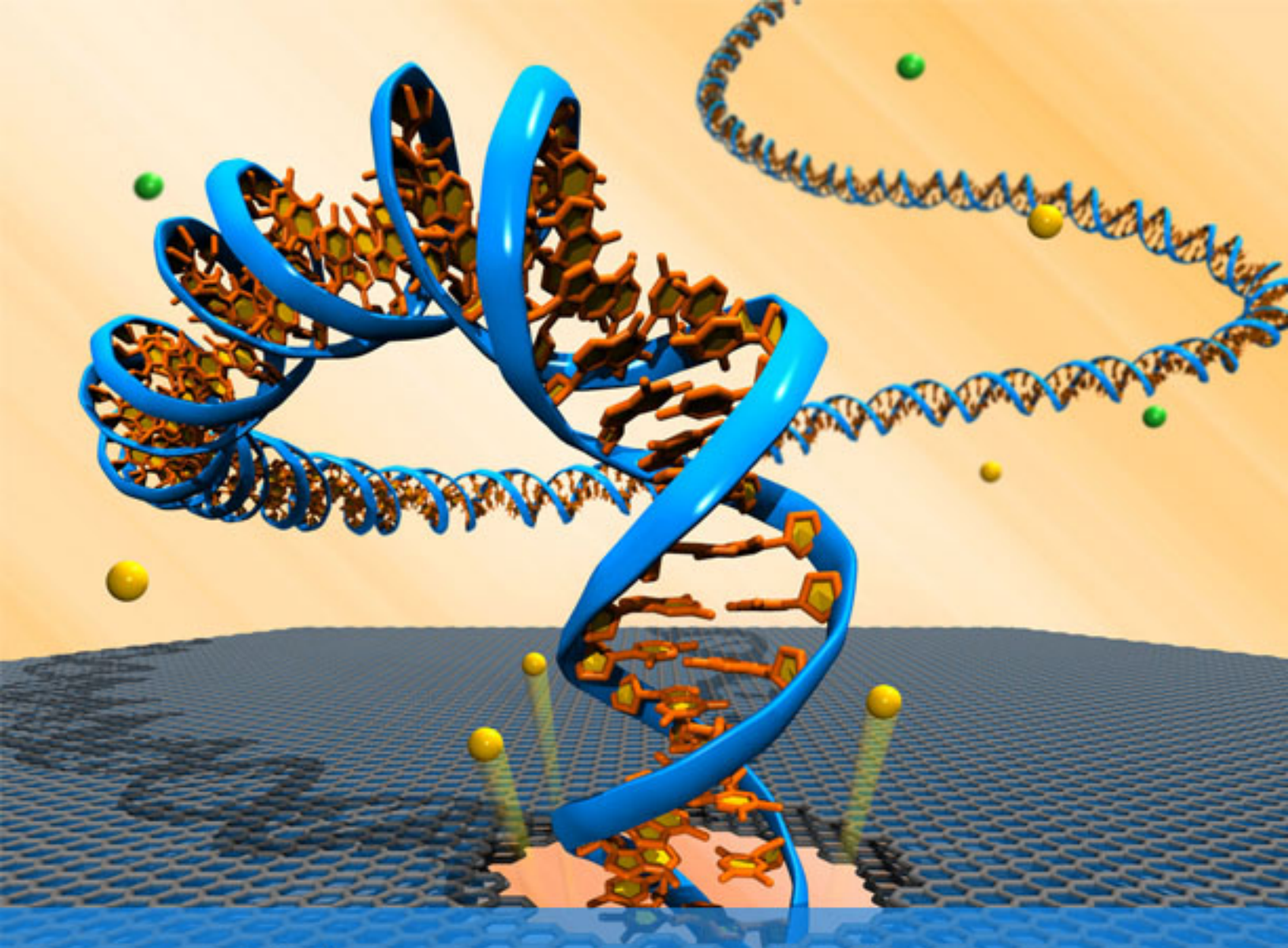

Biomolecules

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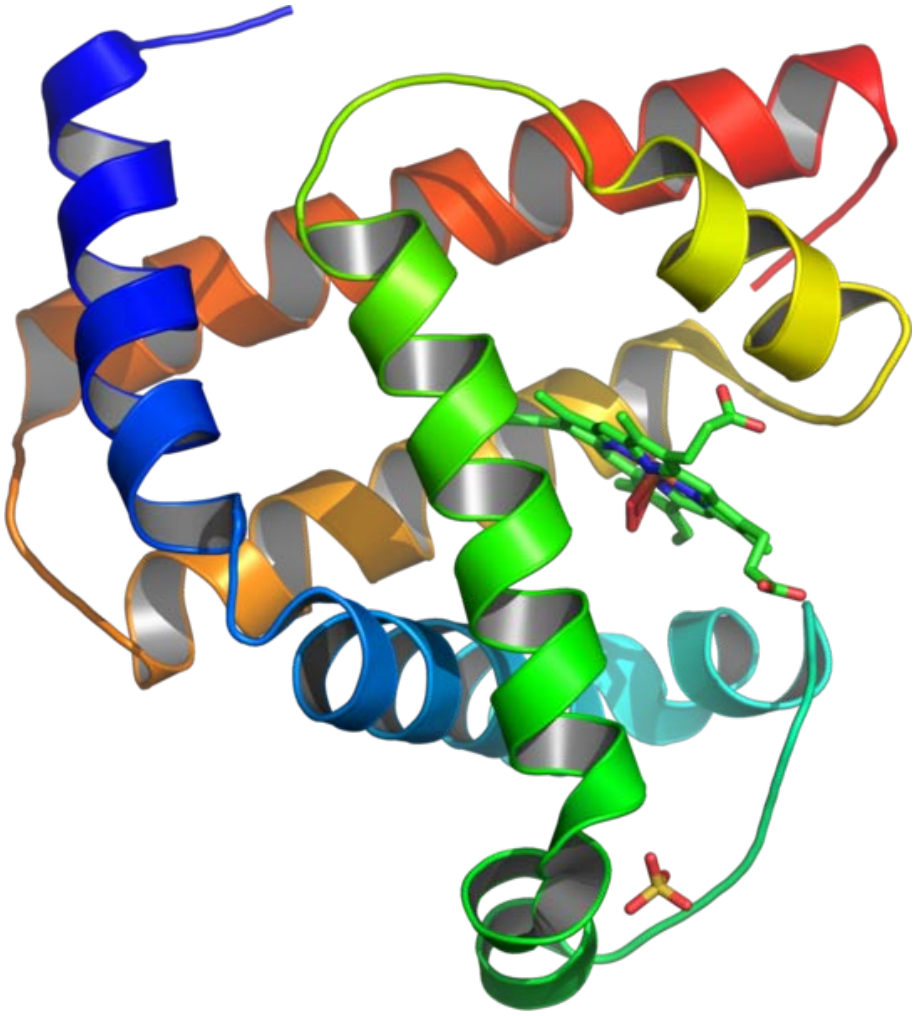
Chapter- 1

Biomolecule



A representation of the 3D structure of myoglobin, showing coloured alpha helices. This protein was the first to have its structure solved by X-ray crystallography by Max Perutz and Sir John Cowdery Kendrew in 1958, for which they received a Nobel Prize in Chemistry.

A **biomolecule** is any organic molecule that is produced by a living organism, including large polymeric molecules such as proteins, polysaccharides, and nucleic acids as well as

small molecules such as primary metabolites, secondary metabolites, and natural products. A more general name for this class of molecules is a biogenic substance.

As organic molecules, biomolecules consist primarily of carbon and hydrogen, nitrogen, and oxygen, and, to a smaller extent, phosphorus and sulfur. Other elements sometimes are incorporated but are much less common.

Types of biomolecules

A diverse range of biomolecules exist, including:

- Small molecules:
  - Lipids, phospholipids, glycolipids, sterols, glycerolipids
  - Vitamins
  - Hormones, neurotransmitters
  - Metabolites

- Monomers, oligomers and polymers:

Biomonomers	Bio-oligomers	Biopolymers	Polymerization process	Covalent Bond name between monomers
Amino acids	Oligopeptides	Polypeptides, proteins (hemoglobin...)	Polycondensation	Peptide bond
Monosaccharides	Oligosaccharides	Polysaccharides (cellulose...)	Polycondensation	Glycosidic bond
Isoprene	Terpenes	Polyterpenes: cis-1,4-polyisoprene natural rubber and trans-1,4-polyisoprene gutta-percha	Polyaddition	
Nucleotides	Oligonucleotides	Polynucleotides, nucleic acids (DNA, RNA)		Phosphodiester bond

Nucleosides and nucleotides

Nucleosides are molecules formed by attaching a nucleobase to a ribose ring. Examples of these include cytidine, uridine, adenosine, guanosine, thymidine and inosine.

Nucleosides can be phosphorylated by specific kinases in the cell, producing nucleotides. Both DNA and RNA are polymers, consisting of long, linear molecules. The repeating structural units, or monomers, of the nucleic acids are called nucleotides.

Each nucleotide is made of an acyclic nitrogenous base, a pentose and one to three phosphate groups. They contain carbon, nitrogen, oxygen, hydrogen and phosphorus. They serve as sources of chemical energy (adenosine triphosphate and guanosine triphosphate), participate in cellular signaling (cyclic guanosine monophosphate and cyclic adenosine monophosphate), and are incorporated into important cofactors of enzymatic reactions (coenzyme A, flavin adenine dinucleotide, flavin mononucleotide, and nicotinamide adenine dinucleotide phosphate).

Saccharides

Monosaccharides are the simplest form of carbohydrates with only one simple sugar. They essentially contain an aldehyde or ketone group in their structure. The presence of an aldehyde group in a monosaccharide is indicated by the prefix *aldo*-. Similarly, a ketone group is denoted by the prefix *keto*-. Examples of monosaccharides are the hexoses glucose, fructose, and galactose and pentoses, ribose, and deoxyribose Consumed fructose and glucose have different rates of gastric emptying, are differentially absorbed and have different metabolic fates, providing multiple opportunities for 2 different saccharides to differentially affect food intake.

Disaccharides are formed when two monosaccharides, or two single simple sugars, form a bond with removal of water. They can be hydrolyzed to yield their saccharin building blocks by boiling with dilute acid or reacting them with appropriate enzymes. Examples of disaccharides include sucrose, maltose, and lactose.

Polysaccharides are polymerized monosaccharides, complex, carbohydrates. They have multiple simple sugars. Examples are starch, cellulose, and glycogen. They are generally large and often have a complex branched connectivity. Because of their size, polysaccharides are not water-soluble, but their many hydroxy groups become hydrated individually when exposed to water, and some polysaccharides form thick colloidal dispersions when heated in water. Shorter polysaccharides, with 3 - 10 monomers, are called oligosaccharides. A fluorescent indicator-displacement molecular imprinting sensor was developed for discriminating saccharides. It successfully discriminated three brands of orange juice beverage. The change in fluorescence intensity of the sensing films resulting is directly related to the saccharide concentration.

Lignin

Lignin is a random polymer composed mainly of aromatic rings with short (up to three) aliphatic carbons chains connecting the rings. Lignin is the second most common biopolymer (after cellulose) and is one of the primary structural components of most plants. It contains subunits derived from *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol and is unusual among biomolecules in that it is racemic i.e. it is not optically active. The lack of optical activity is because the polymerization of lignin occurs via free radical coupling reactions in which there is no preference for either configuration at a chiral center.

Lipids

Lipids are chiefly **fatty acid esters**, and are the basic building blocks of biological membranes. Another biological role is energy storage (e.g., triglycerides). Most lipids consist of a polar or hydrophilic head (typically glycerol) and one to three nonpolar or hydrophobic fatty acid tails, and therefore they are amphiphilic. Fatty acids consist of unbranched chains of carbon atoms that are connected by single bonds alone (**saturated** fatty acids) or by both single and double bonds (**unsaturated** fatty acids). The chains are usually 14-24 carbon groups long, but it is always an even number.

For lipids present in biological membranes, the hydrophilic head is from one of three classes:

- Glycolipids, whose heads contain an oligosaccharide with 1-15 saccharide residues.
- Phospholipids, whose heads contain a positively charged group that is linked to the tail by a negatively charged phosphate group.
- Sterols, whose heads contain a planar steroid ring, for example, cholesterol.

Other lipids include prostaglandins and leukotrienes which are both 20-carbon fatty acyl units synthesized from arachidonic acid. They are also known as fatty acids

Amino acids

Amino acids contain both amino and carboxylic acid functional groups. (In biochemistry, the term amino acid is used when referring to those amino acids in which the amino and carboxylate functionalities are attached to the same carbon, plus proline which is not actually an amino acid).

Amino acids are the building blocks of long polymer chains. With 2-10 amino acids such chains are called peptides, with 10-100 they are often called polypeptides, and longer chains are known as proteins. These protein structures have many structural and enzymatic roles in organisms.

There are twenty amino acids that are encoded by the standard genetic code, but there are more than 500 natural amino acids. When amino acids other than the set of twenty are observed in proteins, this is usually the result of modification after translation (protein synthesis). Only two amino acids other than the standard twenty are known to be incorporated into proteins during translation, in certain organisms:

- Selenocysteine is incorporated into some proteins at a UGA codon, which is normally a stop codon.
- Pyrrolysine is incorporated into some proteins at a UAG codon. For instance, in some methanogens in enzymes that are used to produce methane.

Besides those used in protein synthesis, other biologically important amino acids include carnitine (used in lipid transport within a cell), ornithine, GABA and taurine.

Protein structure

The particular series of amino acids that form a protein is known as that protein's primary structure. This sequence is determined by the genetic makeup of the individual. Proteins have several, well-classified, elements of local structure formed by intermolecular attraction, this forms the secondary structure of protein. They are broadly divided in two, alpha helix and beta sheet, also called beta pleated sheets. Alpha helices are formed of coiling of protein due to attraction between amine group of one amino acid with carboxylic acid group of other. The coil contains about 3.6 amino acids per turn and the alkyl group of amino acid lie outside the plane of coil. Beta pleated sheets are formed by strong continuous hydrogen bond over the length of protein chain. Bonding may be parallel or antiparallel in nature. Structurally, natural silk is formed of beta pleated sheets. Usually, a protein is formed by action of both these structures in variable ratios. Coiling may also be random. The overall 3D structure of a protein is termed its tertiary structure. It is formed as result of various forces like hydrogen bonding, disulfide bridges, hydrophobic interactions, hydrophilic interactions, van der Waals force etc. When two or more different polypeptide chains cluster to form a protein, quaternary structure of protein is formed. Quaternary structure is a unique attribute of polymeric and heteromeric proteins like hemoglobin, which consists of two alpha and two beta peptide chains.

Apoenzymes

An apoenzyme is the inactive storage and generally secretory form of a protein. This is required to protect the secretory cell from the activity of that protein. Apoenzymes becomes active enzyme on addition of a cofactor. Cofactors can be either inorganic (e.g., metal ions and iron-sulfur clusters) or organic compounds, (e.g., flavin and heme). Organic cofactors can be either prosthetic groups, which are tightly bound to an enzyme, or coenzymes, which are released from the enzyme's active site during the reaction.

Isoenzymes

Isoenzymes are enzymes with similar function but different structure. They are products of different genes. They are produced in different organs to perform the same function. LDH are examples of such enzymes. Their varied levels in blood are used to determine any deformity in the organ of secretion.

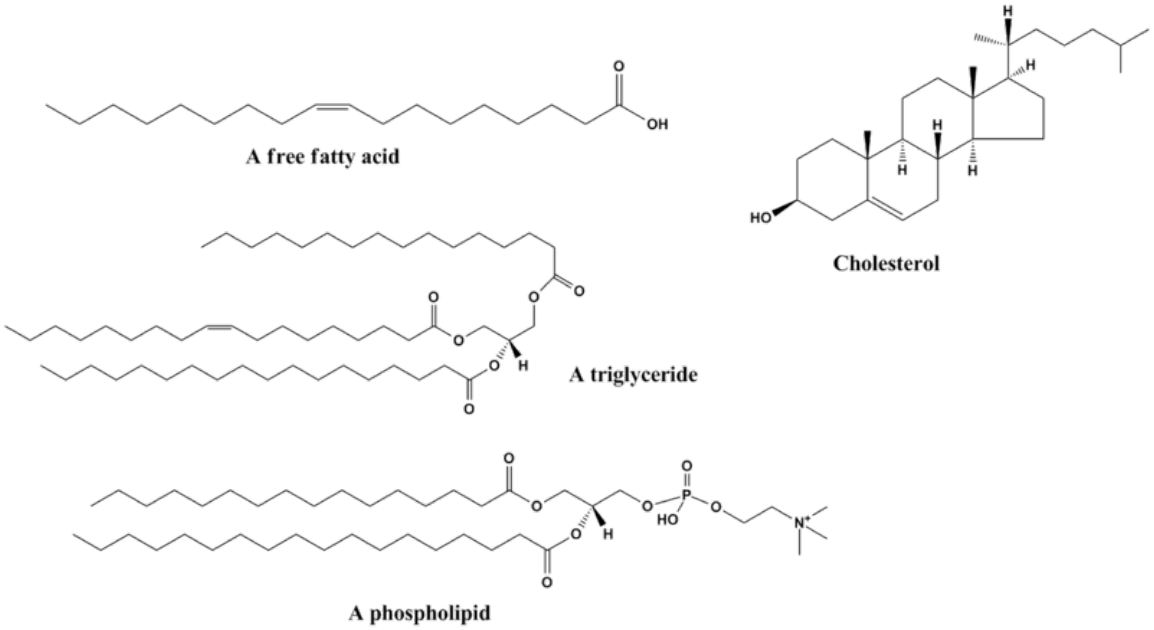
Vitamins

A vitamin is a compound that is generally not synthesized by a given organism but is nonetheless vital to its survival or health (for example coenzymes). These compounds must be absorbed, or eaten, but typically only in trace quantities. When originally proposed by Casimir Funk, a Polish biochemist, he believed them to all be basic and

therefore named them vital amines. The "l" was later dropped to form the word vitamines.

Chapter- 2

Lipid



Structures of some common lipids. At the top are oleic acid and cholesterol. The middle structure is a triglyceride composed of oleoyl, stearoyl, and palmitoyl chains attached to a glycerol backbone. At the bottom is the common phospholipid, phosphatidylcholine.

Lipids are a broad group of naturally occurring molecules which includes fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E and K), monoglycerides, diglycerides, phospholipids, and others. The main biological functions of lipids include energy storage, as structural components of cell membranes, and as important signaling molecules.

Lipids may be broadly defined as hydrophobic or amphiphilic small molecules; the amphiphilic nature of some lipids allows them to form structures such as vesicles, liposomes, or membranes in an aqueous environment. Biological lipids originate entirely or in part from two distinct types of biochemical subunits or "building blocks": ketoacyl and isoprene groups. Using this approach, lipids may be divided into eight categories: fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids and

polyketides (derived from condensation of ketoacyl subunits); and sterol lipids and prenol lipids (derived from condensation of isoprene subunits).

Although the term *lipid* is sometimes used as a synonym for fats, fats are a subgroup of lipids called triglycerides. Lipids also encompass molecules such as fatty acids and their derivatives (including tri-, di-, and monoglycerides and phospholipids), as well as other sterol-containing metabolites such as cholesterol. Although humans and other mammals use various biosynthetic pathways to both break down and synthesize lipids, some essential lipids cannot be made this way and must be obtained from the diet.

Categories of lipids

Fatty acyls

Fatty acyls, a generic term for describing fatty acids, their conjugates and derivatives, are a diverse group of molecules synthesized by chain-elongation of an acetyl-CoA primer with malonyl-CoA or methylmalonyl-CoA groups in a process called fatty acid synthesis. They are made of a hydrocarbon chain that terminates with a carboxylic acid group; this arrangement confers the molecule with a polar, hydrophilic end, and a nonpolar, hydrophobic end that is insoluble in water. The fatty acid structure is one of the most fundamental categories of biological lipids, and is commonly used as a building block of more structurally complex lipids. The carbon chain, typically between four to 24 carbons long, may be saturated or unsaturated, and may be attached to functional groups containing oxygen, halogens, nitrogen and sulfur. Where a double bond exists, there is the possibility of either a *cis* or *trans* geometric isomerism, which significantly affects the molecule's molecular configuration. *Cis*-double bonds cause the fatty acid chain to bend, an effect that is more pronounced the more double bonds there are in a chain. This in turn plays an important role in the structure and function of cell membranes. Most naturally occurring fatty acids are of the *cis* configuration, although the *trans* form does exist in some natural and partially hydrogenated fats and oils.

Examples of biologically important fatty acids are the eicosanoids, derived primarily from arachidonic acid and eicosapentaenoic acid, which include prostaglandins, leukotrienes, and thromboxanes. Other major lipid classes in the fatty acid category are the fatty esters and fatty amides. Fatty esters include important biochemical intermediates such as wax esters, fatty acid thioester coenzyme A derivatives, fatty acid thioester ACP derivatives and fatty acid carnitines. The fatty amides include N-acyl ethanolamines, such as the cannabinoid neurotransmitter anandamide.

Glycerolipids

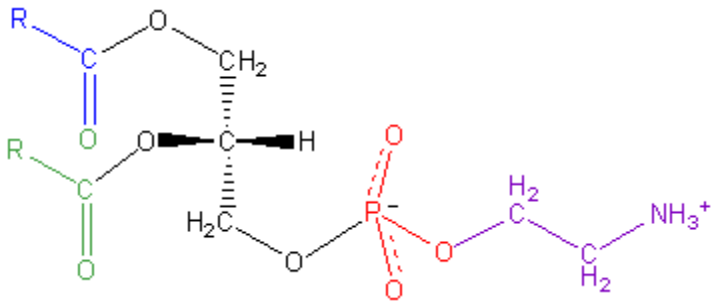
Glycerolipids are composed mainly of mono-, di- and tri-substituted glycerols, the most well-known being the fatty acid esters of glycerol (triacylglycerols), also known as triglycerides. In these compounds, the three hydroxyl groups of glycerol are each esterified, usually by different fatty acids. Because they function as a food store, these lipids comprise the bulk of storage fat in animal tissues. The hydrolysis of the ester bonds

of triacylglycerols and the release of glycerol and fatty acids from adipose tissue is called fat mobilization.

Additional subclasses of glycerolipids are represented by glycosylglycerols, which are characterized by the presence of one or more sugar residues attached to glycerol via a glycosidic linkage. Examples of structures in this category are the digalactosyldiacylglycerols found in plant membranes and seminolipid from mammalian sperm cells.

Glycerophospholipids

Glycerophospholipids, also referred to as phospholipids, are ubiquitous in nature and are key components of the lipid bilayer of cells, as well as being involved in metabolism and cell signaling. Neural tissue (including the brain) contains relatively high amounts of glycerophospholipids, and alterations in their composition has been implicated in various neurological disorders. Glycerophospholipids may be subdivided into distinct classes, based on the nature of the polar headgroup at the *sn*-3 position of the glycerol backbone in eukaryotes and eubacteria, or the *sn*-1 position in the case of archaebacteria.



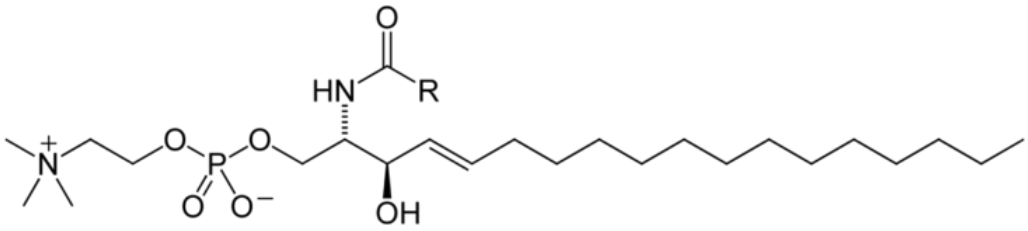
Phosphatidylethanolamine

Examples of glycerophospholipids found in biological membranes are phosphatidylcholine (also known as PC, GPCho or lecithin), phosphatidylethanolamine (PE or GPEtn) and phosphatidylserine (PS or GPSer). In addition to serving as a primary component of cellular membranes and binding sites for intra- and intercellular proteins, some glycerophospholipids in eukaryotic cells, such as phosphatidylinositols and phosphatidic acids are either precursors of, or are themselves, membrane-derived second messengers. Typically, one or both of these hydroxyl groups are acylated with long-chain fatty acids, but there are also alkyl-linked and 1Z-alkenyl-linked (plasmalogen) glycerophospholipids, as well as dialkylether variants in archaebacteria.

Sphingolipids

Sphingolipids are a complex family of compounds that share a common structural feature, a sphingoid base backbone that is synthesized *de novo* from the amino acid serine and a long-chain fatty acyl CoA, then converted into ceramides, phosphosphingolipids, glycosphingolipids and other compounds. The major sphingoid base of mammals is

commonly referred to as sphingosine. Ceramides (N-acyl-sphingoid bases) are a major subclass of sphingoid base derivatives with an amide-linked fatty acid. The fatty acids are typically saturated or mono-unsaturated with chain lengths from 16 to 26 carbon atoms.



Sphingomyelin

The major phosphosphingolipids of mammals are sphingomyelins (ceramide phosphocholines), whereas insects contain mainly ceramide phosphoethanolamines and fungi have phytoceramide phosphoinositols and mannose-containing headgroups. The glycosphingolipids are a diverse family of molecules composed of one or more sugar residues linked via a glycosidic bond to the sphingoid base. Examples of these are the simple and complex glycosphingolipids such as cerebrosides and gangliosides.

Sterol lipids

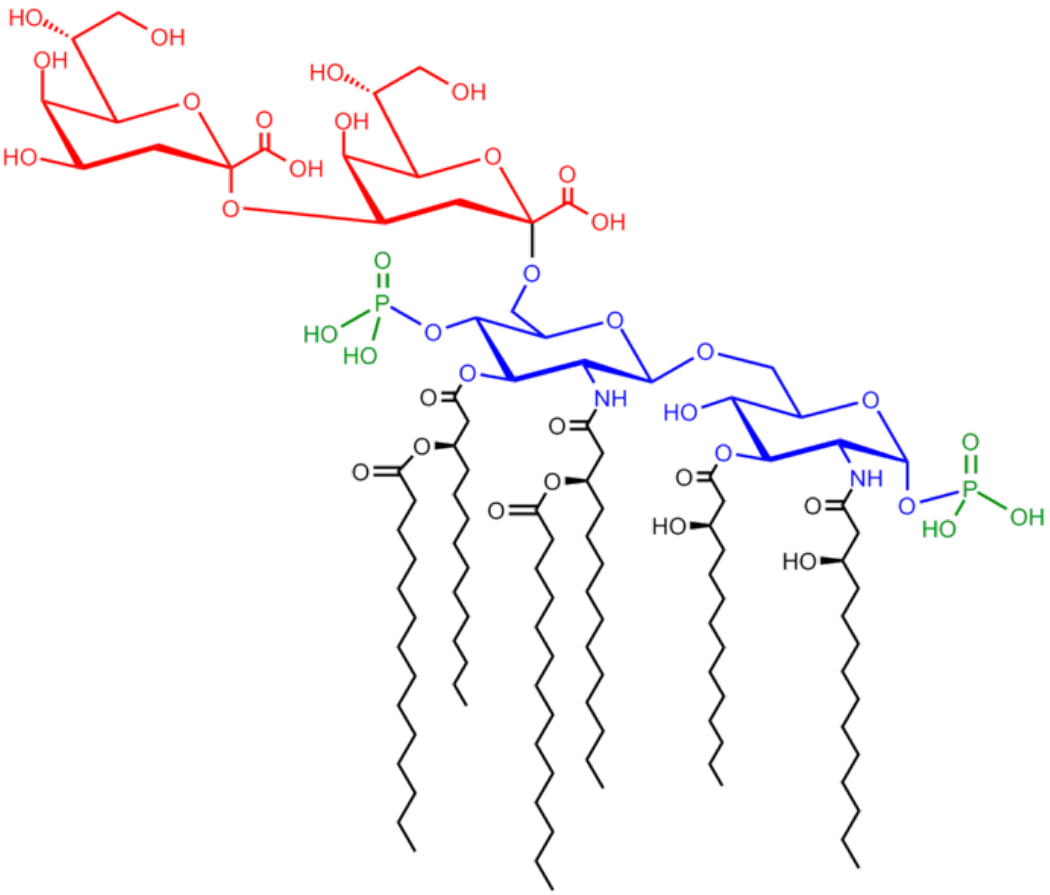
Sterol lipids, such as cholesterol and its derivatives, are an important component of membrane lipids, along with the glycerophospholipids and sphingomyelins. The steroids, all derived from the same fused four-ring core structure, have different biological roles as hormones and signaling molecules. The eighteen-carbon (C18) steroids include the estrogen family whereas the C19 steroids comprise the androgens such as testosterone and androsterone. The C21 subclass includes the progestogens as well as the glucocorticoids and mineralocorticoids. The secosteroids, comprising various forms of vitamin D, are characterized by cleavage of the B ring of the core structure. Other examples of sterols are the bile acids and their conjugates, which in mammals are oxidized derivatives of cholesterol and are synthesized in the liver. The plant equivalents are the phytosterols, such as β-sitosterol, stigmasterol, and brassicasterol; the latter compound is also used as a biomarker for algal growth. The predominant sterol in fungal cell membranes is ergosterol.

Prenol lipids

Prenol lipids are synthesized from the 5-carbon precursors isopentenyl diphosphate and dimethylallyl diphosphate that are produced mainly via the mevalonic acid (MVA) pathway. The simple isoprenoids (linear alcohols, diphosphates, etc.) are formed by the successive addition of C5 units, and are classified according to number of these terpene units. Structures containing greater than 40 carbons are known as polyterpenes.

Carotenoids are important simple isoprenoids that function as antioxidants and as precursors of vitamin A. Another biologically important class of molecules is exemplified by the quinones and hydroquinones, which contain an isoprenoid tail attached to a quinonoid core of non-isoprenoid origin. Vitamin E and vitamin K, as well as the ubiquinones, are examples of this class. Prokaryotes synthesize polyprenols (called bactoprenols) in which the terminal isoprenoid unit attached to oxygen remains unsaturated, whereas in animal polyprenols (dolichols) the terminal isoprenoid is reduced.

Saccharolipids



Structure of the saccharolipid Kdo_2-Lipid A. Glucosamine residues in blue, Kdo residues in red, acyl chains in black and phosphate groups in green.

Saccharolipids describe compounds in which fatty acids are linked directly to a sugar backbone, forming structures that are compatible with membrane bilayers. In the saccharolipids, a monosaccharide substitutes for the glycerol backbone present in glycerolipids and glycerophospholipids. The most familiar saccharolipids are the acylated glucosamine precursors of the Lipid A component of the lipopolysaccharides in Gram-negative bacteria. Typical lipid A molecules are disaccharides of glucosamine, which are derivatized with as many as seven fatty-acyl chains. The minimal lipopolysaccharide

required for growth in *E. coli* is Kdo_2-Lipid A, a hexa-acylated disaccharide of glucosamine that is glycosylated with two 3-deoxy-D-manno-octulosonic acid (Kdo) residues.

Polyketides

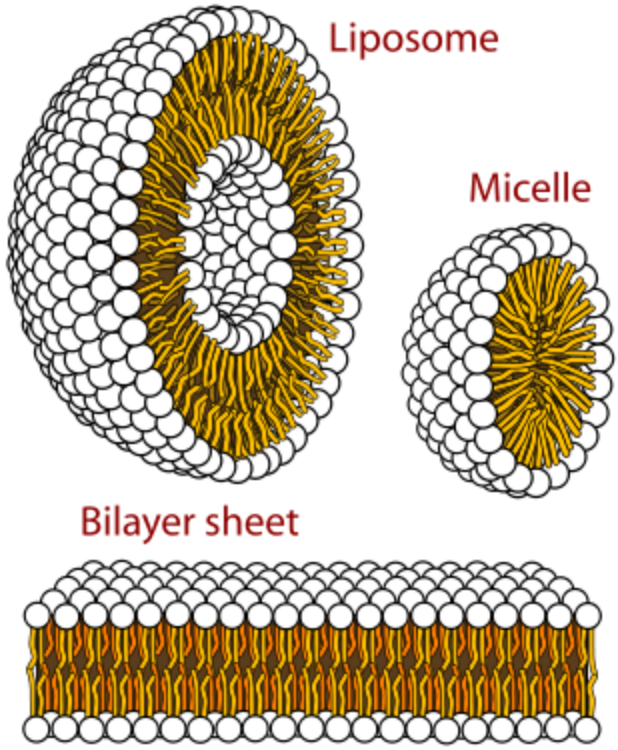
Polyketides are synthesized by polymerization of acetyl and propionyl subunits by classic enzymes as well as iterative and multimodular enzymes that share mechanistic features with the fatty acid synthases. They comprise a large number of secondary metabolites and natural products from animal, plant, bacterial, fungal and marine sources, and have great structural diversity. Many polyketides are cyclic molecules whose backbones are often further modified by glycosylation, methylation, hydroxylation, oxidation, and/or other processes. Many commonly used anti-microbial, anti-parasitic, and anti-cancer agents are polyketides or polyketide derivatives, such as erythromycins, tetracyclines, avermectins, and antitumor epothilones.

Biological functions

Membranes

Eukaryotic cells are compartmentalized into membrane-bound organelles which carry out different biological functions. The glycerophospholipids are the main structural component of biological membranes, such as the cellular plasma membrane and the intracellular membranes of organelles; in animal cells the plasma membrane physically separates the intracellular components from the extracellular environment. The glycerophospholipids are amphipathic molecules (containing both hydrophobic and hydrophilic regions) that contain a glycerol core linked to two fatty acid-derived "tails" by ester linkages and to one "head" group by a phosphate ester linkage. While glycerophospholipids are the major component of biological membranes, other non-glyceride lipid components such as sphingomyelin and sterols (mainly cholesterol in animal cell membranes) are also found in biological membranes. In plants and algae, the galactosyldiacylglycerols, and sulfoquinovosyldiacylglycerol, which lack a phosphate group, are important components of membranes of chloroplasts and related organelles and are the most abundant lipids in photosynthetic tissues, including those of higher plants, algae and certain bacteria.

Bilayers have been found to exhibit high levels of birefringence which can be used to probe the degree of order (or disruption) within the bilayer using techniques such as dual polarisation interferometry



Self-organization of phospholipids: a spherical liposome, a micelle and a lipid bilayer.

A biological membrane is a form of lipid bilayer. The formation of lipid bilayers is an energetically preferred process when the glycerophospholipids described above are in an aqueous environment. In an aqueous system, the polar heads of lipids align towards the polar, aqueous environment, while the hydrophobic tails minimize their contact with water and tend to cluster together, forming a vesicle; depending on the concentration of the lipid, this biophysical interaction may result in the formation of micelles, liposomes, or lipid bilayers. Other aggregations are also observed and form part of the polymorphism of amphiphile (lipid) behavior. Phase behavior is an area of study within biophysics and is the subject of current academic research. Micelles and bilayers form in the polar medium by a process known as the hydrophobic effect. When dissolving a lipophilic or amphiphilic substance in a polar environment, the polar molecules (i.e., water in an aqueous solution) become more ordered around the dissolved lipophilic substance, since the polar molecules cannot form hydrogen bonds to the lipophilic areas of the amphiphile. So in an aqueous environment, the water molecules form an ordered "clathrate" cage around the dissolved lipophilic molecule.

Energy storage

Triacylglycerols, stored in adipose tissue, are a major form of energy storage in animals. The adipocyte, or fat cell, is designed for continuous synthesis and breakdown of triacylglycerols, with breakdown controlled mainly by the activation of hormone-

sensitive enzyme lipase. The complete oxidation of fatty acids provides high caloric content, about 9 kcal/g, compared with 4 kcal/g for the breakdown of carbohydrates and proteins. Migratory birds that must fly long distances without eating use stored energy of triacylglycerols to fuel their flights.

Signaling

In recent years, evidence has emerged showing that lipid signaling is a vital part of the cell signaling. Lipid signaling may occur via activation of G protein-coupled or nuclear receptors, and members of several different lipid categories have been identified as signaling molecules and cellular messengers. These include sphingosine-1-phosphate, a sphingolipid derived from ceramide that is a potent messenger molecule involved in regulating calcium mobilization, cell growth, and apoptosis; diacylglycerol (DAG) and the phosphatidylinositol phosphates (PIPs), involved in calcium-mediated activation of protein kinase C; the prostaglandins, which are one type of fatty-acid derived eicosanoid involved in inflammation and immunity; the steroid hormones such as estrogen, testosterone and cortisol, which modulate a host of functions such as reproduction, metabolism and blood pressure; and the oxysterols such as 25-hydroxy-cholesterol that are liver X receptor agonists.

Other functions

The "fat-soluble" vitamins (A, D, E and K) – which are isoprene-based lipids – are essential nutrients stored in the liver and fatty tissues, with a diverse range of functions. Acyl-carnitines are involved in the transport and metabolism of fatty acids in and out of mitochondria, where they undergo beta oxidation. Polyprenols and their phosphorylated derivatives also play important transport roles, in this case the transport of oligosaccharides across membranes. Polyprenol phosphate sugars and polyprenol diphosphate sugars function in extra-cytoplasmic glycosylation reactions, in extracellular polysaccharide biosynthesis (for instance, peptidoglycan polymerization in bacteria), and in eukaryotic protein N-glycosylation. Cardiolipins are a subclass of glycerophospholipids containing four acyl chains and three glycerol groups that are particularly abundant in the inner mitochondrial membrane. They are believed to activate enzymes involved with oxidative phosphorylation.

Metabolism

The major dietary lipids for humans and other animals are animal and plant triglycerides, sterols, and membrane phospholipids. The process of lipid metabolism synthesizes and degrades the lipid stores and produces the structural and functional lipids characteristic of individual tissues.

Biosynthesis

In animals, when there is an oversupply of dietary carbohydrate, the excess carbohydrate is converted to triacylglycerol. This involves the synthesis of fatty acids from acetyl-CoA

and the esterification of fatty acids in the production of triacylglycerol, a process called lipogenesis. Fatty acids are made by fatty acid synthases that polymerize and then reduce acetyl-CoA units. The acyl chains in the fatty acids are extended by a cycle of reactions that add the acetyl group, reduce it to an alcohol, dehydrate it to an alkene group and then reduce it again to an alkane group. The enzymes of fatty acid biosynthesis are divided into two groups, in animals and fungi all these fatty acid synthase reactions are carried out by a single multifunctional protein, while in plant plastids and bacteria separate enzymes perform each step in the pathway. The fatty acids may be subsequently converted to triacylglycerols that are packaged in lipoproteins and secreted from the liver.

