applications is growing in the biomedical biological and related sciences. Methods of analysis in these fields are also growing, albeit with increasingly unfortunate nomenclature in the form of acronyms such as: FLIM, FLI, FLIE, FRET, FRAP, FCS, PFRAP, smFRET, FIONA, FRIPS, SHREK, SHRIMP.

Gemology, mineralogy and forensics

Gemstones, minerals, fibers and many other materials which may be encountered in forensics or with a relationship to various collectibles may have a distinctive fluorescence or may fluoresce differently under short-wave ultraviolet, long-wave ultra violet, or X-rays.

Many types of calcite will fluoresce under shortwave UV.

Rubies, emeralds, and the Hope Diamond exhibit red fluorescence under short-wave UV light; diamonds also emit light under X ray radiation.

Organic liquids

Organic liquids such as mixtures of anthracene in benzene or toluol, or stilbene in the same solvents, fluoresce with ultraviolet or gamma ray irradiation. The decay times of this fluorescence is of the order of nanoseconds since the duration of the light depends on the lifetime of the excited states of the fluorescent material, in this case anthracene or stilbene.

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Fractionation

Fractionation is a separation process in which a certain quantity of a mixture (solid, liquid, solute or suspension) is divided up in a large number of smaller quantities (fractions) in which the composition changes according to a gradient. Fractions are collected based on differences in a specific property of the individual components. Common trait in fractionations is the need to find an optimum between the amount of fractions collected and the desired purity in each fraction. Fractionation makes it possible to isolate more than two components in a mixture in a single run. This property sets it apart from other separation techniques.

Fractionation is widely employed in many branches of science and technology. Mixtures of liquids and gases are separated by fractional distillation by difference in boiling point. Fractionation of components also takes place in column chromatography by a difference in affinity between stationary phase and the mobile phase. In fractional crystallization and fractional freezing chemical substances are fractionated based on difference in solubility at a given temperature. In cell fractionation, cell components are separated by difference in mass.

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Gram staining

Gram staining (or the **Gram's method**) is an empirical method of differentiating bacterial species into two large groups (Gram-positive and Gram-negative) based on the chemical and physical properties of their cell walls.

The method is named after its inventor, the Danish scientist Hans Christian Gram (1853-1938), who developed the technique in 1884 to discriminate between pneumococci and *Klebsiella pneumoniae* bacteria.

Uses

Research

Gram staining is one of the most useful staining procedures in bacteriological laboratory. The technique is widely used as a tool for differentiating Gram-negative and Gram-positive bacteria, as a first step to determine the identity of a particular bacterial sample.

Medical

Gram stains are performed on body fluid or biopsy when infection is suspected. It yields results much quicker than culture, and is especially important when infection would make an important difference in the patient's treatment and prognosis; examples are cerebrospinal fluid for meningitis and synovial fluid for septic arthritis. It necessitates the 24 hour staffing of microbiological laboratories in hospitals.

Procedure

Staining

- First, an inoculum is taken from a culture using an inoculation loop and put on a slide and then allowed to air dry. If the culture is solid, it is diluted by adding a drop of water or sterile saline on the slide and mixing with the loop. It is important here to take a very small inoculum so that the end result is a sparse single layer of bacteria. It is a common mistake for beginners to put far too much inoculum at this step.
- The specimen is heat-fixed by passing the slide, inoculum side up, through a bunsen flame 1-2 times, without allowing the slide to become hot to the touch.
- A basic dye, crystal violet or gentian violet, is used to stain the slide. This dye is taken up by both Gram-positive and Gram-negative bacteria. Allow to stain for one minute. The slide should look purple to the unaided eye, and if examined microscopically at this point both Gram-positive and Gram-negative

bacteria are purple.
- Rinse off with water for a maximum of five seconds.
- Add iodine (Gram's iodine) solution (1% iodine, 2% potassium iodide in water) for one minute. This acts as a mordant and fixes the dye. Lugol's Solution can also be used as it is an iodine compound.
- Rinse with water.
- Apply 95% ethanol or a mixture of acetone and alcohol. This washes away all the unbound basic dye, (usually crystal violet) and leaves Gram-positive organisms stained purple and Gram-negative organisms unstained (colourless).
- Rinse with water immediately to prevent over-decolourisation (as prolonged exposure to the decolourising agent will remove all the stain from both types of bacteria).
- Apply a suitable counterstain. Suitable stains include safranin or fuchsin. This stain is taken up by both Gram-positive and Gram-negative organisms, but does not alter the colour of Gram-positive organism much, as they are already purple. It does, however, make the Gram-negative organisms pinkish-red.
- Blot gently and allow the slide to dry. Do not smear.

Interpretation

When inspecting the slide under a microscope:

- *Gram-positive* organisms will appear *blue-black* or *purple*.
- *Gram-negative* organisms will appear *red* or *pink*.

Organisms that cannot reliably be differentiated by this staining technique are said to be **Gram-variable**. These are Gram-positive bacteria that lose the stain easily and therefore may appear as a mixture of Gram-positive and Gram-negative bacteria. In addition, mycobacteria - the causative agents of tuberculosis and leprosy - are said to be acid-fast and resistant to Gram staining entirely. Ziehl-Neelsen staining is particularly useful as a Gram stain alternative in these cases.

One-step Gram staining

If a fluorescent microscope is available, the Gram stain can be reduced to a one-step procedure where Gram-positive and Gram-negative cells fluoresce with different colours. This shortens the length of the procedure considerably, which is especially useful if staining a large amount of samples (which is often the case in a clinical laboratory).

Mechanism

Gram-positive bacteria have a thick mesh-like cell wall made of peptidoglycan which is capable of retaining the violet dye/iodine complex. Gram-negative bacteria have a thin cell wall made of a layer of peptidoglycan. In addition to an inner membrane, they also have an outer membrane which contains lipids, and is separated from the cell wall by the periplasmic space.

The decolourising mixture causes dehydration of the multilayered peptidoglycan in the Gram-positive cell wall, thus decreasing the space between the molecules and causing the cell wall to trap the crystal violet-iodine complex within the cell. But in Gram-negative bacteria, the decolourising mixture acts as a lipid solvent and dissolves the outer membrane of the Gram-negative cell wall. The thin layer of peptidoglycan is unable to retain the crystal violet-iodine complex and the Gram-negative cell is decolorized. The decolourisation step is the crucial one, and requires some degree of skill, as being Gram-positive is not an all-or-none phenomenon.

As a general rule of thumb (which has exceptions), Gram-negative bacteria are more dangerous as disease organisms, because their outer membrane is often hidden by a capsule or slime layer which hides the antigens of the cell and so acts as "camouflage" - the human body recognises a foreign body by its antigens; if they are hidden, it becomes harder for the body to detect the invader. Often the presence of a capsule will increase the virulence of a pathogen. Additionally, Gram-negative bacteria have lipopolysaccharide in their outer membrane, an endotoxin which increases the severity of inflammation. This inflammation may be so severe that septic shock may occur. Gram-positive infections are generally less severe because the human body does not contain peptidoglycan; in fact, the human body produces an enzyme called lysozyme which attacks the open peptidoglycan layer of Gram-positive bacteria. Gram-positive bacteria are also frequently much more susceptible to beta-lactam antibiotics, such as penicillin.

