Produced by honeybees from the nectar of flowers, honey is primarily a mixture of the two simple sugars fructose and glucose.
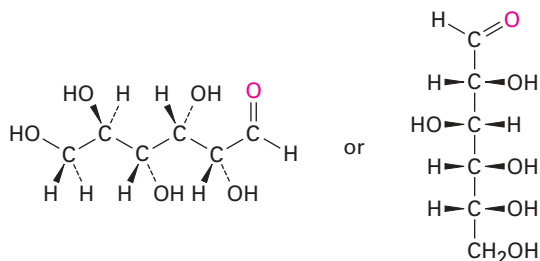
Biomolecules: Carbohydrates

Carbohydrates occur in every living organism. The sugar and starch in food, and the cellulose in wood, paper, and cotton are nearly pure carbohydrate. Modified carbohydrates form part of the coating around living cells, other carbohydrates are part of the nucleic acids that carry our genetic information, and still others are used as medicines.

The word **carbohydrate** derives historically from the fact that glucose, the first carbohydrate to be obtained pure, has the molecular formula $C_6H_{12}O_6$ and was originally thought to be a "hydrate of carbon," $C_6(H_2O)_6$. This view was soon abandoned, but the name persisted. Today, the term *carbohydrate* is used to refer loosely to the broad class of polyhydroxylated aldehydes and ketones commonly called *sugars*. Glucose, also known as *dextrose* in medical work, is the most familiar example.
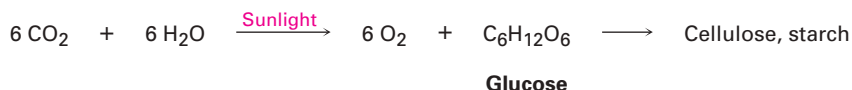
OWL

Online homework for this chapter can be assigned in OWL, an online homework assessment tool.

Glucose (dextrose), a pentahydroxyhexanal

Carbohydrates are synthesized by green plants during photosynthesis, a complex process in which sunlight provides the energy to convert CO_2 and H_2O into glucose plus oxygen. Many molecules of glucose are then chemically linked for storage by the plant in the form of either cellulose or starch. It has been estimated that more than 50% of the dry weight of the earth's biomass—all plants and animals—consists of glucose polymers. When eaten and metabolized, carbohydrates then provide animals with a source of readily available energy. Thus, carbohydrates act as the chemical intermediaries by which solar energy is stored and used to support life.

$$6\,CO_2 \;+\; 6\,H_2O \;\xrightarrow{\text{Sunlight}}\; 6\,O_2 \;+\; \underset{\textbf{Glucose}}{C_6H_{12}O_6} \;\longrightarrow\; \text{Cellulose, starch}$$

WHY THIS CHAPTER?

We've now seen all the common functional groups and reaction types that occur in organic and biological chemistry. In the few remaining chapters, we'll focus on the major classes of biological molecules, beginning in this chapter with a look at the structures and primary biological functions of carbohydrates. In Chapter 17, we'll return to the subject to see how carbohydrates are both synthesized and degraded by organisms.

14.1 Classification of Carbohydrates

Carbohydrates are generally classed as either *simple* or *complex*. **Simple sugars**, or **monosaccharides**, are carbohydrates like glucose and fructose that can't be converted into smaller sugars by hydrolysis. **Complex carbohydrates** are made of two or more simple sugars linked together. Sucrose (table sugar), for example, is a *disaccharide* made up of one glucose linked to one fructose. Similarly, cellulose is a *polysaccharide* made up of several thousand glucose molecules linked together. Enzyme-catalyzed hydrolysis of polysaccharides breaks them down into their constituent monosaccharides.
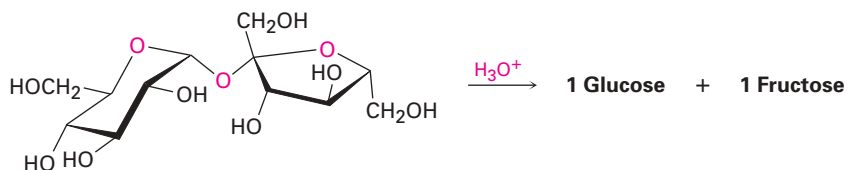

**Sucrose
(a disaccharide)**

$\xrightarrow{\;H_3O^+\;}$ **1 Glucose   +   1 Fructose**
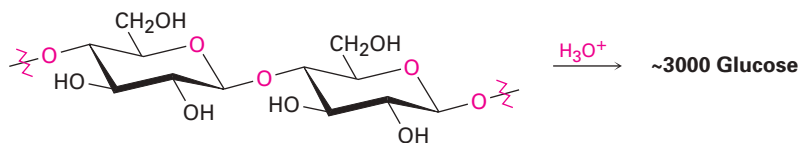
**Cellulose
(a polysaccharide)**

$\xrightarrow{\;H_3O^+\;}$ **~3000 Glucose**

Monosaccharides are further classified as either **aldoses** or **ketoses**. The *-ose* suffix designates a carbohydrate, and the *aldo-* and *keto-* prefixes identify the kind of carbonyl group in the molecule, whether aldehyde or ketone. The number of carbon atoms in the monosaccharide is indicated by the appropriate numerical prefix *tri-*, *tetr-*, *pent-*, *hex-*, and so forth. Thus, glucose is an *aldohexose,* a six-carbon aldehydo sugar; fructose is a *ketohexose,* a six-carbon keto sugar; and ribose is an *aldopentose,* a five-carbon aldehydo sugar. Most of the common simple sugars are either aldopentoses or aldohexoses.

Glucose (an aldohexose)   **Fructose** (a ketohexose)   **Ribose** (an aldopentose)   **Sedoheptulose** (a ketoheptose)
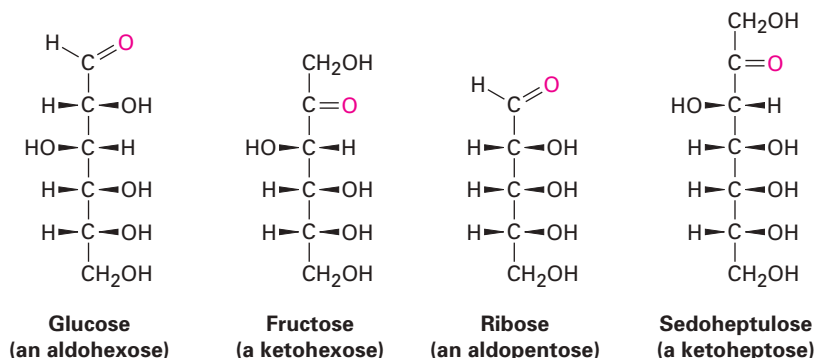
Worked Example 14.1

