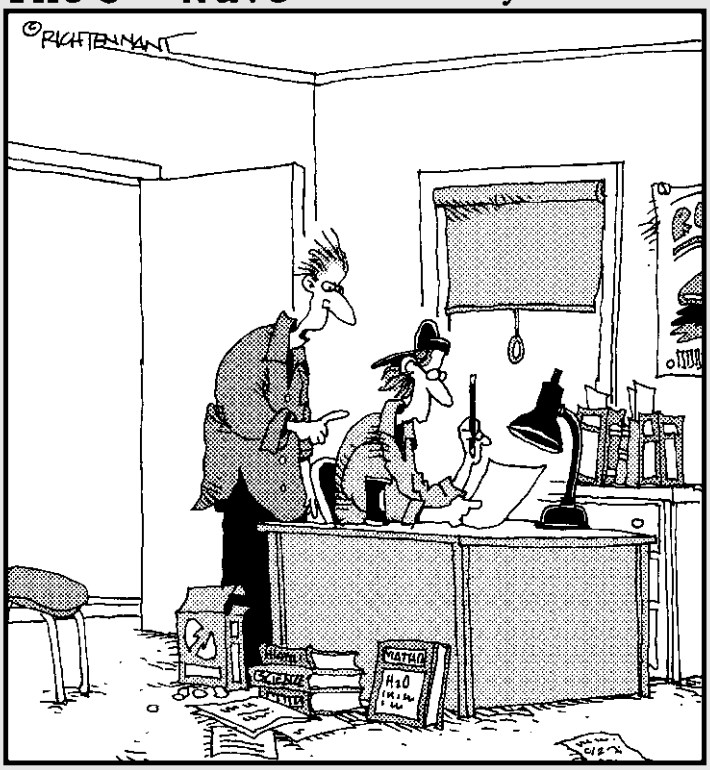
Part III

Carbohydrates, Lipids, Nucleic Acids, and More

The 5th Wave By Rich Tennant



"Your formula for a carbohydrate is close, but not entirely accurate. I'm pretty sure carbohydrates consist of carbon, hydrogen, oxygen, sour cream, and bacon bits."

In this part . . .

We go over many biochemical species. Beginning with carbohydrates, we move on to perhaps less tasty-sounding fare: lipids and steroids. Next up: nucleic acids and that amazing encyclopedia about you that sits on the shelf inside every one of your cells: the genetic code of life, guest starring DNA and RNA. After that we end up talking about vitamins and hormones.

Chapter 7

What We Crave: Carbohydrates

In This Chapter

- Finding out about carbohydrates
- Checking out monosaccharides
- Reviewing oligosaccharides

Admit it: You love your carbohydrates. From simple sugars to complex carbohydrates, a day without carbs is a boring day. And carbs are plentiful: In terms of mass, carbohydrates are the most abundant biochemical.

Carbohydrates are a product of photosynthesis, where inorganic carbon dioxide becomes organic carbon with the utilization of solar energy, accompanied by the release of oxygen gas. The conversion of solar energy to chemical energy produces carbohydrates, which are the primary energy source for metabolic processes. Carbs are not only an important energy source but also are the raw materials for the synthesis of other biochemicals. They have structural uses and are a component of nucleic acids.

The term carbohydrate originally referred to "hydrates of carbon" because the general formula of these compounds was $C_nH_{2n}O_n$ or $C_n(H_2O)_n$. However, some materials with this general formula are *not* carbohydrates, and some carbohydrates do not have this general formula. It is better (though not much more conversational) to define carbohydrates as *polyhydroxyaldehydes and polyhydroxyketones and their derivatives*.

Natural carbohydrates are subdivided into *monosaccharides,* or simple sugars containing three to nine carbon atoms, *polysaccharides,* or polymers of monosaccharides, and an intermediate category of *oligosaccharides,* with two to ten monosaccharide units joined. The most important oligosaccharides to humans economically and biologically are the *disaccharrides.*

Properties of Carbohydrates

In general, the names of most carbohydrates are recognizable by an *-ose* suffix. An *aldose,* for example, is a monosaccharide where the carbonyl group is an aldehyde, whereas in a *ketose* the carbonyl group is a ketone. Chemists also use roots referring to the number of carbon atoms. *Pentoses,* five-carbon atoms, and hexoses, six-carbon atoms, are very important. *Trioses, tetroses,* and so on are also found in nature. It is possible to combine these generic names to give terms such as *aldohexose* and *ketopentose.*

They contain one or more chiral carbons

Chiral carbons are those that have four different groups, atoms or groups of atoms, attached to them. Most carbohydrates contain one or more chiral carbons. For this reason, they are *optically active,* rotating polarized light in different directions and many times having different activity in biological systems. Fischer projections are useful in indicating the asymmetry around each of the chiral carbon atoms. Figure 7-1 illustrates the construction of a Fischer projection. In the Fischer projection, the vertical lines project back, and the horizontal lines project forward. There are two arrangements of groups around a chiral center: These arrangements are called *enantiomers* and represent nonsuperimposable mirror images, like left and right gloves. The enantiomers comprise a D/L pair, where the D form rotates polarized light to the right, and the L form rotates polarized light to the left.

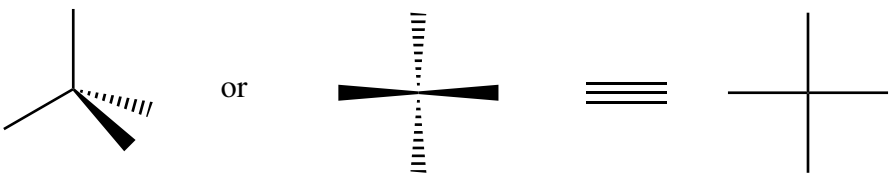


Figure 7-1: The relationship between the three-dimensional structure and the Fischer projection.

Fischer projections are not only useful for representing chiral carbons, but they are useful in identifying which enantiomeric form is present in a sample. To determine whether two projections are enantiomers or just simply two representations of the same molecule, it is necessary to compare the

two drawings. During this comparison, rotate one of the projections by 180° about an axis perpendicular to the plane of the paper (in other words, turn the paper while it's lying on a table). If the diagrams are identical after this rotation, then they are simply two representations of the same molecule. If the diagrams are not identical, they represent a pair of enantiomers.

They have multiple chiral centers

Because many carbohydrates have more than one chiral center (more than one chiral carbon), there can be more than two stereoisomers. The number of stereoisomers is 2^n, where n is the number of chiral carbons. For example, if the compound has two chiral carbons, there are a total of four stereoisomers — two pairs of enantiomers. Although the members of each pair are enantiomers, members of the different pairs are referred to as *diastereomers*.

The structure for D-glucose, a typical monosaccharide, appears in Figure 7-2. In this figure (a Fischer projection), all the carbon atoms except the ones at the top and bottom are chiral — a common way of representing monosaccharides. The carbon atoms appear as a vertical chain with the carbonyl carbon as near the top as possible (it is at the top for an aldose). Numbering the carbon atoms begins at the top, as indicated with the top carbon labeled C_1. The highest-numbered chiral carbon in this case is number five. By convention, if the –OH on this carbon atom appears on the right, it's the D form of the monosaccharide; if it is on the left, it's the L form.

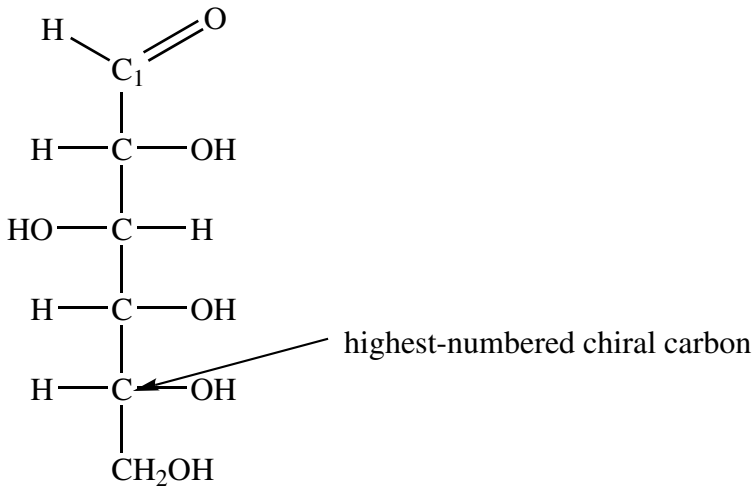


Figure 7-2: Structure of D-glucose.

Any change in the relative positions of the groups attached about any of the chiral carbon atoms in a Fischer projection produces either a different enantiomer or a diastereomer (assuming that the result is not simply a different way of drawing the original structure). In the case of D-glucose, with 4 chiral centers, there are 16 structures. One is D-glucose, and another is its enantiomer: L-glucose. The remaining 14 structures are diastereomers consisting of 7 enantiomeric pairs. Each of the enantiomeric pairs consists of a different monosaccharide. In the case of glucose, you have glucose, allose, altrose, mannose, gulose, idose, galactose, and talose, shown in Figure 7-3. The different D-ketohexoses are in Figure 7-4.

A Sweet Topic: Monosaccharides

The *monosaccharides,* or simple sugars, are an important class of biochemicals. For example, glucose, one of the most common monosaccharides, is the primary form of energy storage in the body. Most monosaccharides taste sweet. The relatively large number of hydroxyl groups and the polar carbonyl group mean that most of these compounds are water-soluble. And, as mentioned earlier, most are optically active.

The most stable monosaccharide structures: Pyranose and furanose forms

The most important monosaccharide is D-glucose (one form of D-glucose appears back in Figure 7-2). This form exists in equilibrium with two slightly different ring forms. The ring form results from an internal cyclization reaction, where a two groups on the same molecule join forming a ring. (The rings appear as planar structures even though the actual structures are not planar.) This cyclization involves a reaction between the carbonyl group and the highest-numbered chiral carbon, producing one of the following structures: a hemiacetal, an acetal, a hemiketal, or a ketal. In the case of D-glucose a pyranose ring forms. Haworth projection formulas are useful when representing the ring forms of a monosaccharide (Figure 7-5).

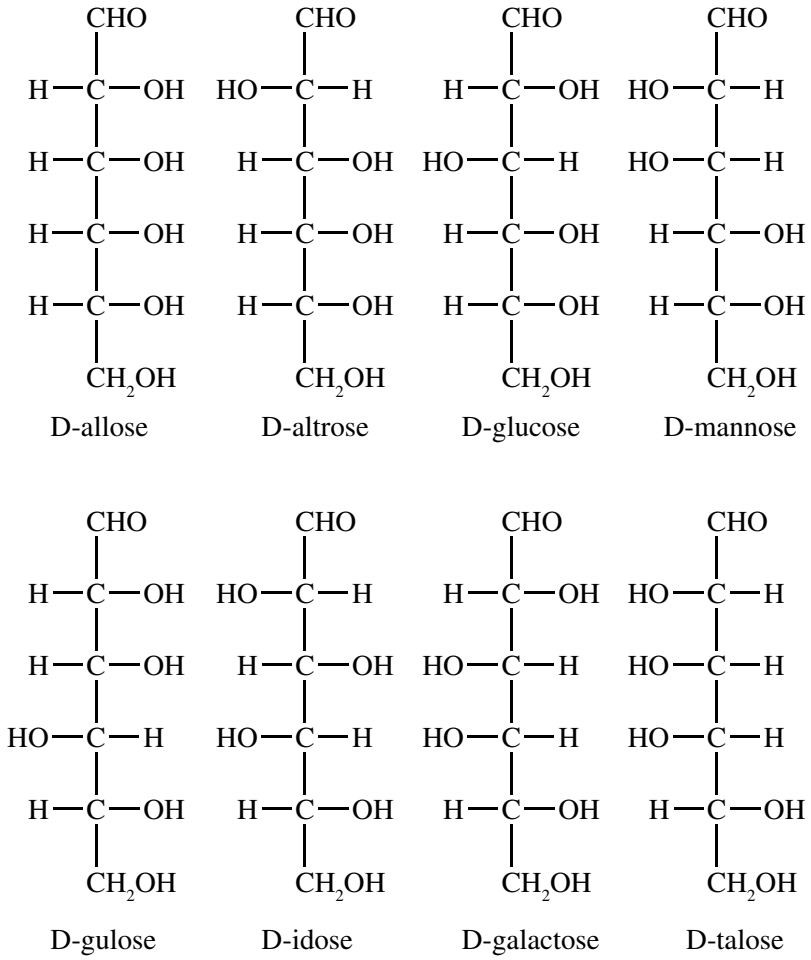


Figure 7-3: Structures of the D-aldohexoses.

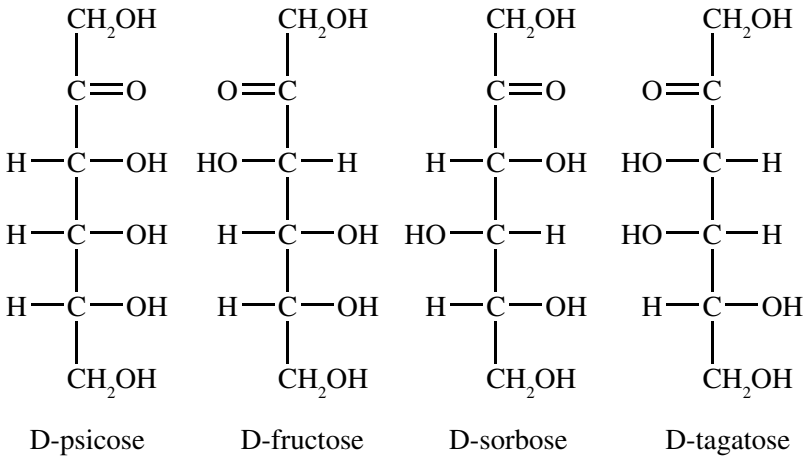


Figure 7-4: Structures of the D-ketohexoses.

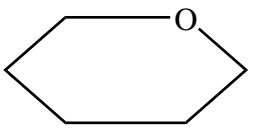


Figure 7-5: A pyranose ring.

There are two possible structures for the pyranose structure of D-glucose (see Figure 7-6), and other monosaccharides. If we examine the Fischer projection for D-glucose, we can see why:

- **Structure 1:** Hydroxyl group on one carbon in the up position.
- **Structure 2:** Hydroxyl group on the corresponding carbon in the down position.

If you "bend" the carbonyl group around and then allow a reaction with the highest numbered chiral carbon, you have two choices: right or left. This gives two forms known as *anomers.* The anomers are labeled α and β. The carbonyl carbon — C_1, in this case – is the anomeric carbon, which should be on the right side of a Haworth projection. The relative positions of –H and –OH about the anomeric carbon determine whether it is the α or β form. The hydroxyl group points down in the α form, and the hydroxyl group points up in the β form. (Reversing the drawing of the rings may give a structure with the opposite orientation of the groups about the anomeric carbon.) In solution, each of the anomers is in equilibrium with the open chain form represented by the Fischer projection. Therefore, there is an interconversion between the α and β forms known as *mutarotation.*

It is also possible to form a five-membered ring, called a *furanose* ring. A simplified furanose structure appears in Figure 7-7. Ribose is an example of a monosaccharide that may form a furanose ring.

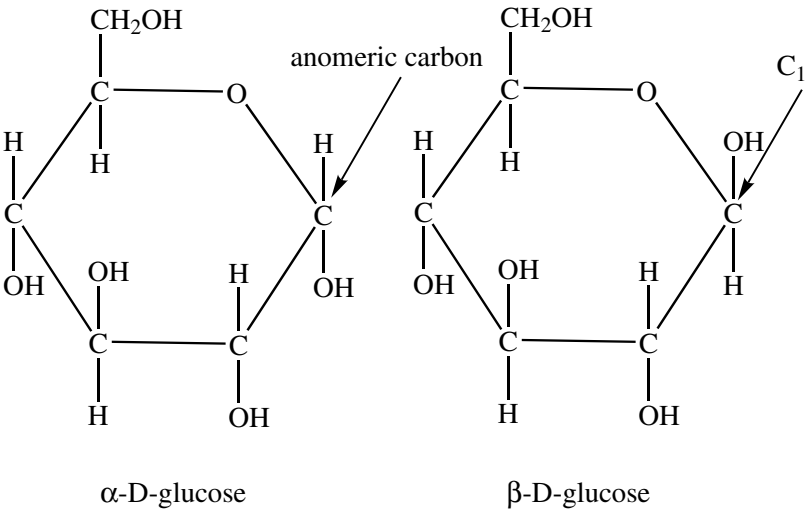


Figure 7-6: The Haworth projections for the pyranose structures of D-glucose.

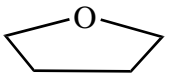


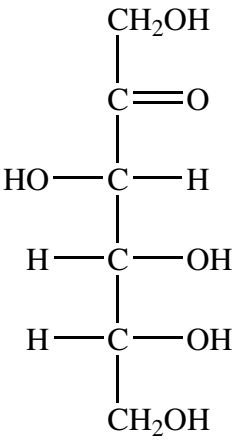
Figure 7-7: A furanose ring.

The pyranose and furanose forms are the thermodynamically more stable forms of the monosaccharides. In general, in the equilibria involving ring and open forms, less than ten percent of the molecules are in the open form. Fructose is a ketose that may form a furanose ring. Structures of D-fructose are shown in Figure 7-8.

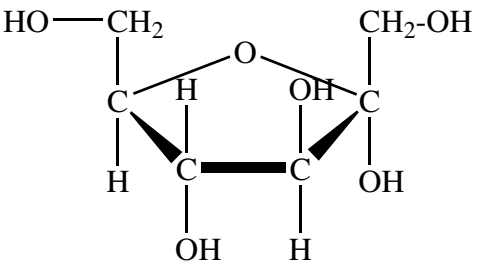
Chemical properties of monosaccharides

Many aldoses, because of the aldehyde group, are reducing sugars — that is, they are reducing agents in certain redox reactions. A number of tests for reducing sugars, include using Fehling's solution or Benedict's solution. These tests are useful to check for glucose in the urine of a diabetic.

The reaction of a monosaccharide with methanol, CH_3OH, in the presence of hydrochloric acid, HCl, replaces the hydrogen atom of the hydroxyl group on C_1 with a methyl group, forming a *glycosidic bond.* (Nitrogen may also be part of a glycosidic bond.) Once the glycoside forms, the ring is "locked," meaning it will not reopen; therefore, mutarotation will no longer take place. A formerly reducing sugar will no longer be a reducing sugar.



D-fructose



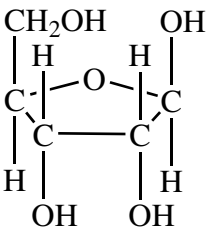
α-D-fructose

Figure 7-8: Two forms of D-fructose.

Derivatives of the monosaccharides

A variety of derivatives of the monosaccharides are formed through the alteration of one or more of the functional groups present. In this section we examine some of these derivatives using D-ribose as the parent monosaccharide. Two forms of the structure of D-ribose appear in Figure 7-9.

The reduction of the carbonyl group to an alcohol yields a reduced sugar (polyhydric alcohol). The reduction of D-ribose forms D-ribitol (Figure 7-10).



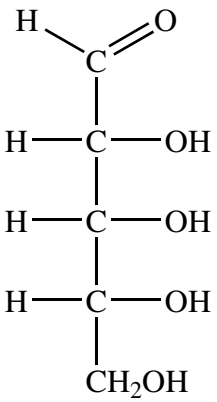


Figure 7-9: Two representations of the structure of D-ribose.

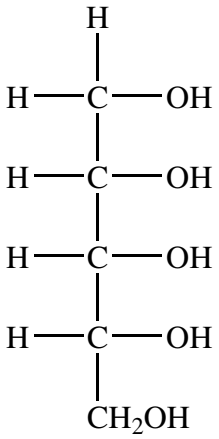


Figure 7-10: D-ribitol.