The synthesis of unsaturated fatty acids involves a desaturation reaction, whereby a double bond is introduced into the fatty acyl chain. For example, in humans, the desaturation of stearic acid by stearoyl-CoA desaturase-1 produces oleic acid. The doubly unsaturated fatty acid linoleic acid as well as the triply unsaturated α-linolenic acid cannot be synthesized in mammalian tissues, and are therefore essential fatty acids and must be obtained from the diet.

Triacylglycerol synthesis takes place in the endoplasmic reticulum by metabolic pathways in which acyl groups in fatty acyl-CoAs are transferred to the hydroxyl groups of glycerol-3-phosphate and diacylglycerol.

Terpenes and isoprenoids, including the carotenoids, are made by the assembly and modification of isoprene units donated from the reactive precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate. These precursors can be made in different ways. In animals and archaea, the mevalonate pathway produces these compounds from acetyl-CoA, while in plants and bacteria the non-mevalonate pathway uses pyruvate and glyceraldehyde 3-phosphate as substrates. One important reaction that uses these activated isoprene donors is steroid biosynthesis. Here, the isoprene units are joined together to make squalene and then folded up and formed into a set of rings to make lanosterol. Lanosterol can then be converted into other steroids such as cholesterol and ergosterol.

Degradation

Beta oxidation is the metabolic process by which fatty acids are broken down in the mitochondria and/or in peroxisomes to generate acetyl-CoA. For the most part, fatty acids are oxidized by a mechanism that is similar to, but not identical with, a reversal of the process of fatty acid synthesis. That is, two-carbon fragments are removed sequentially from the carboxyl end of the acid after steps of dehydrogenation, hydration, and oxidation to form a beta-keto acid, which is split by thiolysis. The acetyl-CoA is then ultimately converted into ATP, CO_2, and H_2O using the citric acid cycle and the electron transport chain.

Hence the Krebs Cycle can start at acetyl-CoA when fat is being broken down for energy if there is little or no glucose available.

The energy yield of the complete oxidation of the fatty acid palmitate is 106 ATP. Unsaturated and odd-chain fatty acids require additional enzymatic steps for degradation.

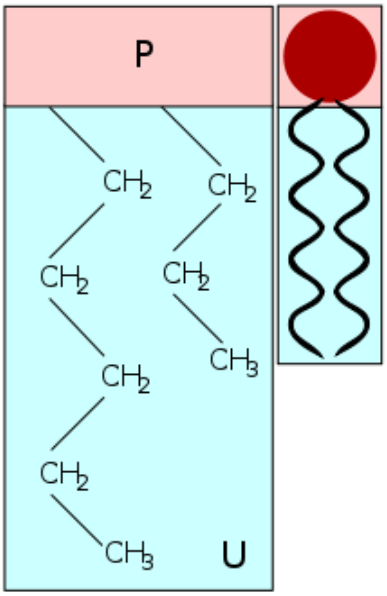
Nutrition and health

Most of the lipid found in food is in the form of triacylglycerols, cholesterol and phospholipids. A minimum amount of dietary fat is necessary to facilitate absorption of fat-soluble vitamins (A, D, E and K) and carotenoids. Humans and other mammals have a dietary requirement for certain essential fatty acids, such as linoleic acid (an omega-6 fatty acid) and alpha-linolenic acid (an omega-3 fatty acid) because they cannot be synthesized from simple precursors in the diet. Both of these fatty acids are 18-carbon polyunsaturated fatty acids differing in the number and position of the double bonds. Most vegetable oils are rich in linoleic acid (safflower, sunflower, and corn oils). Alpha-linolenic acid is found in the green leaves of plants, and in selected seeds, nuts and legumes (particularly flax, rapeseed, walnut and soy). Fish oils are particularly rich in the longer-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A large number of studies have shown positive health benefits associated with consumption of omega-3 fatty acids on infant development, cancer, cardiovascular diseases, and various mental illnesses, such as depression, attention-deficit hyperactivity disorder, and dementia. In contrast, it is now well-established that consumption of trans fats, such as those present in partially hydrogenated vegetable oils, are a risk factor for cardiovascular disease.

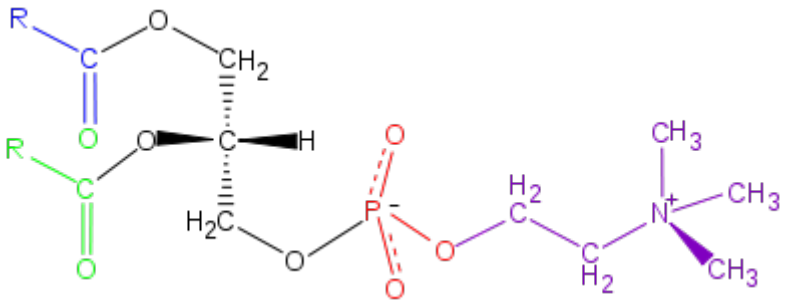
A few studies have suggested that total dietary fat intake is linked to an increased risk of obesity and diabetes. However, a number of very large studies, including the Women's Health Initiative Dietary Modification Trial, an eight year study of 49,000 women, the Nurses' Health Study and the Health Professionals Follow-up Study, revealed no such links. None of these studies suggested any connection between percentage of calories from fat and risk of cancer, heart disease or weight gain. The Nutrition Source, a website maintained by the Department of Nutrition at the Harvard School of Public Health, summarizes the current evidence on the impact of dietary fat: "Detailed research—much of it done at Harvard—shows that the total amount of fat in the diet isn't really linked with weight or disease."

Chapter- 3

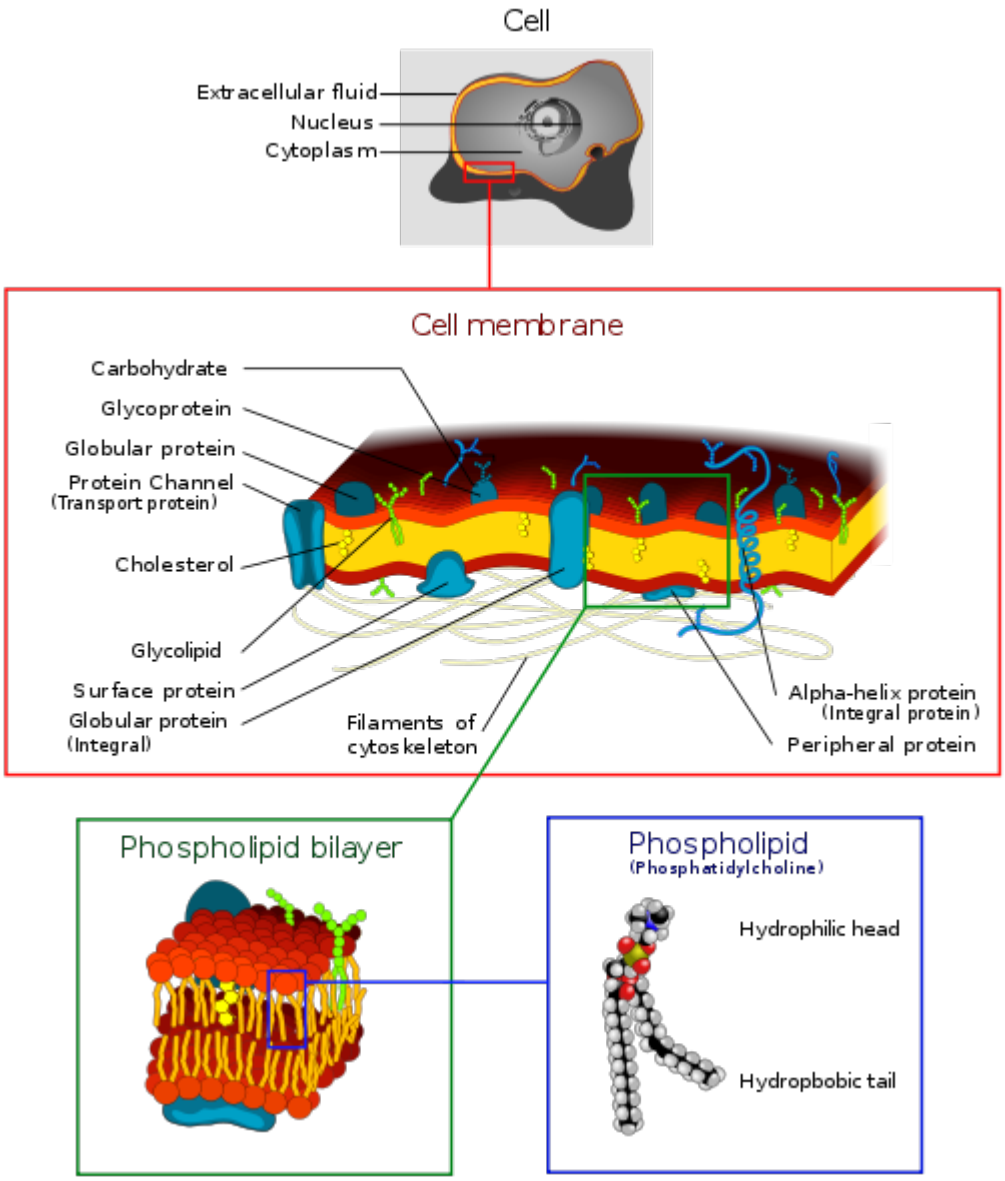
Phospholipid



Polar group of the molecule, highlighted in red.
The **U** indicates the uncharged hydrophobic portion of the molecule, highlighted in blue.



Phosphatidyl choline is the major component of lecithin. It is also a source for choline in the synthesis of acetylcholine in cholinergic neurons.



Cell membranes consist of phospholipid bilayers

Phospholipids are a class of lipids and are a major component of all cell membranes as they can form lipid bilayers. Most phospholipids contain a diglyceride, a phosphate group, and a simple organic molecule such as choline; one exception to this rule is sphingomyelin, which is derived from sphingosine instead of glycerol. The first phospholipid identified as such in biological tissues was lecithin, or phosphatidylcholine, in the egg yolk, by Theodore Nicolas Gobley, a French chemist and pharmacist, in 1847.

Amphipathic character

The 'head' of a phospholipid is hydrophilic (attracted to water), while the hydrophobic 'tails' are repelled by water and are forced to aggregate. The hydrophillic head contains

the negatively charged phosphate group, and may contain other polar groups. The hydrophobic tail usually consists of long fatty acid hydrocarbon chains. When placed in water, phospholipids form a variety of structures depending on the specific properties of the phospholipid. These specific properties allow phospholipids to play an important role in the phospholipid bilayer. In biological systems, the phospholipids often occur with other molecules (e.g., proteins, glycolipids, cholesterol) in a bilayer such as a cell membrane. Lipid bilayers occur when hydrophobic tails line up against one another, forming a membrane with hydrophilic heads on both sides facing the water.

Such movement can be described by the Fluid Mosaic Model, that 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. Cholesterol contributes to membrane fluidity by hindering the packing together of phospholipids. However, this model has now been superseded, as through the study of lipid polymorphism it is now known that the behaviour of lipids under physiological (and other) conditions is not simple.

Types of phospholipid

Diacylglyceride structures

- Phosphatidic acid (phosphatidate) (PA)
- Phosphatidylethanolamine (cephalin) (PE)
- Phosphatidylcholine (lecithin) (PC)
- Phosphatidylserine (PS)
- Phosphoinositides:
    - Phosphatidylinositol (PI)
    - Phosphatidylinositol phosphate (PIP)
    - Phosphatidylinositol bisphosphate (PIP2) and
    - Phosphatidylinositol triphosphate (PIP3).

Phosphosphingolipids

- Ceramide phosphorylcholine (Sphingomyelin) (SPH)
- Ceramide phosphorylethanolamine (Sphingomyelin) (Cer-PE)
- Ceramide phosphorylglycerol

Simulations

Computational simulations of phospholipids are often performed using molecular dynamics with force fields such as GROMOS, CHARMM, or AMBER.

Characterisation

Phospholipids are optically highly birefringent, i.e. their refractive index is different along their axis as opposed to perpendicular to it. Measurement of birefringence can be

achieved using cross polarisers in a microscope to obtain an image of e.g. vesicle walls or using techniques such as dual polarisation interferometry to quantify lipid order or disruption in supported bilayers.

Phospholipid synthesis

Phospholipid synthesis occurs in the cytosol adjacent to ER membrane that is studded with proteins that act in synthesis (GPAT and LPAAT acyl transferases, phosphatase and choline phosphotransferase) and allocation (flippase and floppase). Eventually a vesicle will bud off from the ER containing phospholipids destined for the cytoplasmic cellular membrane on its exterior leaflet and phospholipids destined for the exoplasmic cellular membrane on its inner leaflet.

In signal transduction

Some types of phospholipid can be split to produce products that function as second messengers in signal transduction. Examples include phosphatidylinositol (4,5)-bisphosphate (PIP_2), that can be split by the enzyme Phospholipase C into inositol triphosphate (IP_3) and diacylglycerol (DAG), which both carry out the functions of the G_q type of G protein in response to various stimuli and intervene in various processes from long term depression in neurons to leukocyte signal pathways started by chemokine receptors.

Phospholipids also intervene in prostaglandin signal pathways as the raw material used by lipase enzymes to produce the prostaglandin precursors. In plants they serve as the raw material to produce Jasmonic acid, a plant hormone similar in structure to prostaglandins that mediates defensive responses against pathogens.

Food technology

Phospholipids can also act as an emulsifier, enabling oils to dissolve in water. Phospholipids called lecithin are extracted out of cooking oil and then used as food additives in many things such as bread and can also be purchased separately in a health food store.

Phospholipid derivatives

- Natural phospholipid derivates:

  egg PC, egg PG, soy PC, hydrogenated soy PC, sphingomyelin as natural phospholipids.

- Synthetic phospholipid derivates:
  - Phosphatidic acid (DMPA, DPPA, DSPA)
  - Phosphatidylcholine (DDPC, DLPC, DMPC, DPPC, DSPC, DOPC, POPC, DEPC)

- Phosphatidylglycerol (DMPG, DPPG, DSPG, POPG)
- Phosphatidylethanolamine (DMPE, DPPE, DSPE DOPE)
- Phosphatidylserine (DOPS)
- PEG phospholipid (mPEG-phospholipid, polyglycerin-phospholipid, funcitionalized-phospholipid, terminal activated-phospholipid)

Abbreviations used and chemical information of glycerophospholipids

Abbreviation	CAS	Name	Type
DDPC	3436-44-0	1,2-Didecanoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DEPA-NA	80724-31-8	1,2-Dierucoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DEPC	56649-39-9	1,2-Dierucoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DEPE	988-07-2	1,2-Dierucoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DEPG-NA		1,2-Dierucoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DLOPC	998-06-1	1,2-Dilinoleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DLPA-NA		1,2-Dilauroyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DLPC	18194-25-7	1,2-Dilauroyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DLPE		1,2-Dilauroyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DLPG-NA		1,2-Dilauroyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DLPG-NH4		1,2-Dilauroyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DLPS-NA		1,2-Dilauroyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DMPA-NA	80724-3	1,2-Dimyristoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DMPC	18194-24-6	1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DMPE	988-07-2	1,2-Dimyristoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine

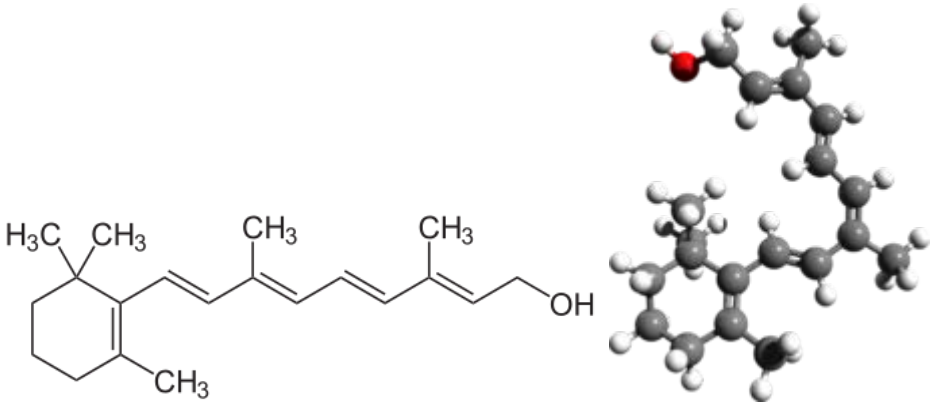
DMPG-NA	67232-80-8	1,2-Dimyristoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DMPG-NH4		1,2-Dimyristoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DMPG-NH4/NA		1,2-Dimyristoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium/Ammonium Salt)	Phosphatidylglycerol
DMPS-NA		1,2-Dimyristoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DOPA-NA		1,2-Dioleoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DOPC	4235-95-4	1,2-Dioleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DOPE	4004-5-1-	1,2-Dioleoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DOPG-NA	62700-69-0	1,2-Dioleoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DOPS-NA	70614-14-1	1,2-Dioleoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DPPA-NA	71065-87-7	1,2-Dipalmitoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DPPC	63-89-8	1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DPPE	923-61-5	1,2-Dipalmitoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DPPG-NA	67232-81-9	1,2-Dipalmitoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DPPG-NH4	73548-70-6	1,2-Dipalmitoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DPPS-NA		1,2-Dipalmitoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DSPA-NA	108321-18-2	1,2-Distearoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DSPC	816-94-4	1,2-Distearoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DSPE	1069-79-0	1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine

DSPG-NA	67232-82-0	1,2-Distearoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DSPG-NH4	108347-80-4	1,2-Distearoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DSPS-NA		1,2-Distearoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
Egg Sphingomyelin empty Liposome			
EPC		Egg-PC	Phosphatidylcholine
HEPC		Hydrogenated Egg PC	Phosphatidylcholine
HSPC		High purity Hydrogenated Soy PC	Phosphatidylcholine
HSPC		Hydrogenated Soy PC	Phosphatidylcholine
LYSOPC MYRISTIC	18194-24-6	1-Myristoyl-*sn*-glycero-3-phosphocholine	Lysophosphatidylcholine
LYSOPC PALMITIC	17364-16-8	1-Palmitoyl-*sn*-glycero-3-phosphocholine	Lysophosphatidylcholine
LYSOPC STEARIC	19420-57-6	1-Stearoyl-*sn*-glycero-3-phosphocholine	Lysophosphatidylcholine
Milk Sphingomyelin MPPC		1-Myristoyl-2-palmitoyl-*sn*-glycero 3-phosphocholine	Phosphatidylcholine
MSPC		1-Myristoyl-2-stearoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine
PMPC		1-Palmitoyl-2-myristoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine
POPC	26853-31-6	1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
POPE		1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
POPG-NA	81490-05-3	1-Palmitoyl-2-oleoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol)...] (Sodium Salt)	Phosphatidylglycerol
PSPC		1-Palmitoyl-2-stearoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine
SMPC		1-Stearoyl-2-myristoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine

SOPC	1-Stearoyl-2-oleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
SPPC	1-Stearoyl-2-palmitoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine

Chapter- 4

Vitamin



The chemical structure of retinol, the most common dietary form of vitamin A

A **vitamin** is an organic compound required as a nutrient in tiny amounts by an organism. In other words, an organic chemical compound (or related set of compounds) is called a vitamin when it cannot be synthesized in sufficient quantities by an organism, and must be obtained from the diet. Thus, the term is conditional both on the circumstances and on the particular organism. For example, ascorbic acid (vitamin C) is a vitamin for humans, but not for most other animals, and biotin and vitamin D are required in the human diet only in certain circumstances. By convention, the term *vitamin* does not include other essential nutrients such as dietary minerals, essential fatty acids, or essential amino acids (which are needed in larger amounts than vitamins), nor does it encompass the large number of other nutrients that promote health but are otherwise required less often. Thirteen vitamins are presently universally recognized.

Vitamins are classified by their biological and chemical activity, not their structure. Thus, each "vitamin" refers to a number of *vitamer* compounds that all show the biological activity associated with a particular vitamin. Such a set of chemicals is grouped under an alphabetized vitamin "generic descriptor" title, such as "vitamin A", which includes the compounds retinal, retinol, and four known carotenoids. Vitamers by definition are convertible to the active form of the vitamin in the body, and are sometimes inter-convertible to one another, as well.

Vitamins have diverse biochemical functions. Some have hormone-like functions as regulators of mineral metabolism (e.g., vitamin D), or regulators of cell and tissue growth

and differentiation (e.g., some forms of vitamin A). Others function as antioxidants (e.g., vitamin E and sometimes vitamin C). The largest number of vitamins (e.g., B complex vitamins) function as precursors for enzyme cofactors, that help enzymes in their work as catalysts in metabolism. In this role, vitamins may be tightly bound to enzymes as part of prosthetic groups: For example, biotin is part of enzymes involved in making fatty acids. Vitamins may also be less tightly bound to enzyme catalysts as coenzymes, detachable molecules that function to carry chemical groups or electrons between molecules. For example, folic acid carries various forms of carbon group – methyl, formyl, and methylene – in the cell. Although these roles in assisting enzyme-substrate reactions are vitamins' best-known function, the other vitamin functions are equally important.

Until the mid-1930s, when the first commercial yeast-extract and semi-synthetic vitamin C supplement tablets were sold, vitamins were obtained solely through food intake, and changes in diet (which, for example, could occur during a particular growing season) can alter the types and amounts of vitamins ingested. Vitamins have been produced as commodity chemicals and made widely available as inexpensive semisynthetic and synthetic-source multivitamin dietary supplements, since the middle of the 20th century.

The term *vitamin* was derived from "vitamine," a combination word made up by Polish scientist Casimir Funk from *vital* and *amine,* meaning amine of life, because it was suggested in 1912 that the organic micronutrient food factors that prevent beriberi and perhaps other similar dietary-deficiency diseases might be chemical amines. This proved incorrect for the micronutrient class, and the word was shortened to vitamin.

History

The discovery dates of the vitamins and their sources

Year of discovery	Vitamin	Food source
1913	Vitamin A (Retinol)	Cod liver oil
1910	Vitamin B_1 (Thiamine)	Rice bran
1920	Vitamin C (Ascorbic acid)	Citrus, most fresh foods
1920	Vitamin D (Calciferol)	Cod liver oil
1920	Vitamin B_2 (Riboflavin)	Meat, eggs
1922	Vitamin E (Tocopherol)	Wheat germ oil, unrefined vegetable oils
1926	Vitamin B_{12} (Cobalamins)	liver, eggs, animal products
1929	Vitamin K_1 (Phylloquinone)	Leafy green vegetables
1931	Vitamin B_5 (Pantothenic acid)	Meat, whole grains, in many foods
1931	Vitamin B_7 (Biotin)	Meat, dairy products, eggs
1934	Vitamin B_6 (Pyridoxine)	Meat, dairy products
1936	Vitamin B_3 (Niacin)	Meat, eggs, grains
1941	Vitamin B_9 (Folic acid)	Leafy green vegetables

The value of eating a certain food to maintain health was recognized long before vitamins were identified. The ancient Egyptians knew that feeding liver to a patient would help cure night blindness, an illness now known to be caused by a vitamin A deficiency. The advancement of ocean voyage during the Renaissance resulted in prolonged periods without access to fresh fruits and vegetables, and made illnesses from vitamin deficiency common among ships' crews.

In 1749, the Scottish surgeon James Lind discovered that citrus foods helped prevent scurvy, a particularly deadly disease in which collagen is not properly formed, causing poor wound healing, bleeding of the gums, severe pain, and death. In 1753, Lind published his *Treatise on the Scurvy*, which recommended using lemons and limes to avoid scurvy, which was adopted by the British Royal Navy. This led to the nickname Limey for sailors of that organization. Lind's discovery, however, was not widely accepted by individuals in the Royal Navy's Arctic expeditions in the 19th century, where it was widely believed that scurvy could be prevented by practicing good hygiene, regular exercise, and maintaining the morale of the crew while on board, rather than by a diet of fresh food. As a result, Arctic expeditions continued to be plagued by scurvy and other deficiency diseases. In the early 20th century, when Robert Falcon Scott made his two expeditions to the Antarctic, the prevailing medical theory was that scurvy was caused by "tainted" canned food.

During the late 18th and early 19th centuries, the use of deprivation studies allowed scientists to isolate and identify a number of vitamins. Lipid from fish oil was used to cure rickets in rats, and the fat-soluble nutrient was called "antirachitic A". Thus, the first "vitamin" bioactivity ever isolated, which cured rickets, was initially called "vitamin A"; however, the bioactivity of this compound is now called vitamin D. In 1881, Russian surgeon Nikolai Lunin studied the effects of scurvy while at the University of Tartu in present-day Estonia. He fed mice an artificial mixture of all the separate constituents of milk known at that time, namely the proteins, fats, carbohydrates, and salts. The mice that received only the individual constituents died, while the mice fed by milk itself developed normally. He made a conclusion that "a natural food such as milk must therefore contain, besides these known principal ingredients, small quantities of unknown substances essential to life." However, his conclusions were rejected by other researchers when they were unable to reproduce his results. One difference was that he had used table sugar (sucrose), while other researchers had used milk sugar (lactose) that still contained small amounts of vitamin B.

The Ancient Egyptians knew that feeding a patient liver (back, right) would help cure night blindness.

In east Asia, where polished white rice was the common staple food of the middle class, beriberi resulting from lack of vitamin B_1 was endemic. In 1884, Takaki Kanehiro, a British trained medical doctor of the Imperial Japanese Navy, observed that beriberi was endemic among low-ranking crew who often ate nothing but rice, but not among officers who consumed a Western-style diet. With the support of the Japanese navy, he experimented using crews of two battleships; one crew was fed only white rice, while the other was fed a diet of meat, fish, barley, rice, and beans. The group that ate only white rice documented 161 crew members with beriberi and 25 deaths, while the latter group had only 14 cases of beriberi and no deaths. This convinced Takaki and the Japanese Navy that diet was the cause of beriberi, but mistakenly believed that sufficient amounts of protein prevented it. That diseases could result from some dietary deficiencies was further investigated by Christiaan Eijkman, who in 1897 discovered that feeding unpolished rice instead of the polished variety to chickens helped to prevent beriberi in the chickens. The following year, Frederick Hopkins postulated that some foods contained "accessory factors" — in addition to proteins, carbohydrates, fats, et cetera — that are necessary for the functions of the human body. Hopkins and Eijkman were awarded the Nobel Prize for Physiology or Medicine in 1929 for their discovery of several vitamins.

In 1910, the first vitamin complex was isolated by Japanese scientist Umetaro Suzuki, who succeeded in extracting a water-soluble complex of micronutrients from rice bran

and named it aberic acid (later *Orizanin*). He published this discovery in a Japanese scientific journal. When the article was translated into German, the translation failed to state that it was a newly discovered nutrient, a claim made in the original Japanese article, and hence his discovery failed to gain publicity. In 1912 Polish biochemist Casimir Funk isolated the same complex of micronutrients and proposed the complex be named "vitamine" (a portmanteau of "vital amine"). The name soon became synonymous with Hopkins' "accessory factors", and, by the time it was shown that not all vitamins are amines, the word was already ubiquitous. In 1920, Jack Cecil Drummond proposed that the final "e" be dropped to deemphasize the "amine" reference, after researchers began to suspect that not all "vitamines" (in particular, vitamin A) has an amine component.

In 1931, Albert Szent-Györgyi and a fellow researcher Joseph Svirbely suspected that "hexuronic acid" was actually vitamin C, and gave a sample to Charles Glen King, who proved its anti-scorbutic activity in his long-established guinea pig scorbutic assay. In 1937, Szent-Györgyi was awarded the Nobel Prize in Physiology or Medicine for his discovery. In 1943, Edward Adelbert Doisy and Henrik Dam were awarded the Nobel Prize in Physiology or Medicine for their discovery of vitamin K and its chemical structure. In 1967, George Wald was awarded the Nobel Prize (along with Ragnar Granit and Haldan Keffer Hartline) for his discovery that vitamin A could participate directly in a physiological process.

In humans

Vitamins are classified as either water-soluble or fat-soluble. In humans there are 13 vitamins: 4 fat-soluble (A, D, E, and K) and 9 water-soluble (8 B vitamins and vitamin C). Water-soluble vitamins dissolve easily in water and, in general, are readily excreted from the body, to the degree that urinary output is a strong predictor of vitamin consumption. Because they are not readily stored, consistent daily intake is important. Many types of water-soluble vitamins are synthesized by bacteria. Fat-soluble vitamins are absorbed through the intestinal tract with the help of lipids (fats). Because they are more likely to accumulate in the body, they are more likely to lead to hypervitaminosis than are water-soluble vitamins. Fat-soluble vitamin regulation is of particular significance in cystic fibrosis.

List of vitamins

Each vitamin is typically used in multiple reactions, and, therefore, most have multiple functions.

Vitamin generic descriptor name	Vitamer chemical name(s) (list not complete)	Solubility	Recommended dietary allowances (male, age 19–70)	Deficiency disease	Upper Intake Level (UL/day)	Overdose disease
Vitamin A	Retinol, retinal, and four carotenoids including beta carotene	Fat	**900 µg**	Night-blindness, Hyperkeratosis, and Keratomalacia	3,000 µg	Hypervitaminosis A
Vitamin B_1	Thiamine	Water	**1.2 mg**	Beriberi, Wernicke-Korsakoff syndrome	N/D	Drowsiness or muscle relaxation with large doses.
Vitamin B_2	Riboflavin	Water	**1.3 mg**	Ariboflavinosis	N/D	
Vitamin B_3	Niacin, niacinamide	Water	**16.0 mg**	Pellagra	35.0 mg	Liver damage (doses > 2g/day) and other problems
Vitamin B_5	Pantothenic acid	Water	5.0 mg	Paresthesia	N/D	Diarrhea; possibly nausea and heartburn.
Vitamin B_6	Pyridoxine, pyridoxamine, pyridoxal	Water	**1.3–1.7 mg**	Anemia peripheral neuropathy.	100 mg	Impairment of proprioception, nerve damage (doses > 100 mg/day)

Vitamin B_7	Biotin	Water	30.0 µg	Dermatitis, enteritis	N/D	
Vitamin B_9	Folic acid, folinic acid	Water	**400 µg**	Megaloblast and Deficiency during pregnancy is associated with birth defects, such as neural tube defects	1,000 µg	May mask symptoms of vitamin B_{12} deficiency; other effects.
Vitamin B_{12}	Cyanocobalamin, hydroxycobalamin, methylcobalamin	Water	**2.4 µg**	Megaloblastic anemia	N/D	Acne-like rash [causality is not conclusively established].
Vitamin C	Ascorbic acid	Water	**90.0 mg**	Scurvy	2,000 mg	Vitamin C megadosage
Vitamin D	Ergocalciferol, cholecalciferol	Fat	5.0 µg–10 µg	Rickets and Osteomalacia	50 µg	Hypervitaminosis D
Vitamin E	Tocopherols, tocotrienols	Fat	**15.0 mg**	Deficiency is very rare; mild hemolytic anemia in newborn infants.	1,000 mg	Increased congestive heart failure seen in one large randomized study.
Vitamin K	phylloquinone, menaquinones	Fat	120 µg	Bleeding diathesis	N/D	Increases coagulation in patients taking warfarin.

In nutrition and diseases

Vitamins are essential for the normal growth and development of a multicellular organism. Using the genetic blueprint inherited from its parents, a fetus begins to develop, at the moment of conception, from the nutrients it absorbs. It requires certain vitamins and minerals to be present at certain times. These nutrients facilitate the chemical reactions that produce among other things, skin, bone, and muscle. If there is serious deficiency in one or more of these nutrients, a child may develop a deficiency disease. Even minor deficiencies may cause permanent damage.

For the most part, vitamins are obtained with food, but a few are obtained by other means. For example, microorganisms in the intestine — commonly known as "gut flora" — produce vitamin K and biotin, while one form of vitamin D is synthesized in the skin with the help of the natural ultraviolet wavelength of sunlight. Humans can produce some vitamins from precursors they consume. Examples include vitamin A, produced from beta carotene, and niacin, from the amino acid tryptophan.

Once growth and development are completed, vitamins remain essential nutrients for the healthy maintenance of the cells, tissues, and organs that make up a multicellular organism; they also enable a multicellular life form to efficiently use chemical energy provided by food it eats, and to help process the proteins, carbohydrates, and fats required for respiration.

Deficiencies

It was suggested that, when plants and animals began to transfer from the sea to rivers and land about 500 million years ago, environmental deficiency of marine mineral antioxidants was a challenge to the evolution of terrestrial life. Terrestrial plants slowly optimized the production of “new” endogenous antioxidants such as ascorbic acid (Vitamin C), polyphenols, flavonoids, tocopherols, etc. Since this age, dietary vitamin deficiencies appeared in terrestrial animals. Humans must consume vitamins periodically but with differing schedules, to avoid deficiency. Human bodily stores for different vitamins vary widely; vitamins A, D, and B_{12} are stored in significant amounts in the human body, mainly in the liver, and an adult human's diet may be deficient in vitamins A and D for many months and B_{12} in some cases for years, before developing a deficiency condition. However, vitamin B_3 (niacin and niacinamide) is not stored in the human body in significant amounts, so stores may last only a couple of weeks. For vitamin C, the first symptoms of scurvy in experimental studies of complete vitamin C deprivation in humans have varied widely, from a month to more than six months, depending on previous dietary history that determined body stores.

Deficiencies of vitamins are classified as either primary or secondary. A **primary deficiency** occurs when an organism does not get enough of the vitamin in its food. A **secondary deficiency** may be due to an underlying disorder that prevents or limits the absorption or use of the vitamin, due to a “lifestyle factor”, such as smoking, excessive alcohol consumption, or the use of medications that interfere with the absorption or use

of the vitamin. People who eat a varied diet are unlikely to develop a severe primary vitamin deficiency. In contrast, restrictive diets have the potential to cause prolonged vitamin deficits, which may result in often painful and potentially deadly diseases.

Well-known human vitamin deficiencies involve thiamine (beriberi), niacin (pellagra), vitamin C (scurvy), and vitamin D (rickets). In much of the developed world, such deficiencies are rare; this is due to (1) an adequate supply of food and (2) the addition of vitamins and minerals to common foods, often called fortification. In addition to these classical vitamin deficiency diseases, some evidence has also suggested links between vitamin deficiency and a number of different disorders.

Side-effects and overdose

In large doses, some vitamins have documented side-effects that tend to be more severe with a larger dosage. The likelihood of consuming too much of any vitamin from food is remote, but overdosing (vitamin poisoning) from vitamin supplementation does occur. At high enough dosages, some vitamins cause side-effects such as nausea, diarrhea, and vomiting. When side-effects emerge, recovery is often accomplished by reducing the dosage. The doses of vitamins different individual can tolerate varies widely, and appear to be related to age and state of health.

In 2008, overdose exposure to all formulations of vitamins and multivitamin-mineral formulations was reported by 68,911 individuals to the American Association of Poison Control Centers (nearly 80% of these exposures were in children under the age of 6), leading to 8 "major" life-threatening outcomes and 0 deaths.

Supplements

Dietary supplements, often containing vitamins, are used to ensure that adequate amounts of nutrients are obtained on a daily basis, if optimal amounts of the nutrients cannot be obtained through a varied diet. Scientific evidence supporting the benefits of some vitamin supplements is well established for certain health conditions, but others need further study. In some cases, vitamin supplements may have unwanted effects, especially if taken before surgery, with other dietary supplements or medicines, or if the person taking them has certain health conditions. Dietary supplements may also contain levels of vitamins many times higher, and in different forms, than one may ingest through food.

There have been mixed studies on the importance and safety of dietary supplementation. A meta-analysis published in 2006 suggested that Vitamin A and E supplements not only provide no tangible health benefits for generally healthy individuals but may actually increase mortality, although two large studies included in the analysis involved smokers, for which it was already known that beta-carotene supplements can be harmful. Another study published in May 2009 found that antioxidants such as vitamins C and E may actually curb some benefits of exercise. While others findings suggest that evidence of Vitamin E toxicity is limited to specific form taken in excess.

Governmental regulation of vitamin supplements

Most countries place dietary supplements in a special category under the general umbrella of *foods*, not drugs. This necessitates that the manufacturer, and not the government, be responsible for ensuring that its dietary supplement products are safe before they are marketed. Regulation of supplements varies widely by country. In the United States, a dietary supplement is defined under the Dietary Supplement Health and Education Act of 1994. In addition, the Food and Drug Administration uses the Adverse Event Reporting System to monitor adverse events that occur with supplements. In the European Union, the Food Supplements Directive requires that only those supplements that have been proven safe can be sold without a prescription

Names in current and previous nomenclatures

Nomenclature of reclassified vitamins

Previous name	Chemical name	Reason for name change
Vitamin B_4	Adenine	DNA metabolite; synthesized in body
Vitamin B_8	Adenylic acid	DNA metabolite; synthesized in body
Vitamin F	Essential fatty acids	Needed in large quantities (does not fit the definition of a vitamin).
Vitamin G	Riboflavin	Reclassified as Vitamin B_2
Vitamin H	Biotin	Reclassified as Vitamin B_7
Vitamin J	Catechol, Flavin	Catechol nonessential; flavin reclassified as B_2
Vitamin L_1	Anthranilic acid	Non essential
Vitamin L_2	Adenylthiomethylpentose	RNA metabolite; synthesized in body
Vitamin M	Folic acid	Reclassified as Vitamin B_9
Vitamin O	Carnitine	Synthesized in body
Vitamin P	Flavonoids	No longer classified as a vitamin
Vitamin PP	Niacin	Reclassified as Vitamin B_3
Vitamin S	Salicylic acid	Proposed inclusion of salicylate as an essential micronutrient
Vitamin U	S-Methylmethionine	Protein metabolite; synthesized in body

The reason that the set of vitamins skips directly from E to K is that the vitamins corresponding to letters F-J were either reclassified over time, discarded as false leads, or renamed because of their relationship to vitamin B, which became a complex of vitamins.

The German-speaking scientists who isolated and described vitamin K (in addition to naming it as such) did so because the vitamin is intimately involved in the *Koagulation* of blood following wounding. At the time, most (but not all) of the letters from F through to J were already designated, so the use of the letter K was considered quite reasonable. The table on the right lists chemicals that had previously been classified as vitamins, as well as the earlier names of vitamins that later became part of the B-complex.

Anti-vitamins

Anti-vitamins are chemical compounds that inhibit the absorption or actions of vitamins. For example, avidin is a protein in egg whites that inhibits the absorption of biotin. Pyrithiamine is similar to thiamine vitamin B1 and inhibits the enzymes that use thiamine.