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Mass spectrometry

How it works: A simple example

Mass spectrometry is an analytical technique used to measure the mass-to-charge ratio of ions. It is most generally used to find the composition of a physical sample by generating a mass spectrum representing the masses of sample components. The technique has several applications, including:

- identifying unknown compounds by the mass of the compound and/or fragments thereof.
- determining the isotopic composition of one or more elements in a compound.
- determining the structure of compounds by observing the fragmentation of the compound.
- quantitating the amount of a compound in a sample using carefully designed methods (mass spectrometry is not inherently quantitative).
- studying the fundamentals of gas phase ion chemistry (the chemistry of ions and neutrals in vacuum).
- determining other physical, chemical or even biological properties of compounds with a variety of other approaches.

A **mass spectrometer** is a device used for mass spectrometry, and produces a mass spectrum of a sample to find its composition. This is normally achieved by ionizing the sample and separating ions of differing masses and recording their relative abundance by measuring intensities of ion flux. A typical mass spectrometer comprises three parts: an ion source, a mass analyzer, and a detector.

How it works: A simple example

Different chemicals have different masses, and this fact is used in a mass spectrometer to determine what chemicals are present in a sample. For example, table salt (NaCl), is vaporized (turned into gas) and ionized (broken down) into electrically charged particles, called ions, in the first part of the mass spectrometer. The sodium ions and chloride ions have specific atomic weights. They also have a charge, which means that they can be moved under the influence of an electric field or magnetic field. These ions are then sent into an ion acceleration chamber and passed through a slit in a metal sheet. A magnetic field is applied to the chamber, which pulls on each ion equally and deflects them (makes them curve instead of travelling straight) onto a detector. The lighter ions deflect farther than the heavy ions because the force on each ion is equal but their masses are not (this is derived from the equation $F = ma$ which states that if the force remains the same, the mass and acceleration are inversely proportional). The detector measures exactly how far each ion has been deflected, and from this measurement, the ion's 'mass to charge ratio' can be worked out. From this information it is possible to determine with a high level of certainty what the chemical composition of the original sample was.

This example was of a sector instrument, however there are many types of mass spectrometers that not only analyze the ions differently but produce different types of ions; however they all use electric and magnetic fields to change the path of ions in some way.

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Southern blot

A **Southern blot** is a method in molecular biology of enhancing the result of an agarose gel electrophoresis by marking specific DNA sequences. The method is named after its inventor, the British biologist Edwin Southern. This caused other blot methods to be named similarly as plays on Southern's name (for example, western blot, northern blot, southwestern blot, or Hawaiian blot).

Method

- The gel from the DNA electrophoresis is treated with an alkaline solution (typically containing sodium hydroxide) to cause the double-stranded DNA to denature, separating it into single strands. Denaturation is necessary so that the DNA will stick to the membrane and be hybridized by the probe. Restriction endonucleases are used to break the DNA strands into fragments.
- A sheet of nitrocellulose (or, alternatively, nylon) membrane is placed on top of the gel. Pressure is applied evenly to the gel (either using suction, or by placing a stack of paper towels and a weight on top of the membrane and gel). This causes the DNA to move from the gel onto the membrane, where it sticks.
- The membrane is then baked (in the case of nitrocellulose) or exposed to ultraviolet radiation (nylon) to permanently crosslink the DNA to the membrane.
- The membrane is now treated with a hybridization probe - an isolated DNA molecule with a specific sequence that pairs with the appropriate sequence. The probe DNA is labelled so that it can be detected, usually by incorporating radioactivity or tagging the molecule with a fluorescent or chromogenic dye. In some cases, the hybridization probe may be made from RNA, rather than DNA.
- After hybridization, excess probe is washed from the membrane, and the pattern of hybridization is visualized on x-ray film by autoradiography in the case of a radioactive or fluorescent probe, or by development of color on the membrane itself if a chromogenic detection is used.

Result

The probe shows which of the fragments of the electrophoresis separation contains a certain DNA sequence.

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Transmembrane receptor

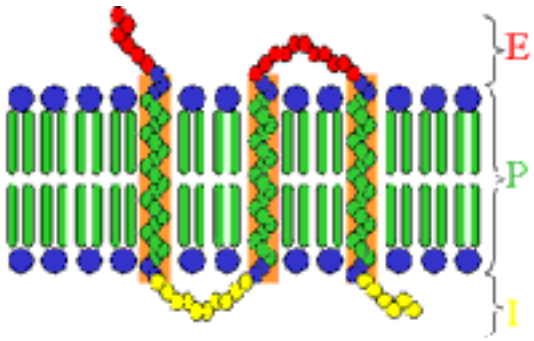
The extracellular domain | The transmembrane domain | The intracellular domain | Regulation of receptor activity

The extracellular domain | The transmembrane domain | The intracellular domain | Regulation of receptor activity

Transmembrane receptors are integral membrane proteins, which reside and operate typically within a cell's plasma membrane, but also in the membranes of some subcellular compartments and organelles. Binding to a signalling molecule or sometimes to a pair of such molecules on one side of the membrane, transmembrane receptors initiate a response on the other side. In this way they play a unique and important role in cellular communications and signal transduction.

Many transmembrane receptors are composed of two or more protein subunits which operate collectively and may dissociate when ligands bind, fall off, or at another stage of their "activation" cycles. They are often classified based on their molecular structure, or because the structure is unknown in any detail for all but a few receptors, based on their hypothesized (and sometimes experimentally verified) membrane topology. The polypeptide chains of the simplest are predicted to cross the lipid bilayer only once, while others cross as many as seven times (the so-called G-protein coupled receptors).

Like any integral membrane protein, a transmembrane receptor may be subdivided into three parts or *domains*.



E=extracellular space; I=intracellular space; P=plasma membrane

The extracellular domain

The extracellular domain is the part of the receptor that sticks out of the membrane on the outside of the cell or organelle. If the polypeptide chain of the receptor crosses the bilayer several times, the external domain can comprise several "loops" sticking out of the membrane. By definition. a receptor's main function is to recognize and respond to a specific ligand, for example, a neurotransmitter or hormone (although certain receptors respond also to changes in transmembrane potential), and in many receptors

these ligands bind to the extracellular domain.

The transmembrane domain

In the majority of receptors for which structural evidence exists, transmembrane alpha helices make up most of the transmembrane domain. In certain receptors, such as the nicotinic acetylcholine receptor, the transmembrane domain forms a protein-lined pore through the membrane, or ion channel. Upon activation of an extracellular domain by binding of the appropriate ligand, the pore becomes accessible to ions, which then pass through. In other receptors, the transmembrane domains are presumed to undergo a conformational change upon binding, which exerts an effect intracellularly. In some receptors, such as members of the 7TM superfamily, the transmembrane domain may contain the ligand binding pocket (evidence for this and for much of what else is known about this class of receptors is based in part on studies of bacteriorhodopsin, the detailed structure of which has been determined by crystallography).

The intracellular domain

The intracellular (or cytoplasmic) domain of the receptor interacts with the interior of the cell or organelle, relaying the signal. There are two fundamentally different ways for this interaction:

- The intracellular domain communicates via specific protein-protein-interactions with *effector proteins*, which in turn send the signal along a signal chain to its destination.
- The intracellular domain has *enzymatic activity*. Often, this is a tyrosine kinase activity. The enzymatic activity can also be located on an enzyme associated with the intracellular domain.

Regulation of receptor activity

There are several ways for the cell to regulate the activity of a transmembrane receptor. Most of them work through the intracellular domain. The most important ways are phosphorylation and internalization.