Classifying Monosaccharides

Classify the following monosaccharide:
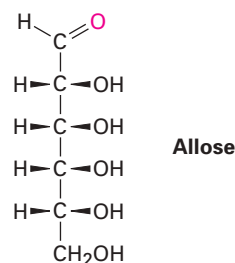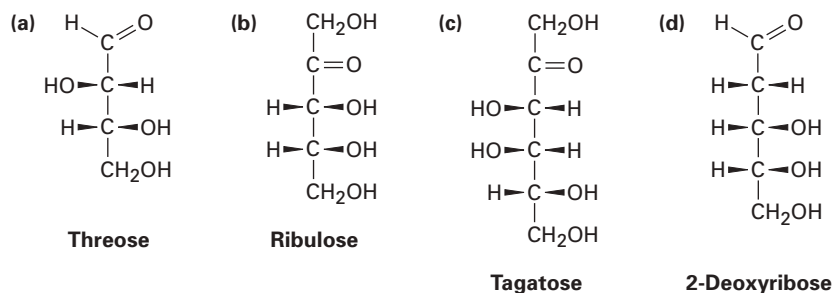

Allose

Solution

Since allose has six carbons and an aldehyde carbonyl group, it is an aldohexose.

Problem 14.1   Classify each of the following monosaccharides:

(a) Threose   **(b)** Ribulose   **(c)** Tagatose   **(d)** 2-Deoxyribose

14.2 Depicting Carbohydrate Stereochemistry: Fischer Projections

Because carbohydrates usually have numerous chirality centers, it was recognized long ago that a quick method for representing stereochemistry is needed. In 1891, the German chemist Emil Fischer suggested a method based on the projection of a tetrahedral carbon atom onto a flat surface. These **Fischer projections** were soon adopted and are now a common means of representing stereochemistry at chirality centers, particularly in carbohydrate chemistry.

A tetrahedral carbon atom is represented in a Fischer projection by two crossed lines. The horizontal lines represent bonds coming out of the page, and the vertical lines represent bonds going into the page.
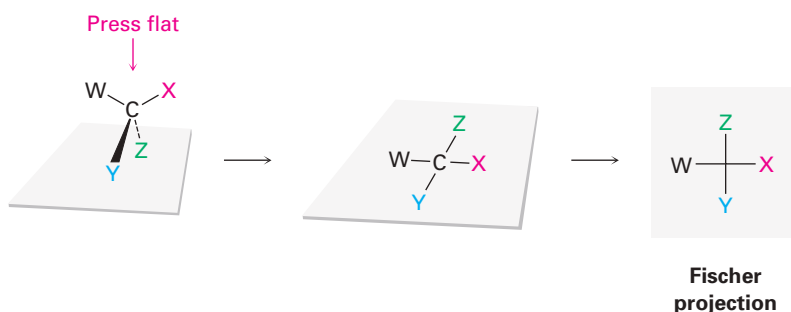
Thus, (*R*)-glyceraldehyde, the simplest monosaccharide, is represented as shown in Figure 14.1.
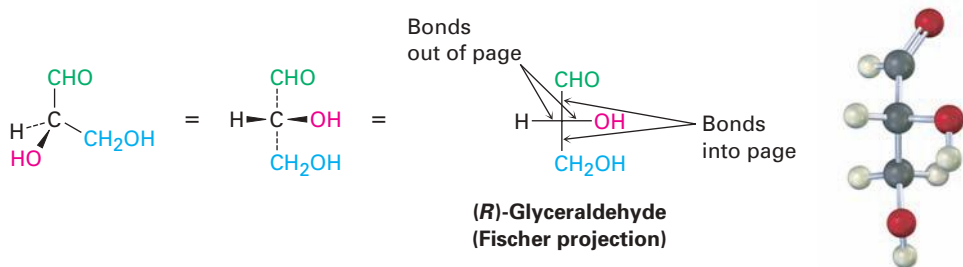

Figure 14.1 A Fischer projection of (*R*)-glyceraldehyde.

Carbohydrates with more than one chirality center are shown in Fischer projections by stacking the centers on top of one another, with the carbonyl carbon at or near the top. Glucose, for example, has four chirality centers stacked on top of one another in a Fischer projection. Such representations
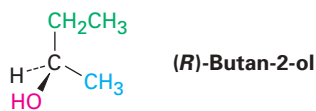
don't, however, give an accurate picture of a molecule's true three-dimensional conformation, which is curled around on itself like a bracelet.

Glucose
(carbonyl group at top)
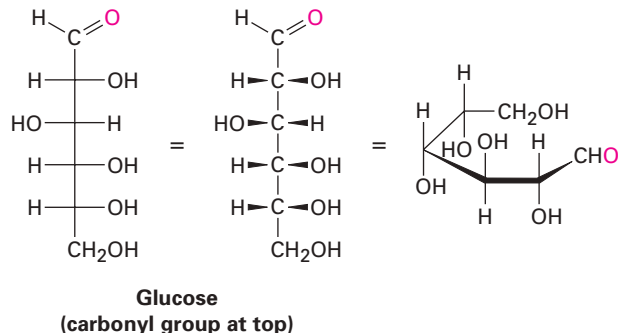
Worked Example 14.2

Drawing a Fischer Projection

Convert the following tetrahedral representation of (R)-butan-2-ol into a Fischer projection:

(R)-Butan-2-ol

Strategy Orient the molecule so that two horizontal bonds are facing you and two vertical bonds are receding away from you. Then press the molecule flat into the paper, indicating the chirality center as the intersection of two crossed lines.

Solution

(R)-Butan-2-ol
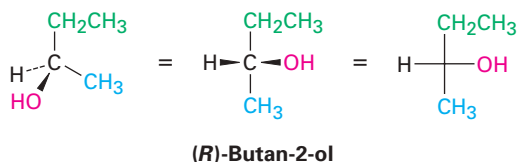
Worked Example 14.3

Interpreting a Fischer Projection

Convert the following Fischer projection of lactic acid into a tetrahedral representation, and indicate whether the molecule is (R) or (S):

Lactic acid

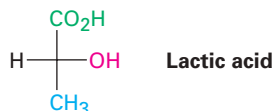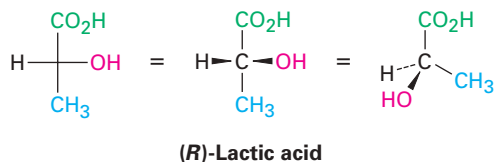**Strategy**   Place a carbon atom at the intersection of the two crossed lines, and imagine that the two horizontal bonds are coming toward you and the two vertical bonds are receding away from you. The projection represents (R)-lactic acid.
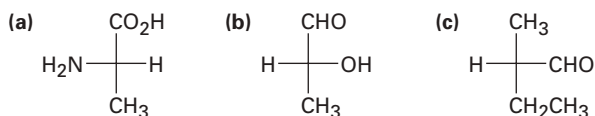
Solution

$$\text{H} {-}\!\!\!\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CO}_2\text{H}}{|}}{|}}\!\!\!{-} \text{OH} \quad = \quad \text{H}{\blacktriangleright}\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CO}_2\text{H}}{|}}{\text{C}}}{\blacktriangleleft}\text{OH} \quad = \quad \underset{\text{HO}}{\overset{\text{H}}{}}\!\!{\cdots}\overset{\overset{\text{CO}_2\text{H}}{|}}{\text{C}}{\diagdown}\text{CH}_3$$