Chapter- 5

Neurotransmitter

Neurotransmitters are endogenous chemicals which transmit signals from a neuron to a target cell across a synapse. Neurotransmitters are packaged into synaptic vesicles clustered beneath the membrane on the presynaptic side of a synapse, and are released into the synaptic cleft, where they bind to receptors in the membrane on the postsynaptic side of the synapse. Release of neurotransmitters usually follows arrival of an action potential at the synapse, but may also follow graded electrical potentials. Low level "baseline" release also occurs without electrical stimulation. Neurotransmitters are synthesized from plentiful and simple precursors, such as amino acids, which are readily available from the diet and which require only a small number of biosynthetic steps to convert.

Discovery

Until the early 20th century, scientists assumed that the majority of synaptic communication in the brain was electrical. However, through the careful histological examinations of Ramón y Cajal (1852–1934), a 20 to 40 nm gap between neurons, known today as the synaptic cleft, was discovered. The presence of such a gap suggested communication via chemical messengers traversing the synaptic cleft, and in 1921 German pharmacologist Otto Loewi (1873–1961) confirmed that neurons can communicate by releasing chemicals. Through a series of experiments involving the vagus nerves of frogs, Loewi was able to manually control the heart rate of frogs by controlling the amount of saline solution present around the vagus nerve. Upon completion of this experiment, Loewi asserted that sympathetic regulation of cardiac function can be mediated through changes in chemical concentrations. Furthermore, Otto Loewi is accredited with discovering acetylcholine (ACh)—the first known neurotransmitter. Some neurons do, however, communicate via electrical synapses through the use of gap junctions, which allow specific ions to pass directly from one cell to another.

Identifying neurotransmitters

The chemical identity of neurotransmitters is often difficult to determine experimentally. For example, it is easy using an electron microscope to recognize vesicles on the presynaptic side of a synapse, but it may not be easy to determine directly what chemical is packed into them. The difficulties led to many historical controversies over whether a

given chemical was or was not clearly established as a transmitter. In an effort to give some structure to the arguments, neurochemists worked out a set of experimentally tractable rules. According to the prevailing beliefs of the 1960s, a chemical can be classified as a neurotransmitter if it meets the following conditions:

- There are precursors and/or synthesis enzymes located in the presynaptic side of the synapse.
- The chemical is present in the presynaptic element.
- It is available in sufficient quantity in the presynaptic neuron to affect the postsynaptic neuron;
- There are postsynaptic receptors and the chemical is able to bind to them.
- A biochemical mechanism for inactivation is present.

Modern advances in pharmacology, genetics, and chemical neuroanatomy have greatly reduced the importance of these rules. A series of experiments that may have taken several years in the 1960s can now be done, with much better precision, in a few months. Thus, it is unusual nowadays for the identification of a chemical as a neurotransmitter to remain controversial for very long.

Types of neurotransmitters

There are many different ways to classify neurotransmitters. Dividing them into amino acids, peptides, and monoamines is sufficient for some classification purposes.

Major neurotransmitters:

- Amino acids: glutamate, aspartate, D-serine, γ-aminobutyric acid (GABA), glycine
- Monoamines and other biogenic amines: dopamine (DA), norepinephrine (noradrenaline; NE, NA), epinephrine (adrenaline), histamine, serotonin (SE, 5-HT)
- Others: acetylcholine (ACh), adenosine, anandamide, nitric oxide, etc.

In addition, over 50 neuroactive peptides have been found, and new ones are discovered regularly. Many of these are "co-released" along with a small-molecule transmitter, but in some cases a peptide is the primary transmitter at a synapse. β-endorphin is a relatively well known example of a peptide neurotransmitter; it engages in highly specific interactions with opioid receptors in the central nervous system.

Single ions, such as synaptically released zinc, are also considered neurotransmitters by some, as are some gaseous molecules such as nitric oxide (NO) and carbon monoxide (CO). These are not classical neurotransmitters by the strictest definition, however, because although they have all been shown experimentally to be released by presynaptic terminals in an activity-dependent way, they are not packaged into vesicles.

By far the most prevalent transmitter is glutamate, which is excitatory at well over 90% of the synapses in the human brain. The next most prevalent is GABA, which is inhibitory at more than 90% of the synapses that do not use glutamate. Even though other transmitters are used in far fewer synapses, they may be very important functionally—the great majority of psychoactive drugs exert their effects by altering the actions of some neurotransmitter systems, often acting through transmitters other than glutamate or GABA. Addictive drugs such as cocaine and amphetamine exert their effects primarily on the dopamine system. The addictive opiate drugs exert their effects primarily as functional analogs of opioid peptides, which, in turn, regulate dopamine levels.

Excitatory and inhibitory

Some neurotransmitters are commonly described as "excitatory" or "inhibitory". The only direct effect of a neurotransmitter is to activate one or more types of receptors. The effect on the postsynaptic cell depends, therefore, entirely on the properties of those receptors. It happens that for some neurotransmitters (for example, glutamate), the most important receptors all have excitatory effects: that is, they increase the probability that the target cell will fire an action potential. For other neurotransmitters (such as GABA), the most important receptors all have inhibitory effects. There are, however, other neurotransmitters, such as acetylcholine, for which both excitatory and inhibitory receptors exist; and there are some types of receptors that activate complex metabolic pathways in the postsynaptic cell to produce effects that cannot appropriately be called either excitatory or inhibitory. Thus, it is an oversimplification to call a neurotransmitter excitatory or inhibitory—nevertheless it is so convenient to call glutamate excitatory and GABA inhibitory that this usage is seen very frequently.

Actions

As explained above, the only direct action of a neurotransmitter is to activate a receptor. Therefore, the effects of a neurotransmitter system depend on the connections of the neurons that use the transmitter, and the chemical properties of the receptors that the transmitter binds to.

Here are a few examples of important neurotransmitter actions:

- Glutamate is used at the great majority of fast excitatory synapses in the brain and spinal cord. It is also used at most synapses that are "modifiable", i.e. capable of increasing or decreasing in strength. Modifiable synapses are thought to be the main memory-storage elements in the brain.
- GABA is used at the great majority of fast inhibitory synapses in virtually every part of the brain. Many sedative/tranquilizing drugs act by enhancing the effects of GABA. Correspondingly glycine is the inhibitory transmitter in the spinal cord.
- Acetylcholine is distinguished as the transmitter at the neuromuscular junction connecting motor nerves to muscles. The paralytic arrow-poison curare acts by blocking transmission at these synapses. Acetylcholine also operates in many regions of the brain, but using different types of receptors.

- Dopamine has a number of important functions in the brain. It plays a critical role in the reward system, but dysfunction of the dopamine system is also implicated in Parkinson's disease and schizophrenia.
- Serotonin is a monoamine neurotransmitter. Most is produced by and found in the intestine (approximately 90%), and the remainder in central nervous system neurons. It functions to regulate appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction, and function of the cardiovascular system and endocrine system. It is speculated to have a role in depression, as some depressed patients are seen to have lower concentrations of metabolites of serotonin in their cerebrospinal fluid and brain tissue.
- Substance P is an undecapeptide responsible for transmission of pain from certain sensory neurons to the central nervous system.

Neurons expressing certain types of neurotransmitters sometimes form distinct systems, where activation of the system affects large volumes of the brain, called *volume transmission*. Major neurotransmitter systems include the noradrenaline (norepinephrine) system, the dopamine system, the serotonin system and the cholinergic system.

Drugs targeting the neurotransmitter of such systems affect the whole system; this fact explains the complexity of action of some drugs. Cocaine, for example, blocks the reuptake of dopamine back into the presynaptic neuron, leaving the neurotransmitter molecules in the synaptic gap longer. Since the dopamine remains in the synapse longer, the neurotransmitter continues to bind to the receptors on the postsynaptic neuron, eliciting a pleasurable emotional response. Physical addiction to cocaine may result from prolonged exposure to excess dopamine in the synapses, which leads to the downregulation of some postsynaptic receptors. After the effects of the drug wear off, one might feel depressed because of the decreased probability of the neurotransmitter binding to a receptor. Prozac is a selective serotonin reuptake inhibitor (SSRI), which blocks re-uptake of serotonin by the presynaptic cell. This increases the amount of serotonin present at the synapse and allows it to remain there longer, hence potentiating the effect of naturally released serotonin. AMPT prevents the conversion of tyrosine to L-DOPA, the precursor to dopamine; reserpine prevents dopamine storage within vesicles; and deprenyl inhibits monoamine oxidase (MAO)-B and thus increases dopamine levels.

Diseases may affect specific neurotransmitter systems. For example, Parkinson's disease is at least in part related to failure of dopaminergic cells in deep-brain nuclei, for example the substantia nigra. Treatments potentiating the effect of dopamine precursors have been proposed and effected, with moderate success.

A brief comparison of the major neurotransmitter systems follows:

Neurotransmitter systems

System	Origin	Effects
Noradrenaline system	*locus coeruleus* Lateral tegmental field	• arousal • reward
Dopamine system	dopamine pathways: • mesocortical pathway • mesolimbic pathway • nigrostriatal pathway • tuberoinfundibular pathway	motor system, reward, cognition, endocrine, nausea
Serotonin system	caudal dorsal raphe nucleus rostral dorsal raphe nucleus	Increase (introversion), mood, satiety, body temperature and sleep, while decreasing nociception.
Cholinergic system	*pontomesencephalotegmental complex* basal optic nucleus of Meynert medial septal nucleus	• learning • short-term memory • arousal • reward

Common neurotransmitters

Category	Name	Abbreviation	Metabotropic	Ionotropic
Small: Amino acids	Aspartate		-	-
Neuropeptides	N-Acetylaspartylglut-amate	NAAG	Metabotropic glutamate receptors; selective agonist of mGluR3	-
Small: Amino acids	Glutamate (glutamic acid)	Glu	Metabotropic glutamate receptor	NMDA receptor, Kainate receptor, AMPA receptor
Small: Amino acids	Gamma-aminobutyric acid	GABA	$GABA_B$ receptor	$GABA_A$, $GABA_A$-ρ receptor
Small: Amino acids	Glycine	Gly	-	Glycine receptor

Small: Acetylcholine	Acetylcholine	Ach	Muscarinic acetylcholine receptor	Nicotinic acetylcholine receptor
Small: Monoamine (Phe/Tyr)	Dopamine	DA	Dopamine receptor	-
Small: Monoamine (Phe/Tyr)	Norepinephrine (noradrenaline)	NE	Adrenergic receptor	-
Small: Monoamine (Phe/Tyr)	Epinephrine (adrenaline)	Epi	Adrenergic receptor	-
Small: Monoamine (Phe/Tyr)	Octopamine		-	-
Small: Monoamine (Phe/Tyr)	Tyramine		-	
Small: Monoamine (Trp)	Serotonin (5-hydroxytryptamine)	5-HT	Serotonin receptor, all but 5-HT3	5-HT3
Small: Monoamine (Trp)	Melatonin	Mel	Melatonin receptor	-
Small: Monoamine (His)	Histamine	H	Histamine receptor	-
PP: Gastrins	Gastrin		-	-
PP: Gastrins	Cholecystokinin	CCK	Cholecystokinin receptor	-
PP: Neurohypophyseals	Vasopressin	AVP	Vasopressin receptor	-
PP: Neurohypophyseals	Oxytocin	OT	Oxytocin receptor	-
PP: Neurohypophyseals	Neurophysin I		-	-
PP: Neurohypophyseals	Neurophysin II		-	-
PP: Neuropeptide Y	Neuropeptide Y	NY	Neuropeptide Y receptor	-
PP: Neuropeptide Y	Pancreatic polypeptide	PP	-	-
PP: Neuropeptide Y	Peptide YY	PYY	-	-
PP: Opioids	Corticotropin (adrenocorticotropic hormone)	ACTH	Corticotropin receptor	-
PP: Opioids	Dynorphin		-	-
PP: Opioids	Endorphin		-	-

PP: Opioids	Enkephaline		-	-
PP: Secretins	Secretin		Secretin receptor	-
PP: Secretins	Motilin		Motilin receptor	-
PP: Secretins	Glucagon		Glucagon receptor	-
PP: Secretins	Vasoactive intestinal peptide	VIP	Vasoactive intestinal peptide receptor	-
PP: Secretins	Growth hormone-releasing factor	GRF	-	-
PP: Somtostatins	Somatostatin		Somatostatin receptor	-
SS: Tachykinins	Neurokinin A		-	-
SS: Tachykinins	Neurokinin B		-	-
SS: Tachykinins	Substance P		-	-
PP: Other	Bombesin		-	-
PP: Other	Gastrin releasing peptide	GRP	-	-
Gas	Nitric oxide	NO	Soluble guanylyl cyclase	-
Gas	Carbon monoxide	CO	-	Heme bound to potassium channels
Other	Anandamide	AEA	Cannabinoid receptor	-
Other	Adenosine triphosphate	ATP	P2Y12	P2X receptor

Precursors of neurotransmitters

While intake of neurotransmitter precursors does increase neurotransmitter synthesis, evidence is mixed as to whether neurotransmitter release (firing) is increased. Even with increased neurotransmitter release, it is unclear whether this will result in a long-term increase in neurotransmitter signal strength, since the nervous system can adapt to changes such as increased neurotransmitter synthesis and may therefore maintain constant firing. Some neurotransmitters may have a role in depression, and there is some evidence to suggest that intake of precursors of these neurotransmitters may be useful in the treatment of mild and moderate depression.

Norepinephrine precursors

For depressed patients where low activity of the neurotransmitter norepinephrine is implicated, there is only little evidence for benefit of neurotransmitter precursor

administration. L-phenylalanine and L-tyrosine are both precursors for dopamine, norepinephrine, and epinephrine. These conversions require vitamin B6, vitamin C, and S-adenosylmethionine. A few studies suggest potential antidepressant effects of L-phenylalanine and L-tyrosine, but there is much room for further research in this area.

Serotonin precursors

Administration of L-tryptophan, a precursor for serotonin, is seen to double the production of serotonin in the brain. It is significantly more effective than a placebo in the treatment of mild and moderate depression. This conversion requires vitamin C.

5-hydroxytryptophan (5-HTP), also a precursor for serotonin, is also more effective than a placebo and nearly as effective or of equal effectiveness to some antidepressants. Interestingly, it takes less than 2 weeks for an antidepressant response to occur, while antidepressant drugs generally take 2–4 weeks. 5-HTP also has no significant side effects.

Administration of 5-HTP bypasses the rate-limiting step in the synthesis of serotonin from tryptophan. Also, 5-HTP readily passes through the blood-brain barrier, and enters the central nervous system without need of a transport molecule. Note, however, that there is some evidence to suggest that a postsynaptic defect in serotonin utilization may be an important factor in depression, not only insufficient serotonin.

It is important to note that not all cases of depression are caused by low levels of serotonin. However, in the subgroup of depressed patients that are serotonin-deficient, there is strong evidence to suggest that 5-HTP is therapeutically useful in treating depression, and more useful than L-tryptophan.

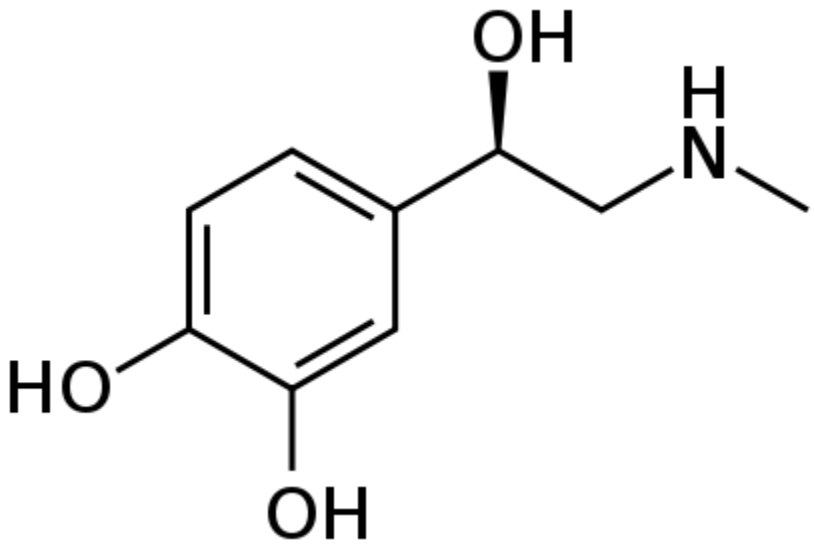
Depression does not have one cause; not all cases of depression are due to low levels of serotonin or norepinephrine. Blood tests for the ratio of tryptophan to other amino acids, as well as red blood cell membrane transport of these amino acids, can be predictive of whether serotonin or norepinephrine would be of therapeutic benefit. Overall, there is evidence to suggest that neurotransmitter precursors may be useful in the treatment of mild and moderate depression.

Degradation and elimination

Neurotransmitter must be broken down once it reaches the post-synaptic cell to prevent further excitatory or inhibitory signal transduction. For example, acetylcholine (ACh), an excitatory neurotransmitter, is broken down by acetylcholinesterase (AChE). Choline is taken up and recycled by the pre-synaptic neuron to synthesize more ACh. Other neurotransmitters such as dopamine are able to diffuse away from their targeted synaptic junctions and are eliminated from the body via the kidneys, or destroyed in the liver. Each neurotransmitter has very specific degradation pathways at regulatory points, which may be the target of the body's own regulatory system or recreational drugs.

Chapter- 6

Hormone



Epinephrine (adrenaline), a catecholamine-type hormone

A **hormone** (from Greek *ὁρμή* - "impetus") is a chemical released by a cell or a gland in one part of the body that sends out messages that affect cells in other parts of the organism. Only a small amount of hormone is required to alter cell metabolism. In essence, it is a chemical messenger that transports a signal from one cell to another. All multicellular organisms produce hormones; plant hormones are also called phytohormones. Hormones in animals are often transported in the blood. Cells respond to a hormone when they express a specific receptor for that hormone. The hormone binds to the receptor protein, resulting in the activation of a signal transduction mechanism that ultimately leads to cell type-specific responses.

Endocrine hormone molecules are secreted (released) directly into the bloodstream, whereas exocrine hormones (or ectohormones) are secreted directly into a duct, and, from the duct, they flow either into the bloodstream or from cell to cell by diffusion in a process known as paracrine signalling.

Recently it has been found that a variety of exogenous modern chemical compounds have hormone-like effects on both humans and wildlife. Their interference with the synthesis,

secretion, transport, binding, action, or elimination of natural hormones in the body are responsible of homeostasis, reproduction, development, and/or behavioural changes sameway as the endogenous produced hormones."

Hormones as a signal

Hormonal signaling involves the following:

1. **Biosynthesis** of a particular hormone in a particular tissue
2. **Storage and secretion** of the hormone
3. **Transport** of the hormone to the target cell(s)
4. **Recognition** of the hormone by an associated cell membrane or intracellular receptor protein
5. **Relay and amplification** of the received **hormonal** signal via a signal transduction process: This then leads to a cellular response. The reaction of the target cells may then be recognized by the original hormone-producing cells, leading to a down-regulation in hormone production. This is an example of a homeostatic negative feedback loop.
6. **Degradation** of the hormone.

Hormone cells are typically of a specialized cell type, residing within a particular endocrine gland, such as thyroid gland, ovaries, and testes. Hormones exit their cell of origin via exocytosis or another means of membrane transport. The hierarchical model is an oversimplification of the hormonal signaling process. Cellular recipients of a particular hormonal signal may be one of several cell types that reside within a number of different tissues, as is the case for insulin, which triggers a diverse range of systemic physiological affects. Different tissue types may also respond differently to the same hormonal signal. Because of this, hormonal signaling is elaborate and hard to dissect.

Interactions with receptors

Most hormones initiate a cellular response by initially combining with either a specific intracellular or cell membrane associated receptor protein. A cell may have several different receptors that recognize the same hormone and activate different signal transduction pathways, or a cell may have several different receptors that recognize different hormones and activate the same biochemical pathway.

For many hormones, including most protein hormones, the receptor is membrane-associated and embedded in the plasma membrane at the surface of the cell. The interaction of hormone and receptor typically triggers a cascade of secondary effects within the cytoplasm of the cell, often involving phosphorylation or dephosphorylation of various other cytoplasmic proteins, changes in ion channel permeability, or increased concentrations of intracellular molecules that may act as secondary messengers (e.g., cyclic AMP). Some protein hormones also interact with intracellular receptors located in the cytoplasm or nucleus by an intracrine mechanism.

For hormones such as steroid or thyroid hormones, their receptors are located intracellularly within the cytoplasm of their target cell. To bind their receptors, these hormones must cross the cell membrane. They can do so because they are lipid-soluble. The combined hormone-receptor complex then moves across the nuclear membrane into the nucleus of the cell, where it binds to specific DNA sequences, effectively amplifying or suppressing the action of certain genes, and affecting protein synthesis. However, it has been shown that not all steroid receptors are located intracellularly. some are associated with the plasma membrane.

An important consideration, dictating the level at which cellular signal transduction pathways are activated in response to a hormonal signal, is the effective concentration of hormone-receptor complexes that are formed. Hormone-receptor complex concentrations are effectively determined by three factors:

1. The number of hormone molecules available for complex formation
2. The number of receptor molecules available for complex formation
3. The binding affinity between hormone and receptor.

The number of hormone molecules available for complex formation is usually the key factor in determining the level at which signal transduction pathways are activated, the number of hormone molecules available being determined by the concentration of circulating hormone, which is in turn influenced by the level and rate at which they are secreted by biosynthetic cells. The number of receptors at the cell surface of the receiving cell can also be varied, as can the affinity between the hormone and its receptor.

Physiology of hormones

Most cells are capable of producing one or more molecules, which act as signaling molecules to other cells, altering their growth, function, or metabolism. The classical hormones produced by cells in the endocrine glands mentioned so far here are cellular products, specialized to serve as regulators at the overall organism level. However, they may also exert their effects solely within the tissue in which they are produced and originally released.

The rate of hormone biosynthesis and secretion is often regulated by a homeostatic negative feedback control mechanism. Such a mechanism depends on factors that influence the metabolism and excretion of hormones. Thus, higher hormone concentration alone cannot trigger the negative feedback mechanism. Negative feedback must be triggered by overproduction of an "effect" of the hormone.

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 the tropic 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, which increases 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., cholecystokinin, leptin, nesfatin-1, obestatin.

To release active hormones quickly into the circulation, hormone biosynthetic cells may produce and store biologically inactive hormones in the form of pre- or prohormones. These can then be quickly converted into their active hormone form in response to a particular stimulus.

Effects of hormones

Hormones have the following effects on the body:

- stimulation or inhibition of growth
- mood swings
- induction or suppression of apoptosis (programmed cell death)
- activation or inhibition of the immune system
- regulation of metabolism
- preparation of the body for mating, fighting, fleeing, and other activity
- preparation of the body for a new phase of life, such as puberty, parenting, and menopause
- control of the reproductive cycle
- hunger cravings

A hormone may also regulate the production and release of other hormones. Hormone signals control the internal environment of the body through homeostasis.

Chemical classes of hormones

Vertebrate hormones fall into three chemical classes:

- 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. More complex protein hormones bear carbohydrate side-chains and are called glycoprotein hormones. Luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone are glycoprotein hormones. There's also another type of hydrophilics hormones. They are called *nonpeptide* hormones. Although they don't have peptide connections, they are assimilated as peptide hormones.

- Lipid and phospholipid-derived hormones derive from lipids such as linoleic acid and arachidonic acid and phospholipids. The main classes are the steroid hormones that derive from cholesterol and the eicosanoids. Examples of steroid hormones are testosterone and cortisol. Sterol hormones such as calcitriol are a homologous system. The adrenal cortex and the gonads are primary sources of steroid hormones. Examples of eicosanoids are the widely studied prostaglandins.
- Monoamines derived from aromatic amino acids like phenylalanine, tyrosine, tryptophan by the action of aromatic amino acid decarboxylase enzymes. Examples of monoamines are thyroxine and adrenaline.

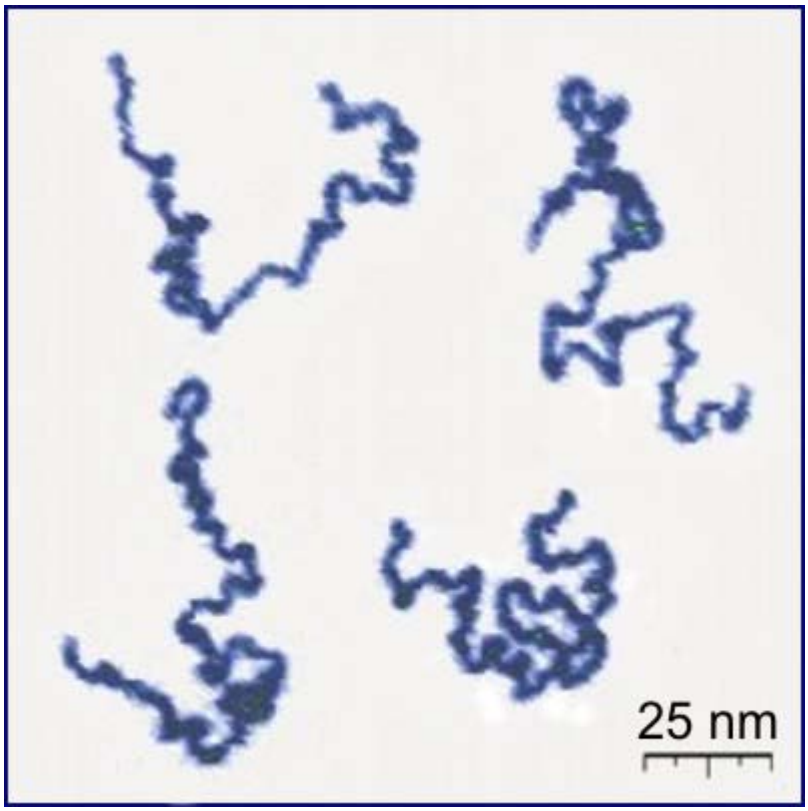
Pharmacology

Many hormones and their analogues are used as medication. The most commonly prescribed hormones are estrogens and progestagens (as methods of hormonal contraception 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.

Chapter- 7

Polymer



Appearance of real linear polymer chains as recorded using an atomic force microscope on surface under liquid medium. Chain contour length for this polymer is ~204 nm; thickness is ~0.4 nm.

A **polymer** is a large molecule (macromolecule) composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. Although the term *polymer* is sometimes taken to refer to plastics, it actually encompasses a large class of natural and synthetic materials with a wide variety of properties.

Because of the extraordinary range of properties of polymeric materials, they play an essential and ubiquitous role in everyday life. This role ranges from familiar synthetic plastics and elastomers to natural biopolymers such as nucleic acids and proteins that are essential for life.

Natural polymeric materials such as shellac, amber, and natural rubber have been used for centuries. A variety of other natural polymers exist, such as cellulose, which is the main constituent of wood and paper. The list of synthetic polymers includes synthetic rubber, Bakelite, neoprene, nylon, PVC, polystyrene, polyethylene, polypropylene, polyacrylonitrile, PVB, silicone, and many more.

Most commonly, the continuously linked backbone of a polymer used for the preparation of plastics consists mainly of carbon atoms. A simple example is polyethylene, whose repeating unit is based on ethylene monomer. However, other structures do exist; for example, elements such as silicon form familiar materials such as silicones, examples being silly putty and waterproof plumbing sealant. Oxygen is also commonly present in polymer backbones, such as those of polyethylene glycol, polysaccharides (in glycosidic bonds), and DNA (in phosphodiester bonds).

Polymers are studied in the fields of polymer chemistry, polymer physics, and polymer science.

Etymology

The word ***polymer*** is derived from the Greek words *πολύ- - poly-* meaning "many"; and *μέρος - meros* meaning "part". The term was coined in 1833 by Jöns Jacob Berzelius, although his definition of a polymer was quite different from the modern definition.

Historical development

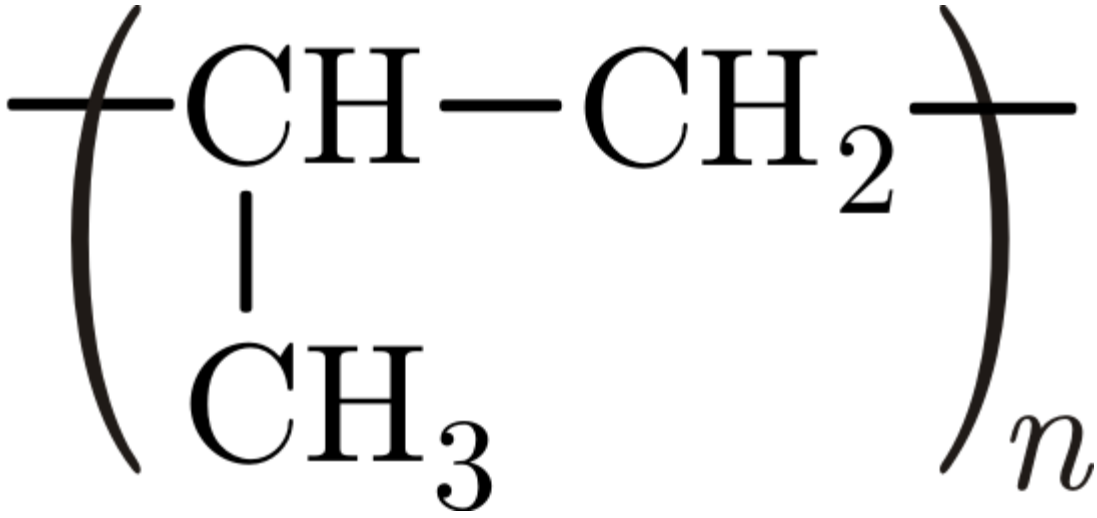
Starting in 1811, Henri Braconnot did pioneering work in derivative cellulose compounds, perhaps the earliest important work in polymer science. The development of vulcanization later in the nineteenth century improved the durability of the natural polymer rubber, signifying the first popularized semi-synthetic polymer. In 1907, Leo Baekeland created the first completely synthetic polymer, Bakelite, by reacting phenol and formaldehyde at precisely controlled temperature and pressure. Bakelite was then publicly introduced in 1909.

Despite significant advances in synthesis and characterization of polymers, a correct understanding of polymer molecular structure did not emerge until the 1920s. Before then, scientists believed that polymers were clusters of small molecules (called colloids), without definite molecular weights, held together by an unknown force, a concept known as association theory. In 1922, Hermann Staudinger proposed that polymers consisted of long chains of atoms held together by covalent bonds, an idea which did not gain wide acceptance for over a decade and for which Staudinger was ultimately awarded the Nobel Prize. Work by Wallace Carothers in the 1920s also demonstrated that polymers could be synthesized rationally from their constituent monomers. An important contribution to synthetic polymer science was made by the Italian chemist Giulio Natta and the German chemist Karl Ziegler, who won the Nobel Prize in Chemistry in 1963 for the development of the Ziegler-Natta catalyst. Further recognition of the importance of polymers came with the award of the Nobel Prize in Chemistry in 1974 to Paul Flory, whose extensive

work on polymers included the kinetics of step-growth polymerization and of addition polymerization, chain transfer, excluded volume, the Flory-Huggins solution theory, and the Flory convention.

Synthetic polymer materials such as nylon, polyethylene, Teflon, and silicone have formed the basis for a burgeoning polymer industry. These years have also shown significant developments in rational polymer synthesis. Most commercially important polymers today are entirely synthetic and produced in high volume on appropriately scaled organic synthetic techniques. Synthetic polymers today find application in nearly every industry and area of life. Polymers are widely used as adhesives and lubricants, as well as structural components for products ranging from children's toys to aircraft. They have been employed in a variety of biomedical applications ranging from implantable devices to controlled drug delivery. Polymers such as poly(methyl methacrylate) find application as photoresist materials used in semiconductor manufacturing and low-k dielectrics for use in high-performance microprocessors. Recently, polymers have also been employed as flexible substrates in the development of organic light-emitting diodes for electronic display.

Polymer synthesis



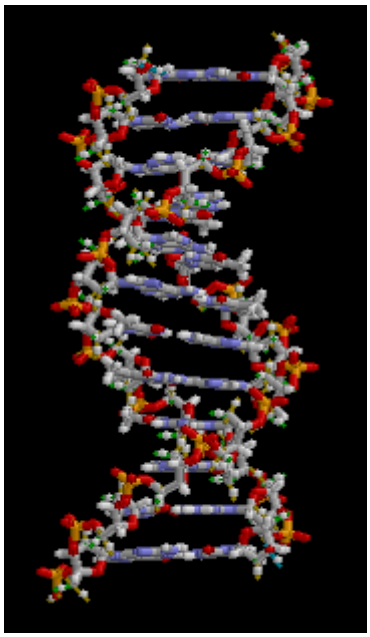
The repeating unit of the polymer polypropylene

Polymerization is the process of combining many small molecules known as monomers into a covalently bonded chain. During the polymerization process, some chemical groups may be lost from each monomer. This is the case, for example, in the polymerization of PET polyester. The monomers are terephthalic acid ($HOOC\text{-}C_6H_4\text{-}COOH$) and ethylene glycol ($HO\text{-}CH_2\text{-}CH_2\text{-}OH$) but the repeating unit is $-OC\text{-}C_6H_4\text{-}COO\text{-}CH_2\text{-}CH_2\text{-}O-$, which corresponds to the combination of the two monomers with the loss of two water molecules. The distinct piece of each monomer that is incorporated into the polymer is known as a repeat unit or monomer residue.

Laboratory synthesis

Laboratory synthetic methods are generally divided into two categories, step-growth polymerization and chain-growth polymerization. The essential difference between the two is that in chain growth polymerization, monomers are added to the chain one at a time only, whereas in step-growth polymerization chains of monomers may combine with one another directly. However, some newer methods such as plasma polymerization do not fit neatly into either category. Synthetic polymerization reactions may be carried out with or without a catalyst. Laboratory synthesis of biopolymers, especially of proteins, is an area of intensive research.

Biological synthesis



Microstructure of part of a DNA double helix **biopolymer**

There are three main classes of biopolymers: polysaccharides, polypeptides, and polynucleotides. In living cells, they may be synthesized by enzyme-mediated processes, such as the formation of DNA catalyzed by DNA polymerase. The synthesis of proteins involves multiple enzyme-mediated processes to transcribe genetic information from the DNA to RNA and subsequently translate that information to synthesize the specified protein from amino acids. The protein may be modified further following translation in order to provide appropriate structure and functioning.

Modification of natural polymers

Many commercially important polymers are synthesized by chemical modification of naturally occurring polymers. Prominent examples include the reaction of nitric acid and

cellulose to form nitrocellulose and the formation of vulcanized rubber by heating natural rubber in the presence of sulfur.

Polymer properties

Polymer properties are broadly divided into several classes based on the scale at which the property is defined as well as upon its physical basis. The most basic property of a polymer is the identity of its constituent monomers. A second set of properties, known as microstructure, essentially describe the arrangement of these monomers within the polymer at the scale of a single chain. These basic structural properties play a major role in determining bulk physical properties of the polymer, which describe how the polymer behaves as a continuous macroscopic material. Chemical properties, at the nano-scale, describe how the chains interact through various physical forces. At the macro-scale, they describe how the bulk polymer interacts with other chemicals and solvents.

Monomers and repeat units

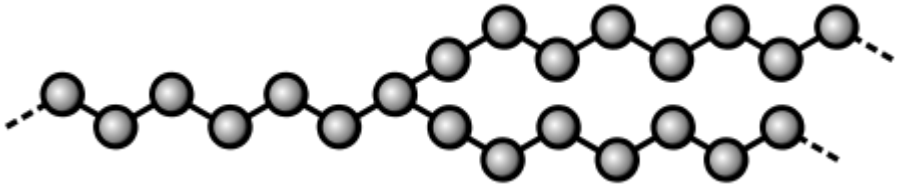
The identity of the monomer residues (repeat units) comprising a polymer is its first and most important attribute. Polymer nomenclature is generally based upon the type of monomer residues comprising the polymer. Polymers that contain only a single type of repeat unit are known as homopolymers, while polymers containing a mixture of repeat units are known as copolymers. Poly(styrene), for example, is composed only of styrene monomer residues, and is therefore classified as a homopolymer. Ethylene-vinyl acetate, on the other hand, contains more than one variety of repeat unit and is thus a copolymer. Some biological polymers are composed of a variety of different but structurally related monomer residues; for example, polynucleotides such as DNA are composed of a variety of nucleotide subunits.

A polymer molecule containing ionizable subunits is known as a polyelectrolyte or ionomer.

Microstructure

The microstructure of a polymer (sometimes called configuration) relates to the physical arrangement of monomer residues along the backbone of the chain. These are the elements of polymer structure that require the breaking of a covalent bond in order to change. Structure has a strong influence on the other properties of a polymer. For example, two samples of natural rubber may exhibit different durability, even though their molecules comprise the same monomers.

Polymer architecture

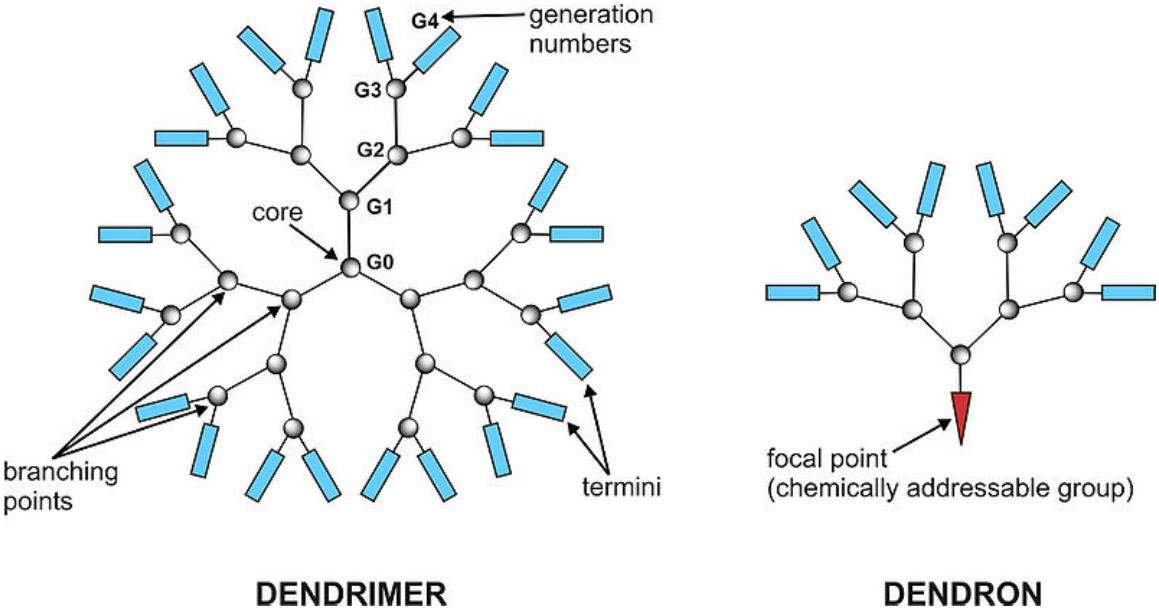


Branch point in a polymer

An important microstructural feature determining polymer properties is the polymer architecture. The simplest polymer architecture is a *linear* chain: a single backbone with no branches. A related unbranching architecture is a *ring* polymer. A branched polymer molecule is composed of a main chain with one or more substituent side chains or branches. Special types of branched polymers include star polymers, comb polymers, brush polymers, dendronized polymers, *ladders*, and dendrimers.