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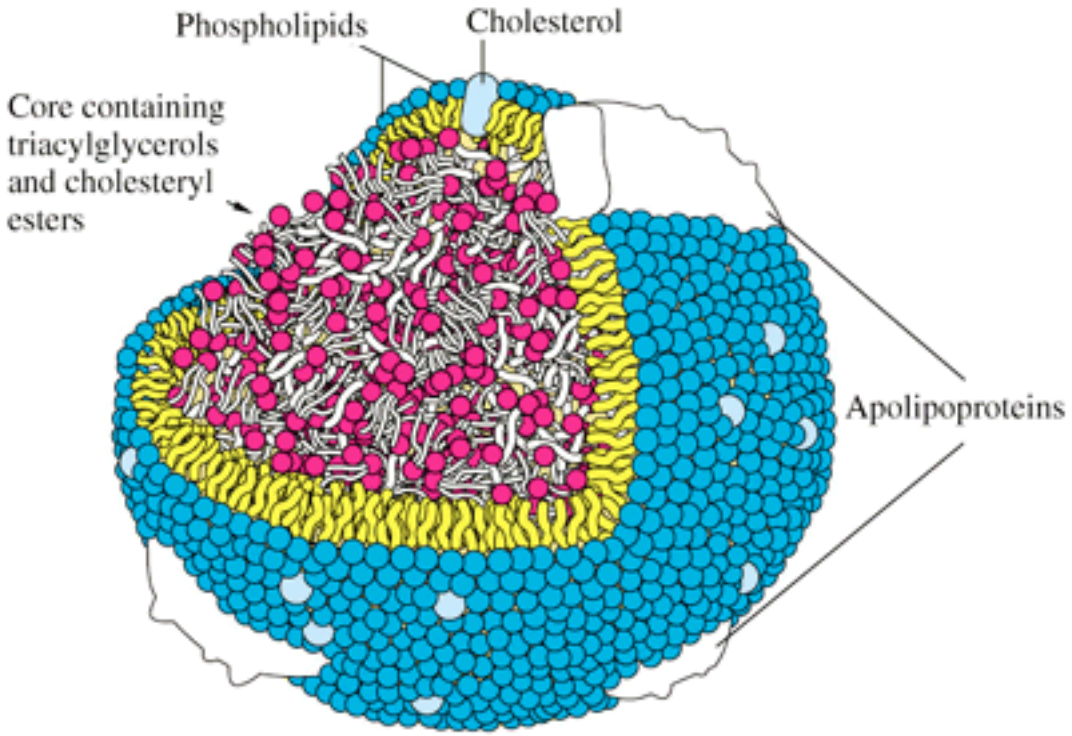
Chylomicron

Contents when released | Changes during circulation

Chylomicrons are large lipoprotein particles (having a diameter of 75 to 1,200nm) that are created by the absorptive cells of the small intestine. Chylomicrons transport exogenous lipids to liver, adipose, cardiac and skeletal tissue where they are broken down by lipoprotein lipase. The chylomicrons are released by exocytosis from enterocytes into lacteals, lymphatic vessels originating in the villi of the small intestine, and are then secreted into the bloodstream at the thoracic duct's connection with the left subclavian vein.



Contents when released

Nascent chylomicrons are primarily composed of triglycerides (85%) and contain some cholesterol and cholesteryl esters. The main apolipoprotein component is apolipoprotein B-48 (APOB48).

Changes during circulation

While circulating in lymph and blood, chylomicron exchanges components with High Density Lipoproteins (HDL). The HDL donates apolipoprotein C-II (APOC2) and apolipoprotein E (APOE) to the nascent chylomicron and thus matures it into a "chylomicron." APOC2 is the cofactor for lipoprotein lipase (LPL) activity. Once triglyceride stores are distributed, the chylomicron returns APOC2 (but keeps APOE) back to the HDL and thus becomes a chylomicron remnant. APOB48 and APOE are

important to identify the chylomicron remnant in the liver for endocytosis and breakdown.

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X-ray crystallography

Inorganic & simple organic structures | Single Crystal Diffraction | Powder Diffraction | Biological structures | Crystallisation | X-ray Diffraction Experiment | Data processing

X-ray crystallography is a technique in crystallography in which the pattern produced by the diffraction of X-rays through the closely spaced lattice of atoms in a crystal is recorded and then analyzed to reveal the nature of that lattice. This generally leads to an understanding of the material and molecular structure of a substance. The spacing in the crystal lattice can be determined using Bragg's law. The electrons that surround the atoms, rather than the atomic nuclei themselves, are the entities which physically interact with the incoming X-ray photons. This technique is widely used in chemistry and biochemistry to determine the structures of an immense variety of molecules, including inorganic compounds, DNA and proteins. X-ray diffraction is commonly carried out using single crystals of a material, but if these are not available, microcrystalline powdered samples may also be used, although this requires different equipment, gives less information, and is much less straightforward.

Inorganic & simple organic structures

In inorganic chemistry, x-ray crystallography is used to determine lattice structures as well as chemical formulas, bond lengths and angles. The primary methods used in inorganic structures are powder diffraction and single-crystal diffraction.

Single Crystal Diffraction

Many complicated inorganic and organometallic systems have been analyzed using single crystal methods, such as fullerenes, metalloporphyrins, and many other complicated compounds. Single crystal is also used in pharmaceutical industry, due to recent problems with polymorphs. The major limitation to the quality of single-crystal data is crystal quality.

Inorganic single-crystal x-ray crystallography is commonly known as small molecule crystallography, as opposed to macromolecular crystallography.

Powder Diffraction

X-ray powder diffraction finds frequent use in materials science because sample preparation is relatively easy, and the test itself is often rapid and non-destructive. The vast majority of engineering materials are crystalline, and even those which are not yield some useful information in diffraction experiments.

The pattern of powder diffraction peaks can be used to quickly identify materials (thanks to the JCPDS pattern database), and changes in peak width or position can be used to determine crystal size, purity,

and texture.

Biological structures

The first protein crystal structure was of sperm whale myoglobin, as determined by Max Perutz and Sir John Cowdery Kendrew in 1958, which led to a Nobel Prize in Chemistry. The X-ray diffraction analysis of myoglobin was originally motivated by the observation of myoglobin crystals in dried pools of blood on the decks of whaling ships. Today X-ray crystallography is used by pharmaceutical companies to determine specifically how drug lead compounds interact with their protein targets. Biological X-ray crystallography is to date the most prolific discipline within the area of Structural biology; out of the ~35000 protein structures solved, X-ray crystallography is responsible for ~29000. NMR spectroscopy has contributed almost 5000 and electron microscopy just over 100. Other Biophysical methods, such as IR spectroscopy and powder diffraction make up the remaining structures, according to the Protein Data Bank (PDB).

Crystallisation

In order to solve a crystal structure, you must first crystallise the compound of interest. This is because a single molecule in solution has insufficient scattering power alone. A crystal can be considered to be an (effectively) infinite repeating array of our molecule of interest. The Laue conditions and Bragg's law show that constructive interference between diffracted X-rays that are in-phase reinforce each other, so that the diffraction pattern becomes detectable. The geometric conditions where diffraction occurs can be visualised using Ewald's sphere.

Crystallization of small molecules has traditionally followed three methods

- Diffusion gradient- solubility or temperature
- Concentration through evaporation
- Sublimation- not recommended due to low quality crystals.

Even though small molecules are relatively more facile to crystallize than macromolecules, there are many compounds reported that have failed to give diffraction quality crystals.