(R)-Lactic acid

Problem 14.2   Convert the following tetrahedral representation of (S)-glyceraldehyde into a Fischer projection:

$$\text{HO}{\cdots}\overset{\overset{\text{CHO}}{|}}{\underset{\text{H}}{\text{C}}}{\diagdown}\text{CH}_2\text{OH}$$ **(S)-Glyceraldehyde**
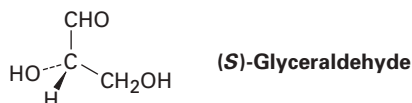
Problem 14.3   Draw Fischer projections of both (R)-2-chlorobutane and (S)-2-chlorobutane.

Problem 14.4   Convert the following Fischer projections into tetrahedral representations, and assign R or S stereochemistry to each:

(a)
$$\text{H}_2\text{N}{-}\!\!\!\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CO}_2\text{H}}{|}}{|}}\!\!\!{-}\text{H}$$

(b)
$$\text{H}{-}\!\!\!\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CHO}}{|}}{|}}\!\!\!{-}\text{OH}$$

(c)
$$\text{H}{-}\!\!\!\underset{\underset{\text{CH}_2\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{|}}\!\!\!{-}\text{CHO}$$

Problem 14.5   Redraw the following molecule as a Fischer projection, and assign R or S configuration to the chirality center (yellow-green = Cl):
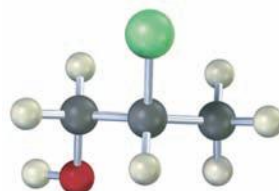
14.3 D,L Sugars

Glyceraldehyde, the simplest aldose, has only one chirality center and thus has two enantiomeric (mirror-image) forms. Only the dextrorotatory enantiomer occurs naturally, however. That is, a sample of naturally occurring glyceraldehyde placed in a polarimeter rotates plane-polarized light in a clockwise direction, denoted (+). Since (+)-glyceraldehyde has been found to have an R configuration at C2, it can be represented as in Figure 14.2. For historical reasons dating from long before the adoption of the R,S system, (R)-(+)-glyceraldehyde is also referred to as D-*glyceraldehyde* (D for dextrorotatory). The

other enantiomer, (*S*)-(−)-glyceraldehyde, is known as L-*glyceraldehyde* (L for levorotatory).

Because of the way that monosaccharides are synthesized in nature, glucose, fructose, ribose, and most other naturally occurring monosaccharides have the same *R* stereochemical configuration as D-glyceraldehyde at the chirality center farthest from the carbonyl group. In Fischer projections, therefore, most naturally occurring sugars have the −OH group at the bottom chirality center pointing to the right (Figure 14.2). Such compounds are referred to as **D sugars**.

Figure 14.2 Some naturally occurring D sugars. The −OH group at the chirality center farthest from the carbonyl group has the same configuration as (*R*)-(+)-glyceraldehyde and points toward the right in Fischer projections.

D-Glyceraldehyde
[(*R*)-(+)-glyceraldehyde]

D-Ribose

D-Glucose

D-Fructose
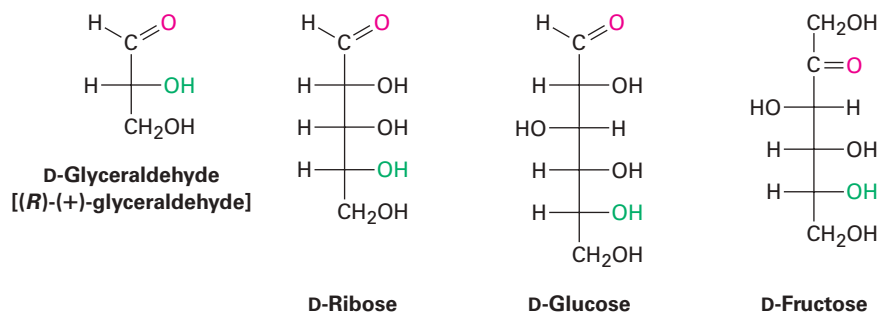
In contrast to D sugars, all **L sugars** have an *S* configuration at the lowest chirality center, with the bottom −OH group pointing to the *left* in Fischer projections. Thus, an L sugar is the mirror image (enantiomer) of the corresponding D sugar and has the opposite configuration at all chirality centers.

L-Glyceraldehyde
[(*S*)-(−)-glyceraldehyde]

L-Glucose
(not naturally occurring)

D-Glucose
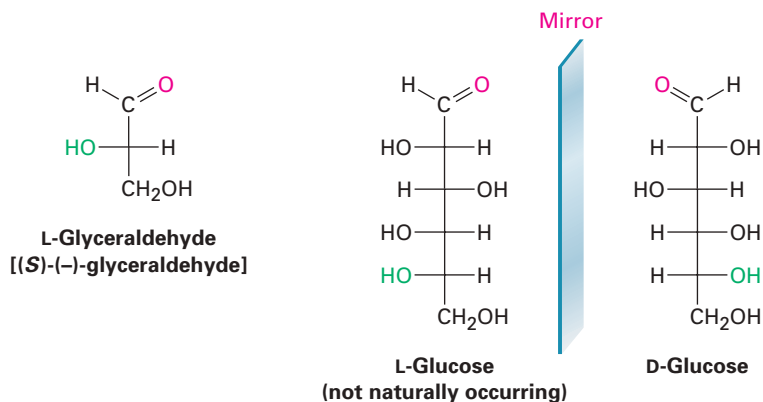
Note that the D and L notations have no relation to the direction in which a given sugar rotates plane-polarized light. A D sugar may be either dextrorotatory or levorotatory. The prefix D indicates only that the stereochemistry of the lowest chirality center is the same as that of D-glyceraldehyde and that the −OH group points to the right when the molecule is drawn in the standard way in a Fischer projection. Note also that the D,L system of carbohydrate nomenclature describes the configuration at only one chirality center and says nothing about the configuration of other chirality centers that may be present.
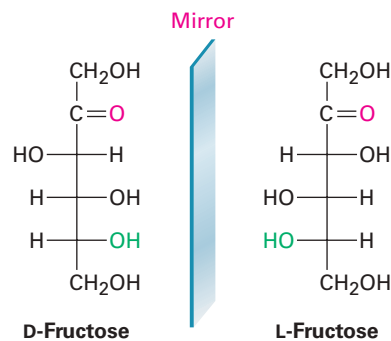
Worked Example 14.4