It is also possible to oxidize a monosaccharide to a carboxylic acid. There are two important oxidations: oxidation of an aldehyde (aldose) to an aldonic acid, and oxidation of the alcohol on the highest-numbered carbon atom to a uronic acid. In the case of D-ribose, it is possible to form D-ribonic acid (Figure 7-11) or D-ribouronic acid (Figure 7-12).

Monosaccharides, like all alcohols, may react with acids to form esters. The combination with phosphoric acid (phosphate sugar) is a biologically important reaction. Any of the alcohol groups may react. Figure 7-13 shows one example: D-ribose-1-phosphate. (The "1" refers to the attachment of the phosphate group to C_1.)

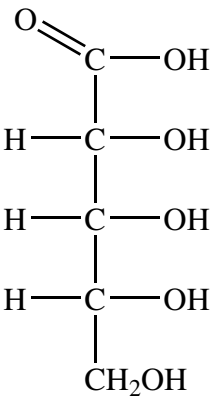


Figure 7-11: D-ribonic acid, an aldonic acid.

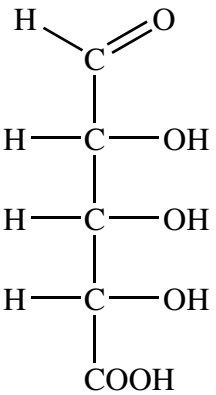


Figure 7-12: D-ribouronic acid, a uronic acid.

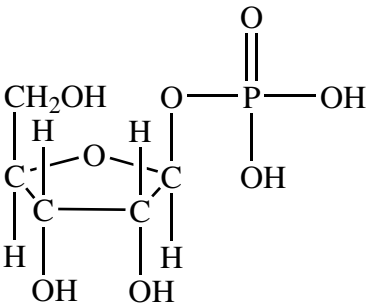


Figure 7-13: D-ribose-1-phosphate.

The most common monosaccharides

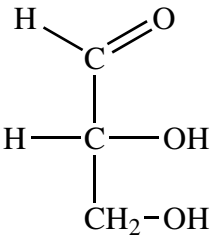
Glucose, or blood sugar, is also known as dextrose. The anomeric carbon is part of a hemiacetal, and the name of the pyranose structure is *glucopyranose.*

Blood is commonly tested for blood glucose levels, which are controlled by the hormone *insulin,* produced within the body in the pancreas. In a healthy human, blood glucose levels rise slightly after eating. The pancreas then releases insulin in order to keep the levels from rising too high. A healthy individual has a fasting blood sugar of 70–99 milligrams of glucose per deciliter of blood and 70–145 mg/dL two hours after eating. The American Diabetes Association associates blood glucose levels of 126 mg/dL (fasting) or 200 mg/dL (two hours after eating) with *diabetes* — the inability of the pancreas to produce enough insulin.

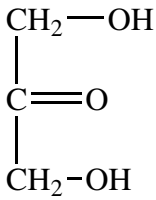
The simplest aldose is glyceraldehyde, and the simplest ketose is dihydroxy acetone. Figure 7-14 shows the structures of these two compounds.

The beginning of life: Ribose and deoxyribose

The monosaccharides D-ribose and D-deoxyribose are important components of the nucleic acids. They are present in these complex molecules in the form of a furanose ring. In addition, they are present as the β anomer. The difference between these two monosaccharides is that there is one less oxygen atom present in deoxyribose, hence the "deoxy." The "missing" oxygen atom is at C_2. The structures of these two sugars appear in Figure 7-15.

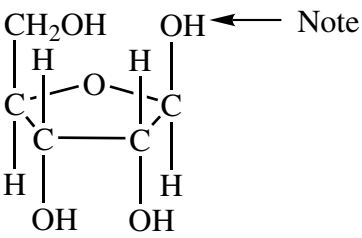


D-glyceraldehyde

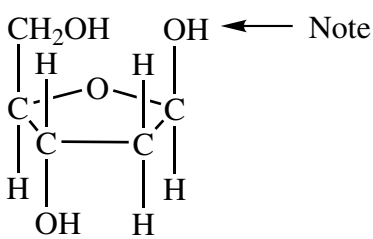


Dihydroxyacetone

Figure 7-14: Glyceraldehyde and dihydroxyacetone.



ribose



deoxyribose

Figure 7-15: The arrows point to the positions of the alcohol groups leading to these becoming the β anomers.

Sugars Joining Hands: Oligosaccharides

The joining of two or more monosaccharides forms an *oligosaccharide,* with two to ten monosaccharide units, or a *polysaccharide,* a polymer having many more monosaccharide units. One or more glycoside linkages hold the monosaccharides together. The simplest, and most common, oligosaccharides are the disaccharides.

Keeping it simple: Disaccharides

A *disaccharide* is an oligosaccharide composed of two monosaccharide units. The best-known disaccharide (and surely the most well liked) is probably sucrose, which you know as table sugar or cane sugar. Each molecule of this sugar is a combination of a glucose molecule and a fructose molecule. There are many other important disaccharides — among them, maltose, malt sugar, and lactose, milk sugar, each of which contains two molecules of glucose. Due to its simplicity,where two identical monosaccharides are joined, we will use maltose to illustrate several points concerning disaccharides, and, by implication, other oligosaccharides and polysaccharides. The structure of maltose appears in Figure 7-16.

The oxygen atom joining the two glucose rings of the maltose molecule in Figure 7-16 is a glycoside linkage — an α(1-4) linkage. The α refers to the anomeric form of the ring on the left. If β-D-glucose were present instead, then lactose would result (see Figure 7-17). The 1-4 indicates that C_1 of the left ring links to C_4 of the right ring. The loss of a water molecule accompanies the formation of the linkage, which locks the left ring so that mutarotation is no longer possible. The locked ring is also no longer a reducing sugar. But mutarotation can still occur on the right ring.

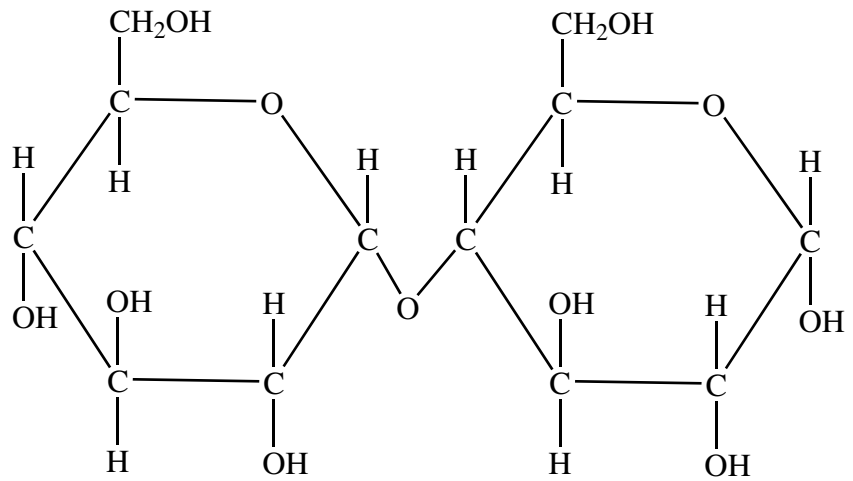


Figure 7-16: The structure of maltose with a α(1-4) linkage present.

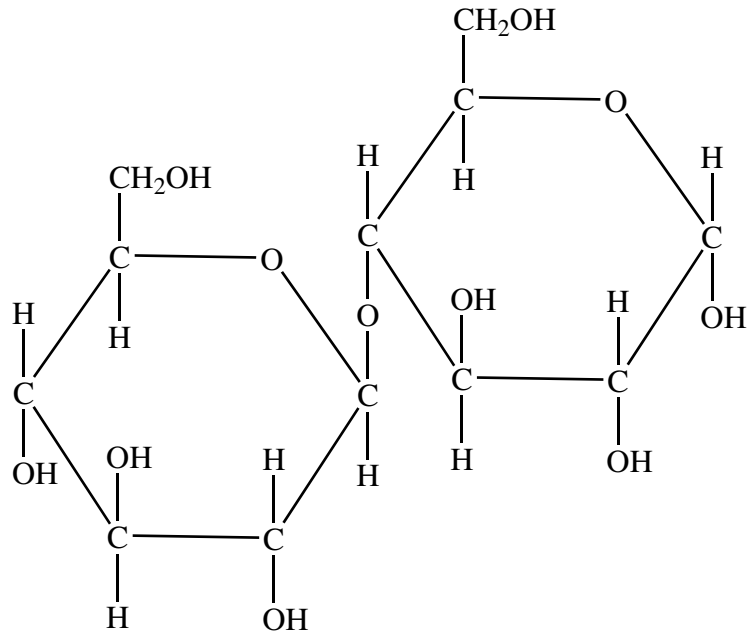


Figure 7-17: Lactose showing its β(1-4) linkage.

Sucrose, table sugar, is a disaccharide like maltose. It forms when D-glucose links to a D-fructose by a α(1-2) linkage. This situation locks both rings so that mutarotation of neither ring can occur. The formation of sucrose appears in Figure 7-18.

If the sweetness of sucrose is 100, then the sweetness level of glucose is 74, and that of fructose, 173. Fructose, found in corn syrup, is the sweetest common sugar — meaning you need less of it to make foods taste sweet. Less sugar translates to fewer calories. There are also naturally occurring, sweet-tasting proteins, some of which are hundreds of times sweeter than sugar.

Quite a few artificial sweeteners are used in commercial products. The best known are *saccharin* (about 500 times as sweet as sucrose, *aspartame* (200 times as sweet as sucrose), and *sucralose* (marketed as Splenda) — which is a whopping 600 times as sweet as sucrose. Sucralose is created by replacing three of the hydroxyl groups of sucrose with chlorines.

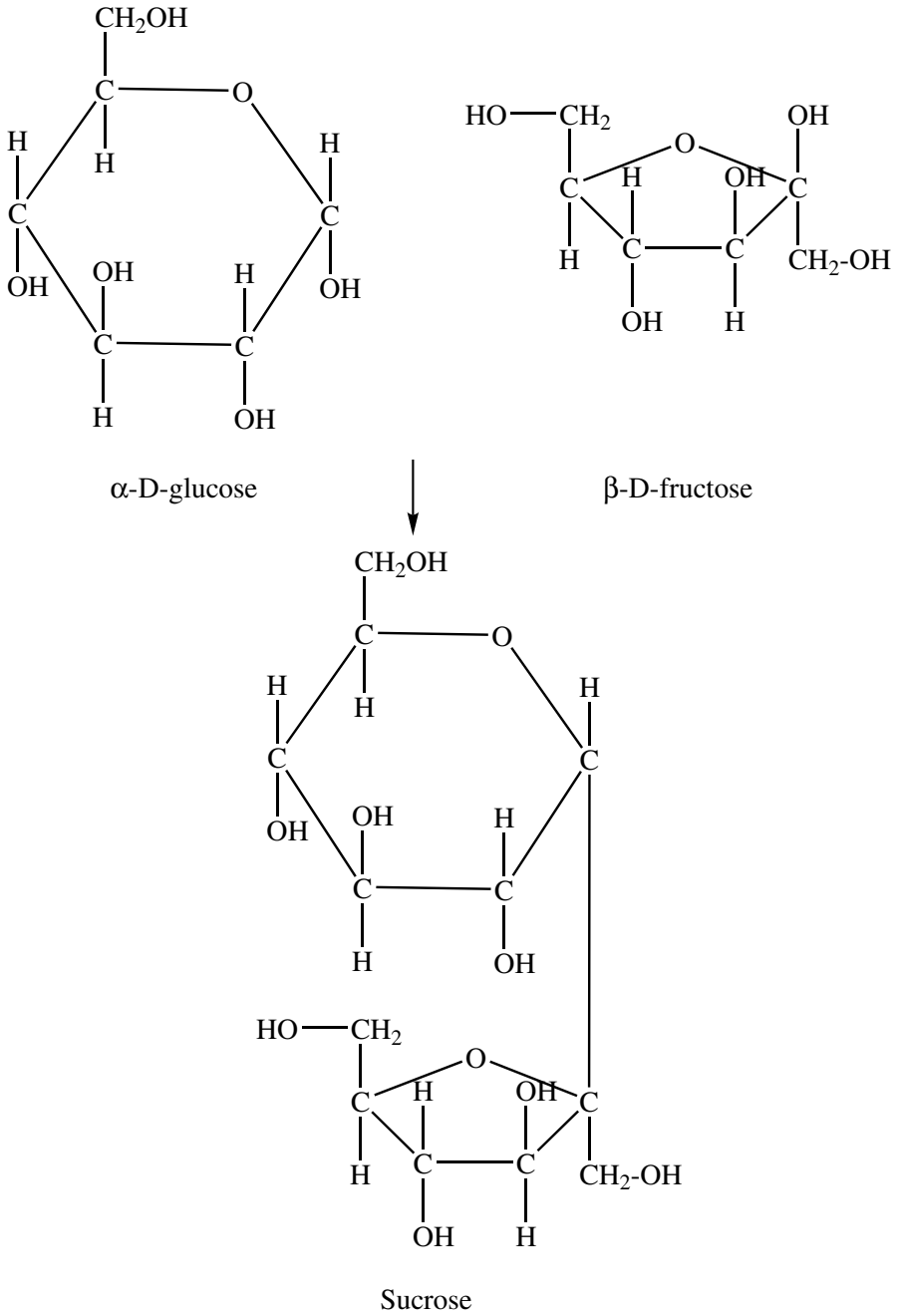


Figure 7-18: Structure of sucrose, formed by joining α-D-glucose and β-D-fructose.

Starch and cellulose: Polysaccharides

The two most important polysaccharides are starch and cellulose. Both of these are polymers of D-glucose. The basic difference between these two polymers is the linkages between the glucose units. Starch is related to maltose and cellulose is related to lactose.

Bread, pasta, and potatoes: Starches

Of all the carbohydrates, we think starches are our favorite. Bring on the potatoes and pastas! The different types of these lovely, delicious polysaccharides are very closely related by the linkages between their monomer units. *Starch* is a polymer of α-D-glucose. There are three common types of starch: amylase, amylopectin, and glycogen. Amylase is the combination of α(1-4) glucose groups. Amylopectin, like amylase, has α((1-4) glucose linkages, but, in addition, it has α((1-6) branches. Glycogen, animal starch, is similar to amylopectin except that it has more branches. All three are useful in storing glucose, and all three give an intense dark blue color in the presence of iodine — a simple and useful test.

Keeping the termites happy: Cellulose

Ever wonder why you can eat a potato but not a tree? *Cellulose* is similar to starch except that the linkages are β(1-4) glucose. The primary use of cellulose in nature is structure. Cleavage of the linkages is only possible with enzymes produced by certain bacteria or fungi. For this reason, only certain creatures, such as termites, and ruminants like cows, who have these bacteria in their GI tracts, can digest and utilize cellulose as an energy source. Cellulose is one of the most abundant biochemicals on earth.

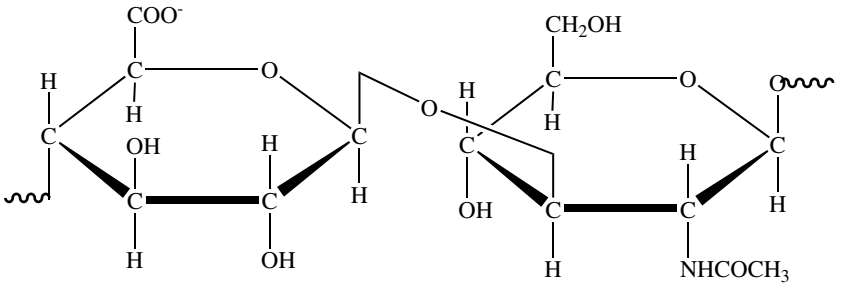
Biological connective tissue: Acidic polysaccharides

One of the major uses of polysaccharies in the body is the area of connective tissues, the compounds that hold our parts together. This group of tissue includes tendons, ligaments, and collagen. (Fuller lips, anyone?) Acidic polysaccharides are important to the structure and function of connective tissue. The repeating units of these polysaccharide derivatives are disaccharides. One of the components of the disaccharide is an *amino sugar* (where an amino group substitutes for an alcohol group). One or both of the components of the disaccharide unit have a negatively charged group (either a sulfate or a carboxylate). Examples are hyaluronic acid and heparin. The hyaluronate and heparin repeating units appear in Figure 7-19.

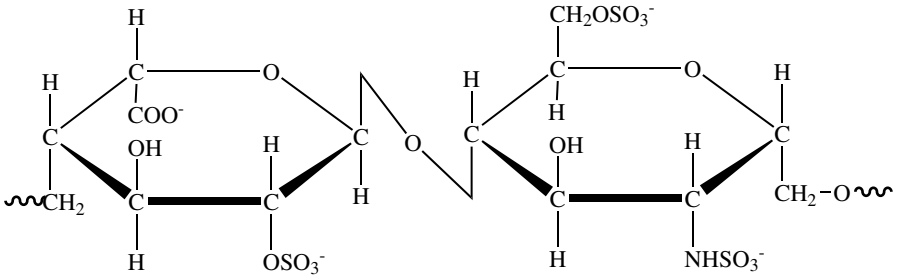
Heparin is used to treat and prevent blood clots from forming, especially in the lungs and legs. It is commonly used after dialysis, after surgery or when the patient has been unable to move for extended periods of time. It acts as an anticoagulant by binding to one of the anti-clotting proteins, increasing its efficiency up to a thousand-fold.

Glycoproteins

Most of the proteins occurring in blood serum are *glycoproteins,* which are proteins with carbohydrates attached. The presence of the carbohydrate tends to increase the hydrophilic nature of the protein. In general, the linkage is by attachment to an asparagine, serine, or threonine residue. Some soluble proteins and some membrane proteins are glycoproteins. We will see glycoproteins again at various times in later chapters.



Hyaluronate



Heparin

Figure 7-19: Disaccharide repeating units in hyaluronate and heparin.

Chapter 8

Lipids and Membranes

In This Chapter

- Living with lipids
- Examining triglycerides
- Finding out about membranes
- Seeing how steroids and other lipids operate

Along with cholesterol, lipids tend to have a bad reputation in today's world, even though they are absolutely necessary to good health. The *lipids* are an exceedingly diverse group of biologically important materials that are distinguished by solubility. A lipid is a member of a group of compounds that are not soluble (or only sparingly soluble) in water but that are soluble in nonpolar solvents or solvents of low polarity. The nonpolar nature of lipids is due to the fact that a large portion of the molecule contains only carbon and hydrogen. If there were significant amounts of oxygen or nitrogen in the structure, the substance would be more polar and hence more soluble in water.

Lovely Lipids: An Overview

Lipids have many important biological roles, including being highly concentrated energy sources, membrane components, and molecular signals. There are lots of kinds of lipids. Figure 8-1 provides a diagram showing the relationship between many of the different categories of lipids. Arachidonic acid, a fatty acid, appears in Figure 8-1 twice — once as the precursor (compound leading) to leukotrienes and prostaglandins and again as a member of the fatty acid group. We double-listed arachidonic acid this way because of its very different roles in these two chemical pathways.