Crystallisation of macromolecules is not trivial. Traditional methods of crystallising inorganic molecules have been modified to be gentle enough for proteins, which are sensitive to temperature and high concentrations of organic solvents.Many methods exist to crystallise proteins, but the two most successful methods are the *microbatch* and *vapour diffusion* techniques. Concentrated solutions of the protein are mixed with various solutions, which typically consist of:

- a buffer to control the pH of the experiment
- a Precipitating agent, to induce supersaturation (typically Poly ethylene glycols, Salts such as Ammonium sulphate or organic alcohols).

- other salts or additives, such as detergents or co-factors

In either *microbatch* or *vapour diffusion* the solutions are allowed to concentrate over time. In solutions of a favourable composition, the protein becomes supersaturated and *crystal nuclei* form, leading to crystal growth. Typically protein crystallographers can screen hundreds or thousands of conditions before a suitable condition is found that leads to a crystal of suitable quality. As a rule of thumb, some useful detail can be gained from a crystal that diffracts with a resolution of better than 4 angstroms (400 picometers).

Many biomolecules of interest still have not been successfully crystallised. Imperfections in the crystal structure, caused by impurities or sample contamination can prevent the acquisition of atomic resolution images. Convection caused by temperature variations within the forming crystal can also cause imperfections, and one of the proposed scientific applications of the International Space Station is the growth of crystals, because convection is reduced in the free fall environment of an orbiting spacecraft.

X-ray Diffraction Experiment

Once prepared the crystals are harvested and often cryocooled with gaseous or liquid nitrogen at a temperature of around 100 kelvins or -172 °C. Liquid helium is occasionally used too, but it is often not necessary to cool crystals that much (and it also costs more). Cryocooling crystals both reduces radiation damage incurred during data collection and decreases thermal motion within the crystal, giving rise to better diffraction limits and higher quality data. Crystals are then mounted on a diffractometer coupled with a machine that emits a beam of X-rays This can either be a rotating-anode type source or a synchrotron. The X-rays are diffracted by their interaction with the electrons in the crystal, and the pattern of diffraction is recorded on film or more recently charge-coupled device detectors and scanned into a computer. Successive images are recorded as a crystal is rotated within the X-ray beam.

Data processing

The data collected from a diffraction experiment is a reciprocal space representation of the crystal lattice. The position of each diffraction 'spot' is governed by the size and shape of the unit cell, and the inherent symmetry within the crystal. The intensity of each diffraction 'spot' is recorded, and is proportional to the square of the *structure factor* amplitude. The *structure factor* is a complex number containing information relating to both the amplitude and phase of a wave. In order to obtain an interpretable *electron density map*, we must first obtain phase estimates (An electron density map allows a crystallographer to build a starting model of our molecule) This is known as the phase problem can be accomplished in a variety of ways.

- Molecular replacement - if a structure exists of a related protein, we can use this structure as a search model and use molecular replacement to determine the orientation and position of our molecules within the unit cell. The phases obtained this way can be used to generate *electron density maps*.
- Heavy atom methods - If we can soak high-molecular weight atoms (not usually found in proteins) into

our crystal we can use direct methods or Patterson-space methods to determine their location and use them to obtain initial phases.
- *Ab Initio* phasing - if we have high resolution data (better than 1.6 angstrom or 160 picometers) we can use direct methods to obtain phase information.

Having obtained initial phases we can build an initial model (our hypothesis) and then refine the Cartesian coordinates of atoms and their respective B-factors (relating to the thermal motion of the atom) to best fit the observed diffraction data. This generates a new (and hopefully more accurate) set of phases and a new electron density map is generated. The model is then revised and updated by the crystallographer and a further round of refinement is carried out. This continues until the correlation between the diffraction data and the model is maximised.

Once the model of a molecule's structure has been finalised, it is often deposited in a crystallographic database such as the Protein Databank or the Cambridge Structure Database. Many structures obtained in private commercial ventures to crystallise medicinally relevant proteins, are not deposited in public crystallographic databases.

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DNA ladder

A **DNA ladder** is a solution of DNA molecules of different lengths used in agarose gel electrophoresis. It is applied to an agarose gel as a reference to estimate the size of unknown DNA molecules. In addition it can be used to approximate the mass of a band by comparison to a special mass ladder.

The DNA ladder is made of 4 different nucleotides which link the 2 sides of the strand. They are called: adenine "A", thymine "T", Cytosine "C" and last Guanine "G."

Different DNA ladders are commercially available depending on expected DNA length. The 1kb ladder with fragment ranging from about 0.5 kbp to 10 or 12 kbp and the 100 bp ladder with fragments ranging from 100 bp to just above 1000 bp are the most frequent. DNA ladders are often produced by a suitable restriction digest of a plasmid. There are special DNA ladders for supercoiled DNA and RNA.

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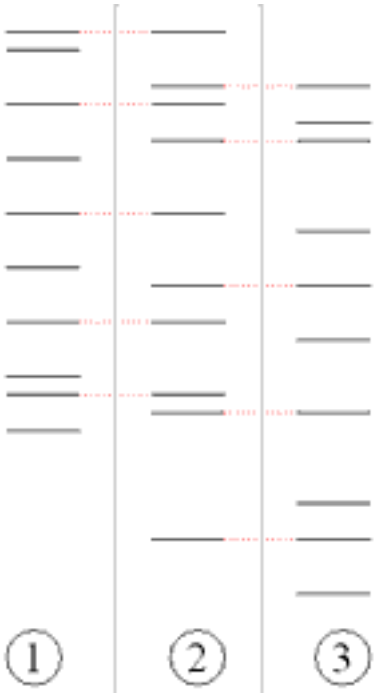
DNA Electrophoresis



Electrophoresis of PCR-amplified DNA fragments. (1) Father. (2) Child. (3) Mother. The child has inherited some, but not all of the fingerprint of each of its parents, giving it a new, unique fingerprint.

DNA electrophoresis is an analytical technique used to separate DNA fragments by size. An electric field forces the fragments to migrate through a gel. DNA molecules normally migrate from negative to positive potential due to the net negative charge of the phosphate backbone of the DNA chain. At the scale of the length of DNA molecules, the gel looks much like a random, intricate network. Longer molecules migrate more slowly because they are more easily 'trapped' in the network.

After the separation is completed, the fractions of DNA fragments of different length are often visualized using a fluorescent dye specific for DNA, such as ethidium bromide. The gel shows bands corresponding to different DNA molecules populations with different molecular weight. Fragment size is usually reported in "nucleotides", "base pairs" or "kb" (for "1000's of base pairs) depending upon whether single- or double-stranded DNA has been separated. Fragment size determination is typically done by comparison to commercially available DNA ladders containing linear DNA fragments of known length.

The types of gel most commonly used for DNA electrophoresis are agarose (for relatively long DNA molecules) and polyacrylamide (for high resolution of short DNA molecules, for example in DNA sequencing). Gels have conventionally been run in a "slab" format such as that shown in the figure, but capillary electrophoresis has become important for applications such as high-throughput DNA sequencing. Electrophoresis techniques used in the assessment of DNA damage include alkaline gel electrophoresis and pulsed field gel electrophoresis. The

measurement and analysis are mostly done with a specialized gel analysis software.

Electrophoresis

Electrophoresis is the movement of an electrically charged substance under the influence of an electric field. This movement is due to the Lorentz force, which may be related to fundamental electrical properties of the body under study and the ambient electrical conditions by the equation given below. *F* is the Lorentz force, *q* is the charge carried by the body, *E* is the electric field :

$$\bar{F}_e = q\bar{E}$$.