Branching of polymer chains affects the ability of chains to slide past one another by altering intermolecular forces, in turn affecting bulk physical polymer properties. Long chain branches may increase polymer strength, toughness, and the glass transition temperature (T_g) due to an increase in the number of entanglements per chain. The effect of such long-chain branches on the size of the polymer in solution is characterized by the branching index. Random length and atactic short chains, on the other hand, may reduce polymer strength due to disruption of organization and may likewise reduce the crystallinity of the polymer.

A good example of this effect is related to the range of physical attributes of polyethylene. High-density polyethylene (HDPE) has a very low degree of branching, is quite stiff, and is used in applications such as milk jugs. Low-density polyethylene (LDPE), on the other hand, has significant numbers of both long and short branches, is quite flexible, and is used in applications such as plastic films.



Dendrimer and dendron

Dendrimers are a special case of polymer where every monomer unit is branched. This tends to reduce intermolecular chain entanglement and crystallization. Alternatively, dendritic polymers are not perfectly branched but share similar properties to dendrimers due to their high degree of branching.

The architecture of the polymer is often physically determined by the **functionality** of the monomers from which it is formed. This property of a monomer is defined as the number of reaction sites at which may form chemical covalent bonds. The basic functionality required for forming even a linear chain is two bonding sites. Higher functionality yields branched or even crosslinked or networked polymer chains.

An effect related to branching is chemical crosslinking - the formation of covalent bonds between chains. Crosslinking tends to increase T_g and increase strength and toughness. Among other applications, this process is used to strengthen rubbers in a process known as vulcanization, which is based on crosslinking by sulfur. Car tires, for example, are highly crosslinked in order to reduce the leaking of air out of the tire and to toughen their durability. Eraser rubber, on the other hand, is not crosslinked to allow flaking of the rubber and prevent damage to the paper.

A cross-link suggests a branch point from which four or more distinct chains emanate. A polymer molecule with a high degree of crosslinking is referred to as a polymer network. Sufficiently high crosslink concentrations may lead to the formation of an infinite network, also known as a gel, in which networks of chains are of unlimited extent—essentially all chains have linked into one molecule.

Chain length

The physical properties of a polymer are strongly dependent on the size or length of the polymer chain. For example, as chain length is increased, melting and boiling temperatures increase quickly. Impact resistance also tends to increase with chain length, as does the viscosity, or resistance to flow, of the polymer in its melt state. Chain length is related to melt viscosity roughly as $1:10^{3.2}$, so that a tenfold increase in polymer chain length results in a viscosity increase of over 1000 times. Increasing chain length furthermore tends to decrease chain mobility, increase strength and toughness, and increase the glass transition temperature (T_g). This is a result of the increase in chain interactions such as Van der Waals attractions and entanglements that come with increased chain length. These interactions tend to fix the individual chains more strongly in position and resist deformations and matrix breakup, both at higher stresses and higher temperatures.

A common means of expressing the length of a chain is the degree of polymerization, which quantifies the number of monomers incorporated into the chain. As with other molecules, a polymer's size may also be expressed in terms of molecular weight. Since synthetic polymerization techniques typically yield a polymer product including a range of molecular weights, the weight is often expressed statistically to describe the distribution of chain lengths present in the same. Common examples are the number average molecular weight and weight average molecular weight. The ratio of these two values is the polydispersity index, commonly used to express the "width" of the molecular weight distribution. A final measurement is contour length, which can be understood as the length of the chain backbone in its fully extended state.

The flexibility of an unbranched chain polymer is characterized by its persistence length.

Monomer arrangement in copolymers

Monomers within a copolymer may be organized along the backbone in a variety of ways.

- **Alternating copolymers** possess regularly alternating monomer residues: $[AB...]_n$ (2).
- **Periodic copolymers** have monomer residue types arranged in a repeating sequence: $[A_nB_m...]$ m being different from n .
- **Statistical copolymers** have monomer residues arranged according to a known statistical rule. A statistical copolymer in which the probability of finding a particular type of monomer residue at an particular point in the chain is independent of the types of surrounding monomer residue may be referred to as a truly **random copolymer** (3).
- **Block copolymers** have two or more homopolymer subunits linked by covalent bonds (4). Polymers with two or three blocks of two distinct chemical species (e.g., A and B) are called diblock copolymers and triblock copolymers, respectively. Polymers with three blocks, each of a different chemical species (e.g., A, B, and C) are termed triblock terpolymers.
- **Graft or grafted copolymers** contain side chains that have a different composition or configuration than the main chain.(5)

Tacticity

Tacticity describes the relative stereochemistry of chiral centers in neighboring structural units within a macromolecule. There are three types: isotactic (all substituents on the same side), atactic (random placement of substituents), and syndiotactic (alternating placement of substituents).

Polymer morphology

Polymer morphology generally describes the arrangement and microscale ordering of polymer chains in space.

Crystallinity

When applied to polymers, the term *crystalline* has a somewhat ambiguous usage. In some cases, the term *crystalline* finds identical usage to that used in conventional crystallography. For example, the structure of a crystalline protein or polynucleotide, such as a sample prepared for x-ray crystallography, may be defined in terms of a conventional unit cell composed of one or more polymer molecules with cell dimensions of hundreds of angstroms or more.

A synthetic polymer may be lightly described as crystalline if it contains regions of three-dimensional ordering on atomic (rather than macromolecular) length scales, usually arising from intramolecular folding and/or stacking of adjacent chains. Synthetic polymers may consist of both crystalline and amorphous regions; the degree of crystallinity may be expressed in terms of a weight fraction or volume fraction of crystalline material. Few synthetic polymers are entirely crystalline.

The crystallinity of polymers is characterized by their degree of crystallinity, ranging from zero for a completely non-crystalline polymer to one for a theoretical completely crystalline polymer. Polymers with microcrystalline regions are generally tougher (can be bent more without breaking) and more impact-resistant than totally amorphous polymers.

Polymers with a degree of crystallinity approaching zero or one will tend to be transparent, while polymers with intermediate degrees of crystallinity will tend to be opaque due to light scattering by crystalline or glassy regions. Thus for many polymers, reduced crystallinity may also be associated with increased transparency.

Chain conformation

The space occupied by a polymer molecule is generally expressed in terms of radius of gyration, which is an average distance from the center of mass of the chain to the chain itself. Alternatively, it may be expressed in terms of pervaded volume, which is the volume of solution spanned by the polymer chain and scales with the cube of the radius of gyration.

Mechanical properties

A polyethylene sample necking under tension.

The bulk properties of a polymer are those most often of end-use interest. These are the properties that dictate how the polymer actually behaves on a macroscopic scale.

Tensile strength

The tensile strength of a material quantifies how much stress the material will endure before suffering permanent deformation. This is very important in applications that rely upon a polymer's physical strength or durability. For example, a rubber band with a higher tensile strength will hold a greater weight before snapping. In general, tensile strength increases with polymer chain length and crosslinking of polymer chains.

Young's modulus of elasticity

Young's Modulus quantifies the elasticity of the polymer. It is defined, for small strains, as the ratio of rate of change of stress to strain. Like tensile strength, this is highly relevant in polymer applications involving the physical properties of polymers, such as rubber bands. The modulus is strongly dependent on temperature.

Transport properties

Transport properties such as diffusivity relate to how rapidly molecules move through the polymer matrix. These are very important in many applications of polymers for films and membranes.

Phase behavior

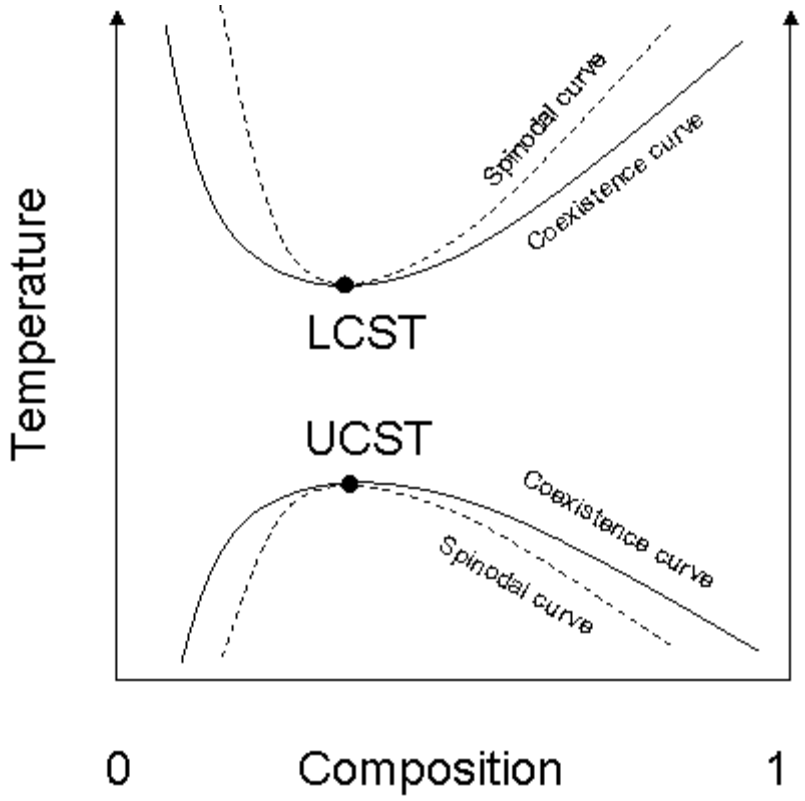
Melting point

The term *melting point*, when applied to polymers, suggests not a solid-liquid phase transition but a transition from a crystalline or semi-crystalline phase to a solid amorphous phase. Though abbreviated as simply T_m, the property in question is more properly called the crystalline melting temperature. Among synthetic polymers, crystalline melting is only discussed with regards to thermoplastics, as thermosetting polymers will decompose at high temperatures rather than melt.

Glass transition temperature

A parameter of particular interest in synthetic polymer manufacturing is the glass transition temperature (T_g), which describes the temperature at which amorphous polymers undergo a transition from a rubbery, viscous amorphous solid, to a brittle, glassy amorphous solid. The glass transition temperature may be engineered by altering the degree of branching or crosslinking in the polymer or by the addition of plasticizer.

Mixing behavior



Phase diagram of the typical mixing behavior of weakly interacting polymer solutions.

In general, polymeric mixtures are far less miscible than mixtures of small molecule materials. This effect results from the fact that the driving force for mixing is usually entropy, not interaction energy. In other words, miscible materials usually form a solution not because their interaction with each other is more favorable than their self-interaction, but because of an increase in entropy and hence free energy associated with increasing the amount of volume available to each component. This increase in entropy scales with the number of particles (or moles) being mixed. Since polymeric molecules are much larger and hence generally have much higher specific volumes than small molecules, the number of molecules involved in a polymeric mixture is far smaller than the number in a small molecule mixture of equal volume. The energetics of mixing, on the other hand, is comparable on a per volume basis for polymeric and small molecule mixtures. This tends to increase the free energy of mixing for polymer solutions and thus make solvation less favorable. Thus, concentrated solutions of polymers are far rarer than those of small molecules.

Furthermore, the phase behavior of polymer solutions and mixtures is more complex than that of small molecule mixtures. Whereas most small molecule solutions exhibit only an upper critical solution temperature phase transition, at which phase separation occurs with cooling, polymer mixtures commonly exhibit a lower critical solution temperature phase transition, at which phase separation occurs with heating.

In dilute solution, the properties of the polymer are characterized by the interaction between the solvent and the polymer. In a good solvent, the polymer appears swollen and occupies a large volume. In this scenario, intermolecular forces between the solvent and monomer subunits dominate over intramolecular interactions. In a bad solvent or poor solvent, intramolecular forces dominate and the chain contracts. In the theta solvent, or the state of the polymer solution where the value of the second virial coefficient becomes 0, the intermolecular polymer-solvent repulsion balances exactly the intramolecular monomer-monomer attraction. Under the theta condition (also called the Flory condition), the polymer behaves like an ideal random coil. The transition between the states is known as a coil-globule transition.

Inclusion of plasticizers

Inclusion of plasticizers tends to lower T_g and increase polymer flexibility. Plasticizers are generally small molecules that are chemically similar to the polymer and create gaps between polymer chains for greater mobility and reduced interchain interactions. A good example of the action of plasticizers is related to polyvinylchlorides or PVCs. A uPVC, or unplasticized polyvinylchloride, is used for things such as pipes. A pipe has no plasticizers in it, because it needs to remain strong and heat-resistant. Plasticized PVC is used for clothing for a flexible quality. Plasticizers are also put in some types of cling film to make the polymer more flexible.

Chemical properties

The attractive forces between polymer chains play a large part in determining a polymer's properties. Because polymer chains are so long, these interchain forces are amplified far beyond the attractions between conventional molecules. Different side groups on the polymer can lend the polymer to ionic bonding or hydrogen bonding between its own chains. These stronger forces typically result in higher tensile strength and higher crystalline melting points.

The intermolecular forces in polymers can be affected by dipoles in the monomer units. Polymers containing amide or carbonyl groups can form hydrogen bonds between adjacent chains; the partially positively charged hydrogen atoms in N-H groups of one chain are strongly attracted to the partially negatively charged oxygen atoms in C=O groups on another. These strong hydrogen bonds, for example, result in the high tensile strength and melting point of polymers containing urethane or urea linkages. Polyesters have dipole-dipole bonding between the oxygen atoms in C=O groups and the hydrogen atoms in H-C groups. Dipole bonding is not as strong as hydrogen bonding, so a polyester's melting point and strength are lower than Kevlar's (Twaron), but polyesters have greater flexibility.

Ethene, however, has no permanent dipole. The attractive forces between polyethylene chains arise from weak van der Waals forces. Molecules can be thought of as being surrounded by a cloud of negative electrons. As two polymer chains approach, their electron clouds repel one another. This has the effect of lowering the electron density on

one side of a polymer chain, creating a slight positive dipole on this side. This charge is enough to attract the second polymer chain. Van der Waals forces are quite weak, however, so polyethylene can have a lower melting temperature compared to other polymers.

Standardized polymer nomenclature

There are multiple conventions for naming polymer substances. Many commonly used polymers, such as those found in consumer products, are referred to by a common or trivial name. The trivial name is assigned based on historical precedent or popular usage rather than a standardized naming convention. Both the American Chemical Society (ACS) and IUPAC have proposed standardized naming conventions; the ACS and IUPAC conventions are similar but not identical. Examples of the differences between the various naming conventions are given in the table below:

Common name	ACS name	IUPAC name
Poly(ethylene oxide) or PEO	Poly(oxyethylene)	Poly(oxyethene)
Poly(ethylene terephthalate) or PET	Poly(oxy-1,2-ethanediyloxycarbonyl-1,4-phenylenecarbonyl)	Poly(oxyetheneoxyterephthaloyl)
Nylon 6	Poly[amino(1-oxo-1,6-hexanediyl)]	Poly[amino(1-oxohexan-1,6-diyl)]

In both standardized conventions, the polymers' names are intended to reflect the monomer(s) from which they are synthesized rather than the precise nature of the repeating subunit. For example, the polymer synthesized from the simple alkene ethene is called polyethylene, retaining the *-ene* suffix even though the double bond is removed during the polymerization process:

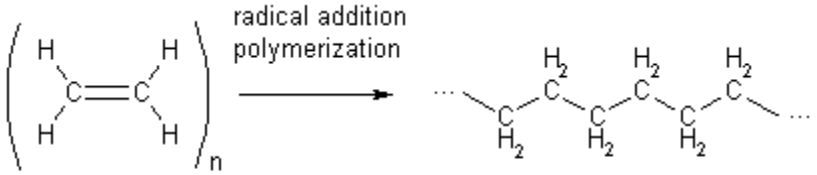
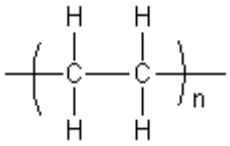


Fig 1: The polymerisation of ethene in to poly(ethene)

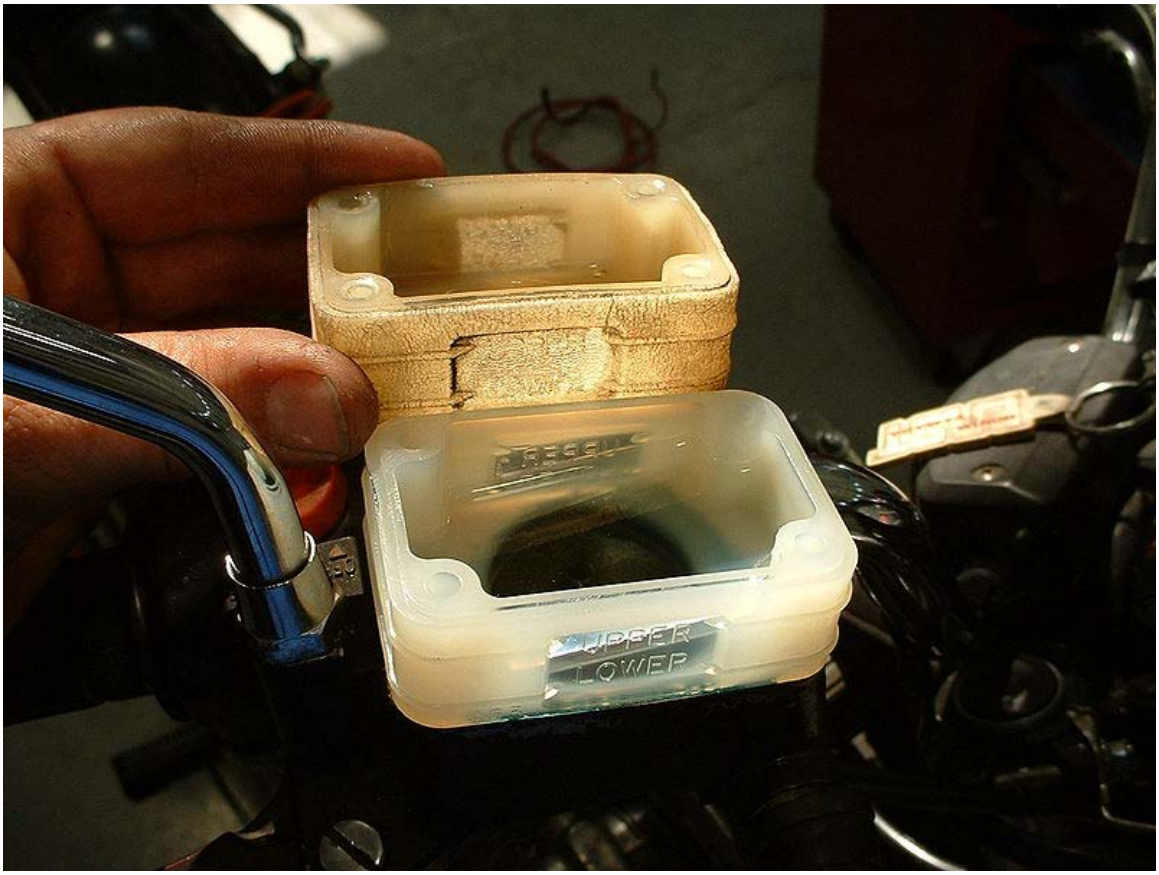


Polymer characterization

The characterization of a polymer requires several parameters which need to be specified. This is because a polymer actually consists of a statistical distribution of chains of varying lengths, and each chain consists of monomer residues which affect its properties.

A variety of lab techniques are used to determine the properties of polymers. Techniques such as wide angle X-ray scattering, small angle X-ray scattering, and small angle neutron scattering are used to determine the crystalline structure of polymers. Gel permeation chromatography is used to determine the number average molecular weight, weight average molecular weight, and polydispersity. FTIR, Raman and NMR can be used to determine composition. Thermal properties such as the glass transition temperature and melting point can be determined by differential scanning calorimetry and dynamic mechanical analysis. Pyrolysis followed by analysis of the fragments is one more technique for determining the possible structure of the polymer. Thermogravimetry is a useful technique to evaluate the thermal stability of the polymer. Detailed analyses of TG curves also allow us to know a bit of the phase segregation in polymers. Rheological properties are also commonly used to help determine molecular architecture (molecular weight, molecular weight distribution and branching)as well as to understand how the polymer will process, through measurements of the polymer in the melt phase. Another polymer characterization technique is Automatic Continuous Online Monitoring of Polymerization Reactions (ACOMP) which provides real-time characterization of polymerization reactions. It can be used as an analytical method in R&D, as a tool for reaction optimization at the bench and pilot plant level and, eventually, for feedback control of full-scale reactors. ACOMP measures in a model-independent fashion the evolution of average molar mass and intrinsic viscosity, monomer conversion kinetics and, in the case of copolymers, also the average composition drift and distribution. It is applicable in the areas of free radical and controlled radical homo- and copolymerization, polyelectrolyte synthesis, heterogeneous phase reactions, including emulsion polymerization, adaptation to batch and continuous reactors, and modifications of polymers.

Polymer degradation



A plastic item with thirty years of exposure to heat and cold, brake fluid, and sunlight. Notice the discoloration, swollen dimensions, and tiny splits running through the material

Polymer degradation is a change in the properties—tensile strength, color, shape, or molecular weight—of a polymer or polymer-based product under the influence of one or more environmental factors, such as heat, light, chemicals and, in some cases, galvanic action. It is often due to the scission of polymer chain bonds via hydrolysis, leading to a decrease in the molecular mass of the polymer.

Although such changes are frequently undesirable, in some cases, such as biodegradation and recycling, they may be intended to prevent environmental pollution. Degradation can also be useful in biomedical settings. For example, a copolymer of polylactic acid and polyglycolic acid is employed in hydrolysable stitches that slowly degrade after they are applied to a wound.

The susceptibility of a polymer to degradation depends on its structure. Epoxies and chains containing aromatic functionalities are especially susceptible to UV degradation while polyesters are susceptible to degradation by hydrolysis, while polymers containing an unsaturated backbone are especially susceptible to ozone cracking. Carbon based polymers are more susceptible to thermal degradation than inorganic polymers such as polydimethylsiloxane and are therefore not ideal for most high-temperature applications.

High-temperature matrices such as bismaleimides (BMI), condensation polyimides (with an O-C-N bond), triazines (with a nitrogen (N) containing ring), and blends thereof are susceptible to polymer degradation in the form of galvanic corrosion when bare carbon fiber reinforced polymer CFRP is in contact with an active metal such as aluminum in salt water environments.

The degradation of polymers to form smaller molecules may proceed by random scission or specific scission. The degradation of polyethylene occurs by random scission—a random breakage of the bonds that hold the atoms of the polymer together. When heated above 450 °C, polyethylene degrades to form a mixture of hydrocarbons. Other polymers, such as poly(alpha-methylstyrene), undergo specific chain scission with breakage occurring only at the ends. They literally unzip or depolymerize back to the constituent monomer.

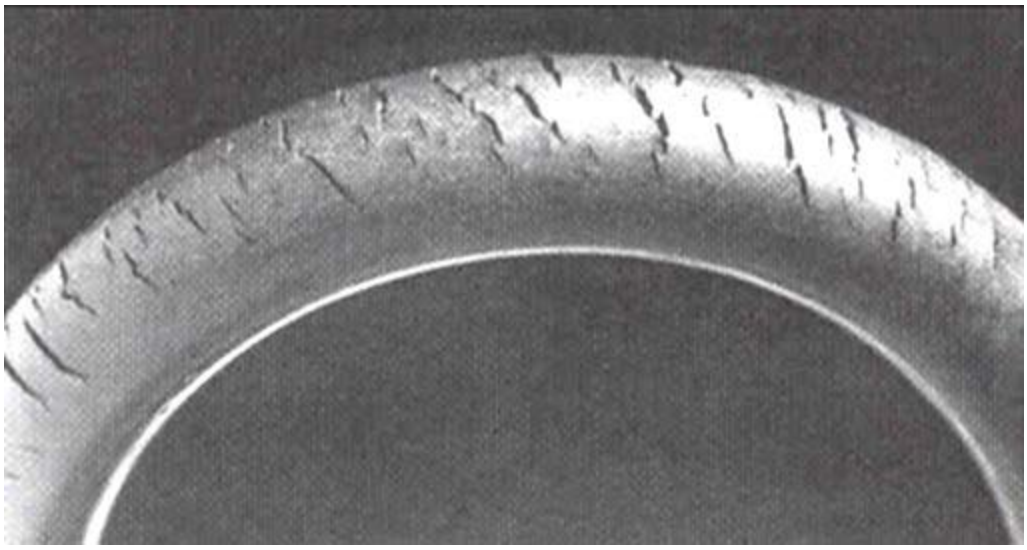
The sorting of polymer waste for recycling purposes may be facilitated by the use of the Resin identification codes developed by the Society of the Plastics Industry to identify the type of plastic.

Product failure

Chlorine attack of acetal resin plumbing joint

In a finished product, such a change is to be prevented or delayed. Failure of safety-critical polymer components can cause serious accidents, such as fire in the case of cracked and degraded polymer fuel lines. Chlorine-induced cracking of acetal resin

plumbing joints and polybutylene pipes has caused many serious floods in domestic properties, especially in the USA in the 1990s. Traces of chlorine in the water supply attacked vulnerable polymers in the plastic plumbing, a problem which occurs faster if any of the parts have been poorly extruded or injection molded. Attack of the acetal joint occurred because of faulty molding, leading to cracking along the threads of the fitting which is a serious stress concentration.



Ozone-induced cracking in natural rubber tubing

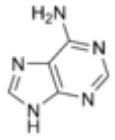
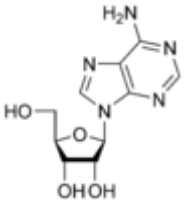
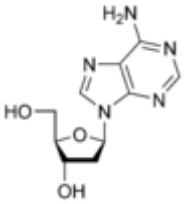
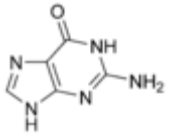
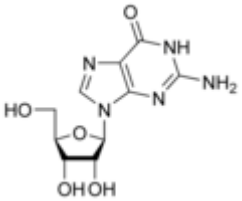
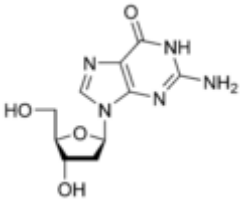
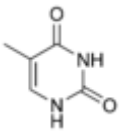
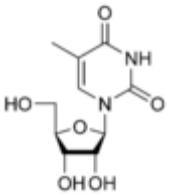
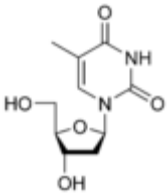
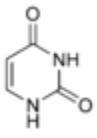
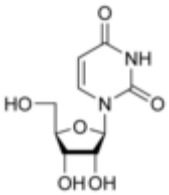
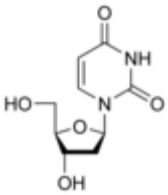
Polymer oxidation has caused accidents involving medical devices. One of the oldest known failure modes is ozone cracking caused by chain scission when ozone gas attacks susceptible elastomers, such as natural rubber and nitrile rubber. They possess double bonds in their repeat units which are cleaved during ozonolysis. Cracks in fuel lines can penetrate the bore of the tube and cause fuel leakage. If cracking occurs in the engine compartment, electric sparks can ignite the gasoline and can cause a serious fire.

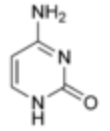
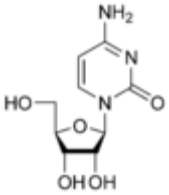
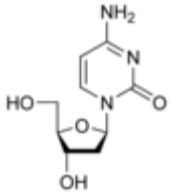
Fuel lines can also be attacked by another form of degradation: hydrolysis. Nylon 6,6 is susceptible to acid hydrolysis, and in one accident, a fractured fuel line led to a spillage of diesel into the road. If diesel fuel leaks onto the road, accidents to following cars can be caused by the slippery nature of the deposit, which is like black ice.

Chapter- 8

Nucleoside and Nucleotide

Nucleoside

Nitrogenous base	Nucleoside	Deoxynucleoside
 Adenine	 Adenosine A	 Deoxyadenosine dA
 Guanine	 Guanosine G	 Deoxyguanosine dG
 Thymine	 5-Methyluridine m^5U	 Thymidine dT
 Uracil	 Uridine U	 Deoxyuridine dU

 Cytosine	 Cytidine C	 Deoxycytidine dC

Nucleosides are glycosylamines consisting of a nucleobase (often referred to as simply *base*) bound to a ribose or deoxyribose sugar via a beta-glycosidic linkage. Examples of nucleosides include cytidine, uridine, adenosine, guanosine, thymidine and inosine.

Nucleosides can be phosphorylated by specific kinases in the cell on the sugar's primary alcohol group (-CH_2-OH), producing nucleotides, which are the molecular building-blocks of DNA and RNA.

Nucleosides can be produced by de novo synthesis pathways, in particular in the liver, but they are more abundantly supplied via ingestion and digestion of nucleic acids in the diet, whereby nucleotidases break down *nucleotides* (such as the thymine nucleotide) into *nucleosides* (such as thymidine) and phosphate. The nucleosides, in turn, are subsequently broken down:

- in the lumen of the digestive system by nucleosidases into nucleobases and ribose or deoxyribose.

In addition, nucleotides can be broken down:

- inside the cell into nitrogenous bases, and ribose-1-phosphate or deoxyribose-1-phosphate.

In medicine several nucleoside analogues are used as antiviral or anticancer agents. The viral polymerase incorporates these compounds with non-canonical bases. These compounds are activated in the cells by being converted into nucleotides, they are administered as nucleosides since charged nucleotides cannot easily cross cell membranes.

In molecular biology, several analogues of the sugar backbone exist. Due to the low stability of RNA, which is prone to hydrolysis, several more stable alternative nucleoside/nucleotide analogues that correctly bind to RNA are used. This is achieved by using a different backbone sugar. These analogues include LNA, morpholino, PNA.

In sequencing, dideoxynucleotides are used. These nucleotides possess the non-canon sugar dideoxyribose, which lacks 3' hydroxyl group (which accepts the phosphate) and therefore cannot bond with the next base, terminating the chain, as DNA polymerases mistake it for a regular deoxyribonucleotide.

Nucleotide

Nucleotides are molecules that, when joined together, make up the structural units of RNA and DNA. In addition, nucleotides play central roles in metabolism. In that capacity, they serve as sources of chemical energy (adenosine triphosphate and guanosine triphosphate), participate in cellular signaling (cyclic guanosine monophosphate and cyclic adenosine monophosphate), and are incorporated into important cofactors of enzymatic reactions (coenzyme A, flavin adenine dinucleotide, flavin mononucleotide, and nicotinamide adenine dinucleotide phosphate).

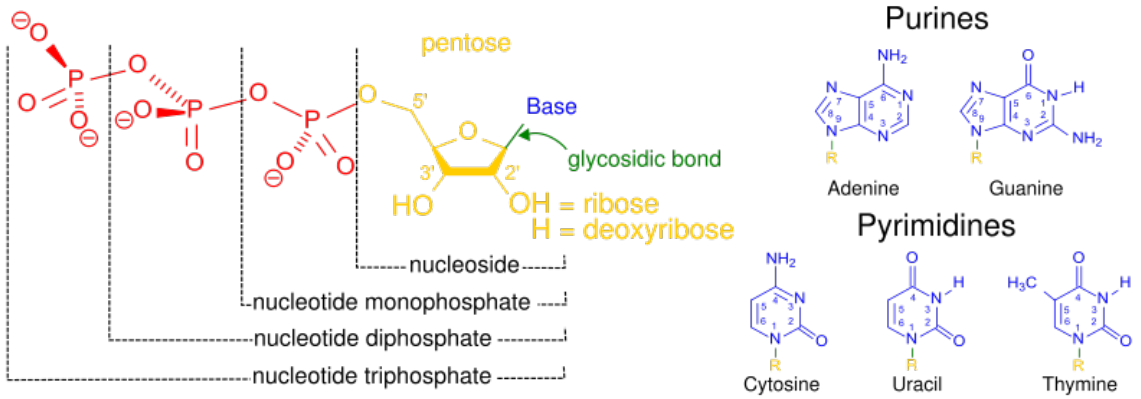


Figure 1: Structural elements of the most common nucleotides

Nucleotide structure

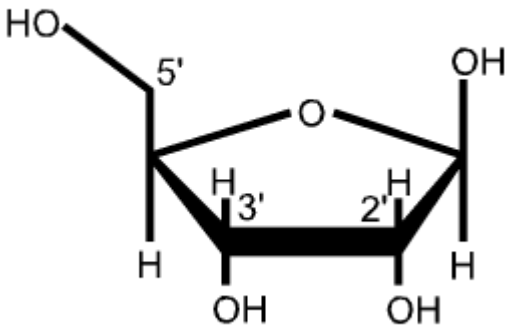


Figure 2: Ribose structure indicating numbering of carbon atoms

A nucleotide is composed of a nucleobase (nitrogenous base), a five-carbon sugar (either ribose or 2'-deoxyribose), and one to three phosphate groups. Together, the nucleobase and sugar comprise a nucleoside. The phosphate groups form bonds with either the 2, 3,

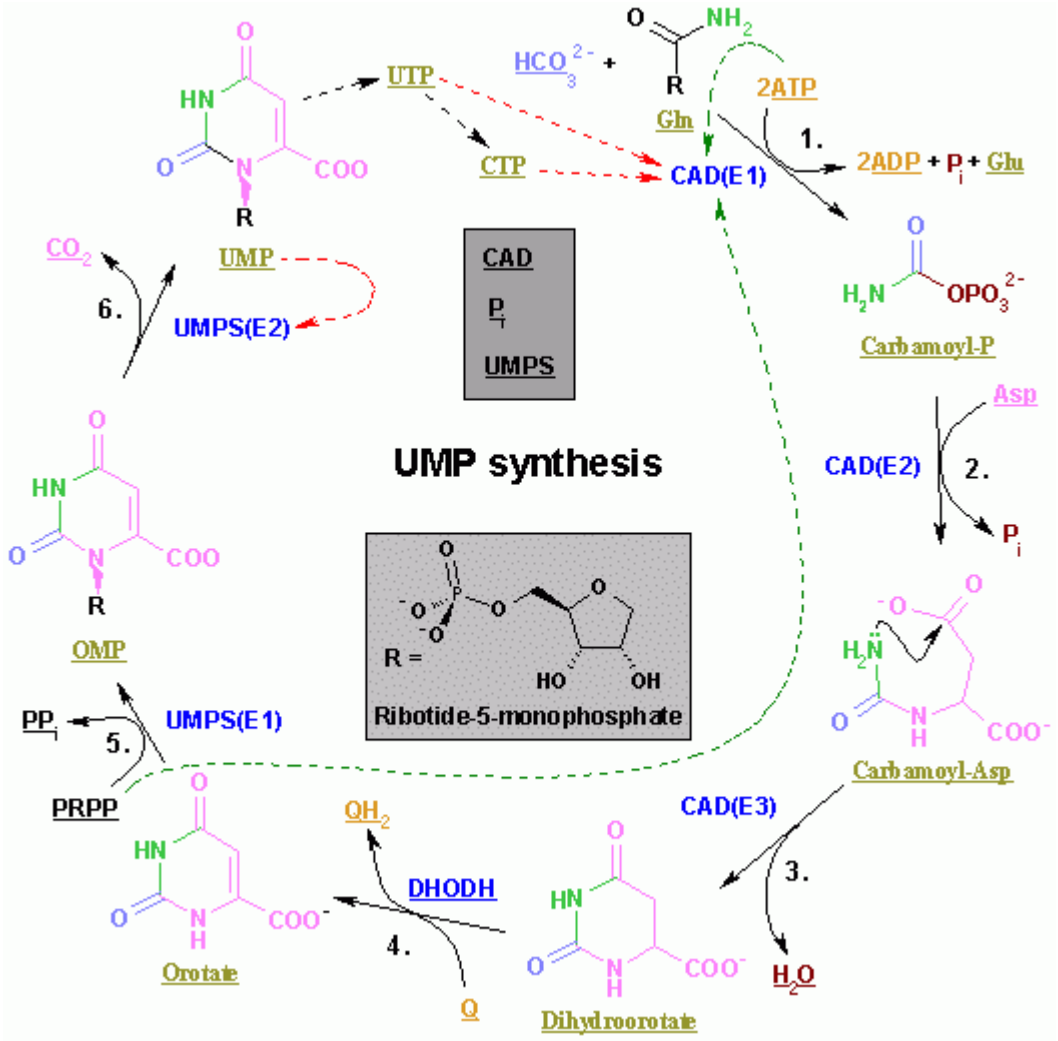
or 5-carbon of the sugar, with the 5-carbon site most common. Cyclic nucleotides form when the phosphate group is bound to two of the sugar's hydroxyl groups. Ribonucleotides are nucleotides where the sugar is ribose, and deoxyribonucleotides contain the sugar deoxyribose. Nucleotides can contain either a purine or a pyrimidine base.

Nucleic acids are polymeric macromolecules made from nucleotide monomers. In DNA, the purine bases are adenine and guanine, while the pyrimidines are thymine and cytosine. RNA uses uracil in place of thymine. Adenine always pairs with thymine by 2 hydrogen bonds, while guanine pairs with cytosine through 3 hydrogen bonds, each due to their unique structures.

Synthesis

Nucleotides can be synthesized by a variety of means both in vitro and in vivo. In vivo, nucleotides can be synthesised de novo or recycled through salvage pathways. Nucleotides undergo breakdown such that useful parts can be reused in synthesis reactions to create new nucleotides. In vitro, protecting groups may be used during laboratory production of nucleotides. A purified nucleoside is protected to create a phosphoramidite, which can then be used to obtain analogues not found in nature and/or to synthesize an oligonucleotide.