Drawing the Fischer Projection of an Enantiomer

Look at the Fischer projection of D-fructose in Figure 14.2, and draw a Fischer projection of L-fructose.
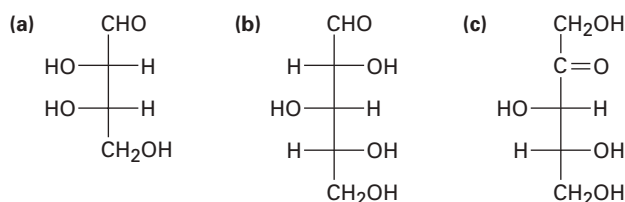
Strategy   Since L-fructose is the enantiomer of D-fructose, simply take the structure of D-fructose and reverse the configuration at every chirality center.

Solution

D-Fructose   L-Fructose

Problem 14.6   Which of the following are L sugars, and which are D sugars?

Problem 14.7   Draw the enantiomers of the carbohydrates shown in Problem 14.6, and identify each as a D sugar or an L sugar.

14.4 Configurations of Aldoses

Aldotetroses are four-carbon sugars with two chirality centers. Thus, there are $2^2 = 4$ possible stereoisomeric aldotetroses, or two D,L pairs of enantiomers, named *erythrose* and *threose*.

Aldopentoses have three chirality centers and a total of $2^3 = 8$ possible stereoisomers, or four D,L pairs of enantiomers. These four pairs are named *ribose, arabinose, xylose,* and *lyxose*. All except lyxose occur widely. D-Ribose is an important part of RNA (ribonucleic acid), L-arabinose is found in many plants, and D-xylose is found in both plants and animals.

Aldohexoses have four chirality centers and a total of $2^4 = 16$ possible stereoisomers, or eight D,L pairs of enantiomers. The names of the eight are *allose, altrose, glucose, mannose, gulose, idose, galactose,* and *talose*. Only D-glucose, from starch and cellulose, and D-galactose, from gums and fruit pectins, are widely distributed in nature. D-Mannose and D-talose also occur naturally, but in lesser abundance.

Fischer projections of the four-, five-, and six-carbon D aldoses are shown in Figure 14.3. Starting from D-glyceraldehyde, we can imagine constructing the two D aldotetroses by inserting a new chirality center just below the aldehyde carbon. Each of the two D aldotetroses then leads to two D aldopentoses (four total), and each of the four D aldopentoses leads to two D aldohexoses (eight total). In addition, each of the D aldoses in Figure 14.3 has a mirror-image L enantiomer, which is not shown.
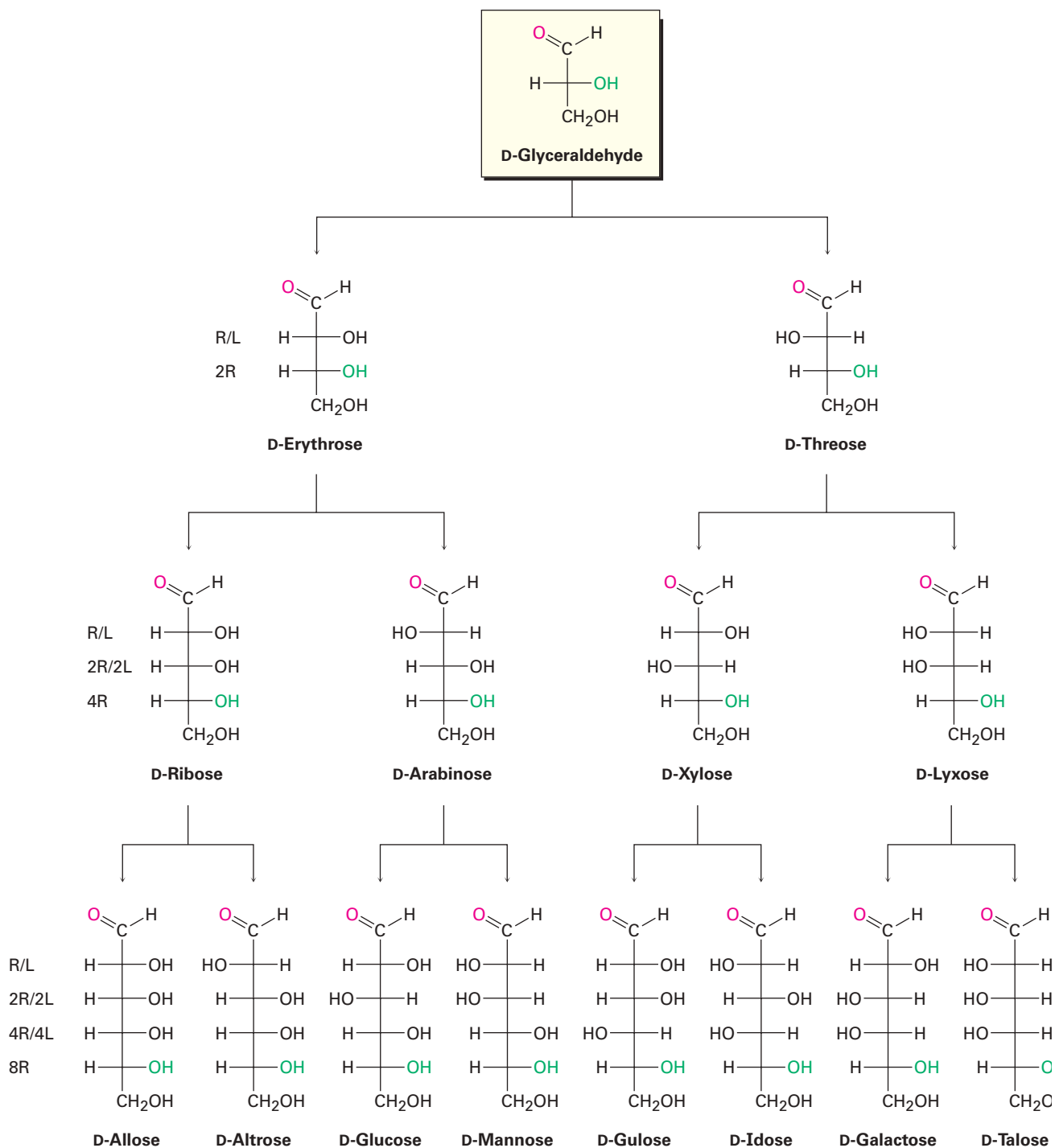
Figure 14.3 Configurations of D aldoses. The structures are arranged from left to right so that the −OH groups on C2 alternate right/left (R/L) in going across a series. Similarly, the −OH groups at C3 alternate two right/two left (2R/2L), the −OH groups at C4 alternate 4R/4L, and the −OH groups at C5 are to the right in all eight (8R). Each D aldose has a mirror-image L enantiomer that is not shown.