The resulting electrophoretic migration is countered by forces of friction such that the rate of migration is constant in a constant and homogeneous electric field:

$$F_f = vf$$

Where *v* is the velocity and *f* is the frictional coefficient.

$$q\bar{E} = vf$$

The electrophoretic mobility μ is defined as followed.

$$\mu = \frac{v}{E} = \frac{q}{f}$$

The expression above applied only to ions at a concentration approaching 0 and in a non-conductive solvent. Polyionic molecules are surrounded by a cloud of counterions which alter the effective electric field applied on the ions to be separated. This render the previous expression a poor approximation of what really happens in an electrophoretic aparatus.

The mobility depends on both the particle properties (e.g., surface charge density and size) and solution properties (e.g., ionic strength, electric permittivity, and pH). For high ionic strengths, an approximate expression for the electrophoretic mobility is given by the Smoluchowski equation,

$$\mu_e = \frac{\epsilon\epsilon_0\zeta}{\eta}$$,

where ε is the dielectric constant of the liquid, ϵ_0 is the permitivitty of free space, η is the viscosity of the liquid, and ζ is the zeta potential (i.e., surface potential) of the particle.

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Polymerase chain reaction

Polymerase chain reaction (**PCR**) is technique for enzymatically replicating DNA without using a living organism, such as *E. coli* or yeast. Like amplification using living organisms, the technique allows a small amount of DNA to be amplified exponentially. As PCR is an *in vitro* technique, it can be performed without restrictions on the form of DNA and it can be extensively modified to perform a wide array of genetic manipulations.

PCR is commonly used in medical and biological research labs for a variety of tasks, such as the detection of hereditary diseases, the identification of genetic fingerprints, the diagnosis of infectious diseases, the cloning of genes, paternity testing, and DNA computing.

PCR was invented by Kary Mullis. At the time he thought up PCR in 1983, Mullis was working in Emeryville, California for Cetus, one of the first biotechnology companies. There, he was charged with making short chains of DNA for other scientists. Mullis has written that he conceived of PCR while cruising along the Pacific Coast Highway 1 one night in his car. He was playing in his mind with a new way of analyzing changes (mutations) in DNA when he realized that he had instead invented a method of amplifying any DNA region. Mullis has said that before his trip was over, he was already savoring the prospects of a Nobel Prize. He shared the Nobel Prize in Chemistry with Michael Smith in 1993.

As Mullis has written in the Scientific American: "Beginning with a single molecule of the genetic material DNA, the PCR can generate 100 billion similar molecules in an afternoon. The reaction is easy to execute. It requires no more than a test tube, a few simple reagents, and a source of heat."

PCR in practice

PCR stands for polymerase chain reaction. It is used to amplify specific regions of a DNA strand. This can be a single gene, just a part of a gene, or non-coding sequence. PCR typically amplifies only short DNA fragments, usually up to 10 kilo base pairs (kb). Certain methods can copy fragments up to 25 kb in size, which is still much less than the chromosomal DNA of a eukaryotic cell - for example, a human cell contains about three billion base pairs (3 Gbp).

PCR, as currently practiced, requires several basic components. These components are:
- *DNA template,* which contains the region of the DNA fragment to be amplified
- Two *primers,* which determine the beginning and end of the region to be amplified (see following section on primers)
- *Taq polymerase* (or another durable polymerase), a DNA polymerase which copies the region to be amplified
- *Deoxynucleotide triphosphates,* (dNTPs) from which the DNA polymerase builds the new DNA
- *Buffer solution,* which provides a suitable chemical environment for the DNA Polymerase
- *Divalent cation,* magnesium or manganese ions

- *Monovalent cation*, potassium ions

The PCR process is carried out in a thermal cycler. This is a machine that heats and cools the reaction tubes within it to the precise temperature required for each step of the reaction. The lid of the thermal cycler is heated to prevent condensation on the inside of the reaction tube caps. Alternatively, a layer of oil may be placed on the reaction mixture to prevent evaporation. Typical reaction volumes range from 15-100 µl.

Primers

The DNA fragment to be amplified is determined by selecting primers. Primers are short, artificial DNA strands - often not more than 50 and usually only 18 to 25 base pairs long - that are complementary to the beginning or the end of the DNA fragment to be amplified. They anneal by adhering to the DNA template at these starting and ending points, where the DNA polymerase binds and begins the synthesis of the new DNA strand.

The choice of the length of the primers and their melting temperature (T_m) depends on a number of considerations. The melting temperature of a primer -- not to be confused with the melting temperature of the template DNA -- is defined as the temperature at which half of the primer binding sites are occupied. Primers that are too short would anneal at several positions on a long DNA template, which would result in non-specific copies. On the other hand, the length of a primer is limited by the maximum temperature allowed to be applied in order to melt it, as melting temperature increases with the length of the primer. Melting temperatures that are too high, i.e., above 80°C, can cause problems since the DNA polymerase is less active at such temperatures. The optimum length of a primer is generally from 15 to 40 nucleotides with a melting temperature between 55°C and 65°C.

Sometimes *degenerate primers* are used. These are actually mixtures of similar, but not identical, primers. They may be convenient if the same gene is to be amplified from different organisms, as the genes themselves are probably similar but not identical. The other use for degenerate primers is when primer design is based on protein sequence. As several different codons can code for one amino acid, it is often difficult to deduce which codon is used in a particular case. Therefore primer sequence corresponding to the amino acid isoleucine might be "ATH", where A stands for adenine, T for thymine, and H for adenine, thymine, or cytosine. (See genetic code for further details about codons.) Use of degenerate primers can greatly reduce the specificity of the PCR amplification. This problem can be partly solved by using touchdown PCR.

The above mentioned considerations make primer design a very exacting process, upon which product yield depends:
- GC-content should be between 40-60%.
- Calculated T_m for both primers used in reaction should not differ >5°C, and T_m of the amplification product should not differ from primers by >10°C (In practice may not be true always).