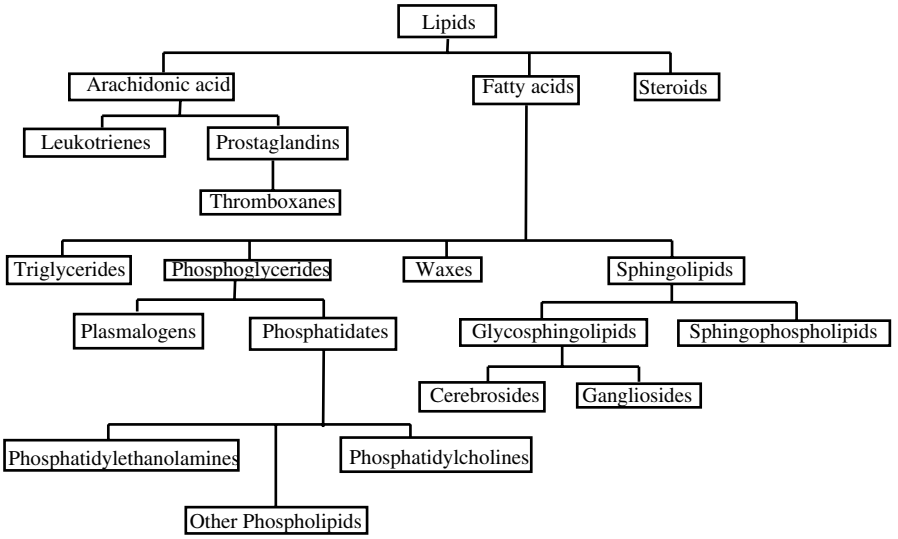


Figure 8-1: The relationships among the many types of lipids.

In the body, lipids provide energy storage and structure (cell membranes) and regulate bodily functions. Many of the lipids work like soap and detergents. Like soaps, lipids have a nonpolar region — usually a fatty acid — and a polar region. Figure 8-2 shows a representation of the structure of a soap.

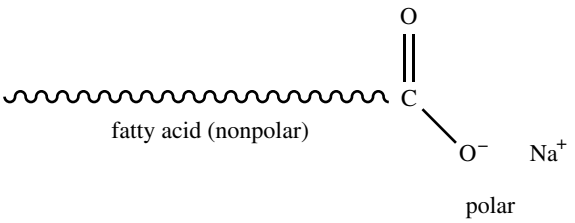


Figure 8-2: Representation of a soap.

In water, soap forms a *micelle,* (see Figure 2-3 in Chapter 2) in which the nonpolar portions of the different molecules coalesce and leave the polar portions on the outside next to the water. If there is any other nonpolar material present, such as grease from dirty dishes, it tends to migrate to the interior of the micelle. With the polar portions of the soap molecules on the outside, the micelle appears as one large polar molecule instead of a number of smaller molecules that have polar and nonpolar regions.

The *dual solubility* nature of soap is why it removes grease or oil from your skin or clothes. The grease or oil is nonpolar and, therefore, is not soluble in water. The soap forms a micelle that surrounds the grease/oil in the nonpolar portion of the micelle. The polar end of the soap micelle is soluble in water,

allowing the grease and oil to be removed during rinsing. Although many different types of lipids exist, our discussion in this chapter focuses on the following four types of lipids:

- **Fatty acids and derivatives (esters):** Fats, oils, and waxes
- **Complex lipids:** Phosphoglycerides and sphingolipids
- **Steroids**
- **Arachidonic acid devivatives:** Prostaglandins, thromboxanes, and eukotrienes

Lipids are important not only as individual molecules but also in terms of their interactions with other lipids and non-lipids in the formation of lipid bilayers or cell membranes. These interactions occur both at the cell boundary and around some interior structures. The fatty acids portions of the lipids are especially important in their physical and chemical properties. The naturally occurring fatty acids have a few key features:

- They are all straight-chained with generally 10–20 (but sometimes more) carbon atoms.
- They have an even number of carbon atoms.
- If carbon-carbon double bonds are present, only the cis-isomer is present.

Table 8-1 lists a few of the common fatty acids.

Table 8-1 Common Fatty Acids

Lauric acid	$CH_3(CH_2)_{10}COOH$
Myristic acid	$CH_3(CH_2)_{12}COOH$
Palmitic acid	$CH_3(CH_2)_{14}COOH$
Palmitoleic acid	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
Stearic acid	$CH_3(CH_2)_{16}COOH$
Oleic acid	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
Linoleic acid	$CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOH$
Linolinic acid	$CH_3(CH_2CH{=}CH)_3(CH_2)_7COOH$
Arachidonic acid	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH$

A *wax* is a simple ester of a fatty acid and a long-chain alcohol. The fatty acid typically contains at least 10 carbon atoms, whereas the alcohol portion is typically 16–30 carbon atoms. In general, a wax, such as the wax in your ears, serves as a protective coating. Because they tend to be somewhat unreactive, we do not discuss waxes in much detail in this book.

A Fatty Subject: Triglycerides

Fats (and oils) are *triglycerides* or *triacylglycerols.* That is, they are triesters of fatty acids with glycerol. *Glycerol* is a trihydroxy alcohol (see Figure 8-3). In a fat, each of the three alcohol groups becomes part of an ester through the reaction with a fatty acid. The fatty acids may or may not be the same.

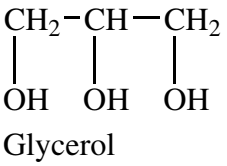


Figure 8-3: Structure of glycerol.

Properties and structures of fats

The basic difference between a fat and an oil is that a fat is a solid at room temperature and an oil is a liquid. That said, two important structural factors distinguish a fat from an oil. One is the size of the fatty acids, and the other is the presence or absence of double bonds. The longer the fatty acid chain, the higher the melting point. The greater the number of carbon-carbon double bonds, the lower the melting point.

A *saturated* fat consists of fatty acids with no carbon-carbon double bonds. An *unsaturated* fat has a double bond while a *polyunsaturated* fat has multiple double bonds.

There are more than 70 known naturally occurring fatty acids. In most natural fats, there is a cis geometry about the double bonds. The presence of double bonds puts "kinks" in the carbon chain, which prevent the fatty acid chains from stacking together as roughly parallel chains. The inability of unsaturated fatty acid chains to stack together inhibits the fat's ability to solidify.

The treatment of an unsaturated fat or oil with hydrogen in the presence of a catalyst such as nickel will lead to hydrogenation of some or all of the carbon-carbon double bonds, forming carbon-to-carbon single bonds. This procedure changes an unsaturated fat into a saturated fat. In most cases, only

partial hydrogenation takes place, and the hydrogenation raises the melting point of the compound. By this procedure, it is possible to convert an oil (liquid) into a fat (solid). Incomplete hydrogenation may change some of the cis arrangements into trans arrangements, producing a *transfat.*

Figure 8-4 shows the structure of a typical fat. Note that that the two upper fatty acid chains (saturated) "stack" next to each other, but the lower chain (unsaturated) does not.

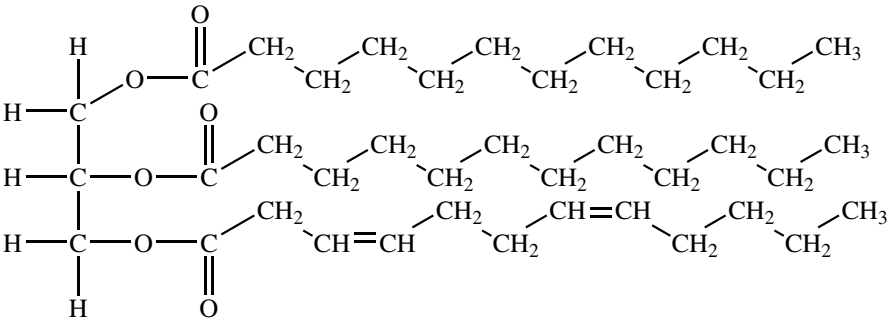


Figure 8-4: Structure of a typical fat: Upper chains are saturated, bottom chain is unsaturated.

Cleaning up: Breaking down a triglyceride

For centuries, the treatment of a fat (commonly animal fat) with a strong base catalyst (generally lye — sodium hydroxide) has been used to produce soap. John's grandmother made soap by boiling hog fat with wood ashes — which contain potassium and sodium hydroxides. She then skimmed off the soap and pressed it into cakes. Unfortunately, Granny wasn't very good at getting all the proportions just right and tended to use too much base, making the soap very alkaline. In this kind of reaction, called a *saponification reaction,* hydrolysis of the ester groups in the presence of a base yields glycerol and the carboxylate ions of the three fatty acids. A soap is really a sodium or potassium salt of a fatty acid. The calcium and magnesium analogues, on the other hand, are insoluble. If the soap is used with *hard* water (containing calcium or magnesium ions), it precipitates as a greasy scum: bathtub ring.

Acids also catalyze the hydrolysis of a fat to produce glycerol and a fatty acid. Acid hydrolysis is reversible, whereas the presence of excess base inhibits the reverse of saponification. During digestion, lipases break down triglycerides, and bile salts make the fatty acid portions soluble. A *lipase* is an enzyme that catalyses the decomposition of a fat. *Bile salts* are oxidation products of cholesterol that act as detergents to make the products of the breakdown soluble. In humans, absorption of the products occurs in the small intestine.

No Simpletons Here: Complex Lipids

So far, we have been discussing simple lipids. However, some lipids are somewhat more complex. In general, complex lipids are esters of glycerol or some other alcohol. The two major categories of complex lipids are the phosphoglycerides and the sphingolipids. The *phosphoglycerides* are the plasmalogens and the phosphatidates. The *sphingolipids* are the glycosphingolipids and the sphingophospholipids. (Further subdivision is shown back in Figure 8-1.) A phospholipid is either a phosphoglyceride or a sphingophospholipid. Phospholipids are major components of membranes. Any carbohydrate-containing lipid is a glycolipid. The classifications of lipids overlap. (As you may have noticed, nothing in biochemistry is ever truly simple.) For this reason, a lipid may fall into more than one subcategory.

Phosphoglycerides

The alcohol here is glycerol, to which two fatty acids and a phosphoric acid are attached as esters. This basic structure is a phosphatidate. *Phosphatidate* is an important intermediate in the synthesis of many phosphoglycerides. The presence of an additional group attached to the phosphate allows for many different phosphoglycerides.

By convention, structures of these compounds show the three glycerol carbon atoms vertically with the phosphate attached to carbon atom number three (at the bottom). The occurrence of phosphoglycerides is almost exclusive to plant and animal cell membranes. Plasmalogens and phosphatidates are examples. These are also known as glycerophospholipids.

Plasmalogens

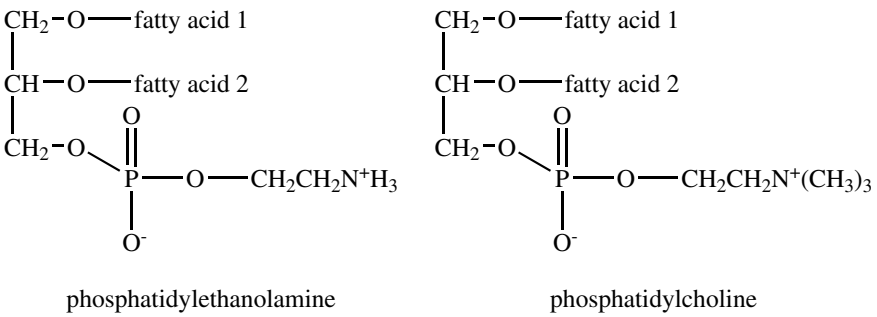
Plasmalogens are a type of phosphoglyceride. The first carbon of glycerol has a hydrocarbon chain attached via an ether, not ester, linkage. Ether linkages are more resistant to chemical attack than ester linkages are. The second (central) carbon atom has a fatty acid linked by an ester. The third carbon links to an ethanolamine or choline by means of a phosphate ester. These compounds are key components of the membranes of muscles and nerves.

Phosphatidates

Phosphatidates are lipids in which the first two carbon atoms of the glycerol are fatty acid esters, and the third is a phosphate ester. The phosphate serves as a link to another alcohol — usually ethanolamine, choline, serine, or a carbohydrate. The identity of the alcohol determines the subcategory of the phosphatidate. There is a negative charge on the phosphate and, in the case of choline or serine, a positive quaternary ammonium ion. (Serine also has a negative carboxylate group.) The presence of charges gives a “head” with an

overall charge. The phosphate ester portion ("head") is hydrophilic, whereas the remainder of the molecule, the fatty acid "tail", is hydrophobic. These are important components for the formation of lipid bilayers.

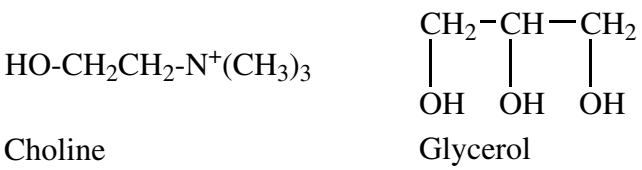
Phosphatidylethanolamines, phosphatidylcholines, and other phospholipids are examples of phosphatidates. Figure 8-5 illustrates examples of a phosphatidylethanolamine and a phosphatidylcholine.



phosphatidylethanolamine phosphatidylcholine

Figure 8-5: Examples of the general formulas of a phosphatidylethanolamine and a phosphatidylcholine.

The structures of some of the alcohols present in lipids appear in Figure 8-6.



Choline Glycerol

Ethanolamine Serine

Figure 8-6: Alcohol components of lipids.

Phosphatidylethanolamines

These are the most common phosphoglycerides in animals and plants. In animals, many of these are the *cephalins,* which are present in nerves and brain tissue. They are also factors involved in blood clotting. Recall that the phosphate has a negative charge and that the nitrogen of the enthanolamine is a quaternary ammonium ion with a positive charge.

Phosphatidylcholines

These are the lecithins. Choline is the alcohol, with a positively charged quaternary ammonium, bound to the phosphate, with a negative charge. Lecithins are present in all living organisms. An egg yolk has a high concentration of lecithins — which are commercially important as an emulsifying agent in products such as mayonnaise. Lecithins are also present in brain and nerve tissue.

Other phospholipids

There are many other phospholipids, some of which are glycolipids. The glycolipids include phosphatidyl sugars where the alcohol functional group is part of a carbohydrate. Phosphatidyl sugars are present in plants and certain microorganisms. A carbohydrate is very hydrophilic due to the large number of hydroxyl groups present.

Sphingolipids

Sphingolipids occur in plants and animals, and are especially abundant in brain and nerve tissue. In these lipids, sphingosine (Figure 8-7) replaces glycerol. The alcohol groups in the sphingosine may form esters just like the similar groups on glycerol. The amino group can form an amide. The combination of a fatty acid and sphingosine, via an amide linkage, is a *ceramide,* which is an intermediate in the formation of other sphingolipids.

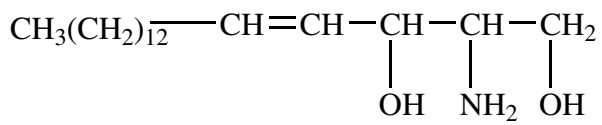


Figure 8-7: Structure of sphingosine.

Glycosphingolipids

A *glycosphingolipid* is an important membrane lipid containing a carbohydrate attached to a ceramide. The carbohydrate serves as a polar (hydrophilic) head. The carbohydrate may be either a monosaccharide or an oligosaccharide. The carbohydrate sequence in the oligosaccharide is important in helping these compounds recognize other compounds in biochemical reactions sequences. The carbohydrate portion is always on the outside of the membrane.

Cerebrosides

A *cerebroside* consists of a monosaccharide attached to a ceramide. The carbohydrate is either glucose or galactose. Cerebrosides are present in nerve and brain cells, though most animal cells contain some of these compounds.

Gangliosides

Gangliosides are sphingolipids with complex structures. The ceramide has an oligosaccharide, containing three to eight monosaccharide units, attached. The monosaccharide units may or may not be substituted. They are very common as part of the outer membranes of nerve cells, where the sugar sequence leads to cell recognition and communication. Small quantities of gangliosides are part of the outer membranes of other cells. When present in a membrane, the carbohydrate portion is always extracellular.

Sphingophospholipids

Sphingophospholipids contain sphingosine, a fatty acid, phosphate, and choline. An example is sphingomyelin, which is an important constituent of the myelin sheath surrounding the axon of all nerve cells. Multiple sclerosis, among other diseases, is a consequence of a fault with the myelin sheath. Sphingomyelin is the most common of the sphingolipids, and it is the only sphingosine phospholipid found in membranes.

Membranes: The Bipolar and the Bilayer

One use of lipids is in the construction of membranes. *Membranes* are used to separate regions both in and around cells — a typical membrane, as shown in Figure 8-8, is a lipid bilayer or bimolecular sheet. The polar portions of the lipids, the heads, are on the outside edges of the bilayer, whereas the nonpolar portions, the tails, are in the interior. The heads of the lipids appear as circles in our illustrations, and the tails appear as strings. The tails are usually long fatty acid chains. The hydrophilic heads, often with a charge, are in contact with aqueous material, and the hydrophobic tails are away from the aqueous material. Interactions between the hydrophobic tails are the key factors leading to the formation of lipid bilayers. *Lipid bilayers* tend to form closed structures or compartments to avoid having exposed hydrophobic edges. The membranes tend to be self-sealing.

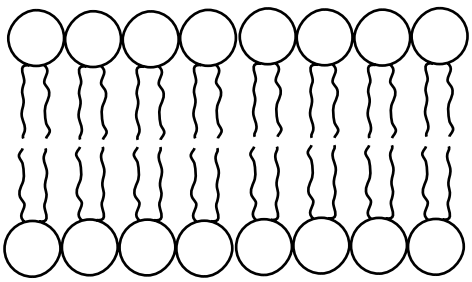


Figure 8-8: A simplified representation of a lipid bilayer.

Actual cell membranes are not as symmetrical as the one shown in Figure 8-8. This asymmetry is due in part to the presence of other components, and in part to differences between the intracellular and extracellular surfaces. If the fatty acid portions are not saturated, the tails will not form parallel structures, and there will be "holes" present within the bilayer. These holes are an essential feature leading to membrane fluidity. Other components include proteins and cholesterol. The carbohydrate portion of glycolipids is on the extracellular side of the bilayer instead of the intracellular side.

Polar materials cannot readily pass through the hydrophobic region of membranes, and nonpolar materials cannot readily pass through the hydrophilic outer region. Water, due to its small size and high concentration, can transverse the bilayer faster than ions and most other polar molecules. In actual cells, certain mechanisms allow material to cross the bilayer but require other components to be present in the bilayer. These components, mostly proteins, give selective permeability of the membranes. In addition, other materials, such as cholesterol, are necessary to serve other functions, such as stiffening the membrane.

Membranes may contain roughly from 20 to 80 percent protein, which may be *peripheral* (on the surface of the membrane) or *integral* (extending into or through the membrane). Integral proteins interact extensively with the hydrophobic portion of the bilayer, as illustrated in Figures 8-9 and 8-10.

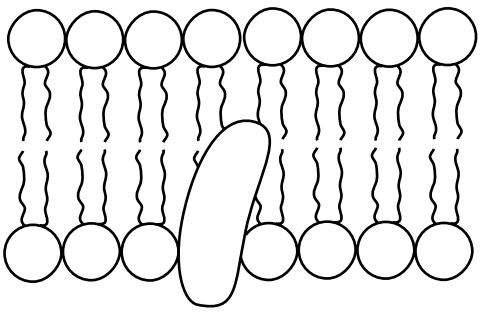


Figure 8-9: An integral protein that does not pass through the membrane.

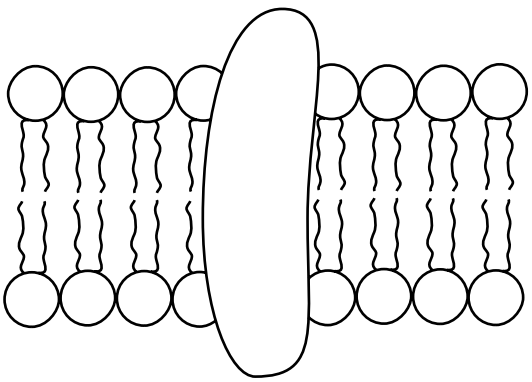


Figure 8-10: An integral protein passing through the membrane.