Problem 14.8   Only the D sugars are shown in Figure 14.3. Draw Fischer projections for the following L sugars:

(a) L-Arabinose   (b) L-Threose   (c) L-Galactose

Problem 14.9   How many aldoheptoses are possible? How many of them are D sugars, and how many are L sugars?

Problem 14.10   Draw Fischer projections for the two D aldoheptoses (Problem 14.9) whose stereochemistry at C3, C4, C5, and C6 is the same as that of glucose at C2, C3, C4, and C5.

Problem 14.11   The following model is that of an aldopentose. Draw a Fischer projection of the sugar, and identify it. Is it a D sugar or an L sugar?
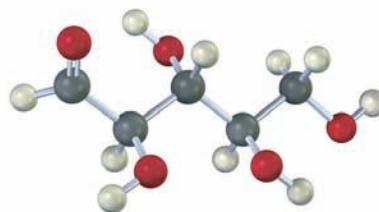
14.5 / Cyclic Structures of Monosaccharides: Hemiacetal Formation

During the discussion of carbonyl-group chemistry in Section 9.8, we said that aldehydes and ketones undergo a rapid and reversible nucleophilic addition reaction with alcohols to form hemiacetals.

**An aldehyde**   **A hemiacetal**
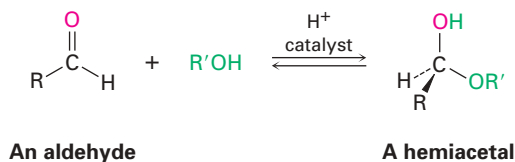
If the carbonyl and the hydroxyl group are in the same molecule, an intramolecular nucleophilic addition can take place, leading to the formation of a *cyclic* hemiacetal. Five- and six-membered cyclic hemiacetals are particularly stable, and many carbohydrates therefore exist in an equilibrium between open-chain and cyclic forms.

Glucose exists in aqueous solution primarily in the six-membered, **pyranose** form resulting from intramolecular nucleophilic addition of the −OH group at C5 to the C1 carbonyl group. Fructose, on the other hand, exists to the extent of about 72% in the pyranose form and about 28% in the five-membered **furanose** form resulting from addition of the −OH group at C5 to the C2 ketone. (The names *pyranose* for a six-membered ring and *furanose* for a five-membered ring are derived from the names of the simple

cyclic ethers pyran and furan.) The cyclic forms of glucose and fructose are shown in Figure 14.4.

Figure 14.4 Glucose and fructose in their cyclic pyranose and furanose forms.

D-Glucose

(Pyranose form)

Pyranose form
(72%)

D-Fructose

Furanose form
(28%)
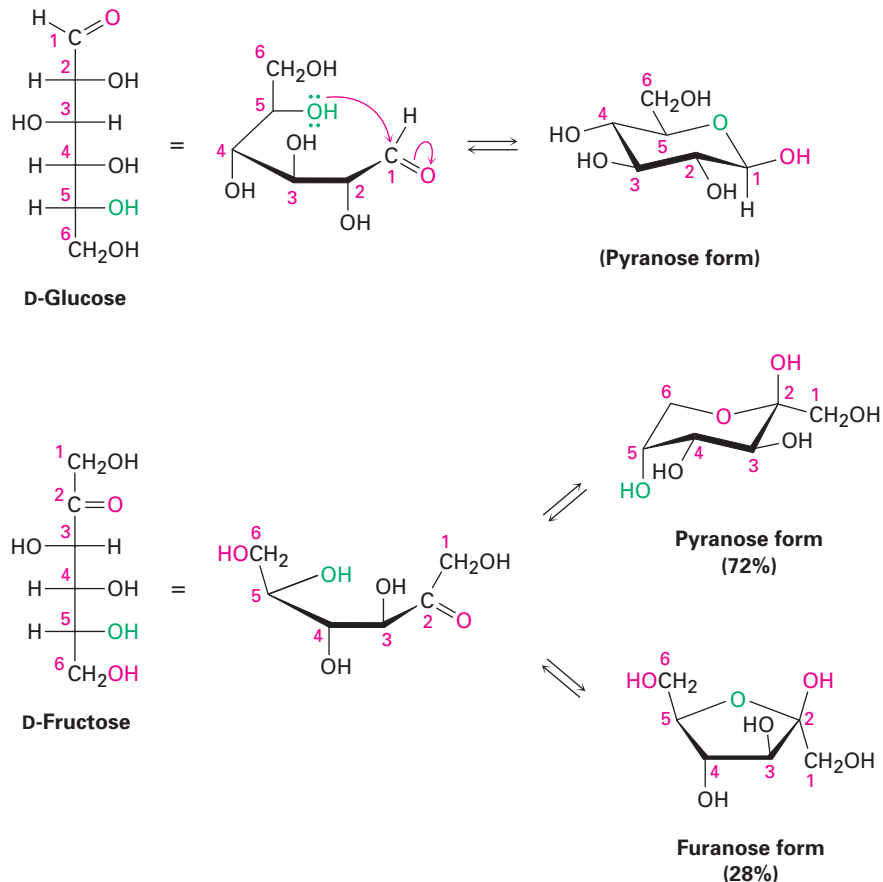
Like cyclohexane rings (Section 2.10), pyranose rings have a chair-like geometry with axial and equatorial substituents. By convention, the rings are usually drawn by placing the hemiacetal oxygen atom at the right rear, as shown in Figure 14.4. Note that an −OH group on the *right* in a Fischer projection is on the *bottom* face of the pyranose ring, and an −OH group on the *left* in a Fischer projection is on the *top* face of the ring. For D sugars, the terminal −CH₂OH group is on the top of the ring, whereas for L sugars, the −CH₂OH group is on the bottom.


Worked Example 14.5

Drawing the Pyranose Form of a Monosaccharide

D-Mannose differs from D-glucose in its stereochemistry at C2. Draw D-mannose in its pyranose form.

Strategy   First draw a Fischer projection of D-mannose. Then lay it on its side, and curl it around so that the −CHO group (C1) is on the right front and the −CH₂OH group (C6) is toward the left rear. Now, connect the −OH at C5 to the

C1 carbonyl group to form the pyranose ring. In drawing the chair form, raise the leftmost carbon (C4) up and drop the rightmost carbon (C1) down.