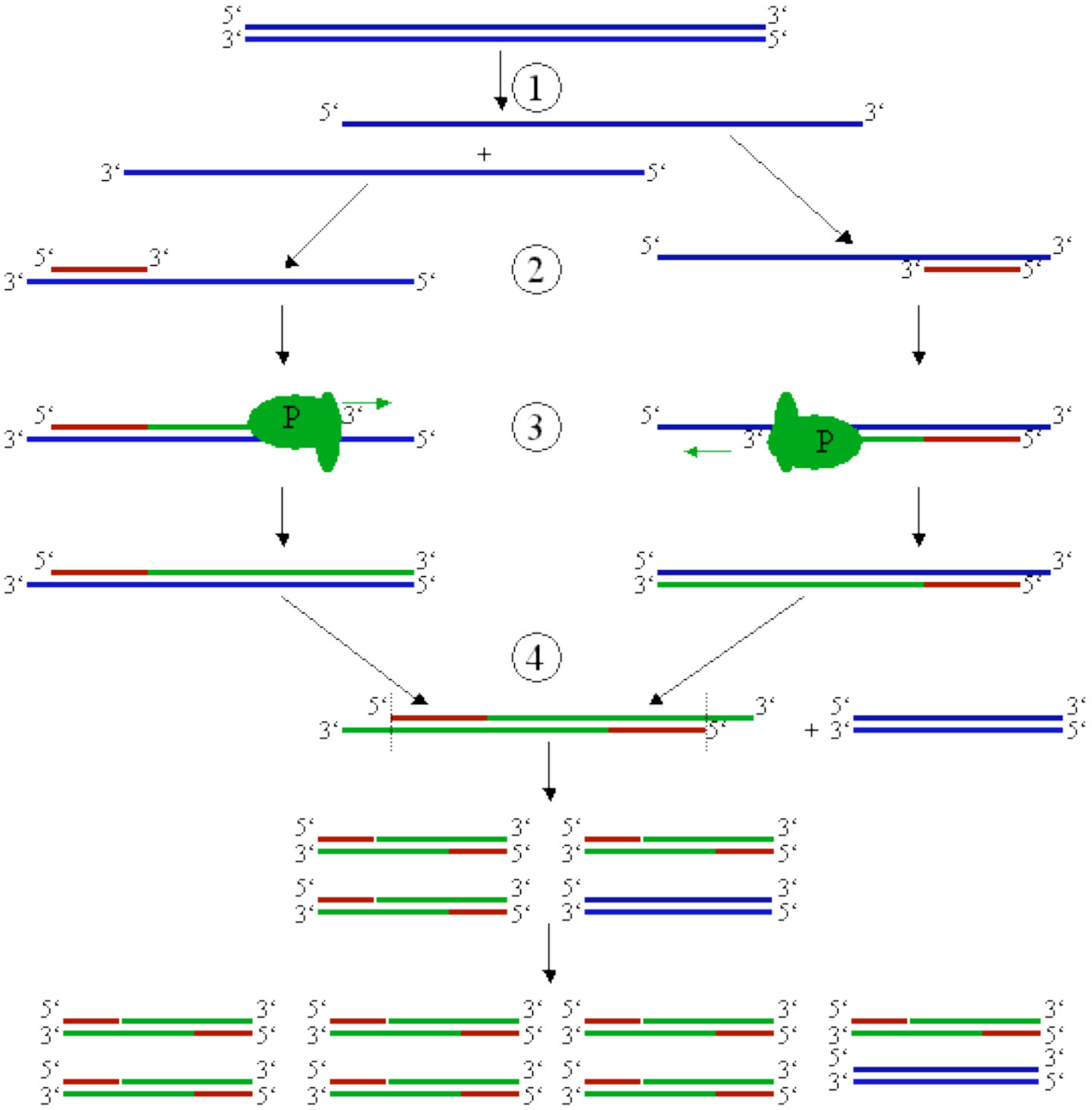
- Annealing temperature usually is 5°C below the calculated lower T_m. However, it should be chosen empirically for individual conditions.
- Inner self-complementary hairpins of >4 and of dimers >8 should be avoided.
- Primer 3' terminus design is critical to PCR success since the primer extends from the 3' end. The 3' end should not be complementary over greater than 3-4 bases to any region of the other primer (or even the same primer) used in the reaction and must provide correct base matching to the template.

There are computer programs to help design primers.

Procedure

The PCR process usually consists of a series of twenty to thirty-five cycles. Each cycle consists of three steps.

1. The double-stranded DNA has to be heated to 94-96°C (or 98°C if extremely thermostable polymerases are used) in order to separate the strands. This step is called *denaturing*; it breaks apart the hydrogen bonds that connect the two DNA strands. Prior to the first cycle, the DNA is often denatured for an extended time to ensure that both the template DNA and the primers have completely separated and are now single-strand only. Time: usually 1-2 minutes, but up to 5 minutes. Also certain polymerases are activated at this step (see hot-start PCR).
2. After separating the DNA strands, the temperature is lowered so the primers can attach themselves to the single DNA strands. This step is called *annealing*. The temperature of this stage depends on the primers and is usually 5°C below their melting temperature (45-65°C). A wrong temperature during the annealing step can result in primers not binding to the template DNA at all, or binding at random. Time: 30 seconds-2 minutes.
3. Finally, the DNA polymerase has to copy the DNA strands. It starts at the annealed primer and works its way along the DNA strand. This step is called *elongation*. The elongation temperature depends on the DNA polymerase. Taq polymerase elongates optimally at a temperature of 72 degrees Celsius. The time for this step depends both on the DNA polymerase itself and on the length of the DNA fragment to be amplified. As a rule-of-thumb, this step takes 1 minute per thousand base pairs. A *final elongation* step is frequently used after the last cycle to ensure that any remaining single stranded DNA is completely copied. This differs from all other elongation steps only in that it is longer--typically 10-15 minutes. This last step is highly recommended if the PCR product is to be ligated into a T vector using TA-cloning.



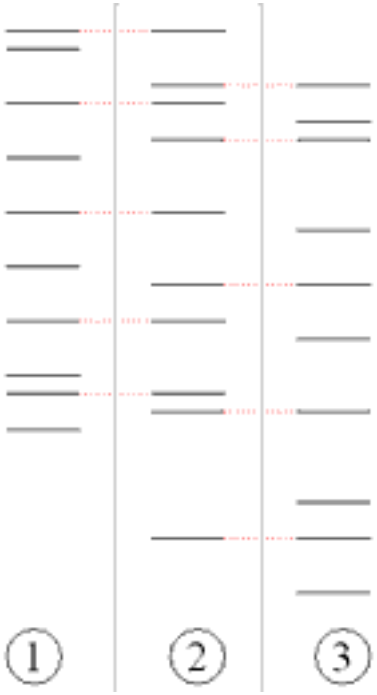
Schematic drawing of the PCR cycle. (1) Denaturing at 94-96°C. (2) Annealing at (eg) 68°C. (3) Elongation at 72°C (P=Polymerase). (4) The first cycle is complete. The two resulting DNA strands make up the template DNA for the next cycle, thus doubling the amount of DNA duplicated for each new cycle (a total of three cycles is shown above).

Uses of PCR

PCR can be used for a broad variety of experiments and analyses. Some examples are discussed below.

Genetic fingerprinting

Genetic fingerprinting is a forensic technique used to identify a person by comparing his or her DNA with a given sample. An example is blood from a crime scene being genetically compared to blood from a suspect. The sample may contain only a tiny amount of DNA (obtained from a source such as blood, semen, saliva, hair, or other organic material)). Theoretically, just a single strand is needed. First, one breaks the DNA sample into fragments; then amplifies them using PCR. The amplified fragments are then separated using gel electrophoresis. The overall layout of the DNA fragments is called a *DNA fingerprint*. Since there is a very tiny possibility that two individuals may have the same sequences (one in several million), the technique is more effective at acquitting a suspect than proving the suspect guilty.



Electrophoresis of PCR-amplified DNA fragments. (1) Father. (2) Child. (3) Mother. The child has inherited some, but not all of the fingerprint of each of its parents, giving it a new, unique fingerprint.

Paternity testing

Although these resulting 'fingerprints' are unique (except for identical twins), genetic relationships, for example, parent-child or siblings, can be determined from two or more genetic fingerprints, which can be used for paternity tests. A variation of this technique can also be used to determine evolutionary relationships between organisms.

Detection of hereditary diseases

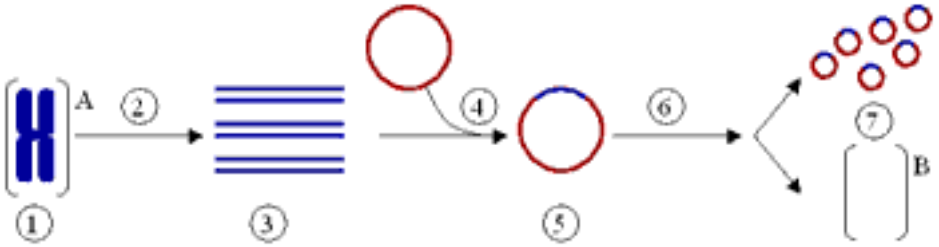
The detection of hereditary diseases in a given genome is a long and difficult process, which can be shortened significantly by using PCR. Each gene in question can easily be amplified through PCR by using the appropriate primers and then sequenced to detect mutations.