Peripheral proteins typically bind to the surface through electrostatic or hydrogen bonding, although covalent interactions are possible. Proteins are important for most membrane processes. If the protein is a glycoprotein, the carbohydrate portion lies on the external side of the membrane and is important to intercellular recognition.

Crossing the wall: Membrane transport

A lipid bilayer is, by its nature, impermeable to polar molecules and ions (hydrophilic species). Nevertheless, cells need to be able to bypass this feature and get hydrophilic materials in and out. There are two ways to circumvent impermeability: A *pump* involves active transport using energy to work against a concentration gradient, and a *channel* involves passive transport or facilitated diffusion using a concentration gradient.

Nonpolar molecules are lipophilic and dissolve in the lipid bilayer. In general, lipophilic materials pass through the membrane by simple diffusion along a concentration gradient. Channels and pumps are mainly to allow hydrophilic species to transverse the hydrophobic region of the bilayer.

Pumps

Pumps require energy to function. In many cases, the hydrolysis of ATP provides the needed energy. The generic name for this type of pump is a P-type ATPase. The name derives from the transfer of a phosphate from an ATP to an intermediate, a step that is essential to the action of the pump. Pumps can transfer other species than ions.

When is a solid a liquid? The fluid mosaic model

The lipid bilayer structure gives much insight into the structure of membranes but little information about their function. Many functions of the membrane depend upon its fluidity, best described by using the *fluid mosaic model.* In this model, the membrane serves as a permeability barrier and as a solvent for the integral proteins. Diffusion along the plane of the membrane — *lateral diffusion* — of the membrane components is often rapid. In general, lipids move more rapidly than proteins, with some proteins being essentially immobile. Diffusion of membrane components across the membrane — *transverse diffusion* — is usually slow.

The fluidity of the membrane depends on a number of factors. Bacteria adjust the fluidity by utilizing fatty acid chains — longer chains are less fluid than are shorter chains. The presence of double bonds makes the membrane more fluid. In animals, cholesterol controls the fluidity: The greater the cholesterol concentration, the less fluid the membrane. The transition from the rigid to the fluid state occurs at a temperature known as the *melting temperature*, T_m.

Most animal cells have a high potassium ion and a low sodium ion concentration relative to the extracellular environment. It requires energy to generate and maintain this gradient. The transport system is the Na^+-K^+ pump, also referred to as Na^+-K^+ ATPase. Hydrolysis of ATP provides the energy to transport potassium ions into the cell and sodium ions out of the cell. Both the sodium and potassium ions must be simultaneously bound to the pump. The pump simultaneously transports three sodium ions out of the cell as it transports two potassium ions in.

Not all pumps require the hydrolysis of ATP to supply energy. Some utilize the transport on one species to facilitate the transport of another. The transport of one species with the concentration gradient can pump another against the concentration gradient. The responsible membrane proteins are the cotransporters or secondary transporters. *Cotransporters* may be either symporters or antiporters. In a symporter, both transported species move in the same direction, whereas in an antiporter, the species move in opposite directions. The sodium-calcium exchanger is an example of an antiporter, which pumps three sodium ions into a cell for every two calcium ions pumped out. Some animal cells use a symporter to pump glucose coupled with sodium ions into the cells.

Channels

A channel provides a means of passively transporting a species across a membrane. It is possible to transport a species through a channel more than 1,000 times as fast as a pump's. A channel is technically a tube running through the membrane, but its behavior is significantly more complicated.

Channels are highly selective. Some select on size — sodium is smaller than potassium — whereas others differentiate between anions and cations. A channel exists in an open state to allow transport and a closed state to inhibit it. Some type of regulation is required to convert a channel between an open and a closed state. When a chemical potential regulates the channel, it is a voltage-regulated gate. The regulation may be due to specific chemicals. Chemically controlled regulation is ligand-gated. After the appropriate regulator is removed, the open channels will spontaneously close.

The best-known ligand-gated channel is the acetylcholine receptor. This channel is important for the transmission of nerve impulses. When a nerve impulse reaches the junction between one nerve and the next — the synapse — it triggers the release of acetylcholine, which transverses the small gap to the next nerve and attaches to acetylcholine receptors. This attachment opens the channel, leading to inward sodium ion diffusion and outward potassium ion diffusion. The change in the ion concentrations transmits the nerve impulse into the second nerve cell.

The increase in the sodium ion concentration in the second nerve cell triggers a mechanism to remove sodium ions from the nerve cell. Later another gate brings potassium ions back into the cell.

Steroids: Pumping up

Steroids are another class of lipids. All steroids have the basic core shown in Figure 8-11. A, B, C, and D are common labels for the rings. Different steroids have additions to this basic structure; these may include side chains, other functional groups, and unsaturation or aromaticity of the rings.

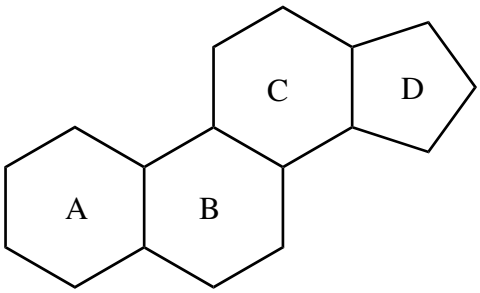


Figure 8-11: Basic structure of a steriod.

Cholesterol is the most abundant steroid. It is a membrane component and serves as the source of other steroids and related materials. Cholesterol comes from the diet, but if insufficient cholesterol is available there, it is synthesized in the liver. The steroid hormones are regulators produced from cholesterol.

Bile salts (mentioned earlier) are a group of materials produced by the oxidation of cholesterol. Unlike cholesterol and the other lipids, bile salts are soluble in water. They are useful as "detergents" to aid in digestion.

The steroids you hear about in the news being used by athletes and bodybuilders are *anabolic steroids,* which increase the body's ability to prevent muscle breakdown and to actually increase the ability to produce muscle. They have structures similar to testosterone, whose function is to enhance male characteristics such as facial hair and muscle mass. However, steroids in large doses have serious side effects: impotence, reduced testicle size, liver tumors, enlargement of the heart, enlargement of the breasts in men, aggressive behavior, and so on. (Sounds great, doesn't it?) Their use without a valid prescription has been illegal since 1991.

Prostaglandins, Thromboxanes, and Leukotrienes: Mopping Up

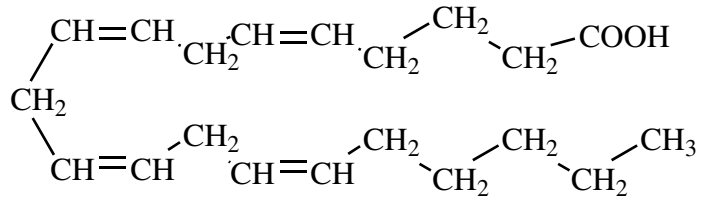
Arachidonic acid, a 20-carbon, polyunsaturated fatty acid, serves as the direct or indirect starting material for the formation of prostaglandins, thromboxanes, and leukotrienes. Cells synthesize both leukotrienes and prostaglandins from arachidonic acid. Additional prostaglandins and thromboxanes come from the prostaglandin derived from arachidonic acid. All three classes of compounds are local hormones. Unlike other hormones, they are not transported via the bloodstream. They are short-lived molecules that alter the activity of the cell producing them and neighboring cells.

All of these compounds are extremely potent chemicals that serve as hormone mediators. They also have many other medical applications and can cause medical problems. They are also known as *eicosanoids* — from the Greek for *twenty,* which alludes to the presence of 20 carbon atoms (Figure 8-12).

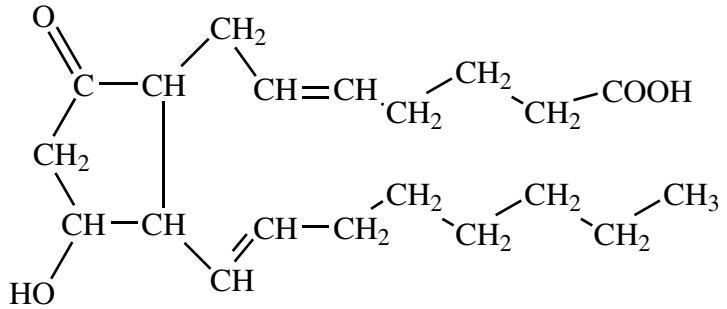
The name *prostaglandin* came from the belief that the prostate gland was its source because they were first isolated from seminal fluid in 1935. Now we know that they are produced in a very wide variety of cells. Prostaglandins differ slightly from each other, but they all contain a five-carbon ring. These minor difference lead to distinct behaviors, although all prostaglandins lower blood pressure, induce contractions in smooth muscles, and are part of the inflammatory response system.

A number of medications are synthetic prostaglandins. For example, derivatives of the prostaglandin PGE_2 are useful in inducing labor. Prostaglandins associated with inflammation are the main cause of the associated redness, pain, and swelling. The half-life of many prostaglandins is only a few minutes or less. Platelets in the blood generate thromboxanes to serve as vasoconstrictors and to induce aggregation of the platelets, two steps leading to the formation of a blood clot. Thromboxane A_2 is an example of one of these agents that induces blood clotting. White blood cells, leukocytes, and other tissues produce leukotrienes, whose name refers to where they were first discovered (leukocytes) and to the presence of three conjugated double bonds (triene). Leukotrienes are associated with allergy attacks.

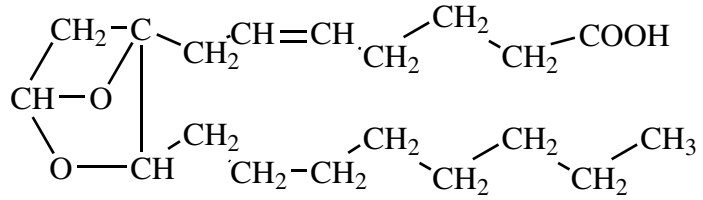
Aspirin interferes with the synthesis of prostaglandins and thromboxanes. Aspirin is an anti-inflammatory agent because it counters the inflammation induced by prostaglandins. The interference with the formation of thromboxanes may be part of the reason why low doses of aspirin help prevent heart attacks and strokes. Low thromboxane levels would inhibit blood clotting. Another anti-inflammatory drug, cortisone, inhibits the release of arachidonic acid from cell membranes, which, in turn, inhibits the formation of the eicosanoids. The fatty acids in fish oils inhibit the formation of the more potent leukotrienes and thromboxanes.



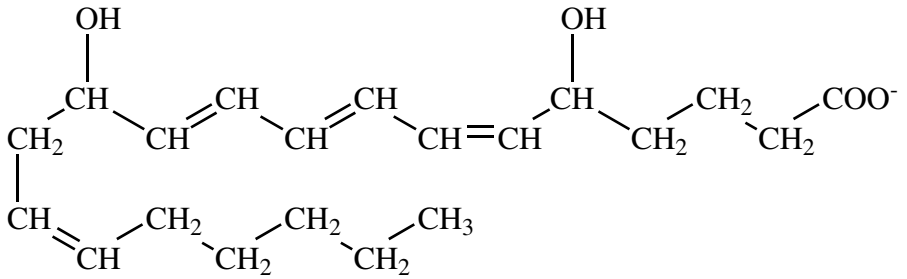
arachidonic acid



a prostaglandin (PGE_2)



a thromboxane (A_2)



a leukotriene (B_4)

Figure 8-12: Structures of arachidonic acid, a typical prostaglandin, thromboxane, and leukotriene.

Chapter 9

Nucleic Acids and the Code of Life

In This Chapter

- Finding out about the structure of proteins
- Understanding amino acid sequencing in proteins
- Going over applications of protein sequencing

Nucleic acids get their name because they were first found in the nuclei of cells. DNA (*deoxyribonucleic acid*) — the most famous nucleic acid — is part of the *chromosomes,* which contain the genes. And the *genes* are ultimately responsible for the synthesis of proteins. Most, if not all, of these proteins are enzymes, each catalyzing a specific chemical reaction occurring in the organism. Indeed, there is a one-gene-one-enzyme hypothesis, where each gene is responsible for the synthesis of one enzyme.

DNA has two direct purposes: It must generate new DNA (replication) so that new generations of cells will have the information necessary to their survival. And it must generate RNA (*ribonucleic acid*). The RNA is involved in the direct synthesis of proteins, called *translation.* These proteins are essential for the maintenance of life.

Nucleotides: The Guts of DNA and RNA

Both DNA and RNA are polymers of nucleotides. A *nucleotide* is a combination of a nitrogen base, a 5-carbon sugar, and a phosphoric acid. There are five different bases present in a nucleotide, and two different sugars. We take a closer look at the components of these nucleotides and then show you how they all fit together.

Reservoir of genetic info: Nitrogen bases

The bases fall into two categories, the general defining structures of which appear in Figure 9-1.

- The purines (adenine and guanine), composed of two fused rings incorporating two nitrogen atoms in each ring and
- The pyramidines (cytosine, thymine, and uracil), composed of a single ring with two nitrogen atoms in the ring structure

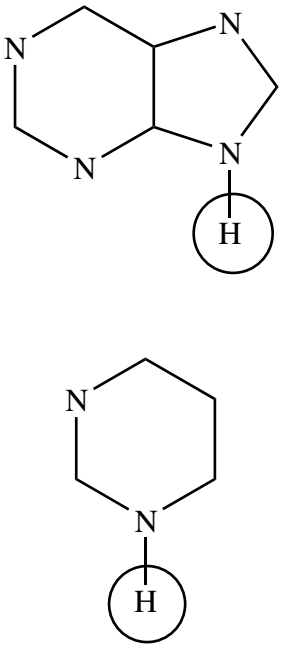
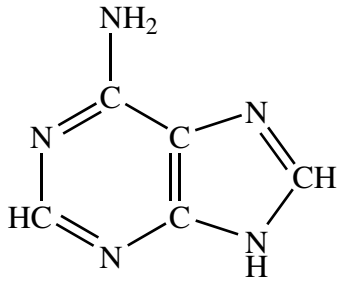


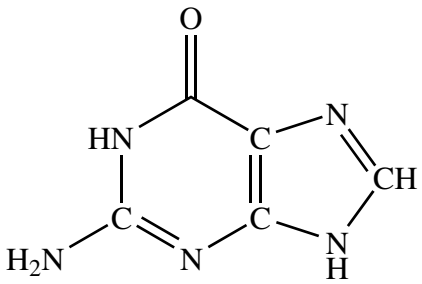
Figure 9-1: Basic purine structure (top) and basic pyramidine structure (bottom).

Adenine (A), guanine (G), and cytosine (C) occur in both DNA and RNA. Thymine (T) is only found in DNA, whereas uracil (U) only occurs in RNA. There are modified forms of some of these bases present in some nucleic acid molecules. The circled hydrogen atoms shown in Figure 9-1 are lost when combining with other components to produce a nucleic acid. The complete structures of the five bases are shown in Figure 9-2. It is the sequence of these bases that stores the genetic information.

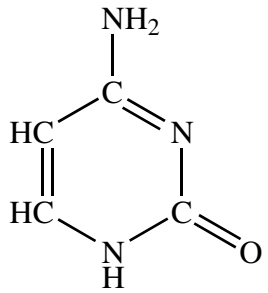
The nitrogen and oxygen atoms present on the nitrogen bases provide a number of sites where hydrogen bonding is possible. Hydrogen bonding is most effective and easily formed between certain combinations of nitrogen bases. Because of this, certain combinations will form, and it is this pattern that is responsible for the transmission of information. The atoms on the nitrogen bases normally use a regular numbering system, whereas the atoms in the sugar component use primed numbers.



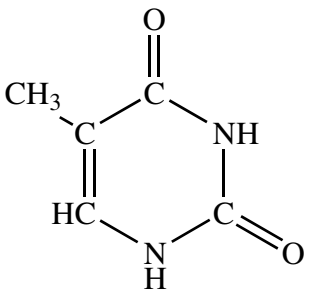
Adenine (A)



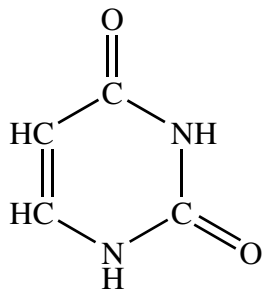
Guanine (G)



Cytosine (C)



Thymine (T)



Uracil (U)

Figure 9-2: Adenine (A), guanine (G), cytosine (C), thymine (T), uracil (U).

The sweet side of life: The sugars

The 5-carbon sugars found in the nucleic acids are D-ribose and D-deoxyribose. The difference between these two sugars is that deoxyribose is missing an oxygen atom on carbon atom number 2'. The structures for these two sugars appear in Figure 9-3. The arrows in the figure point to the alcohol group on carbon atom number 1', the *anomeric* carbon. This is where the nitrogen base will attach. Both sugars adopt the β form of the furanose ring. Numbering of the sugar begins with the anomeric carbon (1') and proceeds clockwise with the $-CH_2OH$ carbon being 5'.

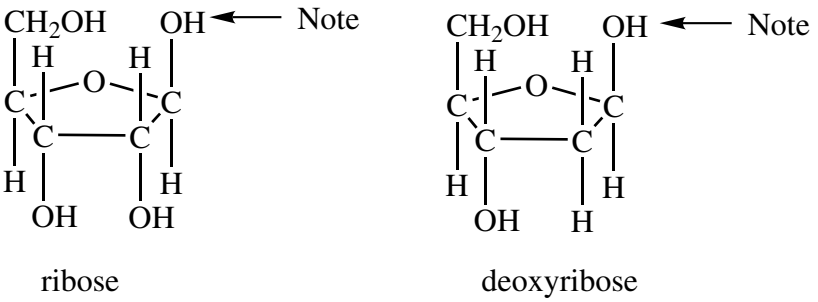


Figure 9-3: Structures of the 5-carbon sugars present in nucleic acids.

The sour side of life: Phosphoric acid

The third component of a nucleotide is a phosphoric acid (Figure 9-4). At physiological pH it does not exist in the fully protonated form shown in the figure. It is responsible for the "acid" in nucleic acid.

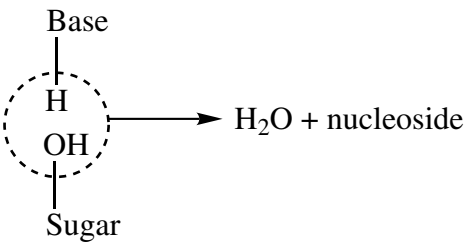


Figure 9-4: Structure of phosphoric acid.

Tracing the Process: From Nucleoside to Nucleotide to Nucleic Acid

Remember Legos and Tinker Toys? Putting together the pieces to get something new? That's what goes on in the construction of nucleic acids. Nature first joins a nitrogen base and a 5-carbon sugar to form a nucleoside; then that nucleoside joins with phosphoric acid to form a nucleotide; finally, the combination of these nucleotides produces a nucleic acid.

First reaction: Nitrogen base + 5-carbon sugar = nucleoside

The combination of a nitrogen base with a 5-carbon sugar is a *nucleoside.* The general reaction appears in Figure 9-5. It is a *condensation* reaction. Remember the condensation reactions you studied in ester formation in organic chemistry? This is exactly the same type. Here a compound containing hydrogen (the nitrogen base) approaches another molecule containing an –OH group (a sugar). The hydrogen combines with the –OH to form water, which is expelled. A bond forms in the remaining fragments.