Solution

D-Mannose   **(Pyranose form)**
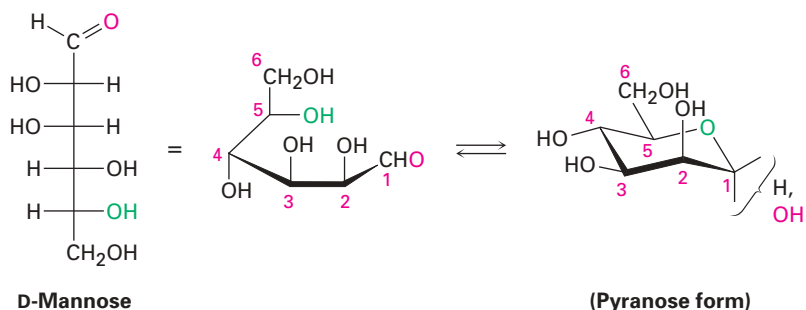
Problem 14.12   D-Galactose differs from D-glucose in its stereochemistry at C4. Draw D-galactose in its pyranose form.

Problem 14.13   Ribose exists largely in a furanose form, produced by addition of the C4 –OH group to the C1 aldehyde. Find the structure of D-ribose in Figure 14.3, and draw it in its furanose form.

14.6 Monosaccharide Anomers: Mutarotation

When an open-chain monosaccharide cyclizes to a pyranose or furanose form, a new chirality center is generated at the former carbonyl carbon. Two diastereomers, called **anomers**, are produced, with the hemiacetal carbon referred to as the **anomeric center**. For example, glucose cyclizes reversibly in aqueous solution to yield a 37:63 mixture of two anomers (Figure 14.5).

**Figure 14.5** Structures of the alpha and beta anomers of glucose.

α-D-Glucopyranose (37.3%)   (0.002%)   β-D-Glucopyranose (62.6%)
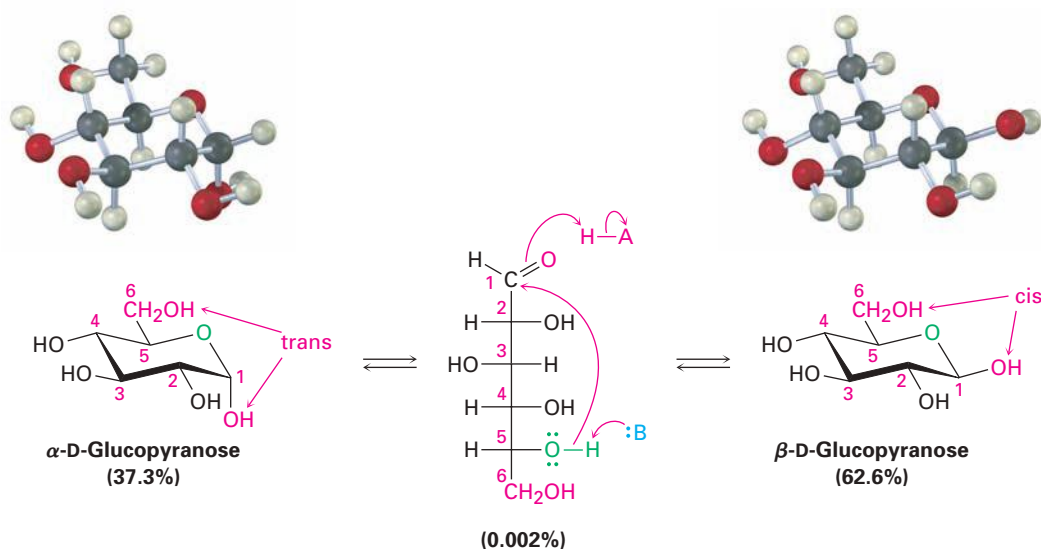
The minor anomer, which has the C1 –OH group trans to the –CH$_2$OH substituent at C5, is called the **alpha (α) anomer**; its full name is α-D-glucopyranose.

The major anomer, which has the C1 –OH group cis to the –CH$_2$OH substituent at C5, is called the **beta (β) anomer**; its full name is β-D-glucopyranose. Note that β-D-glucopyranose has all the substituents on the ring equatorial. Thus, β-D-glucopyranose is the least sterically crowded and most stable of the eight D aldohexoses.

Both anomers of D-glucopyranose can be crystallized and purified. Pure α-D-glucopyranose has a melting point of 146 °C and a specific rotation [α]$_D$ = +112.2; pure β-D-glucopyranose has a melting point of 148–155 °C and a specific rotation [α]$_D$ = +18.7. When a sample of either pure anomer is dissolved in water, however, the optical rotation slowly changes and ultimately reaches a constant value of +52.6. That is, the specific rotation of the α anomer solution decreases from +112.2 to +52.6.°, and the specific rotation of the β anomer solution increases from +18.7 to +52.6.°. Called **mutarotation**, this spontaneous change in optical rotation is caused by the slow interconversion of the pure α and β enantiomers to give the 37 : 63 equilibrium mixture.

Mutarotation occurs by a reversible ring opening of each anomer to the open-chain aldehyde form, followed by reclosure. Although equilibration is slow at neutral pH, it is catalyzed by both acid and base.
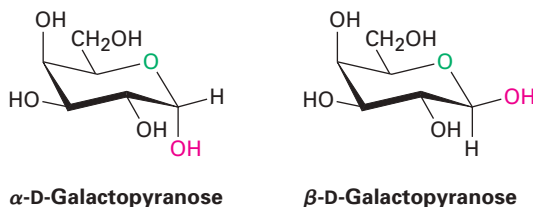

α-**D-Glucopyranose**
[α]$_D$ = +112.2

β-**D-Glucopyranose**
[α]$_D$ = +18.7
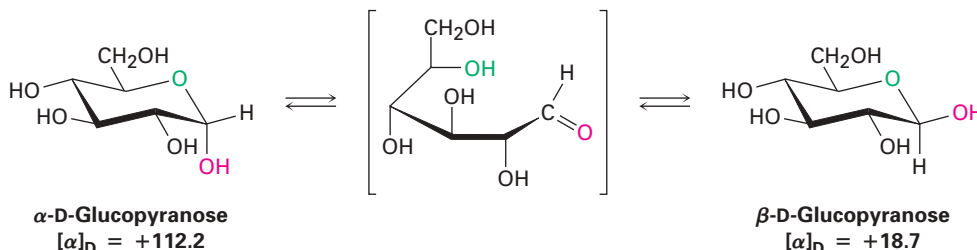
Worked Example 14.6

Drawing Pyranose Anomers

Draw the two pyranose anomers of D-galactose, and identify each as α or β.

Solution   The α anomer has the –OH group at C1 pointing down, trans to the CH$_2$OH, and the β anomer has the –OH group at C1 pointing up, cis to the CH$_2$OH.