Viral diseases, too, can be detected using PCR through amplification of the viral DNA. This analysis is

possible right after infection, which can be from several days to several months before actual symptoms occur. Such early diagnoses give physicians a significant lead in treatment.

Cloning genes

Cloning a gene, not to be confused with cloning a whole organism, describes the process of isolating a gene from one organism and then inserting it into another organism (now termed a genetically modified organism (GMO)). PCR is often used to amplify the gene, which can then be inserted into a vector (a *vector* is a piece of DNA which 'carries' the gene into the GMO) such as a plasmid (a circular DNA molecule). The DNA can then be transferred into an organism (the GMO) where the gene and its product can be studied more closely. Expressing a cloned gene (when a gene is *expressed* the gene product (usually protein or RNA) is produced by the GMO) can also be a way of mass-producing useful proteins, for example medicines or the enzymes in biological washing powders. The incorporation of an affinity tag on a recombinant protein will generate a fusion protein which can be more easily purified by affinity chromatography.



Cloning a gene using a plasmid.
1. Chromosomal DNA of organism A.
PCR.
2. Multiple copies of a single gene from organism A.
3. Insertion of the gene into a plasmid.
4. Plasmid with gene from organism A.
5. Insertion of the plasmid in organism B.
6. Multiplication or expression of the gene, originally from organism A, occurring in organism B.

Mutagenesis

Mutagenesis is a way of making changes to the sequence of nucleotides in the DNA. There are situations in which one is interested in *mutated* (changed) copies of a given DNA strand, for example, when trying to assess the function of a gene or in *in-vitro* protein evolution (also known as Directed evolution). Mutations can be introduced into copied DNA sequences in two fundamentally different ways in the PCR process. *Site-directed mutagenesis* allows the experimenter to introduce a mutation at a specific location on the DNA strand. Usually, the desired mutation is incorporated in the primers used for the PCR program. *Random mutagenesis*, on the other hand, is based on the use of error-prone polymerases in the PCR process. In the case of random mutagenesis, the location and nature of the mutations cannot be controlled. One application of random mutagenesis is to analyze structure-function relationships of a protein. By randomly altering a DNA sequence, one can compare the resulting protein with the original and determine the function of each part of the protein.

Analysis of ancient DNA

Using PCR, it becomes possible to analyze DNA that is thousands of years old. PCR techniques have been successfully used on animals, such as a forty-thousand-year-old mammoth, and also on human DNA, in applications ranging from the analysis of Egyptian mummies to the identification of a Russian Tsar.

Genotyping of specific mutations

Through the use of allele-specific PCR, one can easily determine which allele of a mutation or polymorphism an individual has. Here, one of the two primers is common, and would anneal a short distance away from the mutation, while the other anneals right on the variation. The 3' end of the allele-specific primer is modified, to only anneal if it matches one of the alleles. If the mutation of interest is a T or C single nucleotide polymorphism (T/C SNP), one would use two reactions, one containing a primer ending in T, and the other ending in C. The common primer would be the same. Following PCR, these two sets of reactions would be run out on an agarose gel, and the band pattern will tell you if the individual is homozygous T, homozygous C, or heterozygous T/C. This methodology has several applications, such as amplifying certain haplotypes (when certain alleles at 2 or more SNPs occur together on the same chromosome Linkage Disequilibrium) or detection of recombinant chromosomes and the study of meiotic recombination.

Comparison of gene expression

Researchers have used traditional PCR as a way to estimate changes in the amount of a gene's expression. Ribonucleic acid (RNA) is the molecule into which DNA is transcribed prior to making a protein, and those strands of RNA that hold the instructions for protein sequence are known as messenger RNA (mRNA). Once RNA is isolated it can be reverse transcribed back into DNA (complementary DNA to be precise, known as cDNA), at which point traditional PCR can be applied to amplify the gene, this methodology is called RT-PCR. In most cases if there is more starting material (mRNA) of a gene then during PCR more copies of the gene will be generated. When the products of the PCR process are run on an agarose gel a band, corresponding to a gene, will appear larger on the gel (note that the band remains in the same location relative to the ladder, it will just appear fatter or brighter). By running samples of amplified cDNA from differently treated organisms one can get a general idea of which sample expressed more of the gene of interest. A quantative RT-PCR method has been developed, it is called Real-time PCR.

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Plasmid

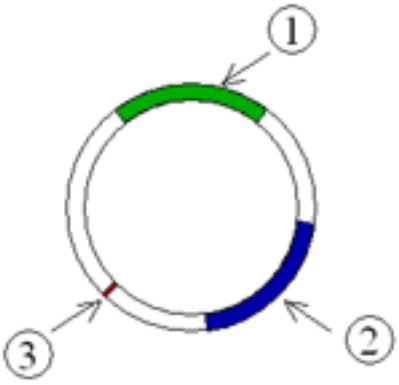
Schematic drawing of a bacterium with plasmids enclosed. Chromosomal DNA is in green. Plasmids are in blue.

A **plasmid** is a DNA molecule separate from the chromosomal DNA and capable of autonomous replication. It is typically circular and double-stranded. It usually occurs in bacteria, sometimes in eukaryotic organisms (e.g., the *2-micrometre-ring* in *Saccharomyces cerevisiae*). Size of plasmids varies from 1 to over 400 kilobase pairs (kbp). There may be one copy, for large plasmids, to hundreds of copies of the same plasmid in a single cell, or even thousands of copies, for certain artificial plasmids selected for high copy number (such as the **pUC** series of plasmids).

The term *plasmid* was first introduced by the American molecular biologist Joshua Lederberg in 1952.

Antibiotic resistance

Plasmids often contain genes or gene cassettes that confer a selective advantage to the bacterium harboring them, such as the ability to make the bacterium antibiotic resistant.



Schematic drawing of a plasmid with antibiotic resistances. 1 & 2 Genes that code for resistance. 3 Ori.

Every plasmid contains at least one DNA sequence that serves as an *origin of replication*, or *ori* (a starting point for DNA replication), which enables the plasmid DNA to be duplicated independently from the chromosomal DNA. The chromosomes of most bacteria are circular, like the plasmid depicted int the Figure above, but linear plasmids are also known, which superficially resemble the chromosomes of most eukaryotes.

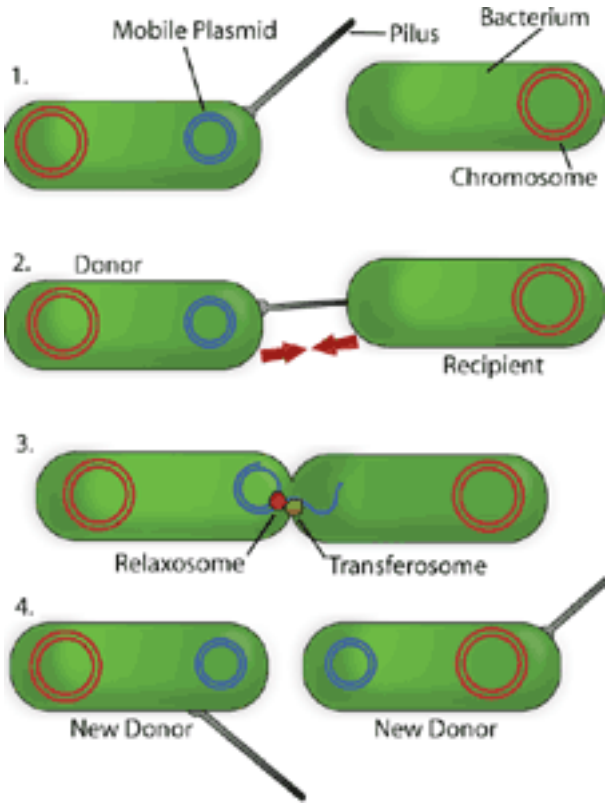
Episomes

An **episome** is a plasmid that can integrate itself into the chromosomal DNA of the host organism. For this reason, it can stay intact for a long time, be duplicated with every cell division of the host, and become a basic part of its genetic makeup. This term is no longer commonly used for plasmids, since it is now clear that a region of homology with the chromosome such as a transposon makes a plasmid into an episome. In mammalian systems, the term episome refers to a circular DNA (such as a viral genome) that is maintained by noncovalent tethering to the host cell chromosome.