Pyrimidine ribonucleotides

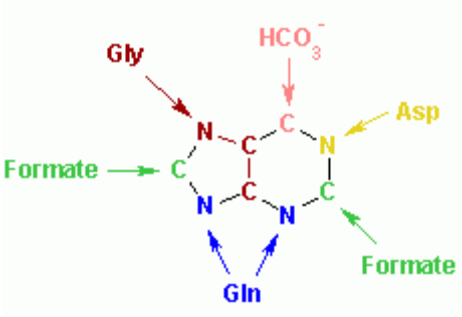


The synthesis of UMP.
The color scheme is as follows: **enzymes, coenzymes, substrate names, inorganic molecules**

Pyrimidine nucleotide synthesis starts with the formation of carbamoyl phosphate from glutamine and CO_2. The cyclisation reaction between carbamoyl phosphate reacts with aspartate, yielding orotate in subsequent steps. Orotate reacts with 5-phosphoribosyl α-diphosphate (PRPP), yielding orotidine monophosphate (OMP), which is decarboxylated to form uridine monophosphate (UMP). It is from UMP that other pyrimidine nucleotides are derived. UMP is phosphorylated to uridine triphosphate (UTP) via two sequential reactions with ATP. Cytidine monophosphate (CMP) is derived from conversion of UTP to cytidine triphosphate (CTP) with subsequent loss of two phosphates.

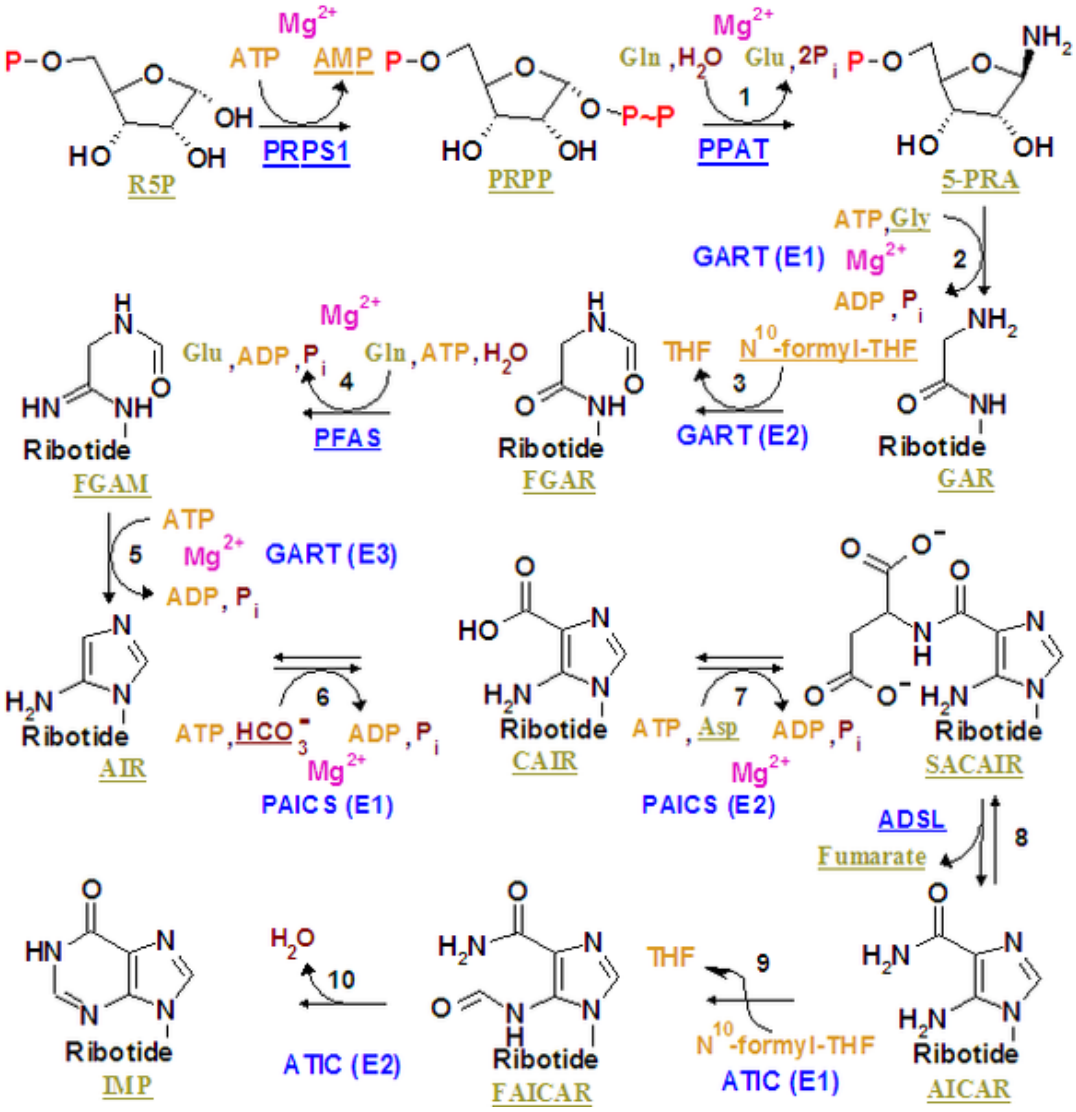
Purine ribonucleotides

The atoms which are used to build the purine nucleotides come from a variety of sources:



The biosynthetic origins of purine ring atoms

N1 arises from the amine group of Asp
C2 and C8 originate from formate
N3 and N9 are contributed by the amide group of Gln
C4, C5 and N7 are derived from Gly
C6 comes from HCO_3^- (CO_2)



The synthesis of IMP. The color scheme is as follows: **enzymes, coenzymes, substrate names, metal ions, inorganic molecules**

The de novo synthesis of purine nucleotides by which these precursors are incorporated into the purine ring proceeds by a 10-step pathway to the branch-point intermediate IMP, the nucleotide of the base hypoxanthine. AMP and GMP are subsequently synthesized from this intermediate via separate, two-step pathways. Thus, purine moieties are initially formed as part of the ribonucleotides rather than as free bases.

Six enzymes take part in IMP synthesis. Three of them are multifunctional:

- GART (reactions 2, 3, and 5)
- PAICS (reactions 6, and 7)
- ATIC (reactions 9, and 10)

Reaction 1. The pathway starts with the formation of PRPP. PRPS1 is the enzyme that activates R5P, which is formed primarily by the pentose phosphate pathway, to PRPP by reacting it with ATP. The reaction is unusual in that a pyrophosphoryl group is directly transferred from ATP to C1 of R5P and that the product has the **α** configuration about C1. This reaction is also shared with the pathways for the synthesis of the pyrimidine nucleotides, Trp, and His. As a result of being on (a) such (a) major metabolic crossroad and the use of energy, this reaction is highly regulated.

Reaction 2. In the first reaction unique to purine nucleotide biosynthesis, PPAT catalyzes the displacement of PRPP's pyrophosphate group (PP_i) by Gln's amide nitrogen. The reaction occurs with the inversion of configuration about ribose C1, thereby forming **β**-5-phosphorybosylamine (5-PRA) and establishing the anomeric form of the future nucleotide. This reaction, which is driven to completion by the subsequent hydrolysis of the released PP_i, is the pathway's flux-generating step and is therefore regulated, too.

Length unit

Nucleotide (abbreviated nt) is a common length unit for single-stranded RNA, similar to how base pair is a length unit for double-stranded DNA.

Abbreviation codes for degenerate bases

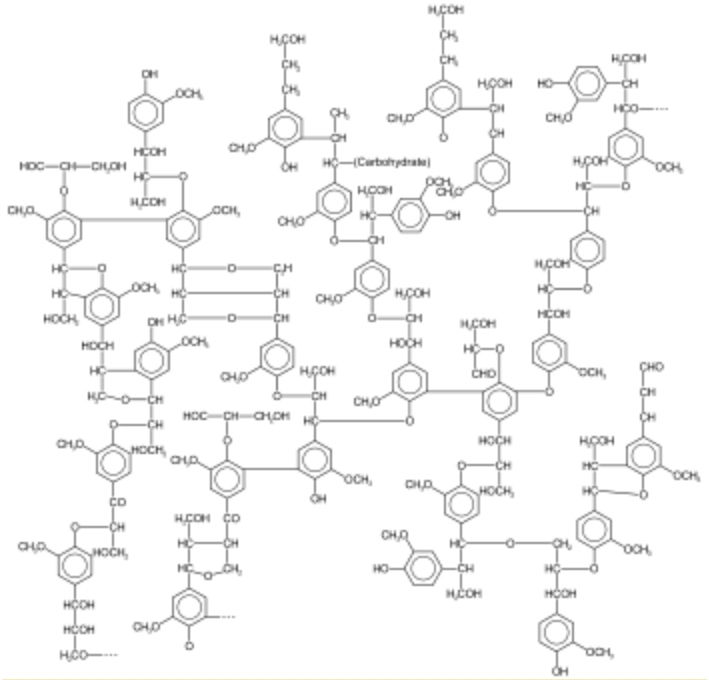
The IUPAC has designated the symbols for nucleotides. Apart from the five (A, G, C, T/U) bases, often degenerate bases are used especially for designing PCR primers. These nucleotide codes are listed here.

IUPAC nucleotide code	Base
A	Adenine
C	Cytosine
G	Guanine

T (or U)	Thymine (or Uracil)
R	A or G
Y	C or T (U)
S	G or C
W	A or T (U)
K	G or T (U)
M	A or C
B	C or G or T (U)
D	A or G or T (U)
H	A or C or T (U)
V	A or C or G
N	any base
. or -	gap

Chapter- 9

Lignin

Lignin	
	
Identifiers	
CAS number	9005-53-2
Properties	
Molecular formula	$C_9H_{10}O_2$, $C_{10}H_{12}O_3$, $C_{11}H_{14}O_4$

Lignin or **lignen** is a complex chemical compound most commonly derived from wood, and an integral part of the secondary cell walls of plants and some algae. The term was introduced in 1819 by de Candolle and is derived from the Latin word *lignum*, meaning wood. It is one of the most abundant organic polymers on Earth, exceeded only by cellulose, employing 30% of non-fossil organic carbon and constituting from a quarter to a third of the dry mass of wood. As a biopolymer, lignin is unusual because of its heterogeneity and lack of a defined primary structure. Its most commonly noted function is the support through strengthening of wood (xylem cells) in trees.

Biological function

Lignin fills the spaces in the cell wall between cellulose, hemicellulose, and pectin components, especially in tracheids, sclereids and xylem. It is covalently linked to hemicellulose and thereby crosslinks different plant polysaccharides, conferring mechanical strength to the cell wall and by extension the plant as a whole. It is particularly abundant in compression wood but 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, whereas lignin is more hydrophobic. The crosslinking of polysaccharides by lignin is an obstacle for water absorption to the cell wall. Thus, lignin makes it possible for the plant's vascular tissue to conduct water efficiently. Lignin is present in all vascular plants, but not in bryophytes, supporting the idea that the original function of lignin was restricted to water transport. However, it is present in red algae, which seems to suggest that the common ancestor of plants and red algae also synthesised lignin. This would suggest that its original function was structural; it plays this role in the red alga *Calliarthron*, where it supports joints between calcified segments.

Ecological function

Lignin plays a significant role in the carbon cycle, sequestering atmospheric carbon into the living tissues of woody perennial vegetation. Lignin is one of the most slowly decomposing components of dead vegetation, contributing a major fraction of the material that becomes humus as it decomposes. The resulting soil humus generally increases the photosynthetic productivity of plant communities growing on a site as the site transitions from disturbed mineral soil through the stages of ecological succession, by providing increased cation exchange capacity in the soil and expanding the capacity of moisture retention between flood and drought conditions.

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. Mechanical, or high yield pulp used to make newsprint contains most of the lignin originally present in the wood. This lignin is responsible for newsprint yellowing with age. Lignin must be removed from the pulp before high quality bleached paper can be manufactured from it.

In sulfite pulping, lignin is removed from wood pulp as sulfonates. These lignosulfonates 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, xylitol sugar and humic acid

- Environmentally sustainable dust suppression agent for roads

The first investigations into commercial use of lignin were reported 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 was operated for many years as Marathon Chemicals. It is now known as LignoTech USA, Inc., and is owned by the Norwegian company, Borregaard, itself a subsidiary of the Norwegian conglomerate Orkla AS.

Lignin removed via the kraft process (sulfate pulping) is usually burned for its fuel value, providing energy to run the mill and its associated processes.

More recently, lignin extracted from shrubby willow has been successfully used to produce expanded polyurethane foam.

In 1998, a German company, Tecnaro, developed a process for turning lignin into a substance, called Arbofoam, which behaves identically to plastic for injection molding. Therefore, it can be used in place of plastic for several applications. When the item is discarded, it can be burned just like wood.

Structure

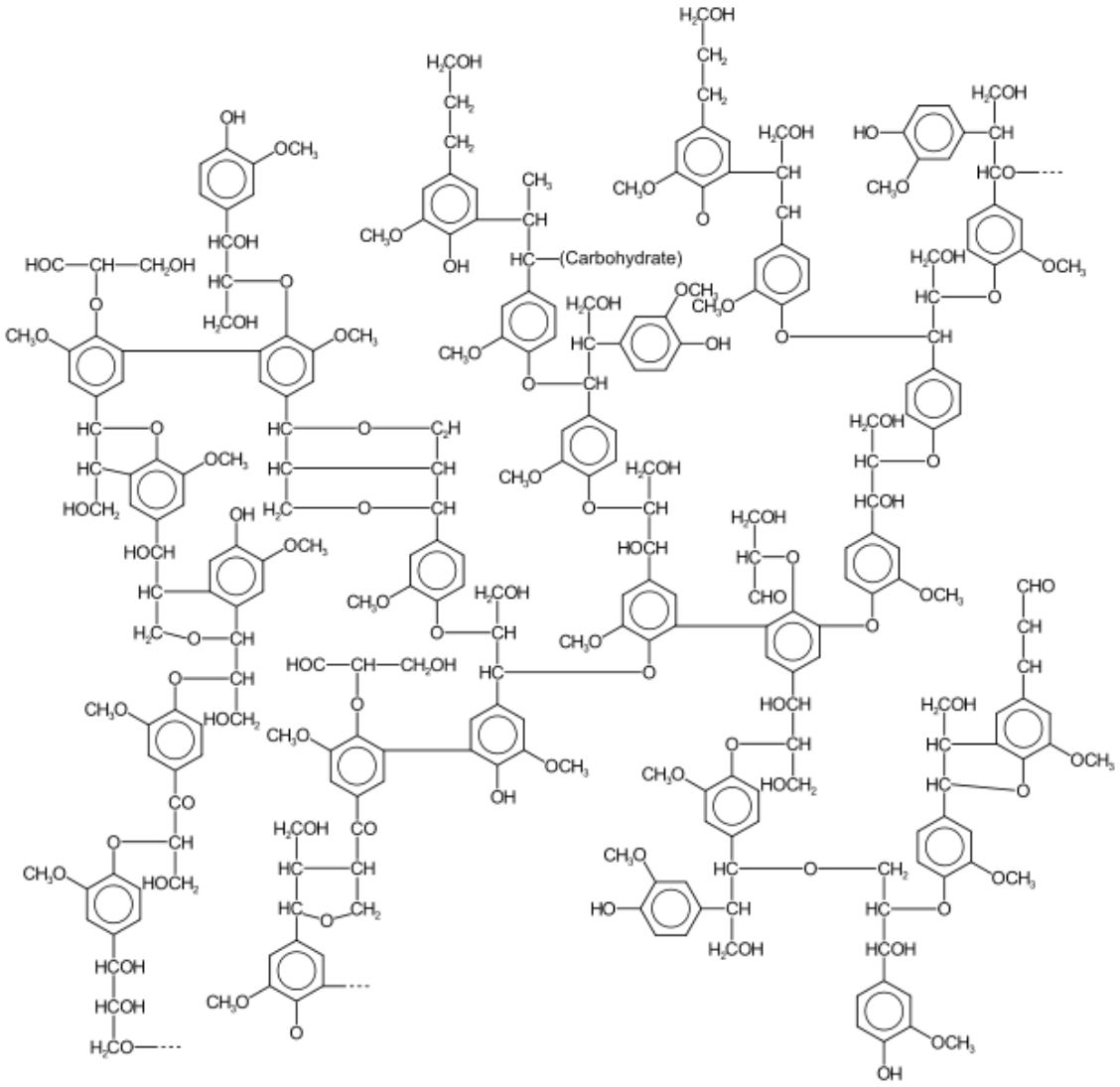


Fig. 1: An example of a possible lignin structure

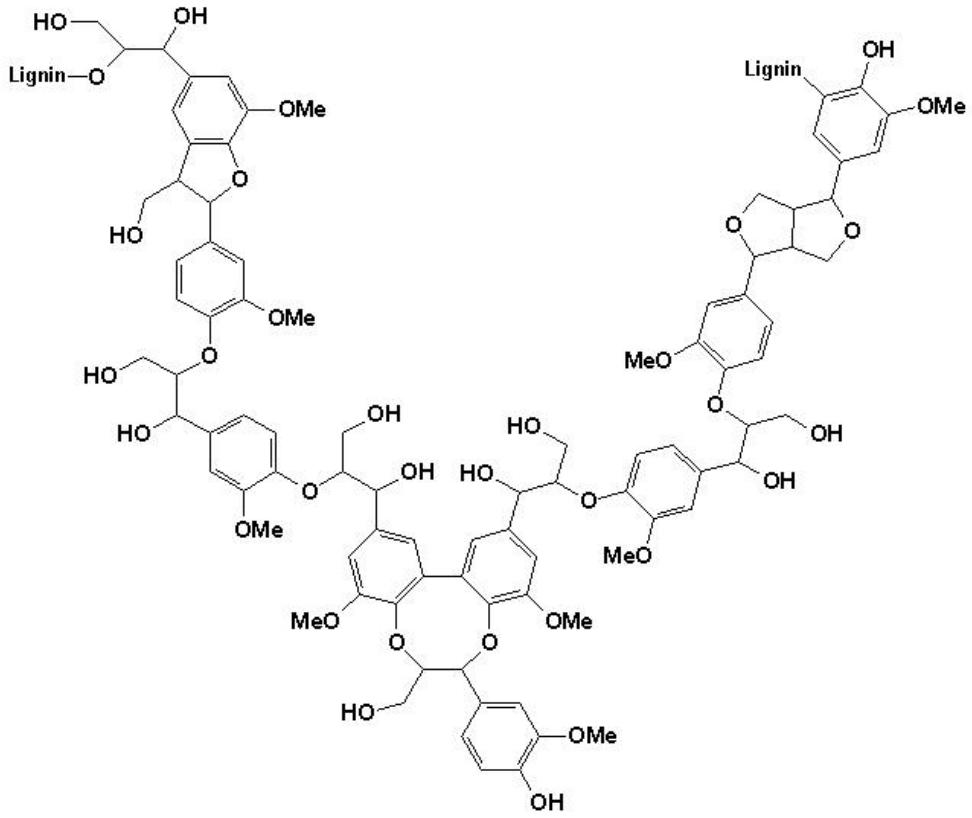


Fig. 2: A small piece of lignin polymer

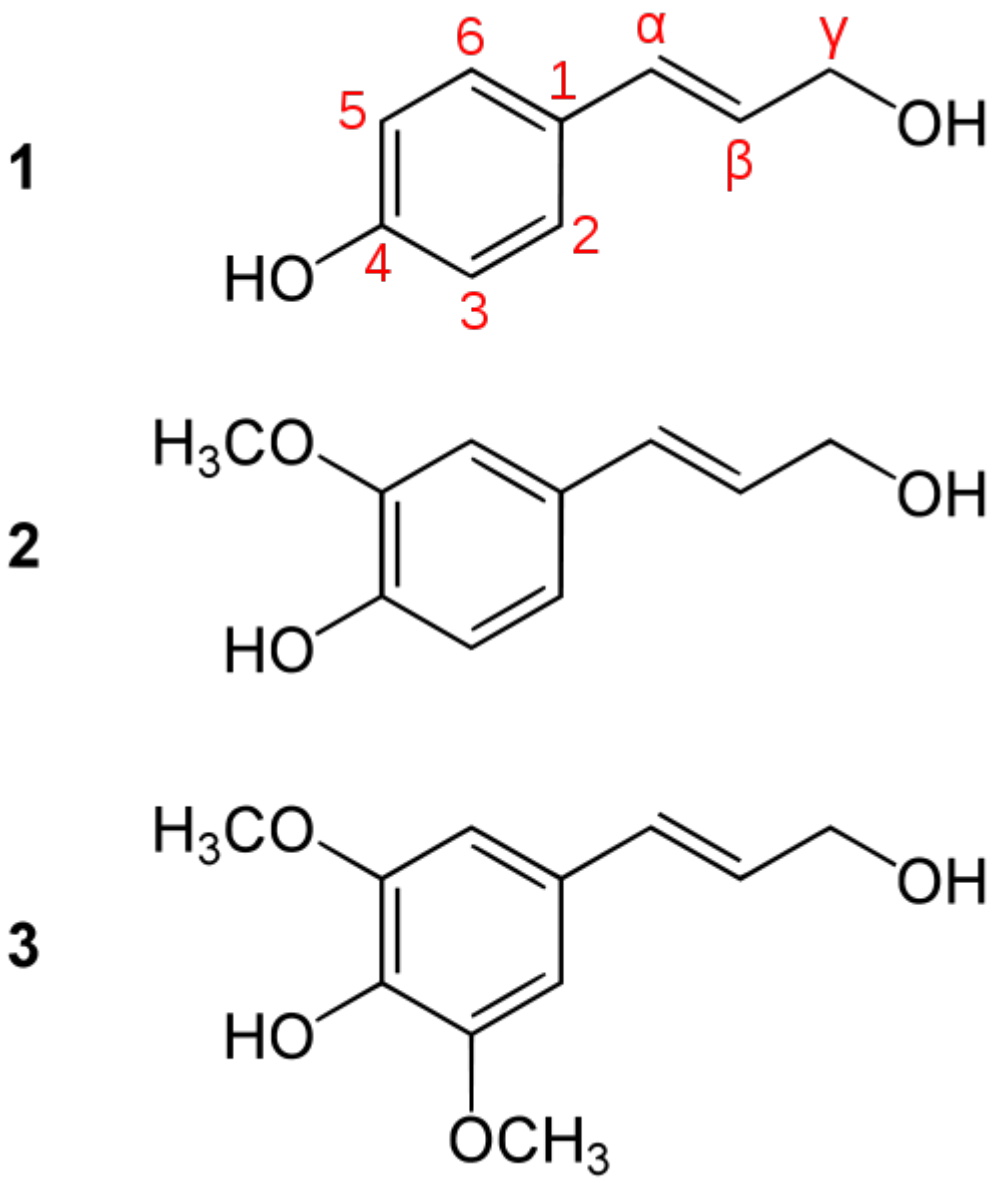


Fig. 3: The three common monolignols: paracoumaryl alcohol (1), coniferyl alcohol (2) and sinapyl alcohol (3)

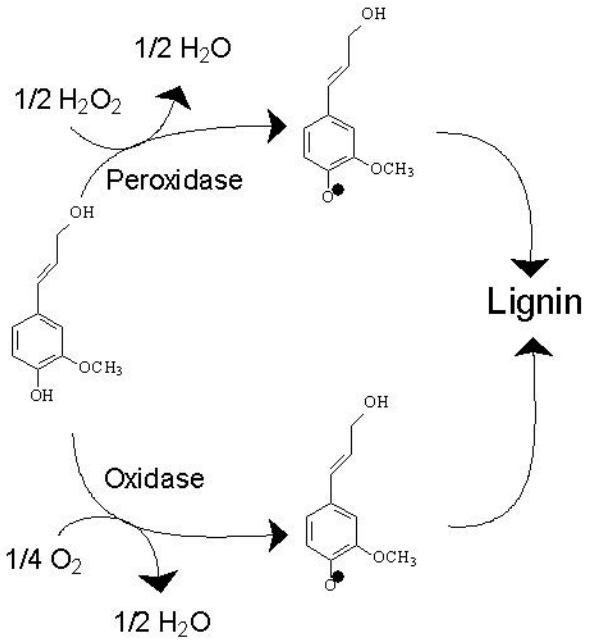


Fig. 4: Polymerisation of coniferyl alcohol to lignin. The reaction has two alternative routes catalysed by two different oxidative enzymes, peroxidases or oxidases.

Lignin is a cross-linked racemic macromolecule with molecular masses in excess of 10,000 u. It is relatively hydrophobic and aromatic in nature. The degree of polymerisation in nature is difficult to measure, since it is fragmented during extraction and the molecule consists of various types of substructures which appear to repeat in a haphazard manner. Different types of lignin have been described depending on the means of isolation.

There are three monolignol monomers, methoxylated to various degrees: *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol (Figure 3). These lignols are incorporated into lignin in the form of the phenylpropanoids *p*-hydroxyphenyl (H), guaiacyl (G), and syringal (S) respectively. Gymnosperms have a lignin that consists almost entirely of G with small quantities of H. That of dicotyledonous angiosperms is more often than not a mixture of G and S (with very little H), and monocotyledonous lignin is a mixture of all three. Many grasses have mostly G, while some palms have mainly S. All lignins contain small amounts of incomplete or modified monolignols, and other monomers are prominent in non-woody plants.

Biosynthesis

Lignin biosynthesis (Figure 4) begins in the cytosol with the synthesis of glycosylated monolignols from the amino acid phenylalanine. These first reactions are shared with the phenylpropanoid pathway. The attached glucose renders them water soluble and less toxic. Once transported through the cell membrane to the apoplast, the glucose is

removed and the polymerisation commences. Much about its anabolism is not understood even after more than a century of study.

The polymerisation step, that is a radical-radical coupling, 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. Low molecular weight oxidants might also be involved. The oxidative enzyme catalyses the formation of monolignol radicals. These radicals are often said to undergo uncatalyzed coupling to form the lignin polymer, but this hypothesis has been recently challenged. The alternative theory that involves an unspecified biological control is however not widely accepted.

Biodegradation

Lignin is indigestible by animal enzymes, but some fungi (such as the Dryad's saddle) and bacteria are able to secrete ligninases which can biodegrade the polymer. The details of the biodegradation are not well understood. The pathway depends on the type of wood decay - in fungi either brown rot, soft rot or white rot. The enzymes involved may employ free radicals for depolymerization reactions. Well understood lignolytic enzymes are manganese peroxidase, lignin peroxidase and cellobiose dehydrogenase. Furthermore, because of its cross-linking with the other cell wall components, it minimizes the accessibility of cellulose and hemicellulose to microbial enzymes. Hence, lignin is generally associated with reduced digestibility of the overall plant biomass, which helps defend against pathogens and pests.

Lignin degradation is made by micro-organisms like fungi and bacteria. Lignin peroxidase (also "ligninase", EC number 1.14.99) is a hemoprotein from the white-rot fungus *Phanerochaete chrysosporium* with a variety of lignin-degrading reactions, all dependent on hydrogen peroxide to incorporate molecular oxygen into reaction products. There are also several other microbial enzymes that are believed to be involved in lignin biodegradation, such as manganese peroxidase, laccase and Cellobiose dehydrogenase (acceptor).

Lignin-related chemicals can be further processed by bacteria. For instance, the aerobic Gram-negative soil bacterium *Sphingomonas paucimobilis* is able to degrade lignin-related biphenyl chemical compounds.

Pyrolysis

Pyrolysis of lignin during the combustion of wood or charcoal production yields a range of products, of which the most characteristic ones are methoxy phenols. Of those, the most important are guaiacol and syringol and their derivatives; their presence can be used to trace a smoke source to a wood fire. In cooking, lignin in the form of hardwood is an important source of these two chemicals which impart the characteristic aroma and taste to smoked foods.

Chapter- 10

Saccharides

Monosaccharide

Monosaccharides (from Greek *monos*: single, *sacchar*: sugar) are the most basic units of biologically important carbohydrates. They are the simplest form of sugar and are usually colorless, water-soluble, crystalline solids. Some monosaccharides have a sweet taste. Examples of monosaccharides include glucose (dextrose), fructose (levulose), galactose, xylose and ribose. Monosaccharides are the building blocks of disaccharides such as sucrose 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 have different chemical and physical properties.

Structure and nomenclature

With few exceptions (e.g., deoxyribose), monosaccharides have the chemical formula $C_x(H_2O)_y$, where x is at least 3. Monosaccharides can be classified by the number x of carbon atoms they contain: triose (3) tetrose (4), pentose (5), hexose (6), heptose (7), and so on.

The most important monosaccharide, glucose, is a hexose. Examples of heptoses include the ketoses mannoheptulose and sedoheptulose. Monosaccharides with eight or more carbons are rarely observed as they are quite unstable.

Linear-chain monosaccharides

Simple monosaccharides have a linear and unbranched carbon skeleton with one carbonyl (C=O) functional group, and one hydroxyl (OH) group on each of the remaining carbon atoms. Therefore, the molecular structure of a simple monosaccharide can be written as $H(CHOH)_n(C=O)(CHOH)_mH$, where $n+1+m = x$; so that its elemental formula is $C_xH_{2x}O_x$.

By convention, the carbon atoms are numbered from 1 to x along the backbone, starting from the end that is closest to the C=O group.

If the carbonyl is at position 1 (that is, *n* or *m* is zero), the molecule begins with an formyl group H(C=O)-, and is technically an aldehyde. In that case, the compound is termed an aldose. Otherwise, the molecule has a keto group, a carbonyl -(C=O)- between two carbons; then it is formally a ketone, and is termed a ketose. Ketoses of biological interest usually have the carbonyl at position 2.

The various classifications above can be combined, resulting in names like "aldohexose" and "ketotriose".

A more general nomenclature for open chain monosaccharides combines a Greek prefix to indicate the number of carbons (tri-, tetr-, pent-, hex-, etc.), with the suffixes '-ose' for aldoses and '-ulose' for ketoses. In the latter case, if the carbonyl is not at position 2, its position is indicated by a numeric infix. So, for example, $H(C=O)(CHOH)_4H$ is pentose, $H(CHOH)(C=O)(CHOH)_3H$ is pentulose, and $H(CHOH)_2(C=O)(CHOH)_2H$ is pent-3-ulose.

Open-chain stereoisomers

Two monosaccharides with equivalent molecular graphs (same chain length and same carbonyl position) may still be distinct stereoisomers, whose molecules differ in the three-dimensional arrangement of the bonds of certain atoms. This happens only if the molecule contains a stereogenic center, specifically a carbon atom that is chiral (connected to four distinct molecular sub-structures). Those four bonds can have any of two configurations in space distinguished by their handedness. In a simple open-chain monosaccharide, every carbon is chiral except the first and the last atoms of the chain, and (in ketoses) the carbon with the keto group.

For example, the triketose H(CHOH)(C=O)(CHOH)H (glycerone, dihydroxyacetone) has no stereogenic center, and therefore exists as a single stereoisomer. The other triose, the aldose $H(C=O)(CHOH)_2H$ (glyceraldehyde), has one chiral carbon — the central one, number 2 — which is bonded to groups -H, -OH, $-C(OH)H_2$, and -(C=O)H. Therefore, it exists as two stereoisomers whose molecules are mirror images of each other (like a left and a right glove). Monosaccharides with four or more carbons may contain multiple chiral carbons, so they typically have more than two stereoisomers. The number of distinct stereoisomers with the same diagram is bounded by 2^c, where c is the number of chiral carbons.

The Fischer projection is a systematic way of drawing the skeletal formula of an acyclic monosaccharide so that the handedness of each chiral carbon is well specified. Each stereoisomer of a simple open-chain monosaccharide can be identified by the positions (right or left) in the Fischer diagram of the chiral hydroxyls (the hydroxyls attached to the chiral carbons).

Most stereoisomers are themselves chiral (distinct from their mirror images). In the Fischer projection, two mirror-image isomers differ by having the positions of all chiral hydroxyls reversed right-to-left. Mirror-image isomers are chemically identical in non-

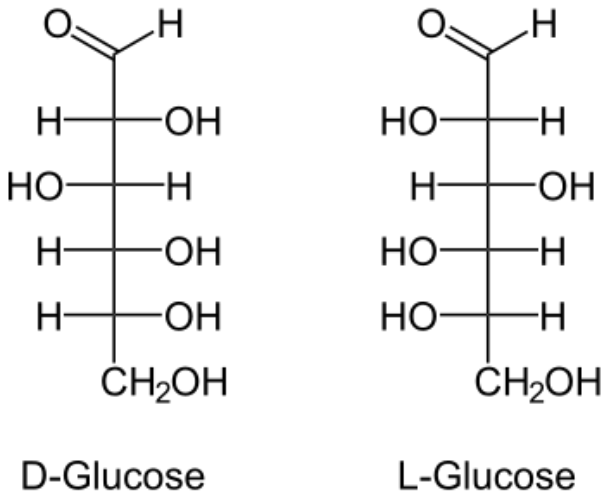
chiral environments, but usually have very different biochemical properties and occurences in nature.

While most stereoisomers can be arranged in pairs of mirror-image forms, there are some non-chiral stereoisomers which are identical to their mirror images, in spite of having chiral centers. This happens whenever the molecular graph is symmetrical, as in the 3-ketopentoses $H(CHOH)_2(CO)(CHOH)_2H$, and the two halves are mirror images of each other. In that case, mirroring is equivalent to a half-turn rotation. For this reason, there are only three distinct 3-ketopentose stereoisomers, even though the molecule has two chiral carbons.

Distinct stereoisomers that are not mirror-images of each other usually have different chamical properties, even in non-chiral environments. Therefore, each mirror pair and each non-chiral stereoisomer may be given a specific monosaccharide name. For example, there are 16 distinct aldohexose stereoisomers, but the name "glucose" means a specific pair of mirror-image aldohexoses. In the Fischer projection, one of the two glucose isomers has the hydroxyl at left on C3, and at right on C4 and C5; while the other isomer has the reversed pattern. These specific monosaccharide names have conventional three-letter abbreviations, like 'Glu' for glucose and 'Thr' for threose.

The D/L nomenclature

Like many chiral molecules, the two stereoisomers of glyceraldehyde will gradually rotate the polarization direction of linearly polarized light as it passes through it, even in solution. The two stereoisomers are identified with the prefixes 'D-' and 'L-', according to the sense of rotation: D-glyceraldehyde is dextrorotary (rotates the polarization axis clockwise), while L-glyceraldehyde is levorotary (rotates it counterclockwise).



D- and L-glucose.

The 'D-' and 'L-' prefixes are also used with other monosaccharides, to distinguish two particular stereoisomers which are mirror-images of each other. For this purpose, one

considers the chiral carbon that is furthest removed from the C=O group. Its four bonds must connect to -H, -OH, -C(OH)H, and to the rest of the molecule. If the molecule can be rotated in space so that the directions of those four groups match those of the analog groups in D-glyceraldehyde's C2, then the isomer receives the 'D-' prefix, otherwise it receives the 'L-' prefix.

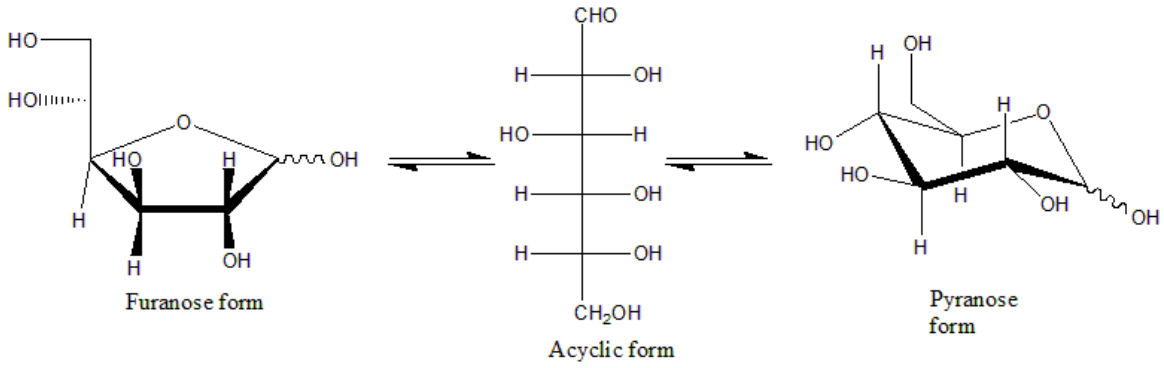
In the Fischer projection, the 'D-' and 'L-' prefixes specifies the configuration at the carbon atom that is second from bottom: 'D-' if the hydroxyl is on the right side, and 'L-' if it is on the left side.

Note that the 'D-' and 'L-' prefixes do not indicate the direction of rotation of polarized light, which is a combined effect of the arrangement at all chiral centers. However, the two isomers will always rotate the light in opposite directions, at the same rate.

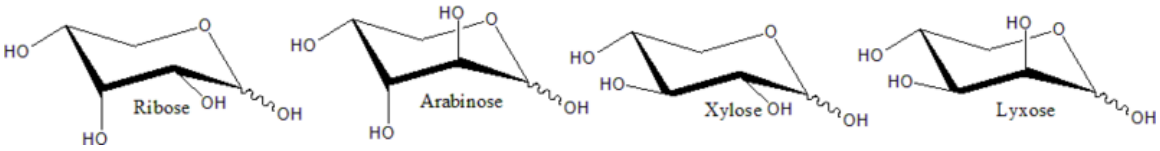
Cyclic isomers

A monosaccharide often switches from the acyclic (open-chain) form to a cyclic form, through a nucleophilic addition reaction between the carbonyl group and one of the hydroxyls of the same molecule. The reaction creates a ring of carbon atoms closed by one bridging oxygen atom. The resulting molecule has an hemiacetal or hemiketal group, depending on whether the linear form was an aldose or a ketose. The reaction is easily reversed, yielding the original open-chain form.

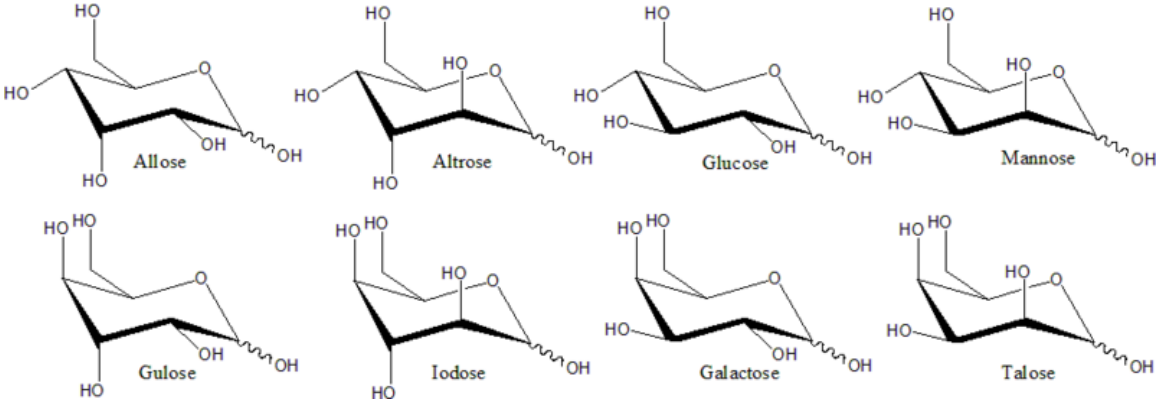
In these cyclic forms, the ring usually has 5 or 6 atoms. These forms are called furanoses and pyranoses, respectively — by analogy with furan and pyran, the simplest compounds with the same carbon-oxygen ring (although they lack the double bonds of these two molecules). For example, the aldohexose glucose may form a hemiacetal linkage between the hydroxyl on carbon 1 and the oxygen on carbon 4, yielding a molecule with a 5-membered ring, called glucofuranose. The same reaction can take place between carbons 1 and 5 to form a molecule with a 6-membered ring, called glucopyranose. Cyclic forms with a 7-atom ring (the same of oxepane), rarely encountered, are called septanoses.