α-**D-Galactopyranose**   β-**D-Galactopyranose**

Problem 14.14   At equilibrium in aqueous solution, D-fructose consists of 70% β-pyranose, 2% α-pyranose, 23% β-furanose, and 5% α-furanose forms. Draw all four.

Problem 14.15   Draw β-D-mannopyranose in its chair conformation, and label all substituents as axial or equatorial. Which would you expect to be more stable, mannose or galactose (Worked Example 14.6)?

14.7 | Reactions of Monosaccharides

Because monosaccharides contain only two kinds of functional groups, hydroxyls and carbonyls, most of the chemistry of monosaccharides is the now-familiar chemistry of these two groups. As we've seen, alcohols can be converted to esters and ethers and can be oxidized; carbonyl compounds can react with nucleophiles and can be reduced.
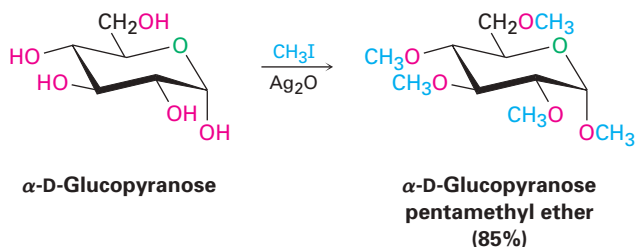
Ester and Ether Formation

Monosaccharides behave as simple alcohols in much of their chemistry. For example, carbohydrate –OH groups can be converted into esters and ethers, which are often easier to work with than the free sugars. Because of their many hydroxyl groups, monosaccharides are usually soluble in water but insoluble in organic solvents such as ether. They are also difficult to purify and have a tendency to form syrups rather than crystals when water is removed. Ester and ether derivatives, however, are soluble in organic solvents and are easily purified and crystallized.

Esterification is carried out by treating the carbohydrate with an acid chloride or acid anhydride in the presence of a base (Sections 10.7 and 10.8). All the –OH groups react, including the anomeric one. For example, β-D-glucopyranose is converted into its pentaacetate by treatment with acetic anhydride in pyridine solution.

β-D-Glucopyranose   Penta-*O*-acetyl-β-D-glucopyranose
                                             (91%)
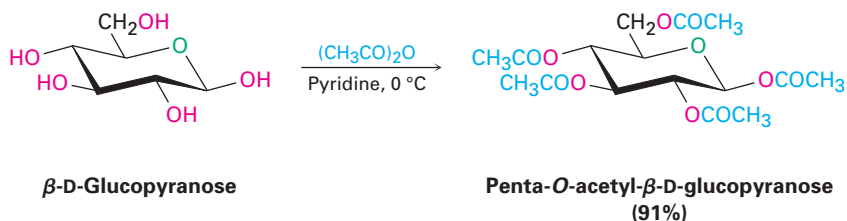
Carbohydrates are converted into ethers by treatment with an alkyl halide in the presence of base (Section 8.4). Silver oxide is a particularly mild and useful base for this reaction because hydroxide and alkoxide bases tend to degrade the sensitive sugar molecules. For example, α-D-glucopyranose is converted into its pentamethyl ether in 85% yield on reaction with iodomethane and Ag_2O.

α-D-Glucopyranose α-D-Glucopyranose
                                  pentamethyl ether
                                  (85%)

Problem 14.16   Draw the products you would obtain by reaction of β-D-ribofuranose with the following:
(a) CH_3I, Ag_2O (b) $(CH_3CO)_2O$, pyridine

β-D-Ribofuranose

Glycoside Formation

We saw in Section 9.8 that treatment of a hemiacetal with an alcohol and an acid catalyst yields an acetal.

A hemiacetal   **An acetal**

In the same way, treatment of a monosaccharide hemiacetal with an alcohol and an acid catalyst yields an acetal in which the anomeric −OH group has been replaced by an −OR group. For example, reaction of glucose with methanol gives a 2:1 mixture of α and β methyl D-glucopyranosides.

β-D-Glucopyranose
(a cyclic hemiacetal)

Methyl α-D-glucopyranoside
(66%)

Methyl β-D-glucopyranoside
(33%)

Called **glycosides**, carbohydrate acetals are named by first citing the alkyl group and then replacing the -*ose* ending of the sugar with -*oside*. Like all acetals, glycosides are stable to water. They aren't in equilibrium with an open-chain form, and they don't show mutarotation. They can, however, be hydrolyzed to give back the free monosaccharide plus alcohol on treatment with aqueous acid.

Glycosides are abundant in nature, and many biologically important molecules contain glycosidic linkages. For example, digitoxin, the active component of the digitalis preparations used for treatment of heart disease, is a glycoside

consisting of a steroid alcohol linked to a trisaccharide. Note also that the three sugars are linked to one another by glycoside bonds.

Digitoxigenin, a glycoside
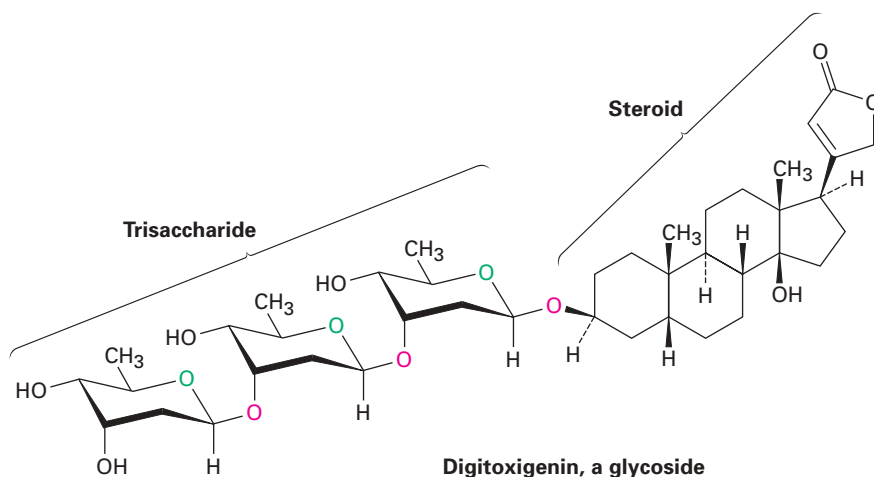
Worked Example 14.7

Predicting the Structure of a Glycoside

What product would you expect from the acid-catalyzed reaction of β-D-ribofuranose with methanol?

Strategy

The acid-catalyzed reaction of a monosaccharide with an alcohol yields a glycoside in which the anomeric −OH group is replaced by the −OR group of the alcohol.