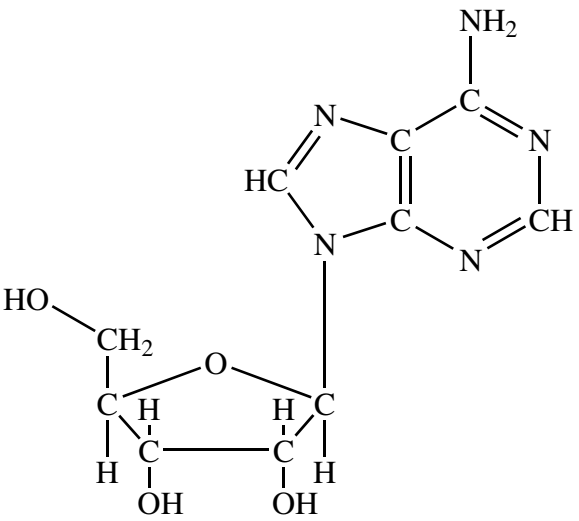


Figure 9-5: General reaction for the formation of a nucleoside.

The name of the nucleoside comes from the nitrogen base if the sugar is ribose; it has a prefix if the sugar is deoxyribose. For example, adenine combines with ribose to form adenosine and combines with deoxyribose to form deoxyadenosine. The structure for the nucleoside adenosine is in Figure 9-6. The hydrogen atom lost from the base was the one circled in Figure 9-1.

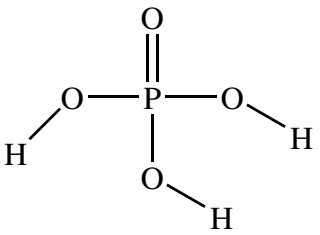


Figure 9-6: Structure of the nucleoside adenosine.

Second reaction: Phosphoric acid + nucleoside = nucleotide

The combination of a phosphoric acid with a nucleoside produces a nucleotide, which is a phosphate ester, as seen in Chapter 3, of a nucleoside. The formation involves a condensation reaction between the phosphoric acid and the alcohol group on carbon number 5, the $-CH_2OH$ (Figure 9-7).

Adenosine monophosphate (AMP) is an example of a nucleotide (Figure 9-8). Nucleotides are the monomers from which nucleic acids form. AMP is not only one of the "Legos" that makes RNA but is also very much involved in the energy transfer process in the cells (much more on AMP in Part IV).

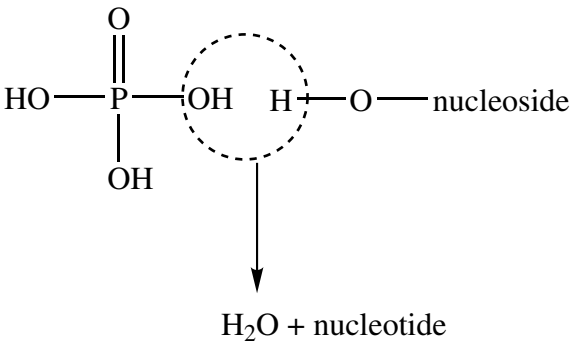


Figure 9-7: Simplified representation of the formation of a nucleotide.

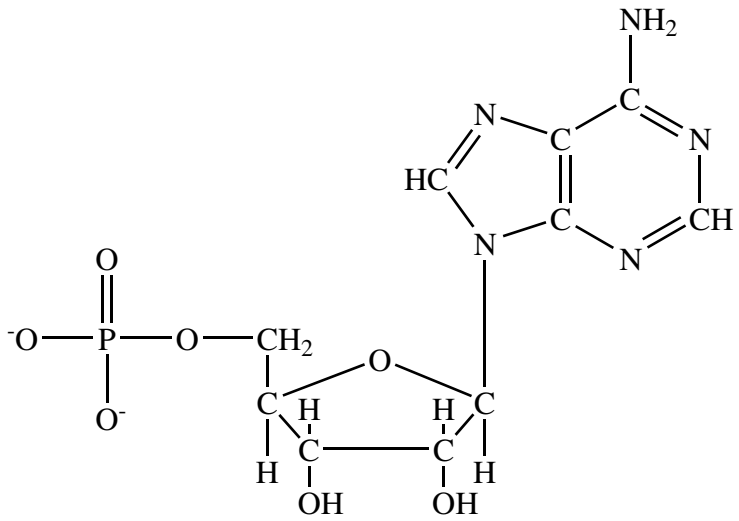


Figure 9-8: Structure of adenosine monophosphate (AMP).

If the sugar is ribose, then the result is one of four ribonucleotides. If the sugar is deoxyribose, the result is one of the four deoxyribonucleotides.

Third reaction: Nucleotide becomes nucleic acid

Nucleic acids form by joining nucleotides using the same condensation reactions we've mentioned. This condensation reaction involves the phosphate of one nucleotide reacting with the alcohol group on carbon atom number 3' of another nucleotide. Figure 9-9 illustrates. Note that the lower –OH, in the circle, is from the phosphoric acid, attached to carbon-5'. The upper –H in the circle is from the alcohol on carbon-3'.

The starting end of the polymer is 5', whereas the terminal end is 3'. Figure 9-10 illustrates the 5' and 3' carbon atoms on adenosine monophosphate.

A Primer on Nucleic Acids

Nucleic acids are responsible for storing and directing the information our cells use for reproduction and growth. They are large molecules found in the cell's nucleus. The genetic information is contained in the DNA, in terms of its primary and secondary structure. As a cell divides and reproduces, the genetic information in the cell is *replicated* to the new cells, which must be done accurately and precisely — no mistakes must be made. RNA's role is to

transfer the genetic information found in the DNA to the ribosomes, where protein synthesis occurs. DNA and RNA allow us to live and function.

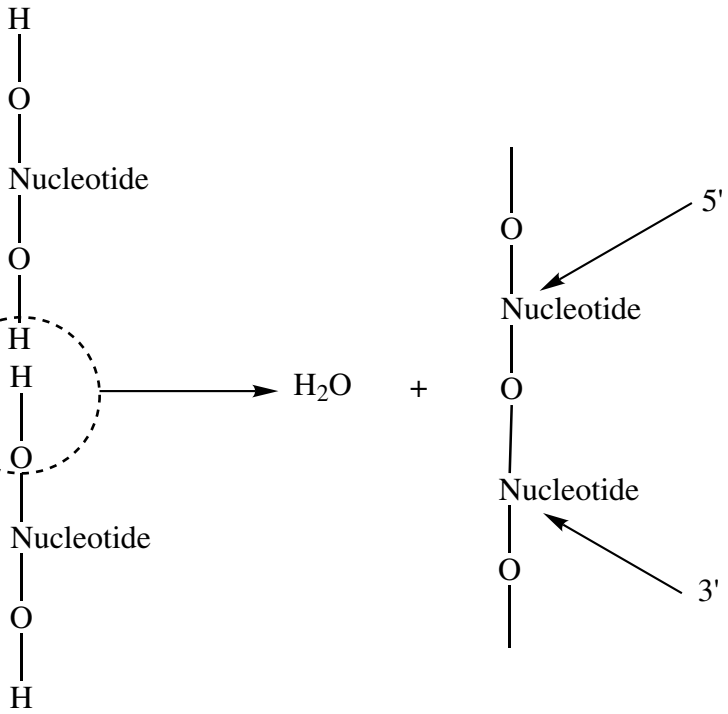


Figure 9-9: Simplified representation of the joining of two nucleotides.

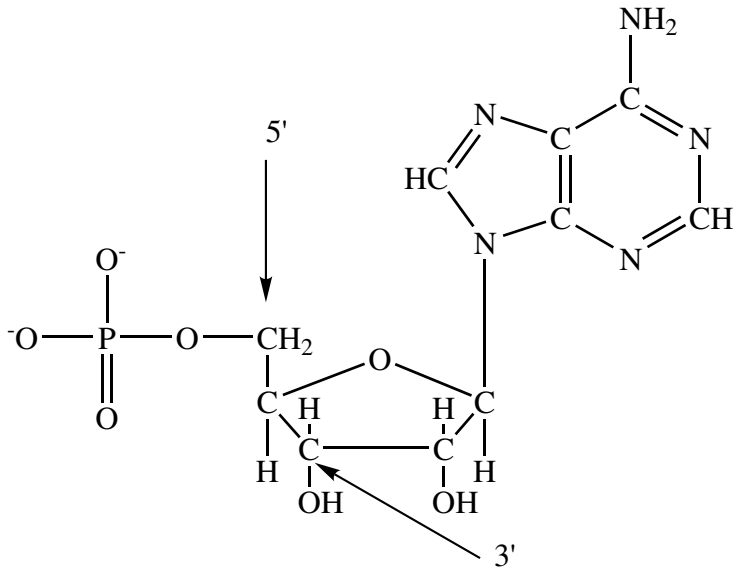


Figure 9-10: 5' and 3' carbon atoms on adenosine monophosphate.

DNA and RNA in the grand scheme of life

Both DNA and RNA are polymers composed of nucleotide subunits. However, DNA is a much larger molecule than RNA. DNA molecules typically have molecular weights in the billions. The human genome contains about 3 billion nucleotides.

As a simplification, the structure of a particular nucleic acid may be represented as 5'-C-G-T-A-3'. This abbreviation indicates that we begin at the 5' end and end at the 3' end (as always), and the nitrogen bases on the nucleotides are, in order, cytosine (C), guanine (G), thymine (T) and adenine (A). There are three different types of RNA, and each one has a specific use:

- Ribosomal RNA (rRNA) is the most common: 75–80 percent occurs within the ribosomes of the cell.
- Transfer RNA (tRNA) accounts for 10–15 percent.
- Messenger RNA (mRNA) makes up the remainder.

All three types are important to protein synthesis — which occurs in the ribosomes, home of ribosomal RNA (rRNA). The amino acids necessary for protein synthesis are transferred to the ribosomes by transfer RNA (tRNA). The message instructing the ribosomes how to assemble the protein travels from the DNA to the ribosome via messenger RNA (mRNA). This message tells the ribosome the sequence of amino acids to make a specific protein.

Transfer RNA contains the fewest nucleotides: 70–90. The average mRNA has about 1,200 nucleotides. There are three subcategories of rRNA ranging from about 120 to over 3,700 nucleotides. (DNA typically has between 1 million and 100 million nucleotides, though viral DNA tends to be smaller.) *Ribonucleotides* have other uses in addition to building RNA. They are present in energy molecules (ATP), in intracellular hormone mediator (cyclic AMP), and in certain coenzymes (FAD and NAD^+). Plants and animals contain both DNA and RNA. Viruses can contain either DNA or RNA.

Nucleic acid structure

The structure of a particular nucleic acid controls its function within the organism. For example, the structure of a particular tRNA determines which specific amino acid it will transfer to the ribosome for protein synthesis. In fact, the difference between DNA and RNA resides in the structure of the molecules. Because of the complexity of these types of molecules, there may be more than one key type of structure present.

The primary structure of the nucleic acids is the sequence of nucleotides, the order in which the individual nucleotides have been joined. This sequencing determines which hydrogen bonds form, and this, in turn, controls much of the function of the nucleic acid. DNA also has an important secondary structure, a consequence of hydrogen bonding between the nitrogen bases on the DNA strands. The result is that DNA consists of a *double helix* — which looks like a ladder twisted lengthwise — where hydrogen bonds (the rungs in the ladder) hold the two primary structures together.

The hydrogen bonds between the two stands of DNA make the two strands *complementary (*paired). Every A is complementary to a T, and every G is complementary to a C in *base pairing.* Base pairing is essential for the function of the nucleic acids.

The two DNA strands are *antiparallel,* which means that the 5' end of one strand connects to the 3' end of its complementary strand. This pairing also places the more polar (more hydrophilic) sugar and phosphate groups on the outside and the less polar (more hydrophobic) nitrogen bases on the inside. (Note that *hydrophilic* and *hydrophobic* as used here are relative terms.) The antiparallel nature affects how DNA produces new DNA (the replication process) and new RNA (the transcription process).

Although each of the nitrogen bases is very efficient at forming hydrogen bonds, certain combinations are extremely effective. In DNA, an adenine is capable of forming two hydrogen bonds to thymine (Figure 9-11), and guanine can form three hydrogen bonds to cytosine (Figure 9-12).

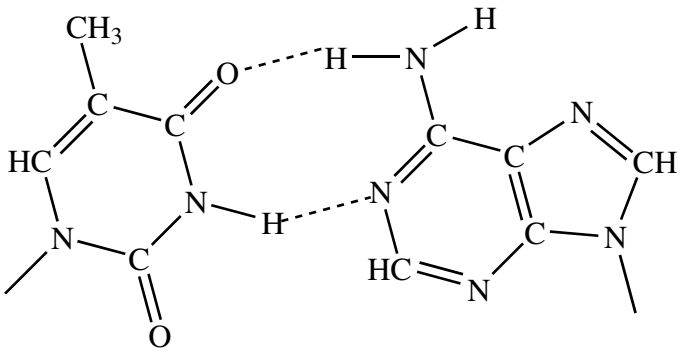


Figure 9-11: Hydrogen bonds (dotted lines) form between adenine (right) and thymine (left).

Adenine is also able to form hydrogen bonds with uracil when DNA interacts with RNA or when two RNA molecules interact. The interaction between adenine and uracil is shown in Figure 9-13.

The ability to form these specific combinations is important in real life — this is the *genetic code* we all have heard so much about. The sequencing of nucleotides in the nucleic acids and the sequencing of amino acids in the proteins all depend on these hydrogen bonds. Without them, the appropriate information would not be transferred precisely, and you might produce kittens instead of kids. The result? DNA, the structure of life (Figure 9-14).

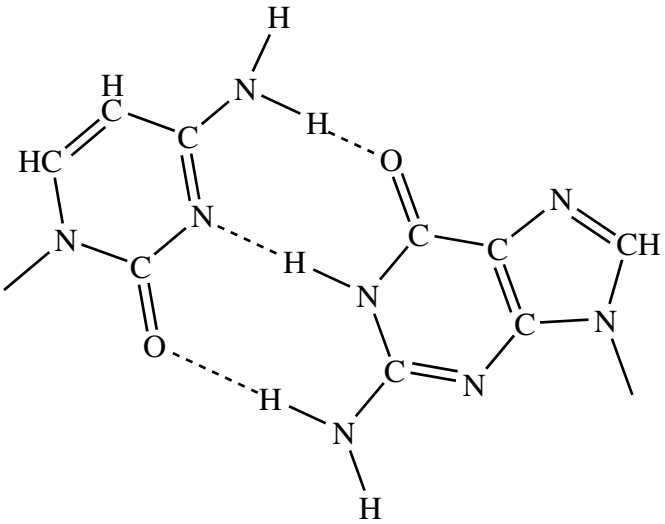


Figure 9-12: Hydrogen bonds (dotted lines) form between guanine (right) and cytosine (left).

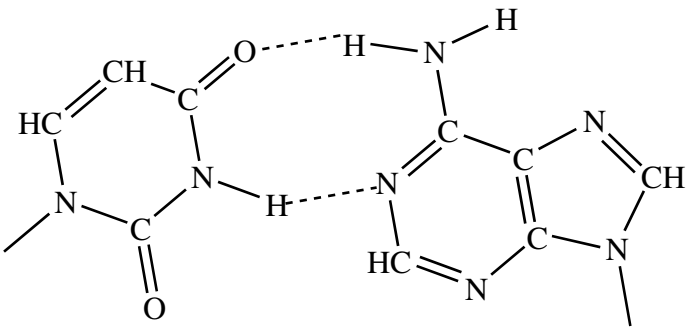


Figure 9-13: Hydrogen bonds (dotted lines) form between adenine (right) and uracil (left).

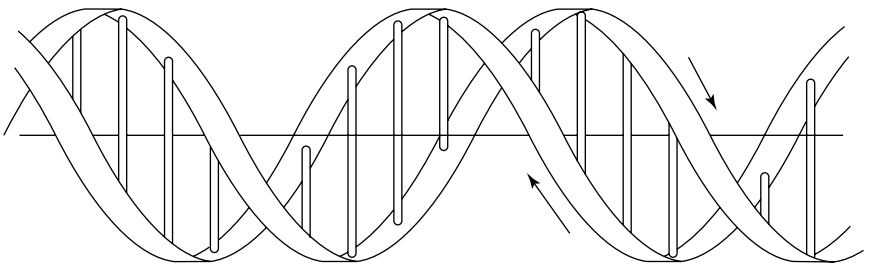


Figure 9-14: The secondary structure of DNA.

Chapter 10

Vitamins and Nutrients

In This Chapter

- Taking a look at the purpose of vitamins
- Understanding B vitamins
- Assessing other vitamins and nutrients

An organism must absorb a variety of materials to live, many of which fall into the category of food, certainly one of *our* favorite categories, especially John's. These foodstuffs required by an organism for life and growth are classified as nutrients. *Nutrients* are the substances in the diet necessary for growth, replacement, and energy. Here are the six general classes of nutrients:

- Carbohydrates
- Lipids
- Proteins
- Vitamins
- Minerals
- Water

Digestion converts large molecules in food into smaller molecules that can be absorbed. During digestion, carbohydrates (with the exception of the monosaccharides), lipids, and proteins are broken down into their components. These components are often used by the organism directly for growth and replacement. For animals, energy comes primarily from carbohydrates and lipids, but proteins can also serve as an energy source.

Vitamins are other organic materials required by an organism, and minerals are inorganic materials required by an organism. In addition, all living organisms require water to survive. Water is a wonderful substance. For more about the unusual properties of water, check out Chapter 2 in this book or *Chemistry For Dummies* by John T. Moore (Wiley).

More than One-a-Day: Basics of Vitamins

Vitamins are organic compounds that are required, in small quantities, for normal metabolism. The term *active form* is used to describe the structural form of the molecule, in this case vitamins, that performs its function (exhibits *activity*) within the organism. In general, humans cannot synthesize sufficient quantities of vitamins; thus, vitamins must come from other sources — through the diet and/or in pill form. A deficiency of a vitamin in the diet leads to a health problem. The general symptoms for any vitamin deficiency include frequent illness, slow healing of wounds, and tiredness. It was not until the early 1900s that the need for trace nutrients such as vitamins and minerals was first established.

There are two categories of vitamins: water-soluble and fat-soluble. *Water-soluble* vitamins include vitamin C and the B vitamins. Vitamins A, D, E, and K comprise the other category, the *fat-soluble* vitamins. Water-soluble vitamins tend to have more oxygen and nitrogen in their structure than fat-soluble vitamins, which have significant hydrocarbon portions in their structure. The majority of water-soluble vitamins either act as coenzymes or are important in the synthesis of coenzymes. Fat-soluble vitamins serve a variety of biochemical functions.

The body can easily eliminate an excess of the water-soluble vitamins, normally in the urine. The bright yellow of the urine of a person taking large doses of vitamin C attests to that fact. Because the body does not store water-soluble vitamins, continual replacement is necessary. The body can store excess amounts of a fat-soluble vitamin in the body's fatty tissue, and therefore elimination is not very easy. Unfortunately, this can lead to an accumulation of these vitamins, sometimes to toxic levels. One should consider this before consuming mega quantities of the fat-soluble vitamins.

To B or Not to B: B Complex Vitamins

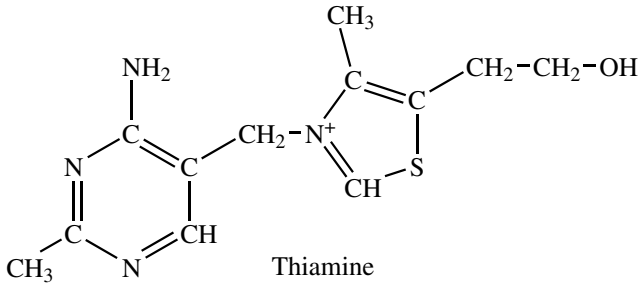
The B vitamins — or B complex — comprise a number of water-soluble vitamins that are found together in a number of sources. Originally, this mixture was thought to be only one vitamin (vitamin B). With the possible exception of vitamin B_6, these appear to be relatively nontoxic. In general, the B complex is important for healthy skin and nervous systems.