Conversion between the furanose, acyclic, and pyranose forms of D-glucose.



Pyranose forms of some pentose sugars.



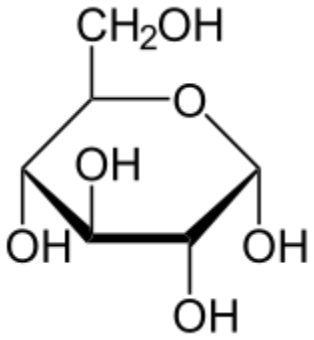
Pyranose forms of some hexose sugars.

For many monosaccharides (including glucose), the cyclic forms predominate, in the solid state and in solutions, and therefore the same name commonly is used for the open- and closed-chain isomers. Thus, for example, the term "glucose" may signify glucofuranose, glucopyranose, the open-chain form, or a mixture of the three.

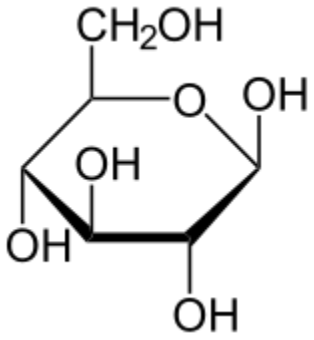
Cyclization creates a new stereogenic center at the carbonyl-bearing carbon The -OH group that replaces the carbonyl's oxygen may end up in two distinct positions relative to the ring's midplane. Thus each open-chain monosaccharide yields two cyclic isomers (anomers), denoted by the prefixes 'α-' and 'β-'. The molecule can change between these two forms by a process called mutarotation, that consists in a reversal of the ring-forming reaction followed by another ring formation.

Haworth projection

The three-dimensional structure of a monosaccharides in cyclic form is usually represented by its Haworth projection. In this diagram, the α-isomer has the OH- of the anomeric carbon below the plane of the carbon atoms, and the β-isomer has the OH- of the anomeric carbon above the plane. Pyranoses typically adopt a chair conformation, similar to cyclohexane. In this conformation the α-isomer has the OH- of the anomeric carbon in an axial position, whereas the β-isomer has the OH- of the anomeric carbon in equatorial position.



α-D-Glucopyranose



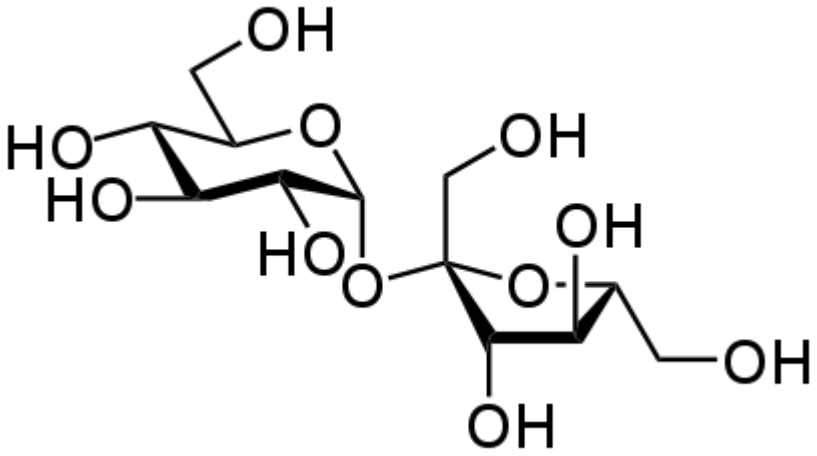
β-D-Glucopyranose

Derivatives

A large number of biologically important modified monosaccharides exist:

- Amino sugars such as:
  - Galactosamine
  - Glucosamine
  - Sialic acid
  - *N*-Acetylglucosamine
- Sulfosugars such as:
  - Sulfoquinovose

Disaccharide



Sucrose, a common disaccharide

A **disaccharide** or *biose* is the carbohydrate formed when two monosaccharides undergo a condensation reaction which involves the elimination of a small molecule, such as water, from the functional groups only. Like monosaccharides, disaccharides also dissolve in water, taste sweet and are called sugars.

'Disaccharide' is one of the four chemical groupings of carbohydrates (monosaccharide, disaccharide, oligosaccharide, and polysaccharide).

Classification

There are two different types of disaccharides: reducing disaccharides, in which one monosaccharide, the reducing sugar, still has a free hemiacetal unit; and non-reducing disaccharides, in which the components bond through an acetal linkage between their anomeric centers and neither monosaccharide has a free hemiacetal unit. Cellobiose and maltose are examples of reducing disaccharides. Sucrose and trehalose are examples of non-reducing disaccharides.

Formation

Disaccharides are formed when two monosaccharides are joined together and a molecule of water is removed. For example; milk sugar (lactose) is made from glucose and galactose whereas the sugar from sugar cane and sugar beets (sucrose) is made from glucose and fructose.

The two monosaccharides are bonded via a dehydration reaction (also called a condensation reaction or dehydration synthesis) that leads to the loss of a molecule of water and formation of a glycosidic bond.

Properties

The glycosidic bond can be formed between any hydroxyl group on the component monosaccharide. So, even if both component sugars are the same (e.g., glucose), different bond combinations (regiochemistry) and stereochemistry (*alpha*- or *beta*-) result in disaccharides that are diastereoisomers with different chemical and physical properties.

Depending on the monosaccharide constituents, disaccharides are sometimes crystalline, sometimes water-soluble, and sometimes sweet-tasting and sticky-feeling.

Common disaccharides

Disaccharide	**Unit 1**	**Unit 2**	**Bond**
Sucrose (*table sugar*, *cane sugar*, *beet sugar*, or *saccharose*)	glucose	fructose	α(1→2)
Lactulose	galactose	fructose	β(1→4)
Lactose (*milk sugar*)	galactose	glucose	β(1→4)
Maltose	glucose	glucose	α(1→4)
Trehalose	glucose	glucose	α(1→1)α
Cellobiose	glucose	glucose	β(1→4)

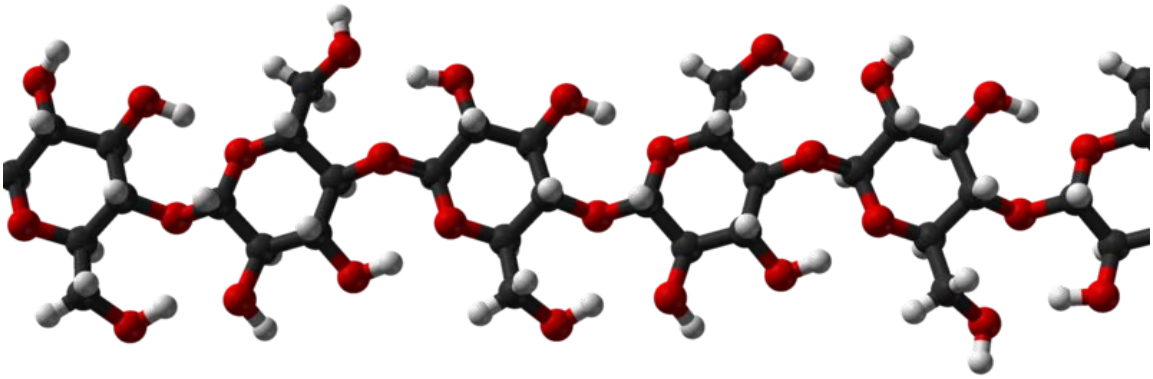
Maltose and cellobiose are hydrolysis products of the polysaccharides, starch and cellulose, respectively.

Less common disaccharides include:

Disaccharide	**Units**	**Bond**
Kojibiose	two glucose monomers	α(1→2)
Nigerose	two glucose monomers	α(1→3)
Isomaltose	two glucose monomers	α(1→6)
β,β-Trehalose	two glucose monomers	β(1→1)β
α,β-Trehalose	two glucose monomers	α(1→1)β
Sophorose	two glucose monomers	β(1→2)
Laminaribiose	two glucose monomers	β(1→3)
Gentiobiose	two glucose monomers	β(1→6)
Turanose	a glucose monomer and a fructose monomer	α(1→3)
Maltulose	a glucose monomer and a fructose monomer	α(1→4)
Palatinose	a glucose monomer and a fructose	α(1→6)

	monomer	
Gentiobiulose	a glucose monomer and a fructose monomer	β(1→6)
Mannobiose	two mannose monomers	either α(1→2), α(1→3), α(1→4), or α(1→6)
Melibiose	a galactose monomer and a glucose monomer	α(1→6)
Melibiulose	a galactose monomer and a fructose monomer	α(1→6)
Rutinose	a rhamnose monomer and a glucose monomer	α(1→6)
Rutinulose	a rhamnose monomer and a fructose monomer	β(1→6)
Xylobiose	two xylopyranose monomers	β(1→4)

Polysaccharide



3D structure of cellulose, a beta-glucan polysaccharide.

Polysaccharides are polymeric carbohydrate structures, formed of repeating units (either mono- or di-saccharides) joined together by glycosidic bonds. These structures are often linear, but may contain various degrees of branching. Polysaccharides are often quite heterogeneous, containing slight modifications of the repeating unit. Depending on the structure, these macromolecules can have distinct properties from their monosaccharide building blocks. They may be amorphous or even insoluble in water.

When all the monosaccharides in a polysaccharide are the same type the polysaccharide is called a *homopolysaccharide*, but when more than one type of monosaccharide is present they are called *heteropolysaccharides*.

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

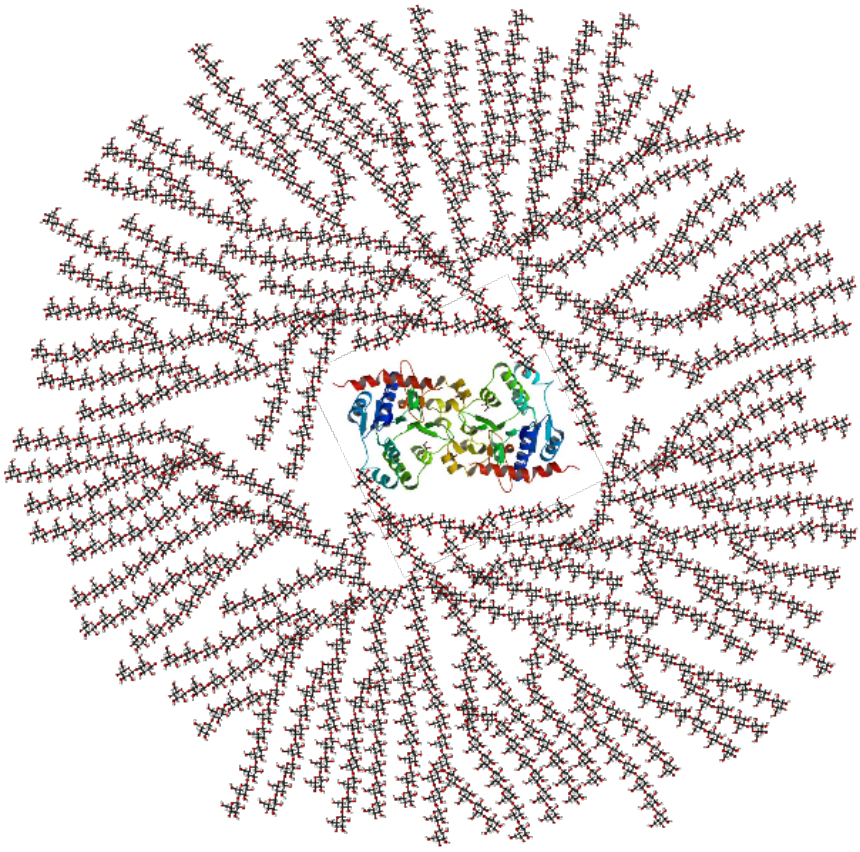
Polysaccharides have a general formula of $C_x(H_2O)_y$ where x is usually a large number between 200 and 2500. Considering that the repeating units in the polymer backbone are often six-carbon monosaccharides, the general formula can also be represented as $(C_6H_{10}O_5)_n$ where $40 \leq n \leq 3000$.

Storage polysaccharides

Starches

Starches are glucose polymers in which glucopyranose units are bonded by *alpha*-linkages. It is made up of a mixture of Amylose (15–20%) and Amylopectin (80–85%). Amylose consists of a linear chain of several hundred glucose molecules and Amylopectin is a branched molecule made of several thousand glucose units (every chain 24–30 glucose unit). Starches are insoluble in water. They can be digested by hydrolysis, catalyzed by enzymes called amylases, which can break the *alpha*-linkages (glycosidic bonds). 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. The formation of starches are the way that plants store glucose.

Glycogen



Glycogen.

Glycogen is a polysaccharide that is found in animals and is composed of a branched chain of glucose residues. It is stored in liver and muscles.

Structural polysaccharides

Cellulose

The structural component 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.

Chitin

Chitin is one of many naturally occurring polymers. It is one of the most abundant natural materials in the world. Over time it is bio-degradable in the natural environment. Its

breakdown may be catalyzed by enzymes called chitinases, secreted by microorganisms such as bacteria and fungi, and produced by some plants. Some of these microorganisms have receptors to simple sugars from the decomposition of chitin. If chitin is detected, they then produce enzymes to digest it by cleaving the glycosidic bonds in order to convert it to simple sugars and ammonia.

Chemically, chitin is closely related to chitosan (a more water-soluble derivative of chitin). It is also closely related to cellulose in that it is a long unbranched chain of glucose derivatives. Both materials contribute structure and strength, protecting the organism.

Arabinoxylans

Arabinoxylans are the copolymers of two pentose sugars - arabinose and xylose.

Acidic polysaccharides

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

Bacterial polysaccharides

Bacterial polysaccharides represent a diverse range of macromolecules that include peptidoglycan, lipopolysaccharides, capsules and exopolysaccharides; compounds whose functions range from structural cell-wall components (e.g. peptidoglycan), and important virulence factors (e.g. Poly-N-acetylglucosamine in *S. aureus*), to permitting the bacterium to survive in harsh environments (e.g. *Pseudomonas aeruginosa* in the human lung). Polysaccharide biosynthesis is a tightly regulated, energy-intensive process and understanding the subtle interplay between the regulation and energy conservation, polymer modification and synthesis, and the external ecological functions is a huge area of research. The potential benefits are enormous and should enable for example the development of novel antibacterial strategies (e.g. new antibiotics and vaccines) and the commercial exploitation to develop novel applications.

Bacterial capsular 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 to 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, welan gum, gellan gum, diutan gum and pullulan.

Most of these polysaccharides exhibit interesting and very useful visco-elastic properties when dissolved in water at very low levels. This gives many foods and various liquid consumer products, like lotions, cleaners and paints, for example, a viscous appearance when stationary, but fluidity when the slightest shear is applied, such as when wiped, poured or brushed. This property is referred to as pseudoplasticity, or shear thinning.

Viscosity of Welan gum

Shear Rate (rpm)	Viscosity (cP)
0.3	23330
0.5	16000
1	11000
2	5500
4	3250
5	2900
10	1700
20	900
50	520

100	310

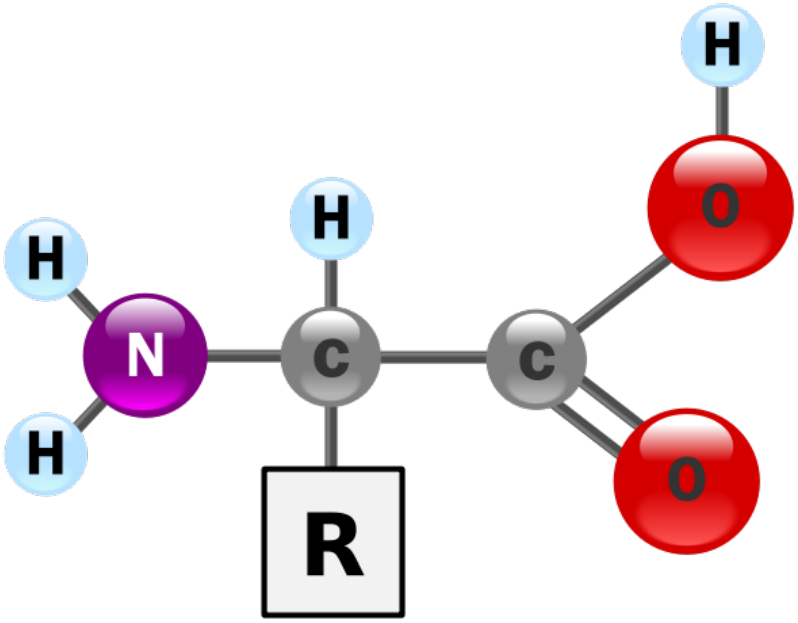
Aqueous solutions of the polysaccharide alone have a curious behavior when stirred. After stopping, the swirl continues due to momentum, then stops, and then reverses direction briefly. This recoil demonstrates the elastic effect of the polysaccharide chains previously streched in solution, returning to their relaxed state.

Cell-surface polysaccharides play diverse roles in bacterial ecology and physiology. They serve as a barrier between the cell wall and the environment, mediate host-pathogen interactions, and form structural components of biofilms. These polysaccharides are synthesized from nucleotide-activated precursors (called nucleotide sugars) and, in most cases, all the enzymes necessary for biosynthesis, assembly and transport of the completed polymer are encoded by genes organized in dedicated clusters within the genome of the organism. Lipopolysaccharide is one of the most important cell-surface polysaccharides, as it plays a key structural role in outer membrane integrity, as well as being an important mediator of host-pathogen interactions.

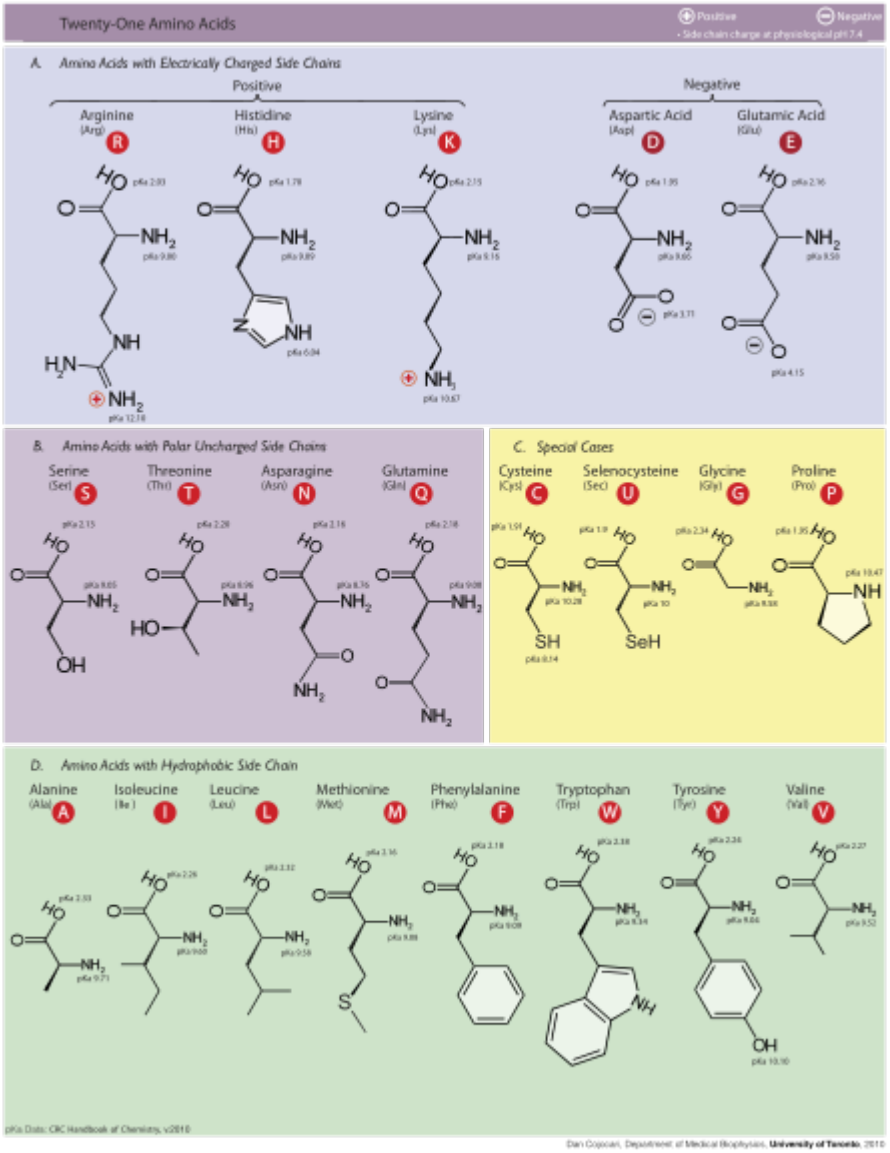
The enzymes that make the *A-band* (homopolymeric) and *B-band* (heteropolymeric) O-antigens have been identified and the metabolic pathways defined. The exopolysaccharide alginate is a linear copolymer of β-1,4-linked D-mannuronic acid and L-guluronic acid residues, and is responsible for the mucoid phenotype of late-stage cystic fibrosis disease. The *pel* and *psl* loci are two recently discovered gene clusters that also encode exopolysaccharides found to be important for biofilm formation. Rhamnolipid is a biosurfactant whose production is tightly regulated at the transcriptional level, but the precise role that it plays in disease is not well understood at present. Protein glycosylation, particularly of pilin and flagellin, is a recent focus of research by several groups and it has been shown to be important for adhesion and invasion during bacterial infection.

Chapter- 11

Amino Acid



The generic structure of an alpha amino acid



The 21 amino acids found in eukaryotes, grouped according to their side chains' pKa's and charge at physiological pH 7.4

Amino acids are molecules containing an amine group, a carboxylic acid group and a side chain that varies between different amino acids. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen. They are particularly important in biochemistry, where the term usually refers to *alpha-amino acids*.

An alpha-amino acid has the generic formula $H_2NCHRCOOH$, where R is an organic substituent; the amino group is attached to the carbon atom immediately adjacent to the carboxylate group (the α–carbon). Other types of amino acid exist when the amino group is attached to a different carbon atom; for example, in gamma-amino acids (such as gamma-amino-butyric acid) the carbon atom to which the amino group attaches is

separated from the carboxylate group by two other carbon atoms. The various alpha-amino acids differ in which side chain (R-group) is attached to their alpha carbon, and can vary in size from just one hydrogen atom in glycine to a large heterocyclic group in tryptophan.

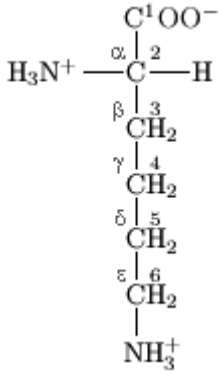
Amino acids are critical to life, and have many functions in metabolism. One particularly important function is to serve as the building blocks of proteins, which are linear chains of amino acids. Amino acids can be linked together in varying sequences to form a vast variety of proteins. Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or standard amino acids Of these, 20 are encoded by the universal genetic code. Eight standard amino acids are called "essential" for humans because they cannot be created from other compounds by the human body, and so must be taken in as food.

Due to their central role in biochemistry, amino acids are important in nutrition and are commonly used in food technology and industry. In industry, applications include the production of biodegradable plastics, drugs, and chiral catalysts.

History

The first few amino acids were discovered in the early 19th century. In 1806, the French chemists Louis-Nicolas Vauquelin and Pierre Jean Robiquet isolated a compound in asparagus that proved to be asparagine, the first amino acid to be discovered. Another amino acid that was discovered in the early 19th century was cystine, in 1810, although its monomer, cysteine, was discovered much later, in 1884. Glycine and leucine were also discovered around this time, in 1820. Usage of the term *amino acid* in the English language is from 1898.

General structure



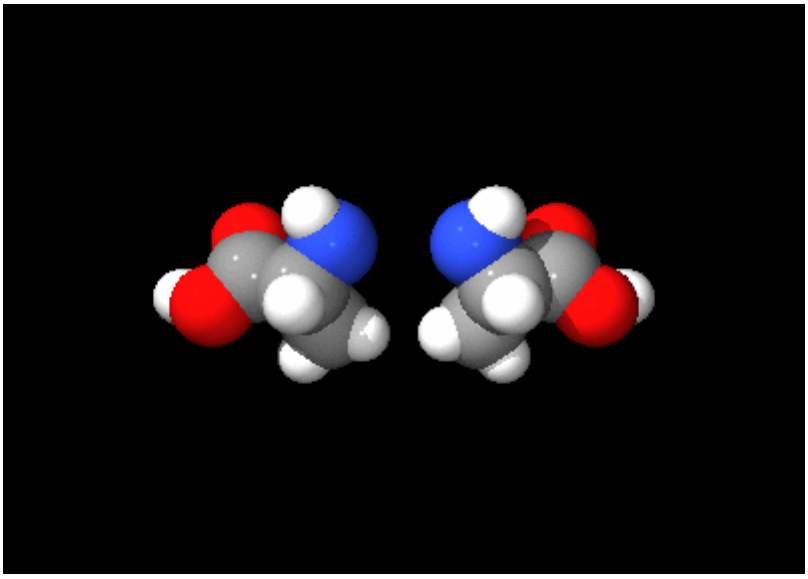
Lysine with the carbon atoms in the side chain labeled

In the structure shown at the top of the page, **R** represents a side chain specific to each amino acid. The carbon atom next to the carboxyl group is called the α–carbon and amino acids with a side chain bonded to this carbon are referred to as *alpha amino acids*. These

are the most common form found in nature. In the alpha amino acids, the α–carbon is a chiral carbon atom, with the exception of glycine. In amino acids that have a carbon chain attached to the α–carbon (such as lysine, shown to the right) the carbons are labeled in order as α, β, γ, δ, and so on. In some amino acids, the amine group is attached to the β or γ-carbon, and these are therefore referred to as *beta* or *gamma amino acids*.

Amino acids are usually classified by the properties of their side chain into four groups. The side chain can make an amino acid a weak acid or a weak base, and a hydrophile if the side chain is polar or a hydrophobe if it is nonpolar. The chemical structures of the 22 standard amino acids, along with their chemical properties, are described more fully in proteinogenic amino acids.

The phrase "branched-chain amino acids" or BCAA refers to the amino acids having aliphatic side chains that are non-linear; these are leucine, isoleucine, and valine. Proline is the only proteinogenic amino acid whose side group links to the α-amino group and, thus, is also the only proteinogenic amino acid containing a secondary amine at this position. Chemically, proline is therefore an imino acid since it lacks a primary amino group, although it is still classed as an amino acid in the current biochemical nomenclature, and may also be called an "N-alkylated alpha-amino acid".

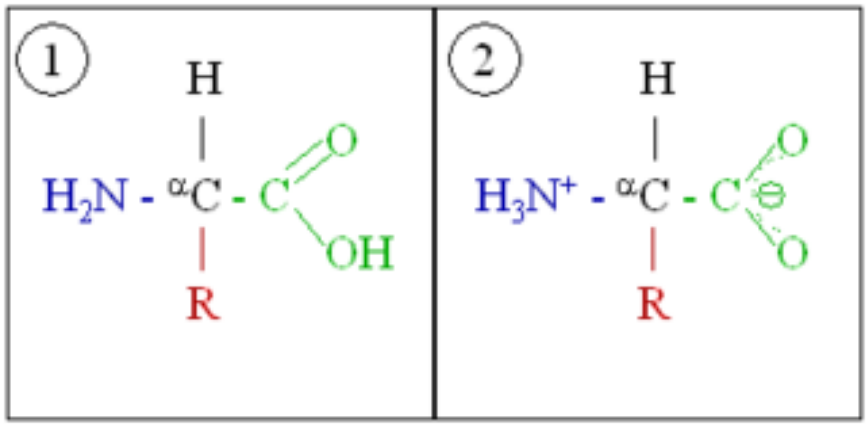


The two optical isomers of alanine, D-Alanine and L-Alanine

Isomerism

Of the standard α-amino acids, all but glycine can exist in either of two optical isomers, called L or D amino acids, which are mirror images of each other. While L-amino acids represent all of the amino acids found in proteins during translation in the ribosome, D-amino acids are found in some proteins produced by enzyme posttranslational modifications after translation and translocation to the endoplasmic reticulum, as in exotic sea-dwelling organisms such as cone snails. They are also abundant components of

the peptidoglycan cell walls of bacteria, and D-serine may act as a neurotransmitter in the brain. The L and D convention for amino acid configuration refers not to the optical activity of the amino acid itself, but rather to the optical activity of the isomer of glyceraldehyde from which that amino acid can theoretically be synthesized (D-glyceraldehyde is dextrorotary; L-glyceraldehyde is levorotary). Alternatively, the *(S)* and *(R)* designators are used to indicate the absolute stereochemistry. Almost all of the amino acids in proteins are *(S)* at the α carbon, with cysteine being *(R)* and glycine non-chiral. Cysteine is unusual since it has a sulfur atom at the second position in its side-chain, which has a larger atomic mass than the groups attached to the first carbon which is attached to the α-carbon in the other standard amino acids, thus the *(R)* instead of *(S)*.

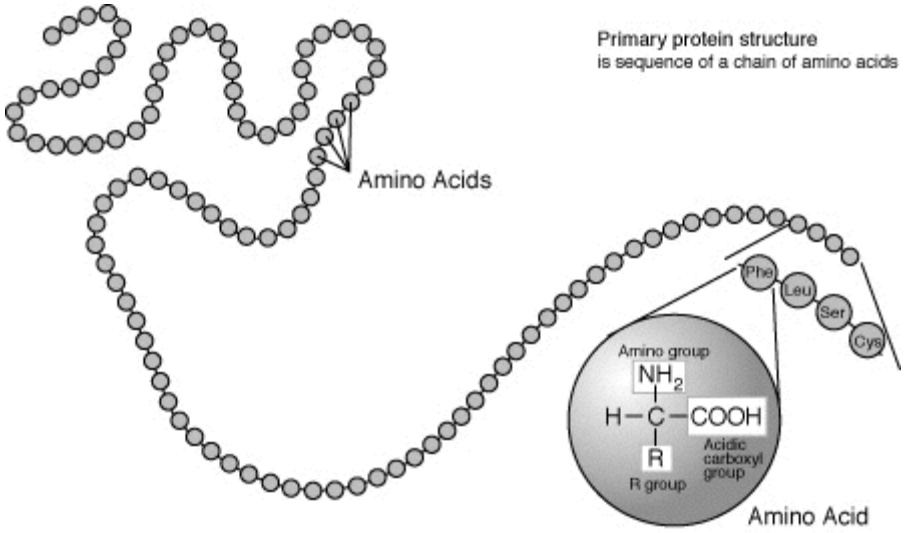


An amino acid in its (1) unionized and (2) zwitterionic forms

Zwitterions

The amine and carboxylic acid functional groups found in amino acids allow it to have amphiprotic properties. At a certain pH, known as the isoelectric point, an amino acid has no overall charge since the number of protonated ammonia groups (positive charges) and deprotonated carboxylate groups (negative charges) are equal. The amino acids all have different isoelectric points. The ions produced at the isoelectric point have both positive and negative charges and are known as a *zwitterion,* which comes from the German word *Zwitter* meaning "hermaphrodite" or "hybrid". Amino acids can exist as zwitterions in solids and in polar solutions such as water, but not in the gas phase. Zwitterions have minimal solubility at their isolectric point and an amino acid can be isolated by precipitating it from water by adjusting the pH to its particular isoelectric point.

Occurrence and functions in biochemistry

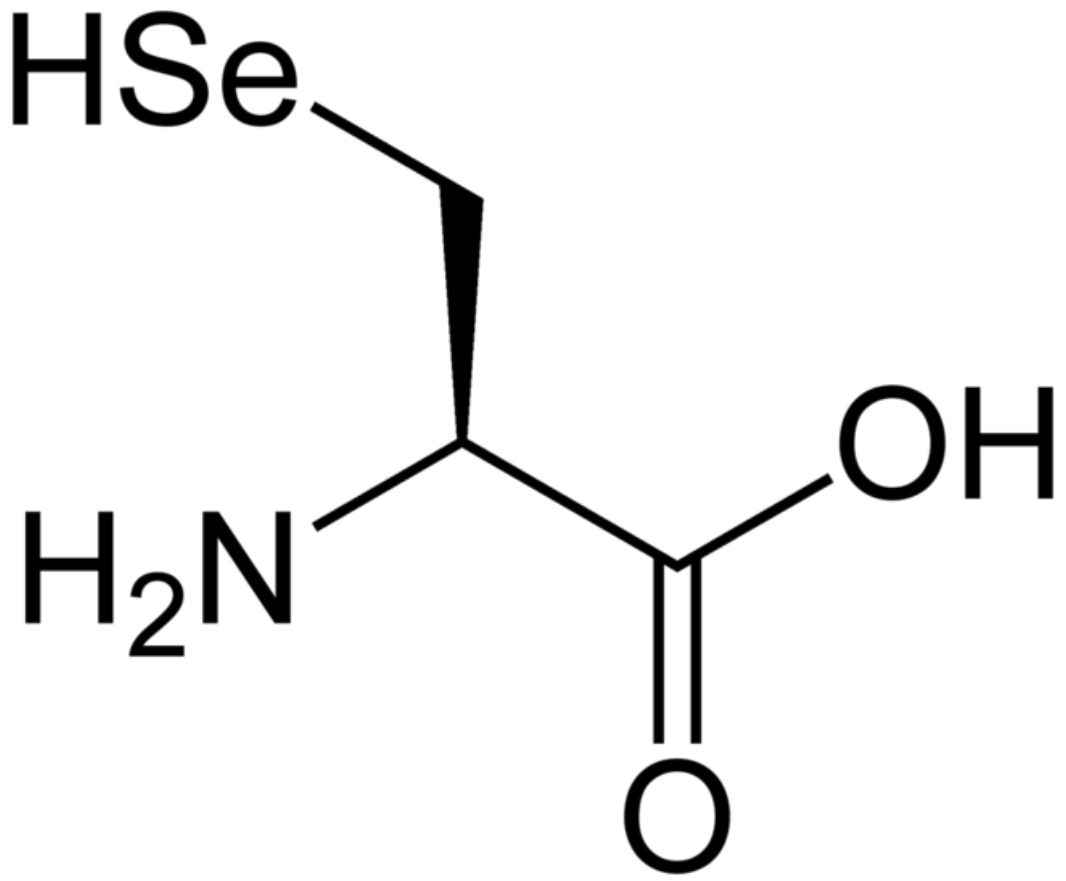


A polypeptide is an unbranched chain of amino acids.

Standard amino acids

Amino acids are the structural units that make up proteins. They join together to form short polymer chains called peptides or longer chains called either polypeptides or proteins. These polymers are linear and unbranched, with each amino acid within the chain attached to two neighboring amino acids. The process of making proteins is called *translation* and involves the step-by-step addition of amino acids to a growing protein chain by a ribozyme that is called a ribosome. The order in which the amino acids are added is read through the genetic code from an mRNA template, which is a RNA copy of one of the organism's genes.

Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or standard amino acids. Of these, 20 are encoded by the universal genetic code. The remaining 2, selenocysteine and pyrrolysine, are incorporated into proteins by unique synthetic mechanisms. Selenocysteine is incorporated when the mRNA being translated includes a SECIS element, which causes the UGA codon to encode selenocysteine instead of a stop codon. Pyrrolysine is used by some methanogenic archaea in enzymes that they use to produce methane. It is coded for with the codon UAG, which is normally a stop codon in other organisms.

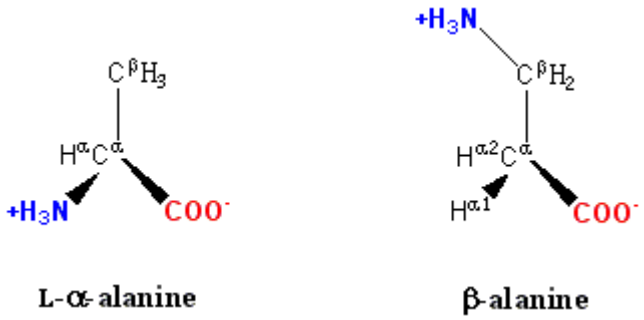


The amino acid selenocysteine

Non-standard amino acids

Aside from the 22 standard amino acids, there are a vast number of other amino acids that are called *non-proteinogenic* or *non-standard*. Those are either not found in proteins (for example carnitine, GABA, or L-DOPA), or are not produced directly and in isolation by standard cellular machinery (for example hydroxyproline and selenomethionine).

Non-standard amino acids that are found in proteins are formed by post-translational modification, which is modification after translation during protein synthesis. These modifications are often essential for the function or regulation of a protein; for example, the carboxylation of glutamate allows for better binding of calcium cations, and the hydroxylation of proline is critical for maintaining connective tissues. Another example is the formation of hypusine in the translation initiation factor EIF5A, through modification of a lysine residue. Such modifications can also determine the localization of the protein, e.g., the addition of long hydrophobic groups can cause a protein to bind to a phospholipid membrane.



β-alanine and its α-alanine isomer

Some nonstandard amino acids are not found in proteins. Examples include lanthionine, 2-aminoisobutyric acid, dehydroalanine and the neurotransmitter gamma-aminobutyric acid. Nonstandard amino acids often occur as intermediates in the metabolic pathways for standard amino acids — for example ornithine and citrulline occur in the urea cycle, part of amino acid catabolism (see below). A rare exception to the dominance of α-amino acids in biology is the β-amino acid beta alanine (3-aminopropanoic acid), which is used in plants and microorganisms in the synthesis of pantothenic acid (vitamin B_5), a component of coenzyme A.

In human nutrition

When taken up into the human body from the diet, the 22 standard amino acids are either used to synthesize proteins and other biomolecules, or are oxidized to urea and carbon dioxide as a source of energy. The oxidation pathway starts with the removal of the amino group by a transaminase, the amino group is then fed into the urea cycle. The other product of transamidation is a keto acid that enters the citric acid cycle. Glucogenic amino acids can also be converted into glucose, through gluconeogenesis.