Vectors

Plasmids used in genetic engineering are called vectors. They are used to transfer genes from one organism to another and typically contain a genetic marker conferring a phenotype that can be selected for or against. Most also contain a polylinker or multiple cloning site (MCS), which is a short region containing several commonly used restriction sites allowing the easy insertion of DNA fragments at this location. See Applications below.

Types



Schematic drawing of bacterial conjugation. 1- Donor cell produces pilus. 2- Pilus attaches to recipient cell, brings the two cells together. 3- The mobile plasmid is nicked and a single strand of DNA is then transferred to the recipent cell. 4- Both cells recircularize their plasmids, synthesize second strands, and reproduce pili; both cells are now viable donors.

One way of grouping plasmids is by their ability to transfer to other bacteria. *Conjugative* plasmids contain so-called *tra-genes*, which perform the complex process of *conjugation*, the sexual transfer of plasmids to another bacterium. *Non-conjugative* plasmids are incapable of initiating conjugation, hence they can only be transferred with the assistance of conjugative plasmids, by 'accident'. An intermediate class of plasmids are *mobilizable*, and carry only a subset of the genes required for transfer. They can 'parasitise' a conjugative plasmid, transferring at high frequency only in its presence.

It is possible for plasmids of different types to coexist in a single cell. Seven different plasmids have been found in *E. coli*. But *related* plasmids are often incompatible, in the sense that only one of them survives in the cell line, due to the regulation of vital plasmid functions. Therefore, plasmids can be assigned into *compatibility groups*.

Another way to classify plasmids is by function. There are five main classes:
- *Fertility-F-plasmids*, which contain tra-genes. They are capable of conjugation.
- *Resistance-(R)plasmids*, which contain genes that can build a resistance against antibiotics or poisons. Historically known as R-factors, before the nature of plasmids was understood.
- *Col-plasmids*, which contain genes that *code for* (determine the production of) colicines, proteins that can kill other bacteria.
- *Degrative plasmids*, which enable the digestion of unusual substances, e.g., toluene or salicylic acid.
- *Virulence plasmids*, which turn the bacterium into a pathogen.

Plasmids can belong to more than one of these functional groups.

Plasmids that exist only as one or a few copies in each bacterium are, upon cell division, in danger of being lost in one of the segregating bacteria. Such single-copy plasmids have systems which attempt to actively distribute a copy to both daughter cells.

Some plasmids include an *addiction system* or "postsegregational killing system (PSK)". They produce both a long-lived poison and a short-lived antidote. Daughter cells that retain a copy of the plasmid survive, while a daughter cell that fails to inherit the plasmid dies or suffers a reduced growth-rate because of the lingering poison from the parent cell.

Applications

Plasmids serve as important tools in genetics and biochemistry labs, where they are commonly used to multiply (make many copies of) or *express* particular genes. Many plasmids are commercially available for such uses.

The gene to be replicated is inserted into copies of a plasmid which contains genes that make cells resistant to particular antibiotics. Next, the plasmids are inserted into bacteria by a process called *transformation*. Then, the bacteria are exposed to the particular antibiotics. Only bacteria which take up copies of the plasmid survive the antibiotic, since the plasmid makes them resistant. In particular, the

protecting genes are expressed (used to make a protein) and the expressed protein breaks down the antibiotics. In this way the antibiotics act as a filter to select only the modified bacteria. Now these bacteria can be grown in large amounts, harvested and lysed to isolate the plasmid of interest.

Another major use of plasmids is to make large amounts of proteins. In this case you grow bacteria containing a plasmid harboring the gene of interest. Just as the bacteria produces proteins to confer its antibiotic resistance, it can also be induced to produce large amounts of proteins from the inserted gene. This is a cheap and easy way of mass-producing a gene or the protein it then codes for, for example, insulin or even antibiotics.

Plasmid DNA extraction

As alluded to above, plasmids are often used to purify a specific sequence, since they can easily be purified away from the rest of the genome. For their use as vectors, and for molecular cloning, plasmids often need to be isolated.

There are several methods to isolate plasmid DNA from bacteria, the archaetypes of which are the **miniprep** and the **maxiprep**. The former can be used to quickly find out whether the plasmid is correct in any of several bacterial clones. The yield is a small amount of impure plasmid DNA, which is sufficient for analysis by restriction digest and for some cloning techniques.

In the latter, much larger volumes of bacterial suspension are grown from which a maxi-prep can be performed. Essentially this is a scaled-up miniprep followed by additional purification. This results in relatively large amounts (several ug) of very pure plasmid DNA.

In recent times many commercial kits have been created to perform plasmid extraction at various scales, purity and levels of automation.

Conformations

Plasmid DNA may appear in one of five conformations, which (for a given size) run at different speeds in a gel during electrophoresis. The conformations are listed below in order of electrophoretic mobility (speed for a given applied voltage) from slowest to fastest:
- "Nicked Open-Circular" DNA has one strand cut.
- "Linear" DNA has free ends, either because both strands have been cut, or because the DNA was linear *in vivo*. You can model this with an electrical extension cord that is not plugged into itself.
- "Relaxed Circular" DNA is fully intact with both strands uncut, but has been enzymatically "relaxed" (supercoils removed). You can model this by letting an extension cord relax and then plugging it into itself.
- "Supercoiled Denatured" DNA is like **supercoiled DNA** (see below), but has unpaired regions that make it slightly less compact; this can result from excessive alkalinity during plasmid preparation. You can model this by twisting a badly frayed extension cord and then plugging it into itself.

- "Supercoiled" (or "Covalently Closed-Circular") DNA is fully intact with both strands uncut, and with a twist built in, resulting in a compact form. You can model this by twisting an extension cord in good condition and then plugging it into itself.

The rate of migration for small linear fragments is directly proportional to the voltage applied at low voltages. At higher voltages, larger fragments migrate at continually increasing yet different rates. Therefore the resolution of a gel decreases with increased voltage.

At a specified, low voltage, the migration rate of small linear DNA fragments is a function of their length. Large linear fragments (over 20kb or so) migrate at a certain fixed rate regardless of length. This is because the molecules 'reptate', with the bulk of the molecule following the leading end through the gel matrix. Restriction digests are frequently used to analyse purified plasmids. These enzymes specifically break the DNA at certain short sequences. The resulting linear fragments form 'bands' after gel electrophoresis. It is possible to purify certain fragments by cutting the bands out of the gel and dissolving the gel to release the DNA fragments.

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Biochemistry from MobileReference

version 8.1

Audience: Intended for everyone interested in Biochemistry, particularly undergraduate and graduate life science students, medical students, nursing students, physician assistants students, and advanced high school students.

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