Vitamin B_1 (thiamine)

Thiamine is important to carbohydrate metabolism. Like the other B vitamins, the body does not store it. In addition, prolonged cooking of food can destroy it. Once absorbed in the body, thiamine is converted to a form that is biologically active through the attachment of a pyrophosphate (diphosphate) group to give thiamine pyrophosphate (TPP). The structures of vitamin B_1 and thiamine pyrophosphate are shown in Figure 10-1.

TPP is a coenzyme used in decarboxylating pyruvate to acetyl-CoA and α-ketoglutarate to succinyl-CoA. In addition, TPP is necessary for the synthesis of ribose.

A deficiency in thiamine leads to beriberi, which causes deterioration in the nervous system. Beriberi was prevalent in regions where rice was a major food source. Rice, particularly polished rice, is low in thiamine. Using brown rice, which has more thiamine, alleviates this problem. Nursing infants are particularly at risk when their mothers have a thiamine deficiency. Many alcoholics also suffer from this condition because many "foods" high in alcohol are particularly low in vitamins.



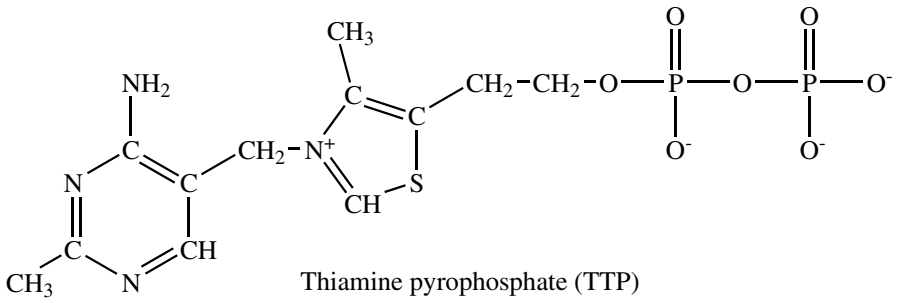


Figure 10-1: Structures of vitamin B^1 (thiamine) and thiamine pyrophosphate (TPP).

Good dietary sources of thiamine include liver, spinach, green peas, navy and pinto beans, whole-grain cereals, and most legumes.

Vitamin B_2 (riboflavin)

Riboflavin is essential to the synthesis of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The structures of these materials are shown in Figure 10-2. FMN and FAD are important coenzymes involved in a number of biochemical redox processes. The name *riboflavin* alludes to the presence of *ribitol,* an alcohol derived from ribose. The other part of riboflavin is the ring system isoalloazine, a flavin derivative.

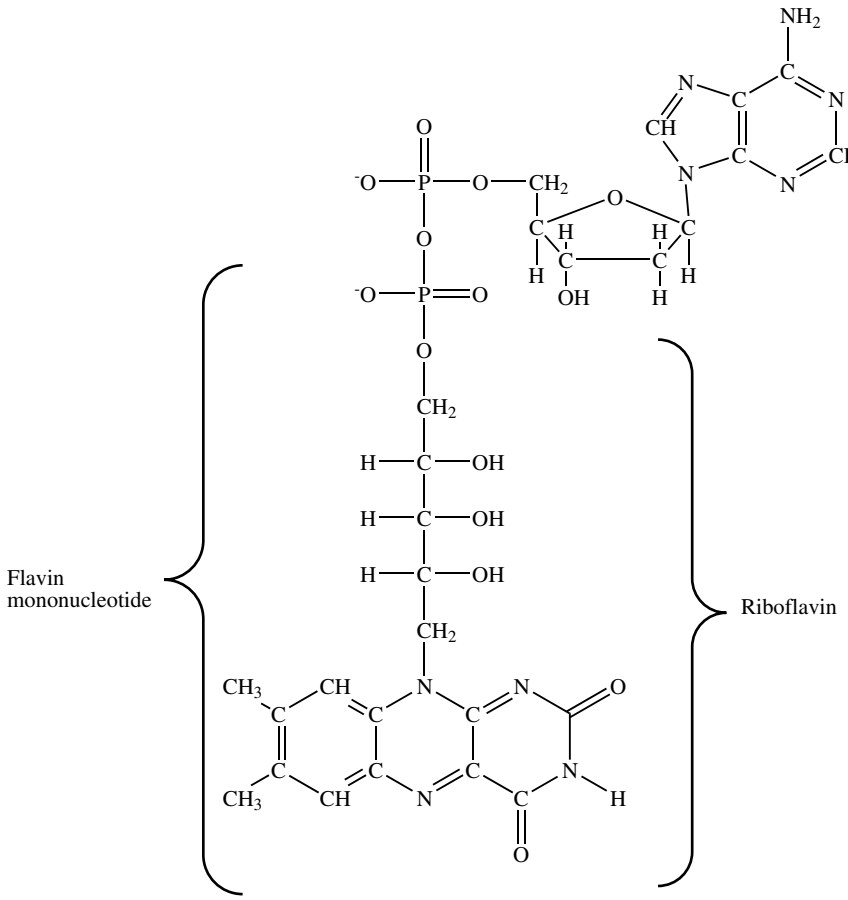


Figure 10-2 : Structure of flavin adenine dinucleotide (the entire structure) and the component materials flavin mononucleotide and riboflavin.

No deficiency diseases are associated with riboflavin; however, a deficiency does lead to burning and itchy eyes, dermatitis, and anemia. Dietary sources of this vitamin include soybeans, liver, milk, cheese and green leafy vegetables. Riboflavin is stable during cooking, but is broken down by light.

Vitamin B_3 (niacin)

The term *niacin* applies to two compounds: nicotinic acid and nicotinamide. These two compounds along with nicotinamide adenine dinucleotide (NAD^+) appear in Figure 10-3. Nicotinamide is part of the coenzymes NAD^+ and nicotinamide dinucleotide phosphate ($NADP^+$). These coenzymes work with a number of enzymes in catalyzing a number of redox processes in the body.

Niacin is one of the few vitamins that the body *can* synthesize. The synthesis utilizes tryptophan and is not very efficient.

Pellagra is a niacin-deficiency disease. Symptoms include loss of appetite, dermatitis, mental disorders, diarrhea, and possibly death. It was common in the southern United States in the early 1900s because many people had a diet of corn, which is neither a good source of niacin or tryptophan.

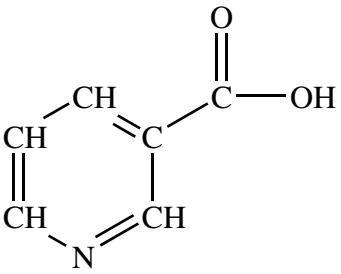
There are many dietary sources for niacin, including most meats and vegetables, milk, cheese, and grains.

Vitamin B_6 (pyridoxine)

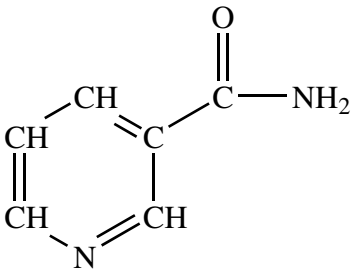
This vitamin consists of three components: pyridoxine, pyridoxal, and pyridoxamine. All three need to be converted to pyridoxal phosphate, a form that is biologically active in the organism. The structures for these compounds appear in Figure 10-4. Pyridoxal phosphate serves as a coenzyme in a variety of processes, including the interconversion of α-keto acids and amino acids.

Avocados, chicken, fish nuts, liver, and bananas are especially good food sources of vitamin B_6. Heating decreases its concentration in food.

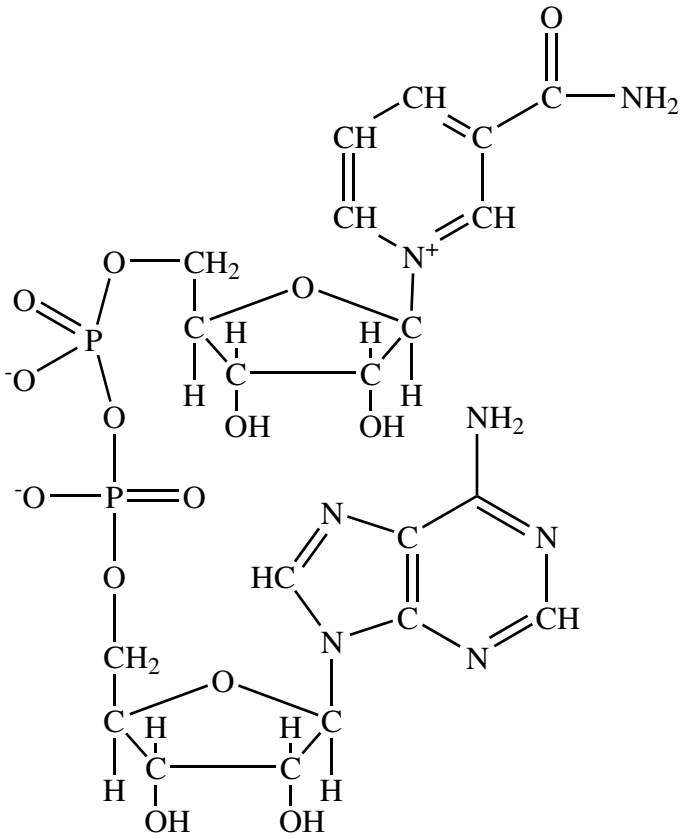
There is no pyridoxine-deficiency disease known; however, low levels can lead to irritability, depression, and confusion. Unlike the other water-soluble vitamins, there is evidence that large doses of vitamin B_6 may lead to health problems. The symptoms of excess vitamin B_6 consumption include irreversible nerve damage.



Nicotinic acid

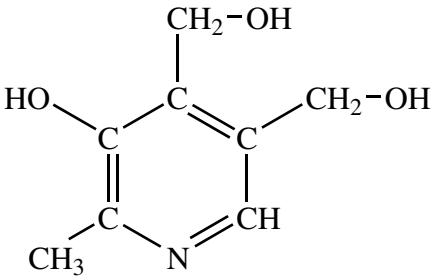


Nicotinamide

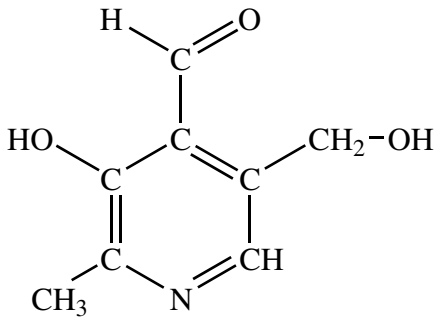


Nicotinamide adenine dinucleotide (NAD^+)

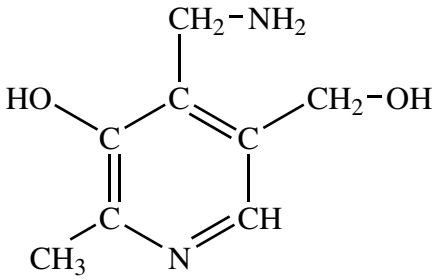
Figure 10-3: Structures of nicotinic acid, nicotinamide, and nicotinamide adenine dinucleotide (NAD^+).



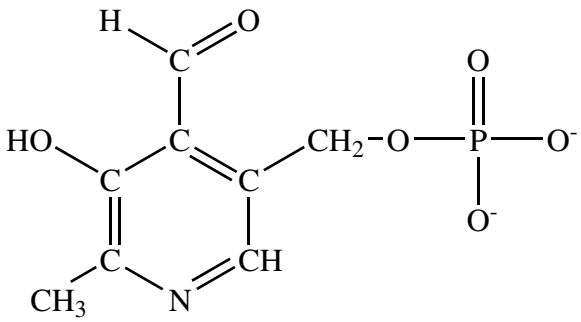
Pyridoxine



Pyridoxal



Pyridoxamine



Pyridoxal phosphate

Figure 10-4: Structures of pyridoxine, pyridoxal, pyridoxamine, and pyridoxal phosphate.

Biotin

Biotin is a coenzyme important to many carboxylation reactions. Biotin is the carbon transporter in both lipid and carbohydrate metabolism.

Bacteria in the intestinal track synthesize biotin in sufficient quantities to minimize the chances for a deficiency. However, antibiotics can inhibit the growth of these bacteria and induce a deficiency. In these circumstances, the symptoms include nausea, dermatitis, depression, and anorexia. Biotin is stable to cooking. Its structure is shown in Figure 10-5.

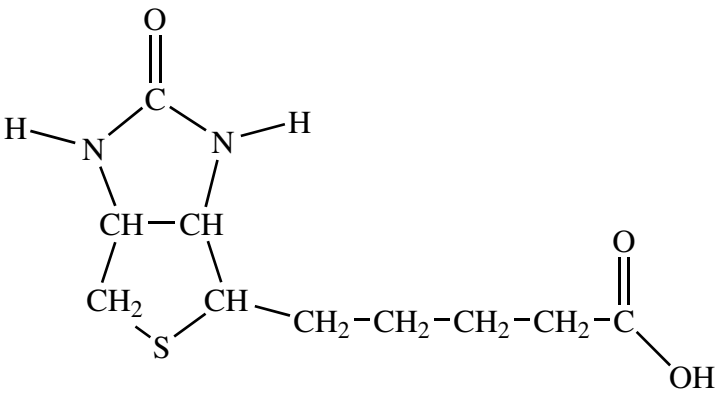


Figure 10-5: Structure of biotin.

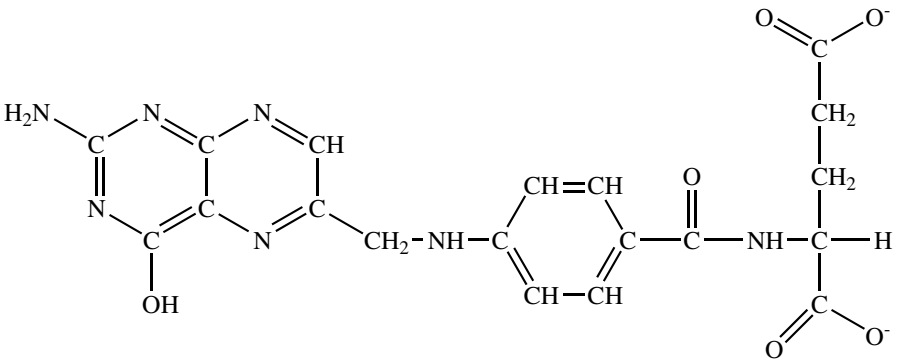
Folic acid

Bacteria in the intestinal track also produce *folic acid;* however, green leafy vegetables, dried beans, and liver are also sources. Reduction of folic acid yields tetrahydrofolic acid, the active form. Both structures are shown in Figure 10-6. The coenzyme transports a carbon, usually as a methyl or formyl, in the synthesis of heme, nucleic acids, choline, and several other compounds. Although cooking easily destroys the compound, intestinal bacteria normally produce sufficient quantities.

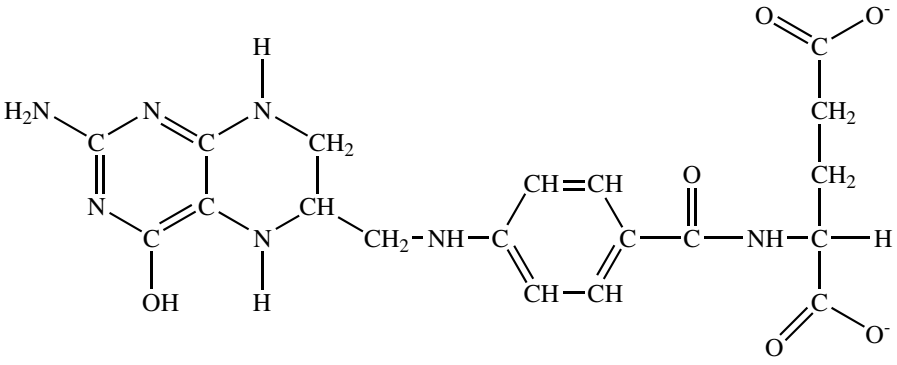
Folic acid is critical to the prevention of malformations of the brain (*anencephaly*) and spine (*spina bifida*). A deficiency of folic acid affects the synthesis of purines — symptoms include gastrointestinal disturbances and anemia. Pregnant women are normally advised to take a vitamin high in folic acid to help in the normal development of the fetus, especially the spine and brain. Sulfa drugs interfere with the formation of folic acid by some pathogens via a form of competitive inhibition.

Pantothenic acid

Pantothenic acid's name derives from a Greek word meaning "from everywhere." As you might expect, then, it has numerous sources, including whole grains, eggs, and meat. Deficiency is virtually unknown. The vitamin is not destroyed by moderate cooking temperatures, but it is not stable at high cooking temperatures. Its structure appears in Figure 10-7.



Folic acid



Tetrahydrofolic acid

Figure 10-6: Structures of folic acid and tetrahydrofolic acid.

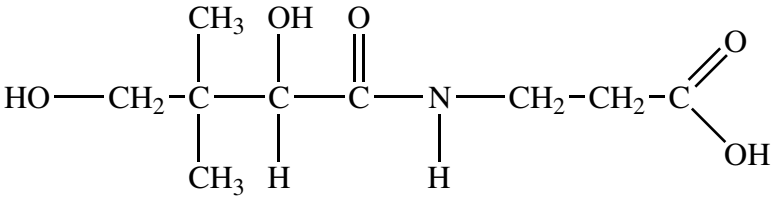


Figure 10-7: Structure of pantothenic acid.

Pantothenic acid is necessary in the biosynthesis of coenzyme A. Coenzyme A is an exceedingly important substance in many biological processes because this coenzyme transfers acyl groups.

The wonders of vitamin B_{12}

Vitamin B_{12} is the only known natural organometallic compound. It does not occur in higher plants, and apparently only bacteria are capable of synthesizing it — bacteria who live in their hosts in a symbiotic relationship. Unfortunately, higher animals including human beings do not have these types of bacteria. Thus, it is necessary to obtain vitamin B_{12} from food. The name *cyanocobalamine* refers to the presence of cyanide. The cyanide is an artifact of the isolation of the compound and is not naturally present. Vitamin B_{12} is necessary to the formation of two coenzymes: methylcobalamin and 5'-deoxyadenosylcobalamin. The structure of methylcobalamin is shown in Figure 10-8.

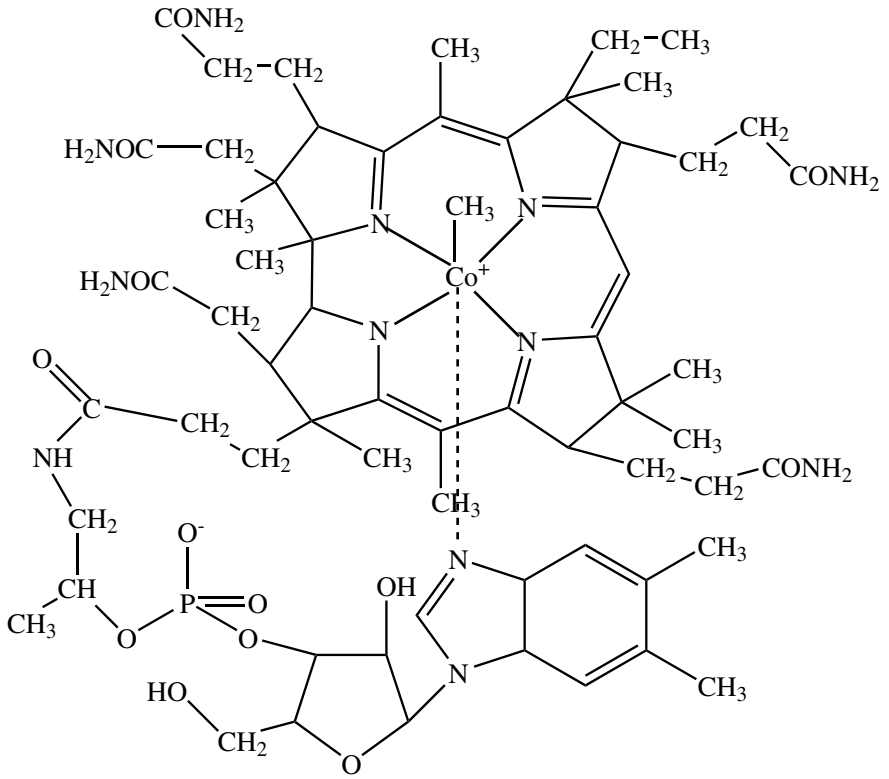


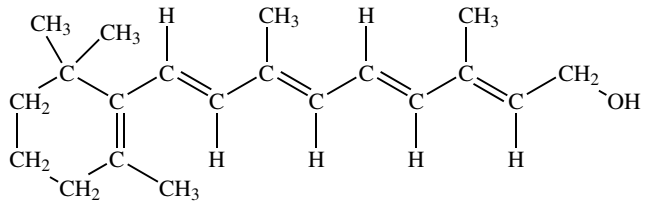
Figure 10-8: Structure of methylcobalamin.