Pyrrolysine trait is restricted to several microbes, and only one organism has both Pyl and Sec. Of the 22 standard amino acids, 8 are called essential amino acids because the human body cannot synthesize them from other compounds at the level needed for normal growth, so they must be obtained from food. In addition, cysteine, taurine, tyrosine, histidine and arginine are semiessential amino-acids in children, because the metabolic pathways that synthesize these amino acids are not fully developed. The amounts required also depend on the age and health of the individual, so it is hard to make general statements about the dietary requirement for some amino acids.

Essential	Nonessential
Isoleucine	Alanine
Leucine	Asparagine
Lysine	Aspartic Acid
Methionine	Cysteine*
Phenylalanine	Glutamic Acid

Threonine	Glutamine*
Tryptophan	Glycine*
Valine	Proline*
	Selenocysteine*
	Serine*
	Tyrosine*
	Arginine*
	Histidine*
	Ornithine*
	Taurine*

(*) Essential only in certain cases.

Non-protein functions

In humans, non-protein amino acids also have important roles as metabolic intermediates, such as in the biosynthesis of the neurotransmitter gamma-aminobutyric acid. Many amino acids are used to synthesize other molecules, for example:

- Tryptophan is a precursor of the neurotransmitter serotonin.
- Tyrosine is a precursor of the neurotransmitter dopamine.
- Glycine is a precursor of porphyrins such as heme.
- Arginine is a precursor of nitric oxide.
- Ornithine and S-adenosylmethionine are precursors of polyamines.
- Aspartate, glycine and glutamine are precursors of nucleotides.
- Phenylalanine is a precursor of various phenylpropanoids which are important in plant metabolism.

However, not all of the functions of other abundant non-standard amino acids are known, for example taurine is a major amino acid in muscle and brain tissues, but although many functions have been proposed, its precise role in the body has not been determined.

Some non-standard amino acids are used as defenses against herbivores in plants. For example canavanine is an analogue of arginine that is found in many legumes, and in particularly large amounts in *Canavalia gladiata* (sword bean). This amino acid protects the plants from predators such as insects and can cause illness in people if some types of legumes are eaten without processing. The non-protein amino acid mimosine is found in other species of legume, particularly *Leucaena leucocephala*. This compound is an analogue of tyrosine and can poison animals that graze on these plants.

Uses in technology

Amino acids are used for a variety of applications in industry but their main use is as additives to animal feed. This is necessary since many of the bulk components of these

feeds, such as soybeans, either have low levels or lack some of the essential amino acids: lysine, methionine, threonine, and tryptophan are most important in the production of these feeds. The food industry is also a major consumer of amino acids, particularly glutamic acid, which is used as a flavor enhancer, and Aspartame (aspartyl-phenylalanine-1-methyl ester) as a low-calorie artificial sweetener. The remaining production of amino acids is used in the synthesis of drugs and cosmetics.

Amino acid derivative	Pharmaceutical application
5-HTP (5-hydroxytryptophan)	Experimental treatment for depression.
L-DOPA (L-dihydroxyphenylalanine)	Treatment for Parkinsonism.
Eflornithine	Drug that inhibits ornithine decarboxylase and is used in the treatment of sleeping sickness.

Expanded genetic code

Since 2001, 40 non-natural amino acids have been added into protein by creating a unique codon (recoding) and a corresponding transfer-RNA:aminoacyl – tRNA-synthetase pair to encode it with diverse physicochemical and biological properties in order to be used as a tool to exploring protein structure and function or to create novel or enhanced proteins.

Chemical building blocks

Amino acids are important as low-cost feedstocks. These compounds are used in chiral pool synthesis as enantiomerically-pure building blocks.

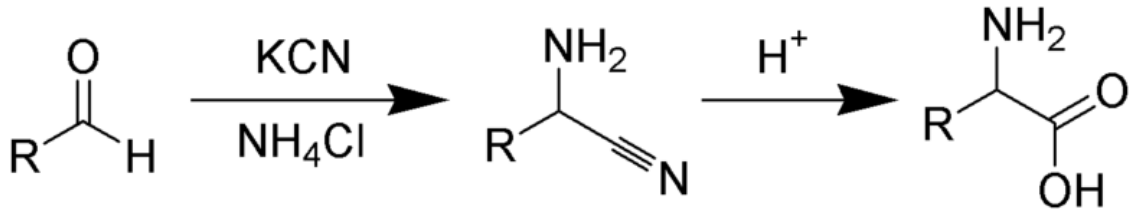
Amino acids have been investigated as precursors chiral catalysts, e.g. for asymmetric hydrogenation reactions, although no commercial applications exist.

Biodegradable plastics

Amino acids are under development as components of a range of biodegradable polymers. These materials have applications as environmentally-friendly packaging and in medicine in drug delivery and the construction of prosthetic implants. These polymers include polypeptides, polyamides, polyesters, polysulfides and polyurethanes with amino acids either forming part of their main chains or bonded as side chains. These modifications alter the physical properties and reactivities of the polymers. An interesting example of such materials is polyaspartate, a water-soluble biodegradable polymer that may have applications in disposable diapers and agriculture. Due to its solubility and ability to chelate metal ions, polyaspartate is also being used as a biodegradeable anti-scaling agent and a corrosion inhibitor. In addition, the aromatic amino acid tyrosine is being developed as a possible replacement for toxic phenols such as bisphenol A in the manufacture of polycarbonates.

Reactions

As amino acids have both a primary amine group and a primary carboxyl group, these chemicals can undergo most of the reactions associated with these functional groups. These include nucleophilic addition, amide bond formation and imine formation for the amine group and esterification, amide bond formation and decarboxylation for the carboxylic acid group. The multiple side chains of amino acids can also undergo chemical reactions. The types of these reactions are determined by the groups on these side chains and are therefore different between the various types of amino acid.



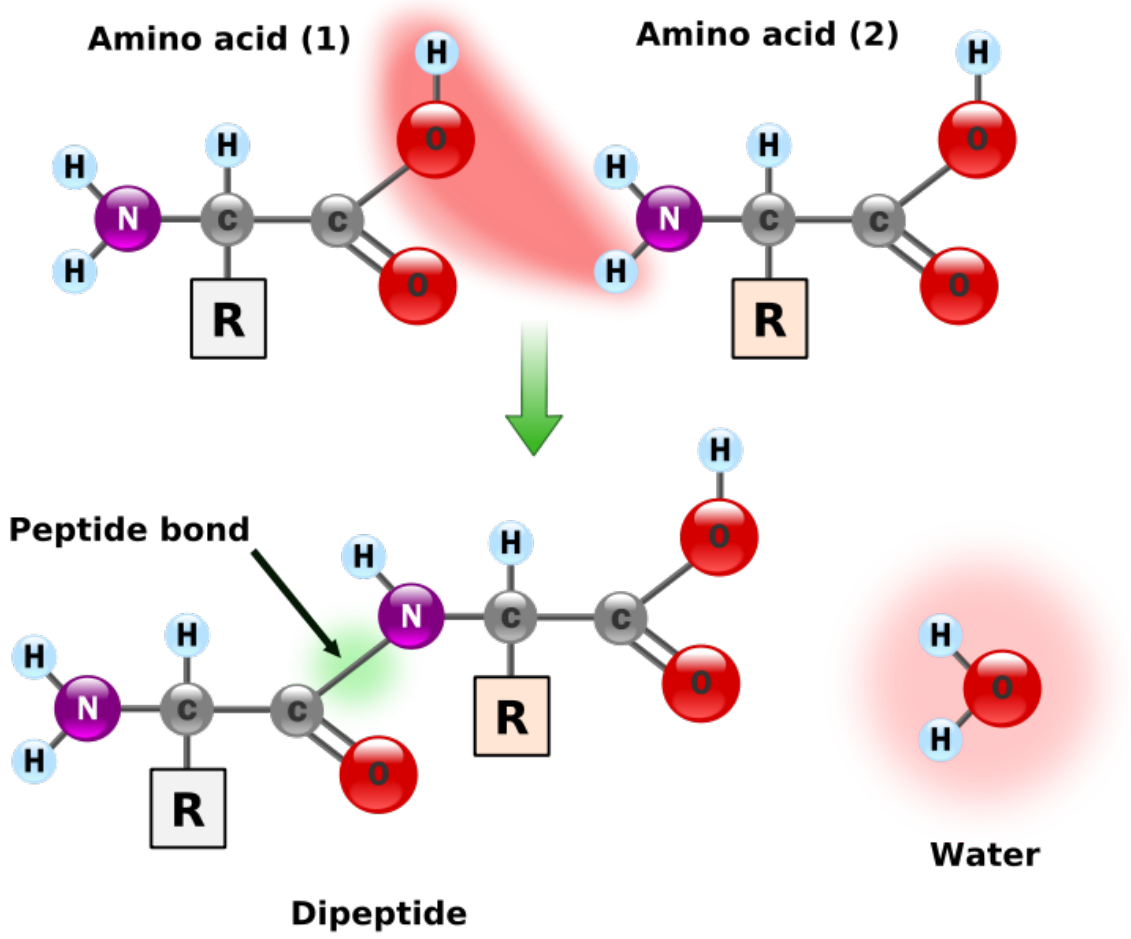
The Strecker amino acid synthesis

Chemical synthesis

Several methods exist to synthesize amino acids. One of the oldest methods, begins with the bromination at the α-carbon of a carboxyic acid. Nucleophilic substitution with ammonia then converts the alkyl bromide to the amino acid. Alternatively, the Strecker amino acid synthesis involves the treatment of an aldehyde with potassium cyanide and ammonia, this produces an α-amino nitrile as an intermediate. Hydrolysis of the nitrile in acid then yields a α-amino acid. Using ammonia or ammonium salts in this reaction gives unsubstituted amino acids, while substituting primary and secondary amines will yield substituted amino acids. Likewise, using ketones, instead of aldehydes, gives α,α-disubstituted amino acids. The classical synthesis gives racemic mixtures of α-amino acids as products, but several alternative procedures using asymmetric auxiliaries or asymmetric catalysts have been developed.

Currently the most adopted method is an automated synthesis on a solid support (e.g. polystyrene beads), using protecting groups (e.g. Fmoc and t-Boc) and activating groups (e.g. DCC and DIC).

Peptide bond formation



The condensation of two amino acids to form a peptide bond

As both the amine and carboxylic acid groups of amino acids can react to form amide bonds, one amino acid molecule can react with another and become joined through an amide linkage. This polymerization of amino acids is what creates proteins. This condensation reaction yields the newly formed peptide bond and a molecule of water. In cells, this reaction does not occur directly; instead the amino acid is first activated by attachment to a transfer RNA molecule through an ester bond. This aminoacyl-tRNA is produced in an ATP-dependent reaction carried out by an aminoacyl tRNA synthetase. This aminoacyl-tRNA is then a substrate for the ribosome, which catalyzes the attack of the amino group of the elongating protein chain on the ester bond. As a result of this mechanism, all proteins made by ribosomes are synthesized starting at their N-terminus and moving towards their C-terminus.

However, not all peptide bonds are formed in this way. In a few cases, peptides are synthesized by specific enzymes. For example, the tripeptide glutathione is an essential part of the defenses of cells against oxidative stress. This peptide is synthesized in two steps from free amino acids. In the first step gamma-glutamylcysteine synthetase

condenses cysteine and glutamic acid through a peptide bond formed between the side-chain carboxyl of the glutamate (the gamma carbon of this side chain) and the amino group of the cysteine. This dipeptide is then condensed with glycine by glutathione synthetase to form glutathione.

In chemistry, peptides are synthesized by a variety of reactions. One of the most used in solid-phase peptide synthesis, which uses the aromatic oxime derivatives of amino acids as activated units. These are added in sequence onto the growing peptide chain, which is attached to a solid resin support. The ability to easily synthesize vast numbers of different peptides by varying the types and order of amino acids (using combinatorial chemistry) has made peptide synthesis particularly important in creating libraries of peptides for use in drug discovery through high-throughput screening.

Biosynthesis and catabolism

In plants, nitrogen is first assimilated into organic compounds in the form of glutamate, formed from alpha-ketoglutarate and ammonia in the mitochondrion. In order to form other amino acids, the plant uses transaminases to move the amino group to another alpha-keto carboxylic acid. For example, aspartate aminotransferase converts glutamate and oxaloacetate to alpha-ketoglutarate and aspartate. Other organisms use transaminases for amino acid synthesis too. Transaminases are also involved in breaking down amino acids. Degrading an amino acid often involves moving its amino group to alpha-ketoglutarate, forming glutamate. In many vertebrates, the amino group is then removed through the urea cycle and is excreted in the form of urea. However, amino acid degradation can produce uric acid or ammonia instead. For example, serine dehydratase converts serine to pyruvate and ammonia.

Nonstandard amino acids are usually formed through modifications to standard amino acids. For example, homocysteine is formed through the transsulfuration pathway or by the demethylation of methionine via the intermediate metabolite S-adenosyl methionine, while hydroxyproline is made by a posttranslational modification of proline.

Microorganisms and plants can synthesize many uncommon amino acids. For example, some microbes make 2-aminoisobutyric acid and lanthionine, which is a sulfide-bridged derivative of alanine. Both of these amino acids are found in peptidic lantibiotics such as alamethicin. While in plants, 1-aminocyclopropane-1-carboxylic acid is a small disubstituted cyclic amino acid that is a key intermediate in the production of the plant hormone ethylene.

Physicochemical properties of amino acids

The 20 amino acids encoded directly by the genetic code can be divided into several groups based on their properties. Important factors are charge, hydrophilicity or hydrophobicity, size and functional groups. These properties are important for protein structure and protein–protein interactions. The water-soluble proteins tend to have their hydrophobic residues (Leu, Ile, Val, Phe and Trp) buried in the middle of the protein,

whereas hydrophilic side chains are exposed to the aqueous solvent. The integral membrane proteins tend to have outer rings of exposed hydrophobic amino acids that anchor them into the lipid bilayer. In the case part-way between these two extremes, some peripheral membrane proteins have a patch of hydrophobic amino acids on their surface that locks onto the membrane. Similarly, proteins that have to bind to positively-charged molecules have surfaces rich with negatively charged amino acids like glutamate and aspartate, while proteins binding to negatively-charged molecules have surfaces rich with positively charged chains like lysine and arginine. There are different hydrophobicity scales of amino acid residues.

Some amino acids have special properties such as cysteine, that can form covalent disulfide bonds to other cysteine residues, proline that forms a cycle to the polypeptide backbone, and glycine that is more flexible than other amino acids.

Many proteins undergo a range of posttranslational modifications, when additional chemical groups are attached to the amino acids in proteins. Some modifications can produce hydrophobic lipoproteins, or hydrophilic glycoproteins. These type of modification allow the reversible targeting of a protein to a membrane. For example, the addition and removal of the fatty acid palmitic acid to cysteine residues in some signaling proteins causes the proteins to attach and then detach from cell membranes.

Table of standard amino acid abbreviations and properties

Amino Acid	3-Letter	1-Letter	Side chain polarity	Side chain charge (pH 7.4)	Hydropathy index	Absorbance λ_{max}(nm)	ε at λ_{max} (x10^{-3} M^{-1} cm^{-1})
Alanine	Ala	A	nonpolar	neutral	1.8		
Arginine	Arg	R	polar	positive	−4.5		
Asparagine	Asn	N	polar	neutral	−3.5		
Aspartic acid	Asp	D	polar	negative	−3.5		
Cysteine	Cys	C	nonpolar	neutral	2.5	250	0.3
Glutamic acid	Glu	E	polar	negative	−3.5		
Glutamine	Gln	Q	polar	neutral	−3.5		
Glycine	Gly	G	nonpolar	neutral	−0.4		
Histidine	His	H	polar	positive(10%) neutral(90%)	−3.2	211	5.9
Isoleucine	Ile	I	nonpolar	neutral	4.5		
Leucine	Leu	L	nonpolar	neutral	3.8		
Lysine	Lys	K	polar	positive	−3.9		
Methionine	Met	M	nonpolar	neutral	1.9		

Phenylalanine	Phe	F	nonpolar	neutral	2.8	257, 206, 188	0.2, 9.3, 60.0
Proline	Pro	P	nonpolar	neutral	−1.6		
Serine	Ser	S	polar	neutral	−0.8		
Threonine	Thr	T	polar	neutral	−0.7		
Tryptophan	Trp	W	nonpolar	neutral	−0.9	280, 219	5.6, 47.0
Tyrosine	Tyr	Y	polar	neutral	−1.3	274, 222, 193	1.4, 8.0, 48.0
Valine	Val	V	nonpolar	neutral	4.2		

Additionally, there are two additional amino acids which are incorporated by overriding stop codons:

21st and 22nd amino acids	**3-Letter**	**1-Letter**
Selenocysteine	Sec	U
Pyrrolysine	Pyl	O

In addition to the specific amino acid codes, placeholders are used in cases where chemical or crystallographic analysis of a peptide or protein can not conclusively determine the identity of a residue.

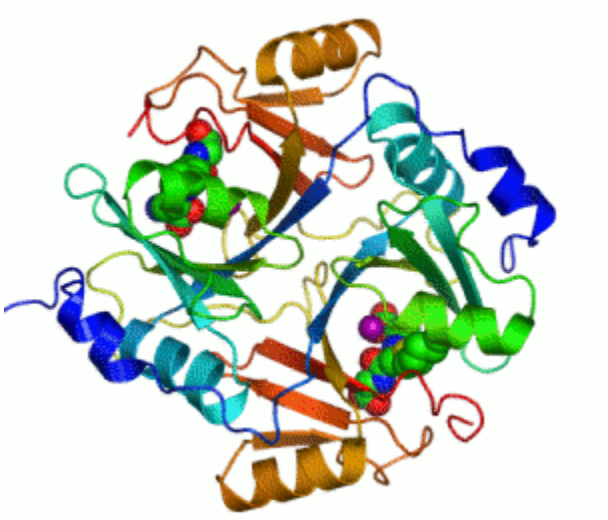
Ambiguous Amino Acids	**3-Letter**	**1-Letter**
Asparagine or aspartic acid	Asx	B
Glutamine or glutamic acid	Glx	Z
Leucine or Isoleucine	Xle	J
Unspecified or unknown amino acid	Xaa	X

Unk is sometimes used instead of **Xaa**, but is less standard.

Additionally, many non-standard amino acids have a specific code. For example, several peptide drugs, such as Bortezomib or MG132 are artificially synthesized and retain their protecting groups, which have specific codes. Bortezomib is Pyz-Phe-boroLeu and MG132 is Z-Leu-Leu-Leu-al. Additionally, To aid in the analysis of protein structure, photocrosslinking amino acid analogues are available. These include photoleucine (**pLeu**) and photomethionine (**pMet**).

Chapter- 12

Enzyme



Human glyoxalase I. Two zinc ions that are needed for the enzyme to catalyze its reaction are shown as purple spheres, and an enzyme inhibitor called *S*-hexylglutathione is shown as a space-filling model, filling the two active sites.

Enzymes are proteins that catalyze (*i.e.*, increase or decrease the rates of) chemical reactions. In enzymatic reactions, the molecules at the beginning of the process are called substrates, and they are converted into different molecules, called the products. Almost all processes in a biological cell need enzymes to occur at significant rates. Since enzymes are selective for their substrates and speed up only a few reactions from among many possibilities, the set of enzymes made in a cell determines which metabolic pathways occur in that cell.

Like all catalysts, enzymes work by lowering the activation energy ($E_a^{\ddagger}$) for a reaction, thus dramatically increasing the rate of the reaction. As a result, products are formed faster and reactions reach their equilibrium state more rapidly. Most enzyme reaction rates are millions of times faster than those of comparable un-catalyzed reactions. As with all catalysts, enzymes are not consumed by the reactions they catalyze, nor do they alter the equilibrium of these reactions. However, enzymes do differ from most other catalysts by being much more specific. Enzymes are known to catalyze about 4,000 biochemical reactions. A few RNA molecules called ribozymes also catalyze reactions,

with an important example being some parts of the ribosome. Synthetic molecules called artificial enzymes also display enzyme-like catalysis.

Enzyme activity can be affected by other molecules. Inhibitors are molecules that decrease enzyme activity; activators are molecules that increase activity. Many drugs and poisons are enzyme inhibitors. Activity is also affected by temperature, chemical environment (*e.g.*, pH), and the concentration of substrate. Some enzymes are used commercially, for example, in the synthesis of antibiotics. In addition, some household products use enzymes to speed up biochemical reactions (*e.g.*, enzymes in biological washing powders break down protein or fat stains on clothes; enzymes in meat tenderizers break down proteins into smaller molecules, making the meat easier to chew).

Etymology and history

Eduard Buchner

As early as the late 18th and early 19th centuries, the digestion of meat by stomach secretions and the conversion of starch to sugars by plant extracts and saliva were known. However, the mechanism by which this occurred had not been identified.

In the 19th century, when studying the fermentation of sugar to alcohol by yeast, Louis Pasteur came to the conclusion that this fermentation was catalyzed by a vital force contained within the yeast cells called "ferments", which were thought to function only within living organisms. He wrote that "alcoholic fermentation is an act correlated with the life and organization of the yeast cells, not with the death or putrefaction of the cells."

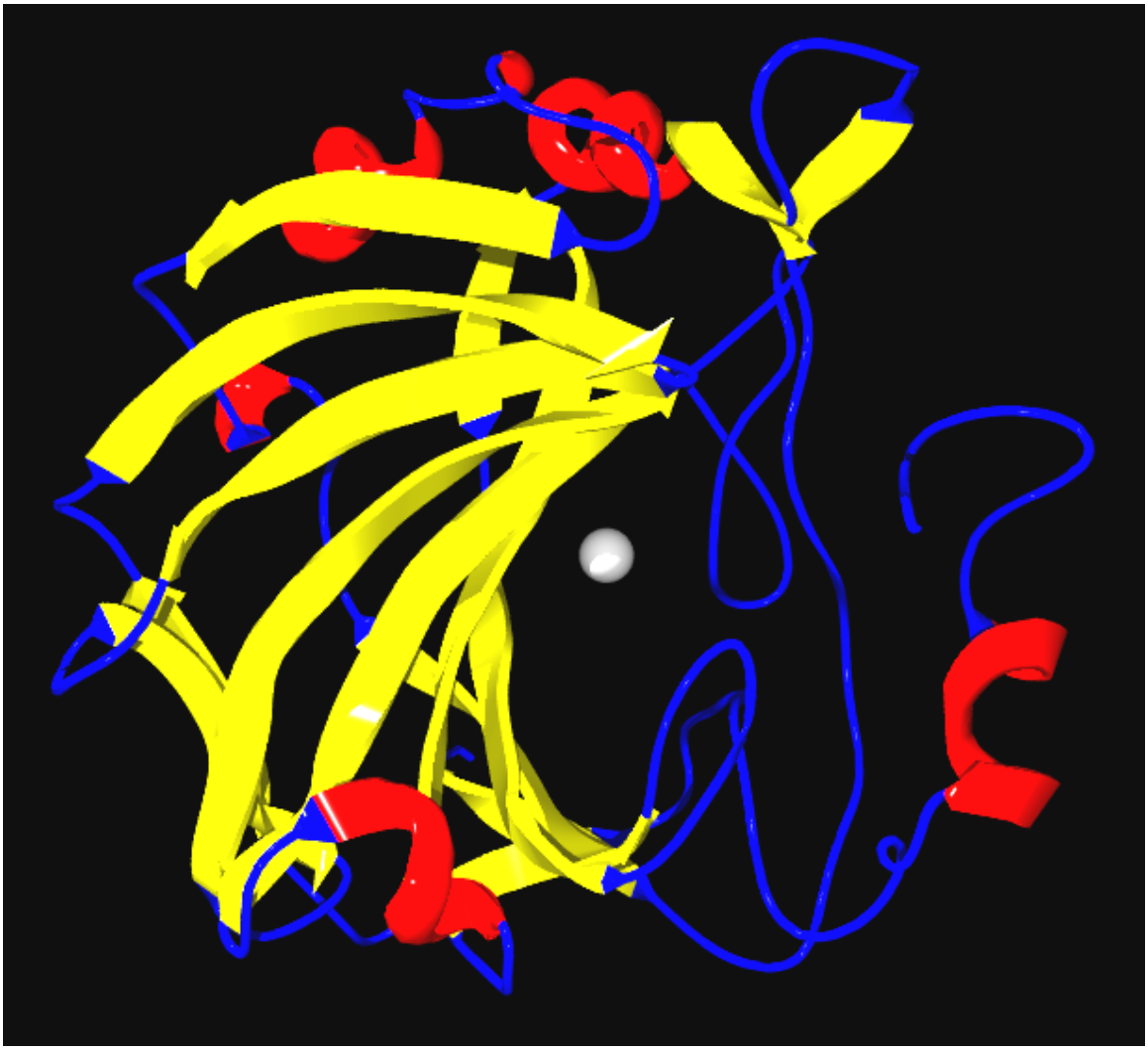
In 1877, German physiologist Wilhelm Kühne (1837–1900) first used the term *enzyme*, which comes from Greek *ενζυμον*, "in leaven", to describe this process. The word *enzyme* was used later to refer to nonliving substances such as pepsin, and the word *ferment* was used to refer to chemical activity produced by living organisms.

In 1897, Eduard Buchner submitted his first paper on the ability of yeast extracts that lacked any living yeast cells to ferment sugar. In a series of experiments at the University of Berlin, he found that the sugar was fermented even when there were no living yeast cells in the mixture. He named the enzyme that brought about the fermentation of sucrose "zymase". In 1907, he received the Nobel Prize in Chemistry "for his biochemical research and his discovery of cell-free fermentation". Following Buchner's example, enzymes are usually named according to the reaction they carry out. Typically, to generate the name of an enzyme, the suffix *-ase* is added to the name of its substrate (*e.g.*, lactase is the enzyme that cleaves lactose) or the type of reaction (*e.g.*, DNA polymerase forms DNA polymers).

Having shown that enzymes could function outside a living cell, the next step was to determine their biochemical nature. Many early workers noted that enzymatic activity was associated with proteins, but several scientists (such as Nobel laureate Richard Willstätter) argued that proteins were merely carriers for the true enzymes and that proteins *per se* were incapable of catalysis. However, in 1926, James B. Sumner showed that the enzyme urease was a pure protein and crystallized it; Sumner did likewise for the enzyme catalase in 1937. The conclusion that pure proteins can be enzymes was definitively proved by Northrop and Stanley, who worked on the digestive enzymes pepsin (1930), trypsin and chymotrypsin. These three scientists were awarded the 1946 Nobel Prize in Chemistry.

This discovery that enzymes could be crystallized eventually allowed their structures to be solved by x-ray crystallography. This was first done for lysozyme, an enzyme found in tears, saliva and egg whites that digests the coating of some bacteria; the structure was solved by a group led by David Chilton Phillips and published in 1965. This high-resolution structure of lysozyme marked the beginning of the field of structural biology and the effort to understand how enzymes work at an atomic level of detail.

Structures and mechanisms



Ribbon diagram showing human carbonic anhydrase II. The grey sphere is the zinc cofactor in the active site. Diagram drawn from PDB 1MOO.

Enzymes are generally globular proteins and range from just 62 amino acid residues in size, for the monomer of 4-oxalocrotonate tautomerase, to over 2,500 residues in the animal fatty acid synthase. A small number of RNA-based biological catalysts exist, with the most common being the ribosome; these are referred to as either RNA-enzymes or ribozymes. The activities of enzymes are determined by their three-dimensional structure. However, although structure does determine function, predicting a novel enzyme's activity just from its structure is a very difficult problem that has not yet been solved.

Most enzymes are much larger than the substrates they act on, and only a small portion of the enzyme (around 3–4 amino acids) is directly involved in catalysis. The region that contains these catalytic residues, binds the substrate, and then carries out the reaction is known as the active site. Enzymes can also contain sites that bind cofactors, which are needed for catalysis. Some enzymes also 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, providing a means for feedback regulation.

Like all proteins, enzymes are long, linear chains of amino acids that fold to produce a three-dimensional product. Each unique amino acid sequence produces a specific structure, which has unique properties. Individual protein chains may sometimes group together to form a protein complex. Most enzymes can be denatured—that is, unfolded and inactivated—by heating or chemical denaturants, which disrupt the three-dimensional structure of the protein. Depending on the enzyme, denaturation may be reversible or irreversible.

Structures of enzymes in complex with substrates or substrate analogs during a reaction may be obtained using Time resolved crystallography methods.

Specificity

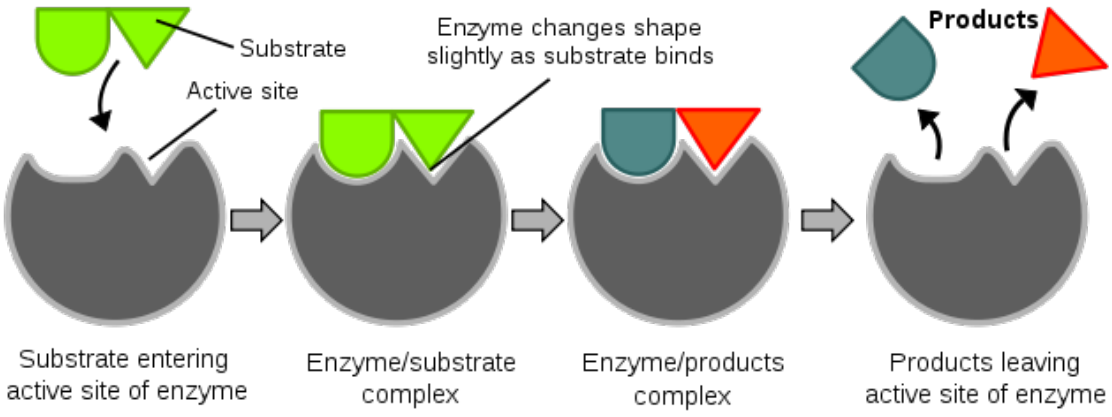
Enzymes are usually very specific as to which reactions they catalyze and the substrates that are involved in these reactions. Complementary shape, charge and hydrophilic/hydrophobic characteristics of enzymes and substrates are responsible for this specificity. Enzymes can also show impressive levels of stereospecificity, regioselectivity and chemoselectivity.

Some of the enzymes showing the highest specificity and accuracy are involved in the copying and expression of the genome. These enzymes have "proof-reading" mechanisms. Here, an enzyme such as DNA polymerase catalyzes a reaction in a first step and then checks that the product is correct in a second step. This two-step process results in average error rates of less than 1 error in 100 million reactions in high-fidelity mammalian polymerases. Similar proofreading mechanisms are also found in RNA polymerase, aminoacyl tRNA synthetases and ribosomes.

Some enzymes that produce secondary metabolites are described as promiscuous, as they can act on a relatively broad range of different substrates. It has been suggested that this broad substrate specificity is important for the evolution of new biosynthetic pathways.

"Lock and key" model

Enzymes are very specific, and it was suggested by the Nobel laureate organic chemist Emil Fischer in 1894 that this was because both the enzyme and the substrate possess specific complementary geometric shapes that fit exactly into one another. This is often referred to as "the lock and key" model. However, while this model explains enzyme specificity, it fails to explain the stabilization of the transition state that enzymes achieve.



Diagrams to show the induced fit hypothesis of enzyme action

In 1958, Daniel Koshland suggested a modification to the lock and key model: since enzymes are rather flexible structures, the active site is continually reshaped by interactions with the substrate as the substrate interacts with the enzyme. As a result, the substrate does not simply bind to a rigid active site; the amino acid side chains which make up the active site are molded into the precise positions that enable the enzyme to perform its catalytic function. In some cases, such as glycosidases, the substrate molecule also changes shape slightly as it enters the active site. The active site continues to change until the substrate is completely bound, at which point the final shape and charge is determined. Induced fit may enhance the fidelity of molecular recognition in the presence of competition and noise via the conformational proofreading mechanism .

Mechanisms

Enzymes can act in several ways, all of which lower $\Delta G^{\ddagger}$:

- Lowering the activation energy by creating an environment in which the transition state is stabilized (e.g. straining the shape of a substrate—by binding the transition-state conformation of the substrate/product molecules, the enzyme distorts the bound substrate(s) into their transition state form, thereby reducing the amount of energy required to complete the transition).
- Lowering the energy of the transition state, but without distorting the substrate, by creating an environment with the opposite charge distribution to that of the transition state.
- Providing an alternative pathway. For example, temporarily reacting with the substrate to form an intermediate ES complex, which would be impossible in the absence of the enzyme.
- Reducing the reaction entropy change by bringing substrates together in the correct orientation to react. Considering $\Delta H^{\ddagger}$ alone overlooks this effect.
- Increases in temperatures speed up reactions. Thus, temperature increases help the enzyme function and develop the end product even faster. However, if heated too

much, the enzyme’s shape deteriorates and the enzyme becomes denatured. Some enzymes like thermolabile enzymes work best at low temperatures.

Interestingly, this entropic effect involves destabilization of the ground state, and its contribution to catalysis is relatively small.

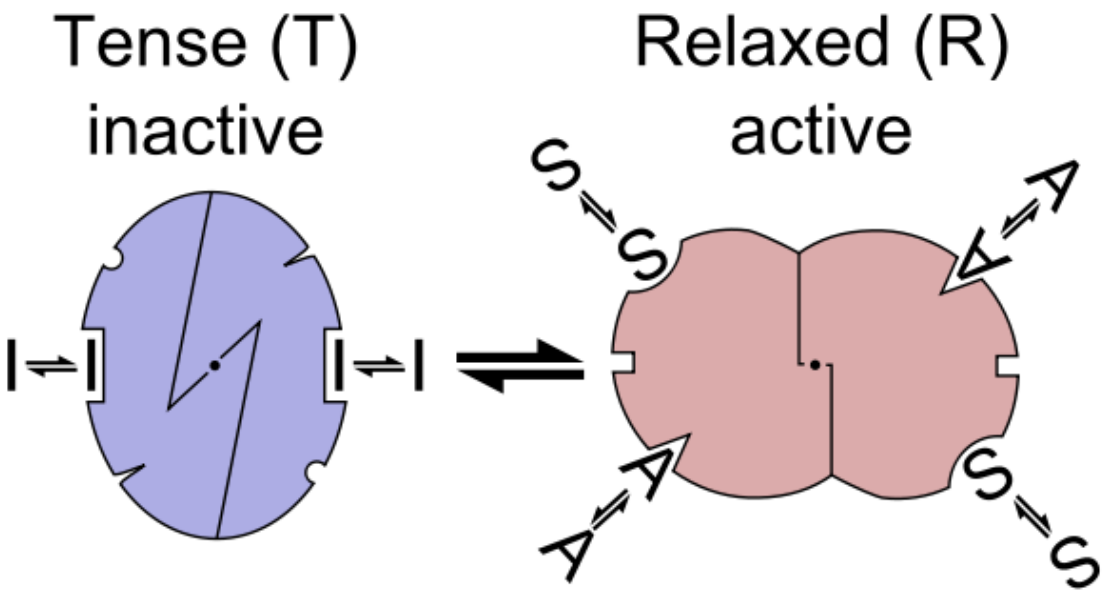
Transition State Stabilization

The understanding of the origin of the reduction of $\Delta G^{\ddagger}$ requires one to find out how the enzymes can stabilize its transition state more than the transition state of the uncatalyzed reaction. Apparently, the most effective way for reaching large stabilization is the use of electrostatic effects, in particular, by having a relatively fixed polar environment that is oriented toward the charge distribution of the transition state. Such an environment does not exist in the uncatalyzed reaction in water.

Dynamics and function

The internal dynamics of enzymes is linked to their mechanism of catalysis. Internal dynamics are the movement of parts of the enzyme's structure, such as individual amino acid residues, a group of amino acids, or even an entire protein domain. These movements occur at various time-scales ranging from femtoseconds to seconds. Networks of protein residues throughout an enzyme's structure can contribute to catalysis through dynamic motions. Protein motions are vital to many enzymes, but whether small and fast vibrations, or larger and slower conformational movements are more important depends on the type of reaction involved. However, although these movements are important in binding and releasing substrates and products, it is not clear if protein movements help to accelerate the chemical steps in enzymatic reactions. These new insights also have implications in understanding allosteric effects and developing new drugs.

Allosteric modulation



Allosteric transition of an enzyme between R and T states, stabilized by an agonist, an inhibitor and a substrate (the MWC model)

Allosteric sites are sites on the enzyme that bind to molecules in the cellular environment. The sites form weak, noncovalent bonds with these molecules, causing a change in the conformation of the enzyme. This change in conformation translates to the active site, which then affects the reaction rate of the enzyme. Allosteric interactions can both inhibit and activate enzymes and are a common way that enzymes are controlled in the body.

Cofactors and coenzymes

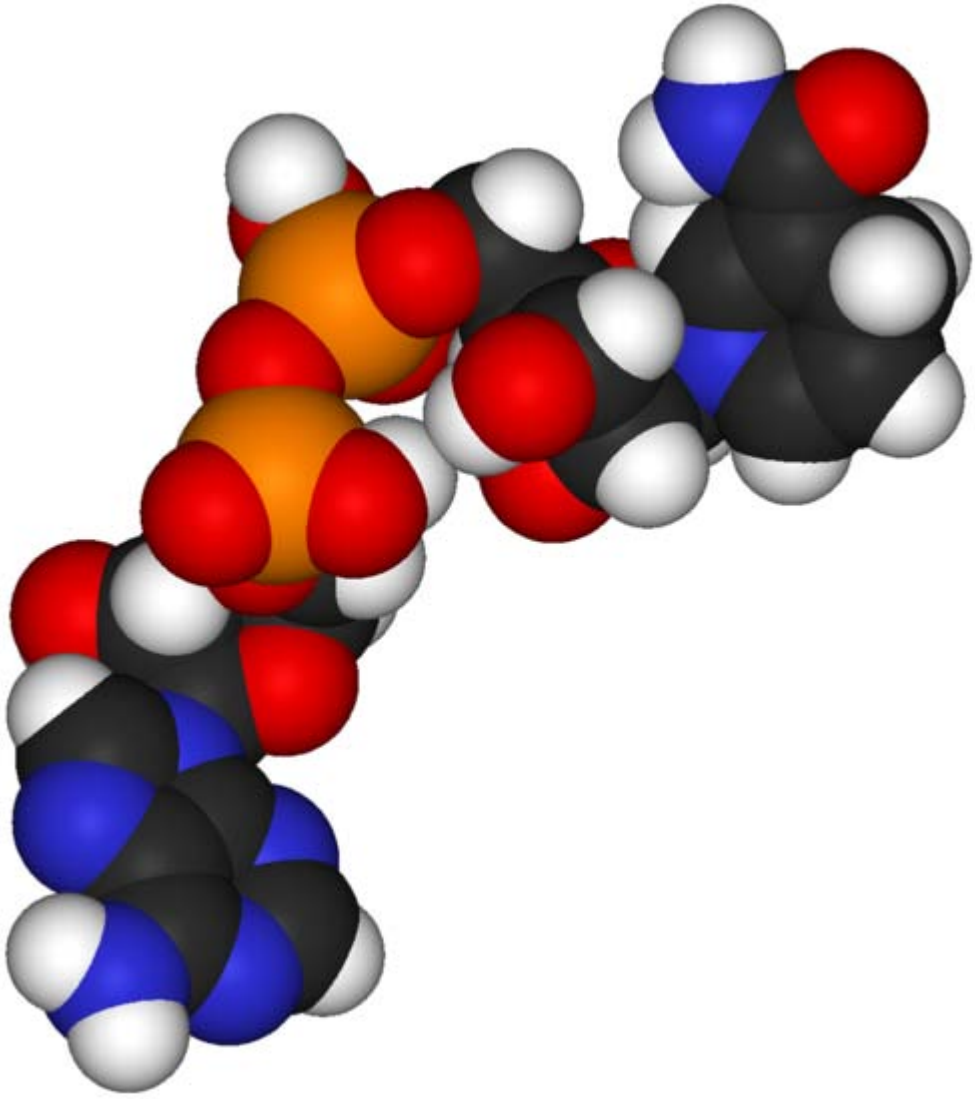
Cofactors

Some enzymes do not need any additional components to show full activity. However, others require non-protein molecules called cofactors to be bound for activity. Cofactors can be either inorganic (*e.g.*, metal ions and iron-sulfur clusters) or organic compounds (e.g., flavin and heme). Organic cofactors can be either prosthetic groups, which are tightly bound to an enzyme, or coenzymes, which are released from the enzyme's active site during the reaction. Coenzymes include NADH, NADPH and adenosine triphosphate. These molecules transfer chemical groups between enzymes.

An example of an enzyme that contains a cofactor is carbonic anhydrase, and is shown in the ribbon diagram above with a zinc cofactor bound as part of its active site. These tightly bound molecules are usually found in the active site and are involved in catalysis. For example, flavin and heme cofactors are often involved in redox reactions.

Enzymes that require a cofactor but do not have one bound are called *apoenzymes* or *apoproteins*. An apoenzyme together with its cofactor(s) is called a *holoenzyme* (this is the active form). Most cofactors are not covalently attached to an enzyme, but are very tightly bound. However, organic prosthetic groups can be covalently bound (*e.g.*, thiamine pyrophosphate in the enzyme pyruvate dehydrogenase). The term "holoenzyme" can also be applied to enzymes that contain multiple protein subunits, such as the DNA polymerases; here the holoenzyme is the complete complex containing all the subunits needed for activity.

Coenzymes



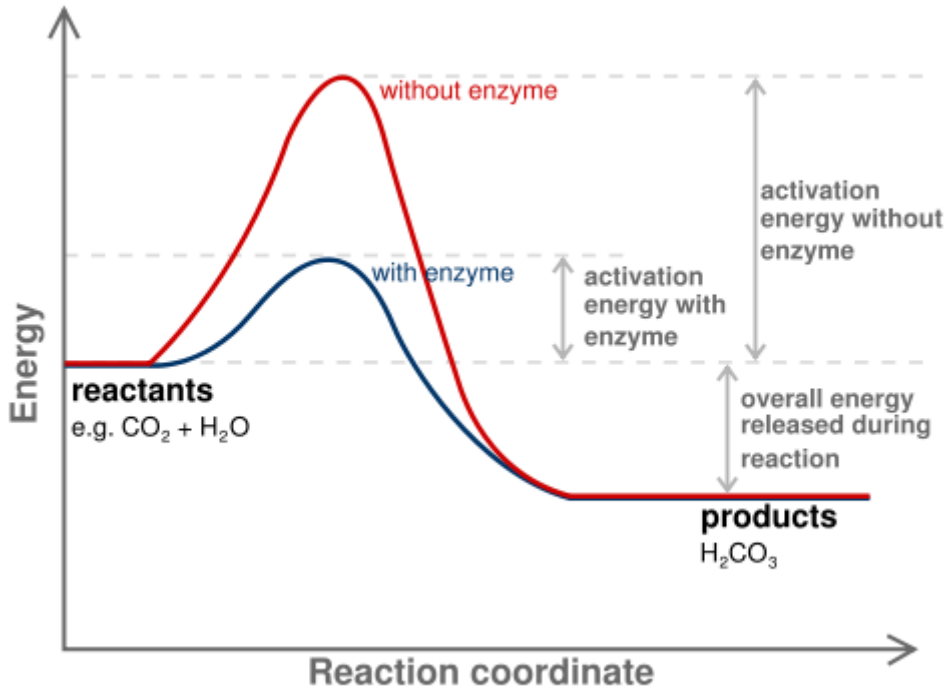
Space-filling model of the coenzyme NADH

Coenzymes are small organic molecules that can be loosely or tightly bound to an enzyme. Tightly bound coenzymes can be called allosteric groups. Coenzymes are transport chemical groups from one enzyme to another. Some of these chemicals such as riboflavin, thiamine and folic acid are vitamins (compounds which cannot be synthesized by the body and must be acquired from the diet). The chemical groups carried include the hydride ion (H^-) carried by NAD or $NADP^+$, the phosphate group carried by adenosine triphosphate, the acetyl group carried by coenzyme A, formyl, methenyl or methyl groups carried by folic acid and the methyl group carried by S-adenosylmethionine.

Since coenzymes are chemically changed as a consequence of enzyme action, it is useful to consider coenzymes to be a special class of substrates, or second substrates, which are common to many different enzymes. For example, about 700 enzymes are known to use the coenzyme NADH.

Coenzymes are usually continuously regenerated and their concentrations maintained at a steady level inside the cell: for example, NADPH is regenerated through the pentose phosphate pathway and *S*-adenosylmethionine by methionine adenosyltransferase. This continuous regeneration means that even small amounts of coenzymes are used very intensively. For example, the human body turns over its own weight in ATP each day.

Thermodynamics



The energies of the stages of a chemical reaction. Substrates need a lot of energy to reach a transition state, which then decays into products. The enzyme stabilizes the transition state, reducing the energy needed to form products.

As all catalysts, enzymes do not alter the position of the chemical equilibrium of the reaction. Usually, in the presence of an enzyme, the reaction runs in the same direction as it would without the enzyme, just more quickly. However, in the absence of the enzyme, other possible uncatalyzed, "spontaneous" reactions might lead to different products, because in those conditions this different product is formed faster.

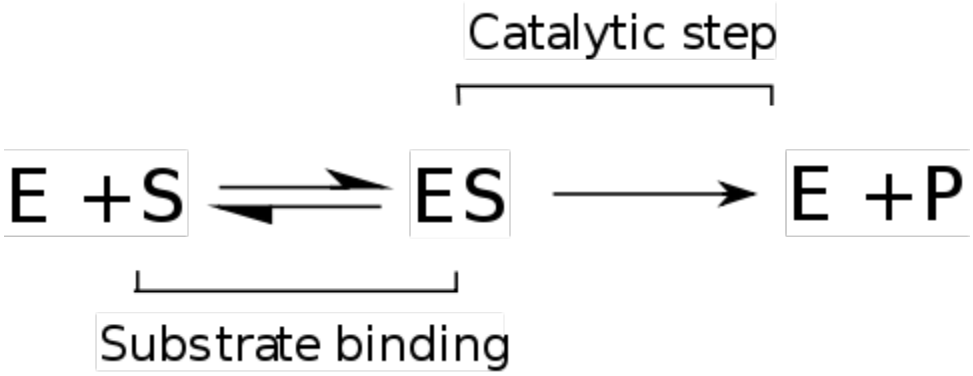
Furthermore, enzymes can couple two or more reactions, so that a thermodynamically favorable reaction can be used to "drive" a thermodynamically unfavorable one. For example, the hydrolysis of ATP is often used to drive other chemical reactions.

Enzymes catalyze the forward and backward reactions equally. They do not alter the equilibrium itself, but only the speed at which it is reached. For example, carbonic anhydrase catalyzes its reaction in either direction depending on the concentration of its reactants.

$$CO_2 + H_2O \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3 \text{(in tissues; high } CO_2 \text{ concentration)}$$
$$H_2CO_3 \xrightarrow{\text{Carbonic anhydrase}} CO_2 + H_2O \text{(in lungs; low } CO_2 \text{ concentration)}$$

Nevertheless, if the equilibrium is greatly displaced in one direction, that is, in a very exergonic reaction, the reaction is *effectively* irreversible. Under these conditions the enzyme will, in fact, only catalyze the reaction in the thermodynamically allowed direction.

Kinetics



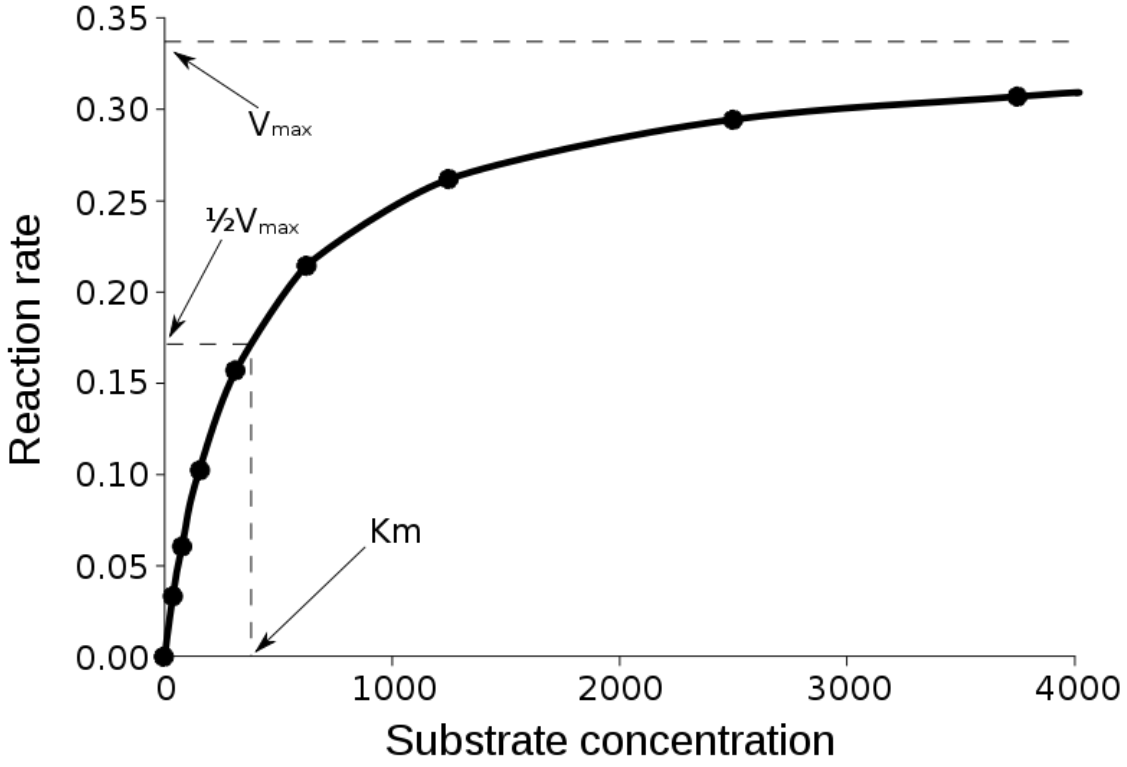
Mechanism for a single substrate enzyme catalyzed reaction. The enzyme (E) binds a substrate (S) and produces a product (P).

Enzyme kinetics is the investigation of how enzymes bind substrates and turn them into products. The rate data used in kinetic analyses are obtained from enzyme assays.

In 1902 Victor Henri proposed a quantitative theory of enzyme kinetics, but his experimental data were not useful because the significance of the hydrogen ion concentration was not yet appreciated. After Peter Lauritz Sørensen had defined the logarithmic pH-scale and introduced the concept of buffering in 1909 the German

chemist Leonor Michaelis and his Canadian postdoc Maud Leonora Menten repeated Henri's experiments and confirmed his equation which is referred to as Henri-Michaelis-Menten kinetics (sometimes also Michaelis-Menten kinetics). Their work was further developed by G. E. Briggs and J. B. S. Haldane, who derived kinetic equations that are still widely used today.

The major contribution of Henri was to think of enzyme reactions in two stages. In the first, the substrate binds reversibly to the enzyme, forming the enzyme-substrate complex. This is sometimes called the Michaelis complex. The enzyme then catalyzes the chemical step in the reaction and releases the product.



Saturation curve for an enzyme reaction showing the relation between the substrate concentration (S) and rate (v)

Enzymes can catalyze up to several million reactions per second. For example, the uncatalyzed decarboxylation of orotidine 5'-monophosphate has a half life of 78 million years. However, when the enzyme orotidine 5'-phosphate decarboxylase is added, the same process takes just 25 milliseconds. Enzyme rates depend on solution conditions and substrate concentration. Conditions that denature the protein abolish enzyme activity, such as high temperatures, extremes of pH or high salt concentrations, while raising substrate concentration tends to increase activity. To find the maximum speed of an enzymatic reaction, the substrate concentration is increased until a constant rate of product formation is seen. This is shown in the saturation curve on the right. Saturation happens because, as substrate concentration increases, more and more of the free enzyme

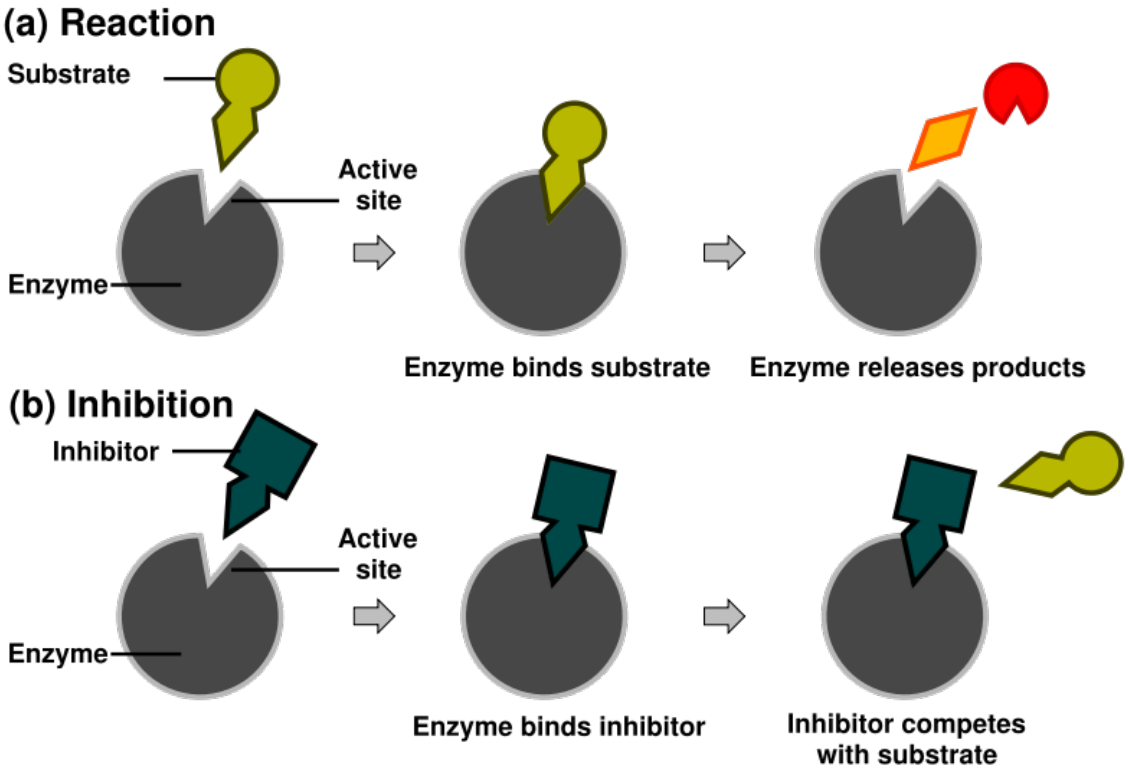
is converted into the substrate-bound ES form. At the maximum velocity (V_{max}) of the enzyme, all the enzyme active sites are bound to substrate, and the amount of ES complex is the same as the total amount of enzyme. However, V_{max} is only one kinetic constant of enzymes. The amount of substrate needed to achieve a given rate of reaction is also important. This is given 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, and this can show how tight the binding of the substrate is to the enzyme. Another useful constant is k_{cat}, which is the number of substrate molecules handled by one active site per second.

The efficiency of an enzyme can be expressed in terms of k_{cat}/K_m. This is also called the specificity constant and incorporates the rate constants for all steps in the reaction. Because the specificity constant reflects both affinity and catalytic ability, it is useful for comparing different enzymes against each other, or the same enzyme with different substrates. The theoretical maximum for the specificity constant is called the diffusion limit and 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 with this property are called *catalytically perfect* or *kinetically perfect*. Example of such enzymes are triose-phosphate isomerase, carbonic anhydrase, acetylcholinesterase, catalase, fumarase, β-lactamase, and superoxide dismutase.

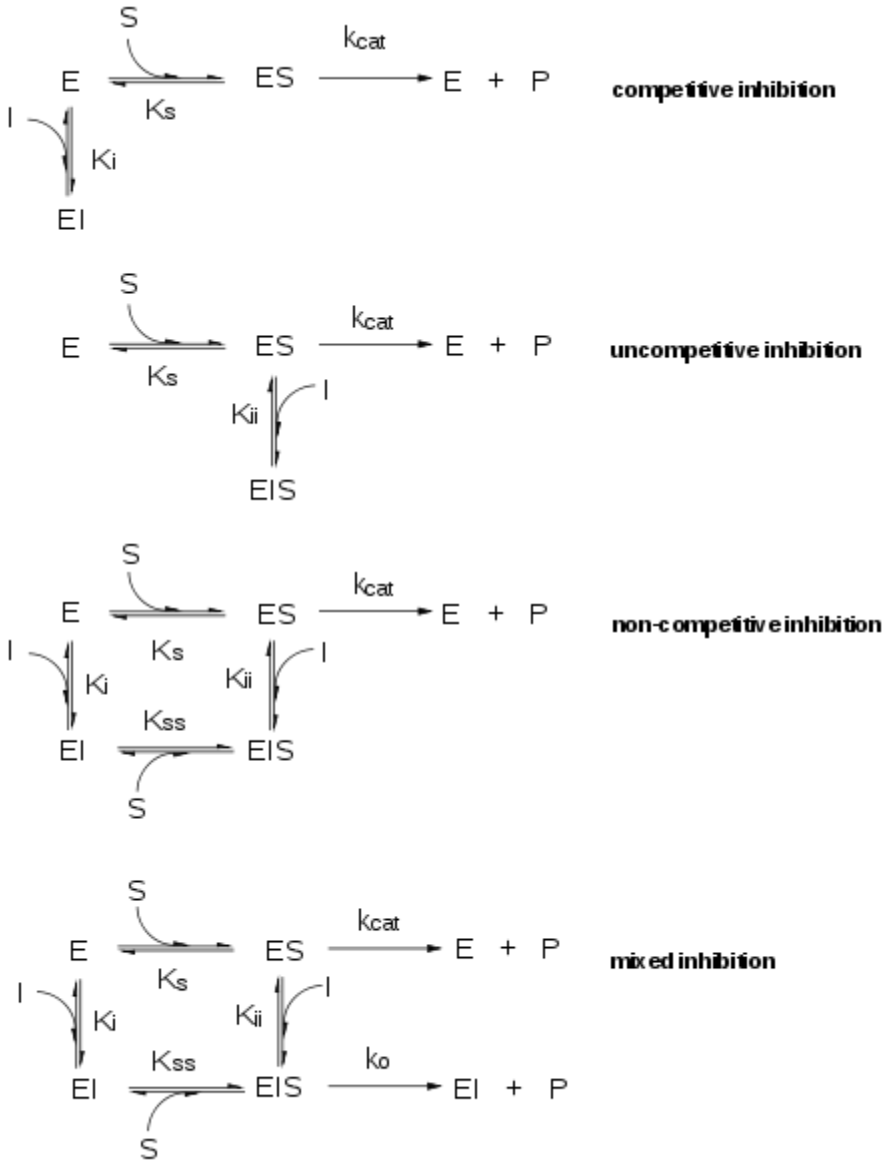
Michaelis-Menten kinetics relies on the law of mass action, which is derived from the assumptions of free diffusion and thermodynamically driven random collision. However, many biochemical or cellular processes deviate significantly from these conditions, because of macromolecular crowding, phase-separation of the enzyme/substrate/product, or one or two-dimensional molecular movement. In these situations, a fractal Michaelis-Menten kinetics may be applied.

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 pre-orienting them by using dipolar electric fields. Other models invoke a quantum-mechanical tunneling explanation, whereby a proton or an electron can tunnel through activation barriers, although for proton tunneling this model remains somewhat controversial. Quantum tunneling for protons has been observed in tryptamine. This suggests that enzyme catalysis may be more accurately characterized as "through the barrier" rather than the traditional model, which requires substrates to go "over" a lowered energy barrier.

Inhibition



Competitive inhibitors bind reversibly to the enzyme, preventing the binding of substrate. On the other hand, binding of substrate prevents binding of the inhibitor. Substrate and inhibitor compete for the enzyme.



Types of inhibition. This classification was introduced by W.W. Cleland.

Enzyme reaction rates can be decreased by various types of enzyme inhibitors.

Competitive inhibition

In competitive inhibition, the inhibitor and substrate compete for the enzyme (i.e., they can not bind at the same time). Often competitive inhibitors strongly resemble the real substrate of the enzyme. For example, methotrexate is a competitive inhibitor of the enzyme dihydrofolate reductase, which catalyzes the reduction of dihydrofolate to tetrahydrofolate. The similarity between the structures of folic acid and this drug are shown in the figure to the *right* bottom. Note that binding of the inhibitor need *not* be to the substrate binding site (as frequently stated), if binding of the inhibitor changes the

conformation of the enzyme to prevent substrate binding and *vice versa*. In competitive inhibition the maximal velocity of the reaction is not changed, but higher substrate concentrations are required to reach a given velocity, increasing the apparent K_m.

Uncompetitive inhibition

In uncompetitive inhibition the inhibitor can not bind to the free enzyme, but only to the ES-complex. The EIS-complex thus formed is enzymatically inactive. This type of inhibition is rare, but may occur in multimeric enzymes.

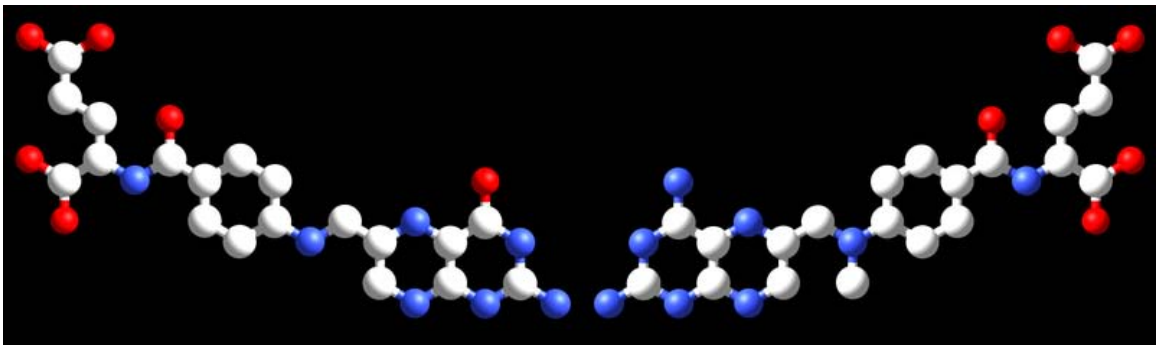
Non-competitive inhibition

Non-competitive inhibitors can bind to the enzyme at the binding site at the same time as the substrate,but not to the active site. Both the EI and EIS complexes are enzymatically inactive. Because the inhibitor can not be driven from the enzyme by higher substrate concentration (in contrast to competitive inhibition), the apparent V_{max} changes. But because the substrate can still bind to the enzyme, the K_m stays the same.

Mixed inhibition

This type of inhibition resembles the non-competitive, except that the EIS-complex has residual enzymatic activity.This type of inhibitor does not follow Michaelis-Menten equation.

In many organisms inhibitors may act as part of a feedback mechanism. If an enzyme produces too much of one substance in the organism, that substance may act as an inhibitor for the enzyme at the beginning of the pathway that produces it, causing production of the substance to slow down or stop when there is sufficient amount. This is a form of negative feedback. Enzymes which are subject to this form of regulation are often multimeric and have allosteric binding sites for regulatory substances. Their substrate/velocity plots are not hyperbolar, but sigmoidal (S-shaped).



The coenzyme folic acid (left) and the anti-cancer drug methotrexate (right) are very similar in structure. As a result, methotrexate is a competitive inhibitor of many enzymes that use folates.

Irreversible inhibitors react with the enzyme and form a covalent adduct with the protein. The inactivation is irreversible. These compounds include eflornithine a drug used to treat the parasitic disease sleeping sickness. Penicillin and Aspirin also act in this manner. With these drugs, the compound is bound in the active site and the enzyme then converts the inhibitor into an activated form that reacts irreversibly with one or more amino acid residues.

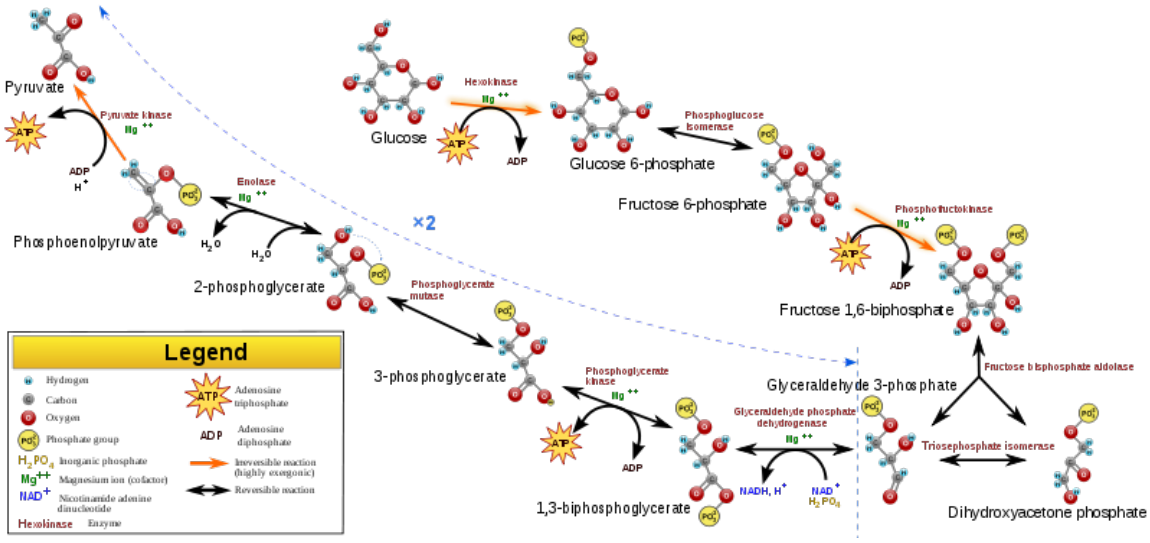
Uses of inhibitors

Since inhibitors modulate the function of enzymes they are often used as drugs. An common example of an inhibitor that is used as a drug is aspirin, which inhibits the COX-1 and COX-2 enzymes that produce the inflammation messenger prostaglandin, thus suppressing pain and inflammation. However, other enzyme inhibitors are poisons. For example, the poison cyanide is an irreversible enzyme inhibitor that combines with the copper and iron in the active site of the enzyme cytochrome c oxidase and blocks cellular respiration.

Biological function

Enzymes serve a wide variety of functions inside living organisms. They are indispensable for signal transduction and cell regulation, often via kinases and phosphatases. They also generate movement, with myosin hydrolysing ATP to generate muscle contraction and also moving cargo around the cell as part of the cytoskeleton. Other ATPases in the cell membrane are ion pumps involved in active transport. Enzymes are also involved in more exotic functions, such as luciferase generating light in fireflies. Viruses can also contain enzymes for infecting cells, such as the HIV integrase and reverse transcriptase, or for viral release from cells, like the influenza virus neuraminidase.

An important function of enzymes is in the digestive systems of animals. Enzymes such as amylases and proteases break down large molecules (starch or proteins, respectively) into smaller ones, so they can be absorbed by the intestines. Starch molecules, for example, are too large to be absorbed from the intestine, but enzymes hydrolyse the starch chains into smaller molecules such as maltose and eventually glucose, which can then be absorbed. Different enzymes digest different food substances. In ruminants which have herbivorous diets, microorganisms in the gut produce another enzyme, cellulase to break down the cellulose cell walls of plant fiber.



Glycolytic enzymes and their functions in the metabolic pathway of glycolysis

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. Sometimes more than one enzyme can catalyze the same reaction in parallel, this can allow more complex regulation: with for example a low constant activity being provided by one enzyme but an inducible high activity from a second enzyme.

Enzymes determine what steps occur in these pathways. Without enzymes, metabolism would neither progress through the same steps, nor be fast enough to serve the needs of the cell. Indeed, a metabolic pathway such as glycolysis could not exist independently of enzymes. Glucose, for example, can react directly with ATP to become phosphorylated at one or more of its carbons. In the absence of enzymes, this occurs so slowly as to be insignificant. However, if hexokinase is added, these slow reactions continue to take place except that phosphorylation at carbon 6 occurs so rapidly that if the mixture is tested a short time later, glucose-6-phosphate is found to be the only significant product. Consequently, the network of metabolic pathways within each cell depends on the set of functional enzymes that are present.

Control of activity

There are five main ways that enzyme activity is controlled in the cell.

1. **Enzyme production** (transcription and translation of enzyme genes) can be enhanced or diminished by a cell in response to changes in the cell's environment. This form of gene regulation is called enzyme induction and inhibition. For example, bacteria may become resistant to antibiotics such as penicillin because enzymes called beta-lactamases are induced that hydrolyse the crucial beta-lactam ring within the penicillin molecule. Another example are enzymes in the liver

called cytochrome P450 oxidases, which are important in drug metabolism. Induction or inhibition of these enzymes can cause drug interactions.

2. Enzymes can be **compartmentalized**, with different metabolic pathways occurring in different cellular compartments. For example, fatty acids are synthesized by one set of enzymes in the cytosol, endoplasmic reticulum and the Golgi apparatus and used by a different set of enzymes as a source of energy in the mitochondrion, through β-oxidation.
3. Enzymes can be regulated by **inhibitors and activators**. For example, the end product(s) of a metabolic 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 allocate materials and energy economically, and prevents the manufacture of excess end products. The control of enzymatic action helps to maintain a stable internal environment in living organisms.
4. Enzymes can be regulated through **post-translational modification**. This can include phosphorylation, myristoylation and glycosylation. For example, in the response to insulin, the phosphorylation of multiple enzymes, including glycogen synthase, helps control the synthesis or degradation of glycogen and allows the cell to respond to changes in blood sugar. Another example of post-translational modification is the cleavage 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 stops the enzyme from digesting the pancreas or other tissues before it enters the gut. This type of inactive precursor to an enzyme is known as a zymogen.
5. Some enzymes may become **activated when localized to a different environment** (e.g. from a reducing (cytoplasm) to an oxidizing (periplasm) environment, high pH to low pH etc.). For example, hemagglutinin in the influenza virus is activated by a conformational change caused by the acidic conditions, these occur when it is taken up inside its host cell and enters the lysosome.

Involvement in disease

Phenylalanine hydroxylase. Created from PDB 1KW0

Since the tight control of enzyme activity is essential for homeostasis, any malfunction (mutation, overproduction, underproduction or deletion) of a single critical enzyme can lead to a genetic disease. The importance of enzymes is shown by the fact that a lethal illness can be caused by the malfunction of just one type of enzyme out of the thousands of types present in our bodies.

One example is the most common type of phenylketonuria. A mutation of a single amino acid in the enzyme phenylalanine hydroxylase, which catalyzes the first step in the degradation of phenylalanine, results in build-up of phenylalanine and related products. This can lead to mental retardation if the disease is untreated.

Another example is when germline mutations in genes coding for DNA repair enzymes cause hereditary cancer syndromes such as xeroderma pigmentosum. Defects in these enzymes cause cancer since the body is less able to repair mutations in the genome. This causes a slow accumulation of mutations and results in the development of many types of cancer in the sufferer.

Naming conventions

An enzyme's name is often derived from its substrate or the chemical reaction it catalyzes, with the word ending in ***-ase***. Examples are lactase, alcohol dehydrogenase and DNA polymerase. This may result in different enzymes, called isozymes, with the same function having the same basic name. Isoenzymes have a different amino acid sequence and might be distinguished by their optimal pH, kinetic properties or immunologically. Isoenzyme and isozyme are homologous proteins. Furthermore, the normal physiological reaction an enzyme catalyzes may not be the same as under artificial conditions. This can result in the same enzyme being identified with two different names. *E.g.* Glucose isomerase, used industrially to convert glucose into the sweetener fructose, is a xylose isomerase *in vivo*.

The International Union of Biochemistry and Molecular Biology have 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 top-level classification is

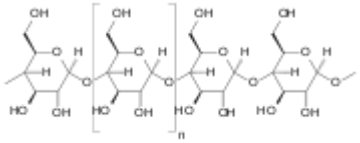
- EC 1 *Oxidoreductases*: catalyze oxidation/reduction reactions
- EC 2 *Transferases*: transfer a functional group (*e.g.* a methyl or phosphate group)
- EC 3 *Hydrolases*: catalyze the hydrolysis of various bonds
- EC 4 *Lyases*: cleave various bonds by means other than hydrolysis and oxidation
- EC 5 *Isomerases*: catalyze isomerization changes within a single molecule
- EC 6 *Ligases*: join two molecules with covalent bonds.

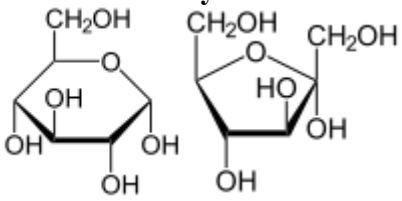
According to the naming conventions, enzymes are generally classified into six main family classes and many sub-family classes. Some web-servers, e.g., EzyPred and bioinformatics tools have been developed to predict which main family class and sub-family class an enzyme molecule belongs to according to its sequence information alone via the pseudo amino acid composition.

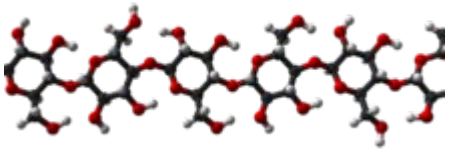
Industrial applications

Enzymes are used in the chemical industry and other industrial applications when extremely specific catalysts are required. However, enzymes in general are limited in the number of reactions they have evolved to catalyze and also by their lack of stability in organic solvents and at high temperatures. Consequently, protein engineering is an active area of research and involves attempts to create new enzymes with novel properties,

either through rational design or *in vitro* evolution. These efforts have begun to be successful, and a few enzymes have now been desiged "from scratch" to catalyze reactions that do not occur in nature.

Application	Enzymes used	Uses
Food processing  Amylases catalyze the release of simple sugars from starch.	Amylases from fungi and plants	Production of sugars from starch, such as in making high-fructose corn syrup. In baking, catalyze breakdown of starch in the flour to sugar. Yeast fermentation of sugar produces the carbon dioxide that raises the dough.
	Proteases	Biscuit manufacturers use them to lower the protein level of flour.
Baby foods	Trypsin	To predigest baby foods
Brewing industry  Germinating barley used for malt	Enzymes from barley are released during the mashing stage of beer production.	They degrade starch and proteins to produce simple sugar, amino acids and peptides that are used by yeast for fermentation.
	Industrially produced barley enzymes	Widely used in the brewing process to substitute for the natural enzymes found in barley.
	Amylase, glucanases, proteases	Split polysaccharides and proteins in the malt.
	Betaglucanases and arabinoxylanases	Improve the wort and beer filtration characteristics.
	Amyloglucosidase and pullulanases	Low-calorie beer and adjustment of fermentability.
	Proteases	Remove cloudiness produced during storage of beers.
	Acetolactatedecarboxylase (ALDC)	Increases fermentation efficiency by reducing diacetyl formation.
Fruit juices	Cellulases, pectinases	Clarify fruit juices.

Dairy industry  Roquefort cheese	Rennin, derived from the stomachs of young ruminant animals (like calves and lambs)	Manufacture of cheese, used to hydrolyze protein
	Microbially produced enzyme	Now finding increasing use in the dairy industry
	Lipases	Is implemented during the production of Roquefort cheese to enhance the ripening of the blue-mould cheese.
	Lactases	Break down lactose to glucose and galactose.
Meat tenderizers	Papain	To soften meat for cooking
Starch industry  Glucose Fructose	Amylases, amyloglucosideases and glucoamylases	Converts starch into glucose and various syrups.
	Glucose isomerase	Converts glucose into fructose in production of high fructose syrups from starchy materials. These syrups have enhanced sweetening properties and lower calorific values than sucrose for the same level of sweetness.
Paper industry  A paper mill in South Carolina	Amylases, Xylanases, Cellulases and ligninases	Degrade starch to lower viscosity, aiding sizing and coating paper. Xylanases reduce bleach required for decolorising; cellulases smooth fibers, enhance water drainage, and promote ink removal; lipases reduce pitch and lignin-degrading enzymes remove lignin to soften paper.
Biofuel industry	Cellulases	Used to break down cellulose into sugars that can be fermented
	Ligninases	Use of lignin waste



Cellulose in 3D

Biological detergent	Primarily proteases, produced in an extracellular form from bacteria	Used for presoak conditions and direct liquid applications helping with removal of protein stains from clothes
	Amylases	Detergents for machine dish washing to remove resistant starch residues
	Lipases	Used to assist in the removal of fatty and oily stains
	Cellulases	Used in biological fabric conditioners
Contact lens cleaners	Proteases	To remove proteins on contact lens to prevent infections
Rubber industry	Catalase	To generate oxygen from peroxide to convert latex into foam rubber
Photographic industry	Protease (ficin)	Dissolve gelatin off scrap film, allowing recovery of its silver content.
Molecular biology  Part of the DNA double helix	Restriction enzymes, DNA ligase and polymerases	Used to manipulate DNA in genetic engineering, important in pharmacology, agriculture and medicine. Essential for restriction digestion and the polymerase chain reaction. Molecular biology is also important in forensic science.