Both coenzymes assist in reactions involving rearrangements. Methylcobalamin is useful in methyl transfer reactions. The coenzyme 5'-deoxyadenosylcobalamin works in some rearrangement reactions where a hydrogen atom and a group attached to an adjacent carbon exchange positions.

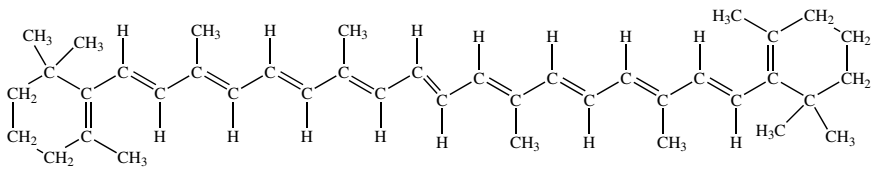
Pernicious anemia usually results from poor absorption of vitamin B_{12}. Normal stomach cells produce a glycoprotein that aids in the absorption of the vitamin in the intestine. It is the lack of this intrinsic factor that leads to the vitamin deficiency and not the lack of the vitamin in the diet. Elderly people may have difficulty in generating sufficient quantities of the intrinsic factor, and strict vegetarians also may develop symptoms. The symptoms of pernicious anemia include lesions on the spinal cord leading to a loss of muscular coordination and gastrointestinal problems. The blood contains large, fragile, and immature red blood cells. Dietary sources include meat, eggs, milk and cereals. This vitamin is stable to cooking.

Vitamin A

Vitamin A is not a single compound — a number of compounds are biologically active, that is they undergo biological reactions within the organism. The parent compound is 11-trans-retinol, found in milk and eggs. Vitamin A is exclusive to animals, and the plant pigment β-carotene can serve as a precursor (Figure 10-9). As a precursor, it is a *provitamin.* Cleavage of β-carotene yields two vitamin A active species. Any β-carotene that doesn't become vitamin A is used as an antioxidant.



11-trans-retinol



β-carotene

Figure 10-9: Structures of 11-trans-retinol and β-carotene. Note that carbon 11 is the fifth from the right in the main chain.

Vitamin A is especially important to vision. Part of the vision process involves the absorption of light. This absorption causes the geometry on the double bond between carbon atoms 11 and 12 to change from cis to trans. The isomerization triggers a series of events, giving rise to a nerve impulse. An enzyme reverses the isomerization so the molecule may be reused. In addition to being directly involved in vision, vitamin A also promotes the development of the epithelial cells producing the mucous membranes, which protect the eyes and many other organs from infections and irritants. Vitamin A also helps in the changes in the bone structures that occur as an infant matures.

A deficiency in vitamin A begins with night blindness, followed by other eye problems, which could lead to blindness. An extreme deficiency may lead to *xerophthalmia,* inflammation of the eyelids and eyes, which can cause infections and blindness. Young animals require vitamin A for growth, and adults are capable of storing several months' supply of it, primarily in the liver. The livers of some animals, such as polar bears and seals, may have such a high vitamin A concentration that they are toxic to humans. Excessive dosages of vitamin A may lead to acute toxicity, and as a fat-soluble vitamin, it is not easily eliminated. Symptoms include nausea, vomiting, blurred vision, and headaches. Large doses have been linked to birth defects and spontaneous abortions. The provitamin, β-carotene, is not toxic.

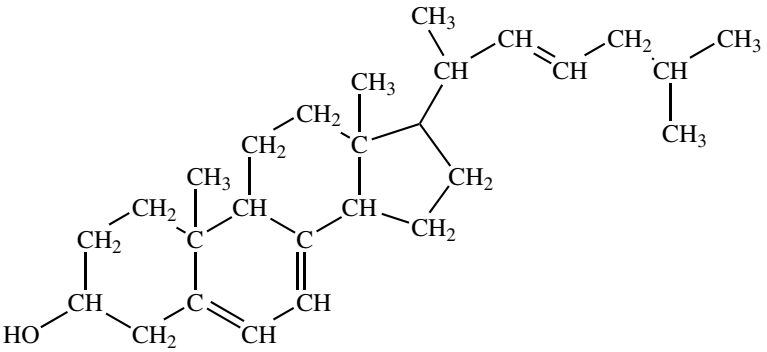
Vitamin D

Vitamin D is sometimes called the *sunshine vitamin*. It can be produced in the body through the action of sunlight, which is ultraviolet radiation. Individuals walking around outside nude or semi-nude normally have very little trouble with vitamin D deficiency. The rest of us, however, depend on vitamin D-fortified foods, especially milk.

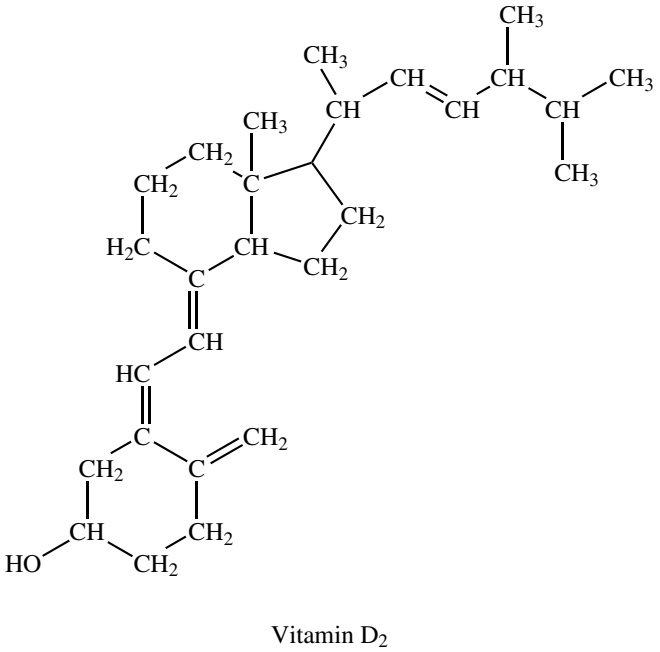
Several compounds exhibit vitamin D activity. Only two of them — actually provitamins — occur commonly in food: ergosterol and 7-dehydrocholesterol. Irradiation with ultraviolet light converts ergosterol into vitamin D_2, *ergocalciferol.* Ultraviolet irradiation, particularly in the skin of animals, converts 7-dehydrocholesterol into vitamin D_3, *cholecalciferol.* (A little confusingly, vitamin D_1 is a mixture of vitamin D_2 and vitamin D_3.) The structures of ergosterol, vitamin D_2, 7-dehydrocholesterol, and vitamin D_3 appear in Figure 10-10.

The body's ability to absorb calcium and phosphorus is tied to vitamin D. Teeth and bone have large amounts of these two elements and are the first parts of the body affected by a vitamin D deficiency. Osteomalacia, a condition in which a softening of the bones may lead to deformities, may also result. (In infants and children, osteomalacia is called rickets.) A vitamin D

deficiency is more serious in children than in adults because growth requires larger quantities of calcium and phosphorus. Persons with some portion of their skin routinely exposed to sunlight seldom develop a deficiency.

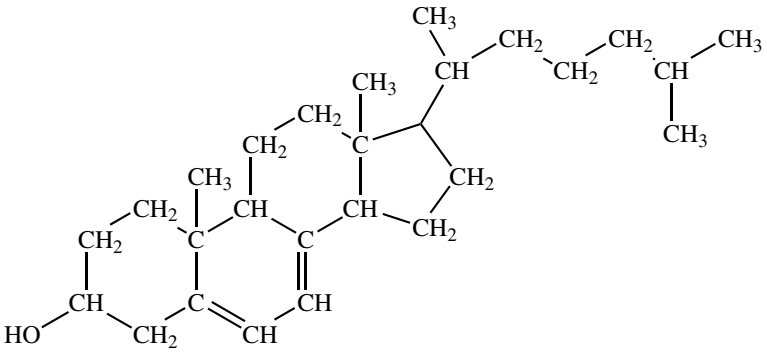


Ergosterol

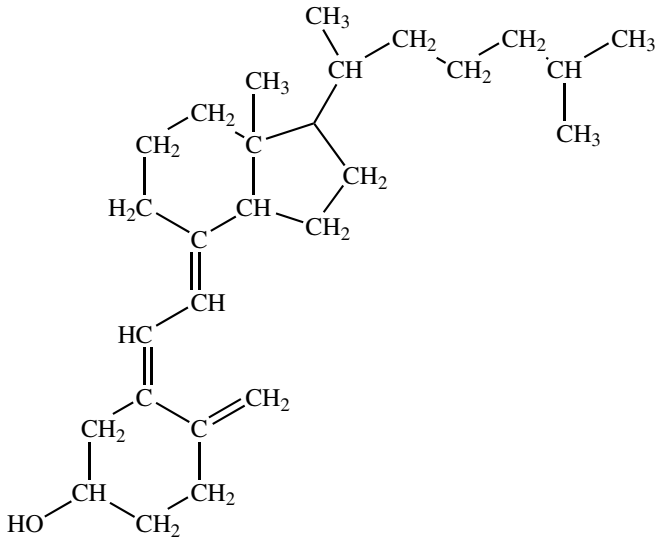


Vitamin D_2

Figure 10-10: Structures of ergosterol, vitamin D_2, 7-dehydrocholesterol, and vitamin D_3.



7-Dehydrocholesterol



Vitamin D_3

Figure 10-10: (continued)

Excess vitamin D is toxic. It is not easy to eliminate this fat-soluble vitamin. Symptoms of excessive amounts of vitamin D include nausea, diarrhea, kidney stones and other deposits, and sometimes even death.

Vitamin E

The *tocopherols* are a group of compounds that exhibit vitamin E activity. The most effective is α-tocopherol (see Figure 10-11). Vitamin E comes from a number of sources, vegetable oils, nuts, whole grains, leafy vegetables, to name a few. Deficiencies are rare except in individuals on a no-fat diet or who, for medical reasons, cannot efficiency absorb fat. Cystic fibrosis may interfere with fat absorption.

Vitamin E serves as an effective anti-oxidant. *Anti-oxidants* are necessary to minimize the damage caused by oxidants present in the body — many problems associated with aging are apparently due to oxidants. Vitamin E may also help prevent cholesterol deposits in the arteries. There are no well-documented problems with the use of large doses; however, some recent studies, although disputed, warn against taking mega doses of vitamin E.

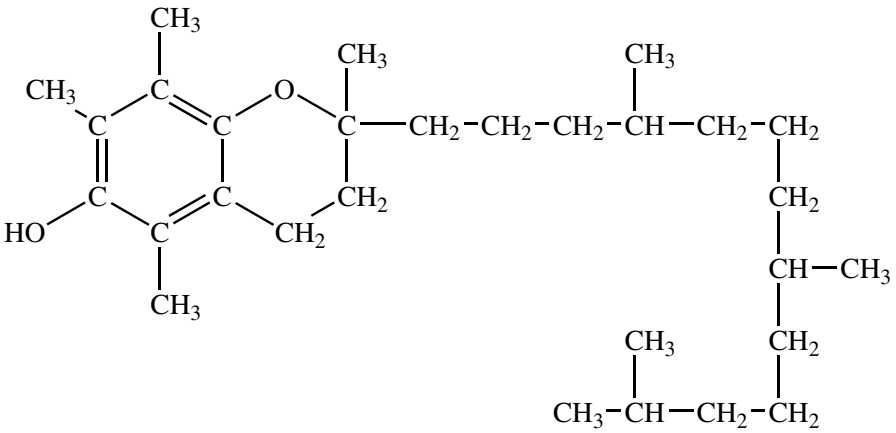


Figure 10-11: Structure of α-tocopherol (vitamin E).

Vitamin K

Vitamin K_1 (Figure 10-12) is one of many compounds that exhibit vitamin K activity and differ in the side-chains attached to the ring system. One chain is usually a methyl; the other typically has at least 20 carbon atoms.

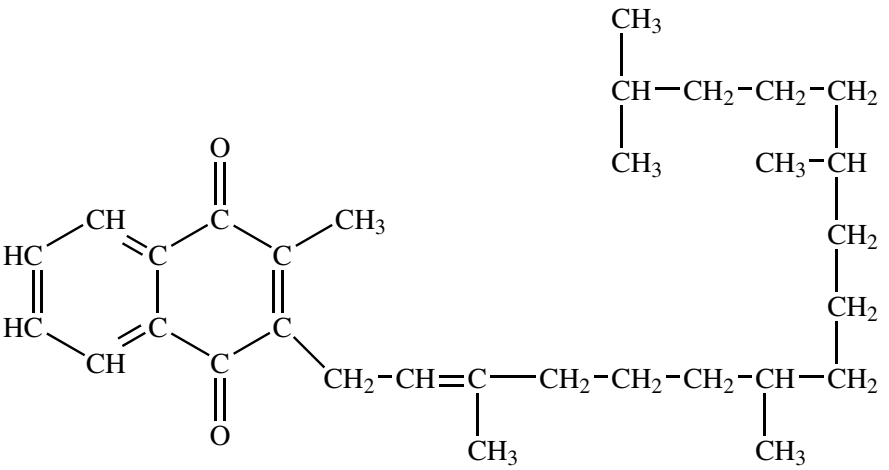


Figure 10-12: Structure of vitamin K_1.

Vitamin K is necessary to produce the proenzyme *prothrombin,* which helps blood clot. A vitamin K deficiency is uncommon because intestinal bacteria normally produce sufficient quantities, although several foods are also good sources, including green leafy vegetables, cauliflower, broccoli, organ meats (love that liver!), milk, soybeans, avocados, and bananas. Two tablespoons of parsley contains almost twice your recommended daily amount of vitamin K. Prolonged use of antibiotics can decrease the number of these vitamin K-producing bacteria and lead to a reduction in vitamin K in the body. One symptom of a deficiency is an increase in the time necessary to form a blood clot, and such individuals are prone to develop serious bruises from even minor injuries. Infants with a deficiency have been known to die from brain hemorrhage. Increasing the vitamin K intake of the mothers decreases the likelihood of this occurrence.

Vitamin C

Vitamin C is another name for *ascorbic acid* (Figure 10-13). Dehydroascorbic acid also has vitamin C activity. Vitamin C is water-soluble — thus the body can readily eliminate excess, and large doses are not toxic.

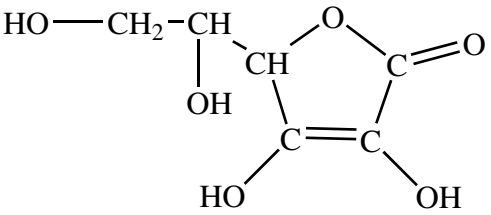


Figure 10-13: Structure of vitamin C.

A deficiency in vitamin C leads to the disease *scurvy,* symptoms of which include a weakening of the collagen — an important protein in connective tissues such as ligaments and tendons. Many foods contain vitamin C, especially plants and citrus fruits, so it is easy to prevent scurvy. For years, British ships carried limes as a source of vitamin C (leading, incidentally, to the slang term *limey* to refer to a British sailor). Many mammals (other than humans) synthesize vitamin C from glucose. Cooking, especially prolonged cooking, destroys vitamin C. Vitamin C is an antioxidant. Like vitamin E, it helps prevent damage produced by oxidants. It also helps in the absorption of iron, and keeps the iron in the +2 state. Vitamin C helps convert some of the proline in collagen C to hydroxyproline, which stabilizes the collagen.

Chapter 11

Be Quiet: Hormones

In This Chapter

- Examining the structures of hormones
- Finding out about some important hormones
- Discovering how hormones function

We *know* with this chapter title you are expecting several jokes, but we'll try to restrain ourselves and play it straight.

Hormones are materials produced in one area of the body and used in a different area. They are molecular messengers that are created in certain glands in the body and then travel through the bloodstream to the target organ. Other substances, called *paracrine factors* or *growth and differentiation factors* (GDFs), also convey biochemical information within a particular organ (a bit like passing a note in class). This conveyance is accomplished by simple diffusion over a small distance. Some biochemical substances may be both a hormone and a paracrine factor.

The endocrine glands produce most — but not all — hormones. Endocrine glands include the hypothalamus, pituitary, pancreas, adrenal, liver, testes, and ovaries. Now surely that got your attention! Some glands produce a single hormone, whereas others produce more than one. The simplified viewpoint (and we are all about keeping it simple) is that the pituitary gland acts as the central control for the endocrine system. Hormones from the pituitary gland do cause other glands to produce hormones that affect other systems — however, there are glands that have the same effect on the pituitary gland.

Structures of Some Key Hormones

There are three groups of hormones:

- Proteins, such as insulin
- Steroids, materials derived from cholesterol
- Amines, such as epinephrine

These materials allow one part of the body to influence what occurs elsewhere. These molecules are so efficient that only very low concentrations, typically 10^{-7} to 10^{-10} M, are necessary. That's a really small amount! The low concentrations make identification and isolation of these substances difficult.

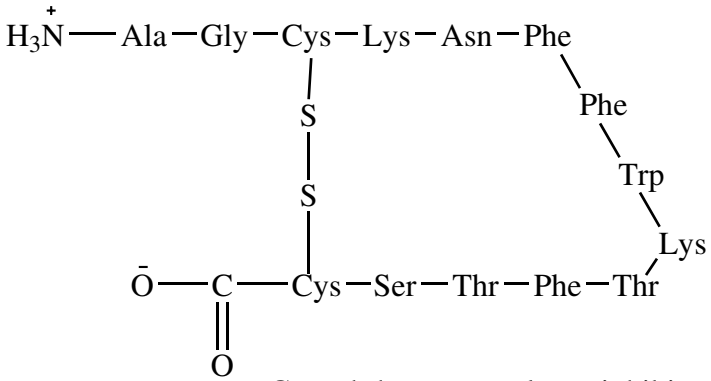
Proteins

The *protein,* or *polypeptide,* hormones, typically produced by the pituitary and hypothalamus glands, vary greatly in size — from simple tripeptides to larger molecules with more than 200 amino acid residues. Protein hormones are a diverse collection of molecules, including insulin (the structure of which you can see in Chapter 5).

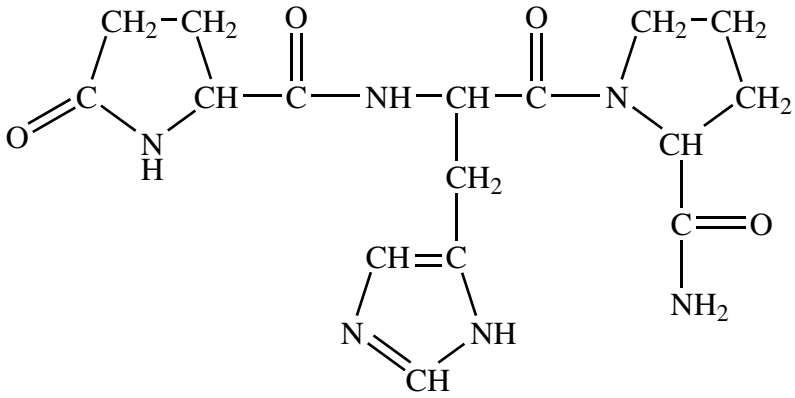
Others include the *thyrotropin-releasing factor,* which induces the release or production of a biochemical (thyrotropin, in this case). The thyrotropin-releasing factor hormone is a tripeptide containing glutamine (modified), histidine, and proline (modified). Another one is the *growth-hormone-release-inhibitory factor,* which inhibits the release or production of a chemical species. Together (Figure 11-1), these types of hormones provide a mechanism to start and stop an action. The idea is to maintain a tight biochemical control of biochemical processes, such as growth.

Steroids

You have no doubt read about steroid use among athletes, where it is used to increase muscle mass — to "pump-up," in other words. *Steroid* hormones, produced by the body's ovaries, testes, and adrenal glands, are cholesterol derivatives of about the same size as the parent molecule. They include the *estrogens* (female sex hormones), the *androgens* (male sex hormones), and the *adrenal cortical* hormones, such as aldosterone and cortisol. The estrogens and androgens are responsible for the development of the secondary sex characteristics of both females and males, respectively. These characteristics include enlargement of the breasts of females and development of facial hair in males.



Growth-hormone-release-inhibitory factor



Thyrotropin-releasing factor

Figure 11-1: Structures of the growth-hormone-release-inhibitory factor and thyrotropin-releasing factor.

The adrenal cortical hormones (Figure 11-2), which include the glucocorticoids and the mineralocorticoids, have a variety of functions. The glucocorticoids, such as cortisol, are important to several metabolic pathways. The mineralocorticoids, such as aldosterone, are important to the transport of inorganic species, such as sodium or potassium ions.

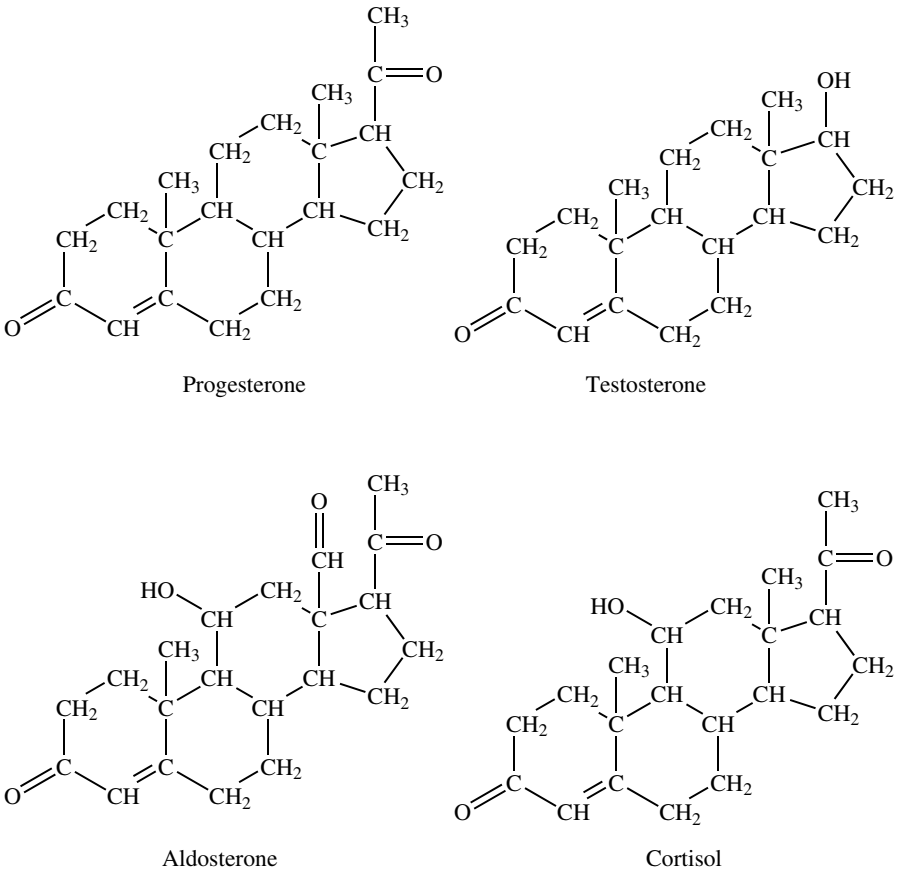
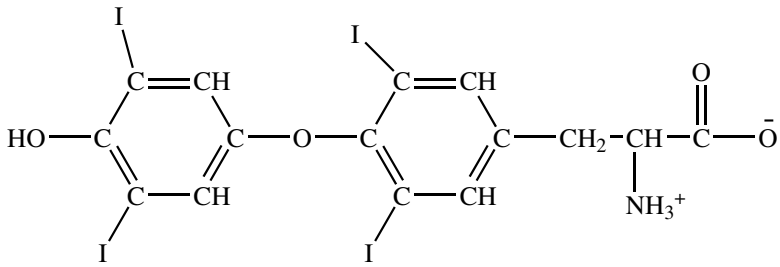


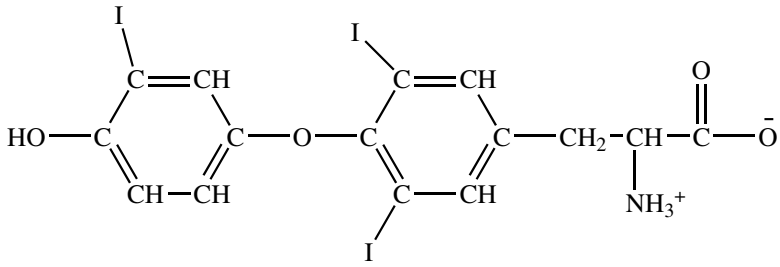
Figure 11-2: Structures of progesterone (an estrogen), testosterone (an androgen), and aldosterone and cortisol, adrenal cortical hormones.

Amines

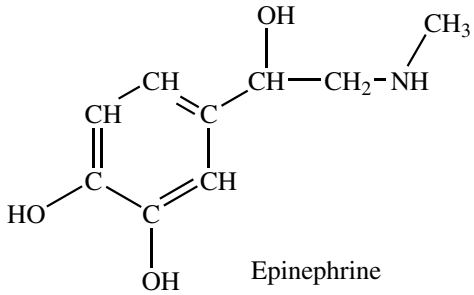
The *amine* hormones, typically produced by the thyroid and adrenal glands, are small molecules, many of which are derivatives of tyrosine. These hormones include *thyroxine* and *triiodthyronine,* produced by the thyroid gland, and *epinephrine* and *norepinephrine* produced by the adrenal gland. Figure 11-3 illustrates the structures of these hormones. Thyroxine and triiodothyronine are important metabolic-rate regulators. In fact, thyroxine is one of the most important substances in the body. It influences carbohydrate metabolism as well as protein synthesis and is involved in cardiovascular, brain, and renal function. Epinephrine and norepinephrine are important to control heart rate, blood flow, and metabolic rate.



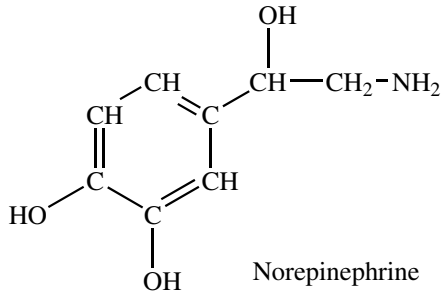
Thyroxine



Triiodothyroxine



Epinephrine



Norepinephrine

Figure 11-3: Structures of thyroxine, triiodothyronine, epinephrine, and norepinephrine.

Before and After: Prohormones

The synthesis of some hormones, like some enzymes, does not begin by producing the molecule in its active form. Instead, a *prohormone* forms, which remains unreactive and dormant until activated — sort of like us in the morning until we get our first cups of coffee. This process allows the body to build a store of a hormone for quick activation. Activating the prohormone requires less time than would the total synthesis of the molecule.

Proinsulin

Proinsulin is an example of a prohormone. *Insulin* is the hormone responsible for controlling blood sugar levels. Too much insulin results in a low blood sugar level (hypoglycemia), whereas too little insulin leads to elevated blood sugar levels (hyperglycemia). Your body needs to have a supply of insulin readily available for when you eat a piece of candy, such as a large chocolate-hazelnut truffle. If all of this insulin were already in your bloodstream, upon eating the candy you would become hypoglycemic. If the insulin were not present at all, you might become hyperglycemic until your body was able to synthesize sufficient insulin from the individual amino acids. Both hypoglycemia and hyperglycemia can lead to serious medical problems. The presence of a quantity of inactive insulin, ready to jump into action at a moment's notice, is the solution.

Bovine insulin (insulin produced from cows) contains two polypeptide chains, A and B, linked by disulfide linkages, with a total of 51 amino acid residues. Bovine proinsulin has 30 more amino acid residues than insulin does. Proinsulin is a single polypeptide chain with the insulin disulfide linkages. By removing a polypeptide sequence from the central region of this chain (residues 31–60), insulin forms. The excised portion originally connected one end of the A chain of insulin to the end of the B chain. The conversion of proinsulin to insulin requires the cleavage of two peptide bonds.

Angiotensinogen

Angiotensinogen is the prohormone of angiotensin II, a hormone that signals the adrenal cortex to release aldosterone. (In addition, angiotensin II is the most potent known vasoconstrictor.) The conversion of the prohormone to the hormone requires two steps. The first step uses the enzyme rennin. This peptidase, produced in the kidney, specifically cleaves a peptide bond between two leucine residues, the result of which is the decapeptide angiotensin I.

The second step utilizes the peptidase known as the angiotensin-converting enzyme. This enzyme, which occurs primarily in the lungs, cleaves the C-terminal dipeptide from angiotensin I to yield angiotensin II. These biochemical reactions can occur very rapidly, ensuring that the hormone can be quickly activated when needed by the body.

Fight or Flight: Hormone Function

The endocrine system, which generates the hormones, consists of a number of apparently unrelated organs: the liver, the ovaries or testes, the thyroid, the pancreas, and a number of other glands — components that are part of a complex, integrated network. A malfunction of one affects others.

Opening the letter: Hormonal action

Several mechanisms lead to the regulation of hormones. A *control loop* is the simplest. In many cases, one hormone stimulates the production of others so that many actions may occur before some type of control occurs.

Simple control loops

We are all familiar with *control loops.* You study for a test, but get a so-so grade. So you study harder for the next exam. Your grade provides *feedback,* causing your study habits to (hopefully) change. In the body, a control loop process begins with an external stimulus signaling a gland to generate a hormone. This hormone then influences its target site. Action by the target leads to a change, which signals the gland to stop. The action of the hormone causing the stop signal provides a negative feedback. An example of this type of loop is the production of insulin by the pancreas. The presence of high glucose levels in the bloodstream signals the pancreas to release insulin. The released insulin lowers the glucose level in the bloodstream. The reduced glucose level signals the pancreas to stop releasing insulin. The low glucose level is the negative feedback. This is a simplification; other factors may trigger the release of insulin. In addition, high glucose levels can trigger other biochemical functions, such as the synthesis of glycogen in the liver.

Hypothalamus-pituitary control

The hypothalamus-pituitary system is a very complex example of the other extreme of hormone control. The hypothalamus and the pituitary glands are in such close proximity that they behave almost as a single unit.

Initially, the central nervous system signals the hypothalamus to release a hormone called a *hormone-releasing factor,* which signals the pituitary. The pituitary, thus signaled, releases another hormone into the bloodstream. This hormone may target a specific organ or signal another part of the endocrine system to secrete yet another hormone. The presence of this final hormone serves as a negative feedback signal to the hypothalamus to stop secreting the hormone-releasing factor to the pituitary. Again, this is a simplistic view of a complicated system. An analogy might be your parents seeing your so-so exam grade. They freak out and force you to study harder. You are being influenced by an external force, in this case, your parents.

Figure 11-4 gives a more detailed representation of this system. Although the pituitary gland is known as the "master gland," this figure indicates that it is, in fact, the hypothalamus that deserves this honor.

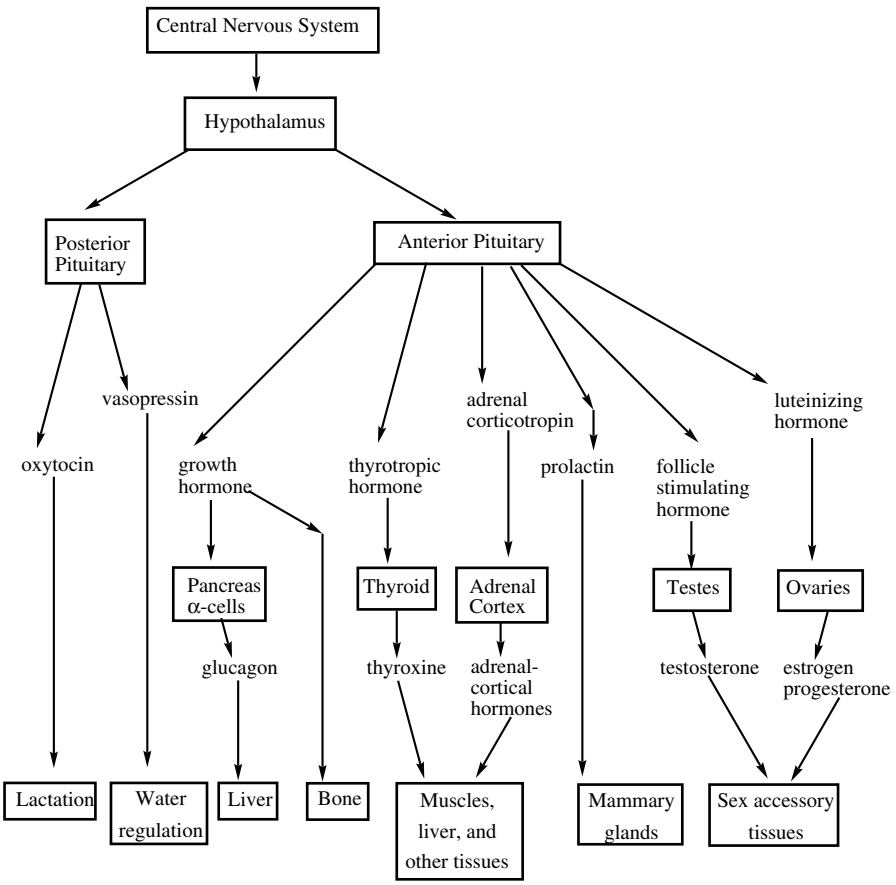


Figure 11-4: Schematic of hormone control in the body.

Models of hormonal action

Two models have been proposed to account for the molecular action of hormones. The first is the *two-messenger hypothesis,* which applies primarily to polypeptide and amine hormones. The other, *steroid hormonal action,* applies primarily to steroids. We use a simplistic approach (the KISS rule: Keep It Simple, Silly) for each model to emphasize their basic concepts. The actual processes involve many more changes.

The two-messenger model: Like the mail

Studies into the hormonal action of epinephrine (adrenaline) led to the development of this model. Later work indicated that the model applies to other hormonal systems as well. In the two-messenger model, a hormone binds to a receptor site on the exterior of a cell. This binding induces the release of another agent within the cell. The hormone is the first messenger, and the other agent in the second messenger.

For example, the adrenal medulla releases epinephrine, the "fight or flight" hormone, in vertebrate animals. This release initiates a number of responses, including glycogenolysis, the breakdown of glycogen. Glycogenolysis releases glucose for use in rapid energy production. As with other hormones, the concentration of hormone required is very low. For epinephrine, it is about 10^{-9} M. The released epinephrine acts as the first messenger (the extracellular one). Molecules of epinephrine bind to specific receptor sites on the surface of the target cells — primarily the skeletal muscles and, to a lesser extent, liver. The binding of epinephrine to the outside of liver cells induces the enzyme adenylate cyclase, bound to the interior of the cell membrane, to synthesize cyclic AMP (see Figure 11-5). Cyclic AMP, or cAMP, is the second messenger (the intracellular one). The second messenger initiates a series of events terminating in the release of glucose (glycogenolysis).

Initially, the cAMP binds to the regulatory subunit of protein kinase, and this activates the membrane-bound enzyme. The released protein kinase then activates phosphorylase kinase. This process requires calcium ion and ATP. (Muscular action releases calcium ion, which aids the process.) Phosphorylase kinase, with aid of ATP and magnesium ion, converts inactive phosphorylase b to active phosphorylase a. The increased presence of this enzyme accelerates the breakdown of glycogen with the release of D-glucose-1-phosphate. Phosphoglucomutase then converts D-glucose-1-phosphate to D-glucose-6-phosphate. Finally, D-glucose-6-phosphatase catalyzes the loss of the phosphate to release glucose, which may be used in the cell or, more importantly, may enter the bloodstream. Whew!

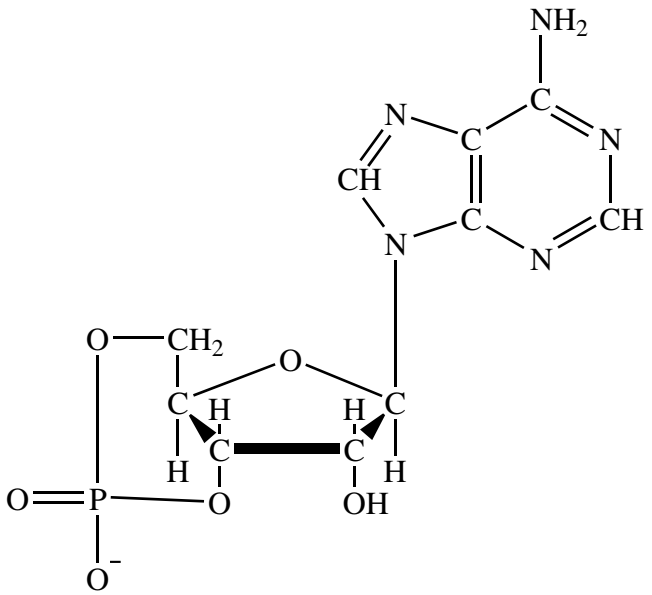


Figure 11-5: Structure of cyclic AMP.

The enzyme protein kinase also catalyzes the conversion of glycogen synthase (active) to phosphor-glycogen synthase (inactive). Thus, while the level of protein kinase is high, the production of new glycogen ceases. The inhibition of glycogen synthesis also means that more glucose will be available for rapid actions, such as running away from an angry pit bull.

Steroid hormonal action

Unlike hormones in the two-messenger system, steroid hormones cross the membrane and enter the cell. This mechanism applies to other hormones as well, such as thyroid hormones, in addition to the steroid hormones.

The first system described by this model was the action of estradiol on uterine tissue in mammals. The estradiol, an estrogen, enters the cell where it binds to an estrogen-receptor protein. The binding does not involve covalent bonding, but induces instead a conformational change in the protein. The change in the shape of the protein allows it to pass through the "door" into the cell nucleus. The hormone-protein complex then enters the cell nucleus where it binds to a specific site on a chromosome. This binding to the chromosome stimulates transcription to produce mRNA, which, in turn, exits the nucleus and synthesizes protein molecules through translation.

Three basic factors differentiate the steroid system from the two-messenger system. First, in the steroid system the hormone enters the cell. Second, there is a specific receptor molecule within the cytosol, the fluid inside the cell. Finally, the hormone action is at the chromosome level.