Solution

β-D-Ribofuranose → Methyl β-D-ribofuranoside + H₂O
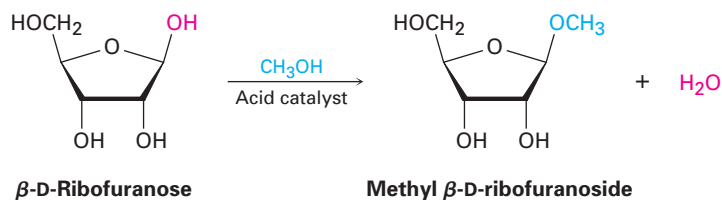
Problem 14.17

Draw the product you would obtain from the acid-catalyzed reaction of β-D-galactopyranose with ethanol.

Biological Ester Formation: Phosphorylation

In living organisms, carbohydrates occur not only in their free form but also linked through their anomeric center to other biological molecules such as lipids (*glycolipids*) or proteins (*glycoproteins*). Collectively called *glycoconjugates*, these sugar-linked molecules are components of cell walls and are crucial to the mechanism by which different cell types recognize one another.

Glycoconjugate formation occurs by reaction of the lipid or protein with a glycosyl nucleoside diphosphate. This diphosphate is itself formed by initial reaction of a monosaccharide with adenosine triphosphate (ATP) to give a

glycosyl monophosphate, followed by reaction with uridine triphosphate (UTP). (We'll see the structures of nucleoside phosphates in Section 16.5.) The purpose of the phosphorylation is to activate the anomeric −OH group of the sugar and make it a better leaving group in a nucleophilic substitution reaction with a protein or lipid (Figure 14.6).

Figure 14.6 Glycoprotein formation occurs by initial reaction of the starting carbohydrate with ATP to give a glycosyl monophosphate, followed by reaction with UTP to form a glycosyl uridine 5′-diphosphate. Nucleophilic substitution by an −OH (or −NH$_2$) group on a protein then gives the glycoprotein.
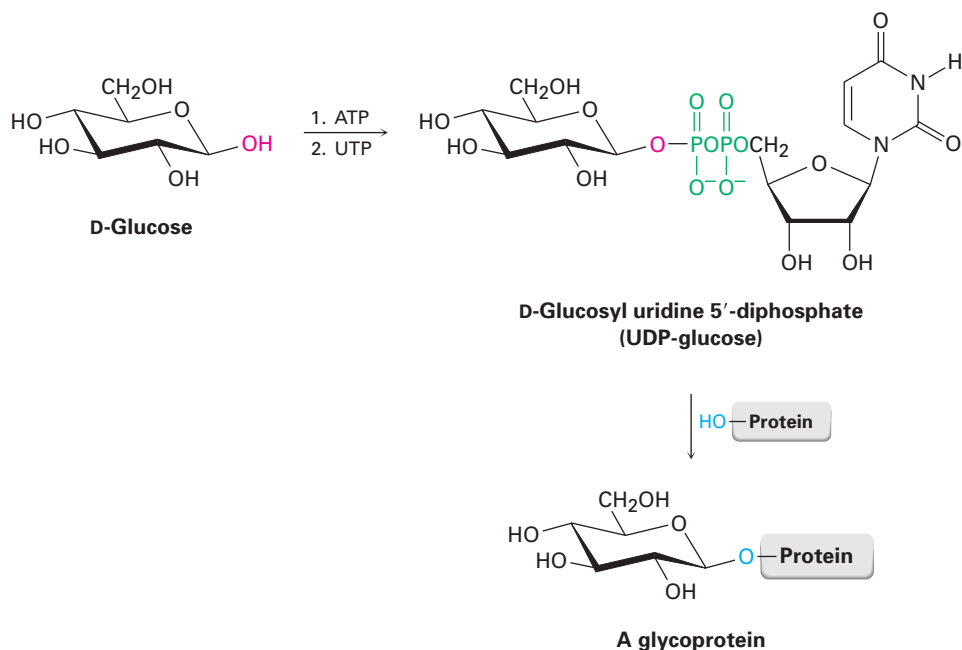
Reduction of Monosaccharides

Treatment of an aldose or a ketose with NaBH$_4$ reduces it to a polyalcohol called an **alditol**. The reaction occurs by reaction of the open-chain form present in the aldehyde ⇌ hemiacetal equilibrium.
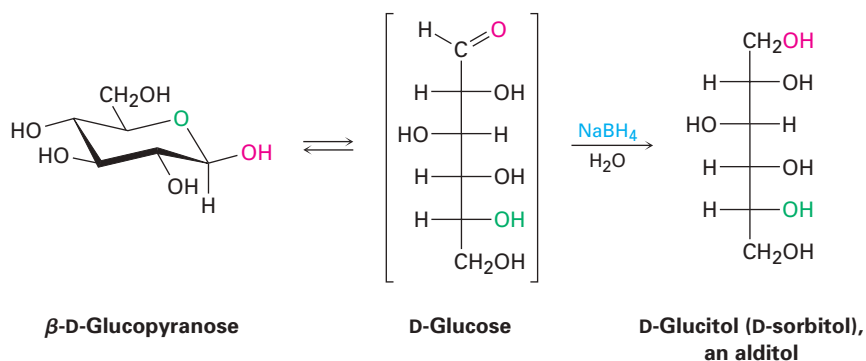
D-Glucitol, the alditol produced on reduction of D-glucose, is itself a naturally occurring substance that has been isolated from many fruits and berries. It is used under the name D-sorbitol as a sweetener and sugar substitute in many foods.

Worked Example 14.8

Drawing the Structure of an Alditol

Show the structure of the alditol you would obtain from reduction of D-galactose.

Strategy

First draw D-galactose in its open-chain form. Then convert the −CHO group at C1 into a −CH₂OH group.

Solution

D-Galactose   **D-Galactitol**
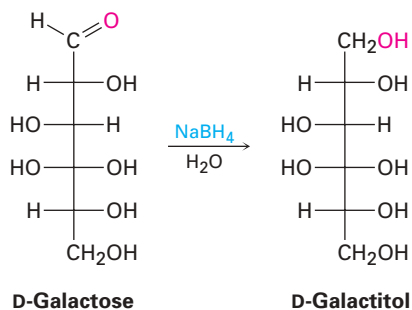
Problem 14.18

How can you account for the fact that reduction of D-glucose leads to an optically active alditol (D-glucitol), whereas reduction of D-galactose leads to an optically inactive alditol (see Section 6.7)?

Problem 14.19

Reduction of L-gulose with NaBH₄ leads to the same alditol (D-glucitol) as reduction of D-glucose. Explain.

Oxidation of Monosaccharides

Like other aldehydes, aldoses can be oxidized to yield the corresponding carboxylic acids, called **aldonic acids**. For laboratory purposes, a buffered solution of aqueous Br_2 is often used.

D-Glucose   **D-Gluconic acid**
                               (an aldonic acid)
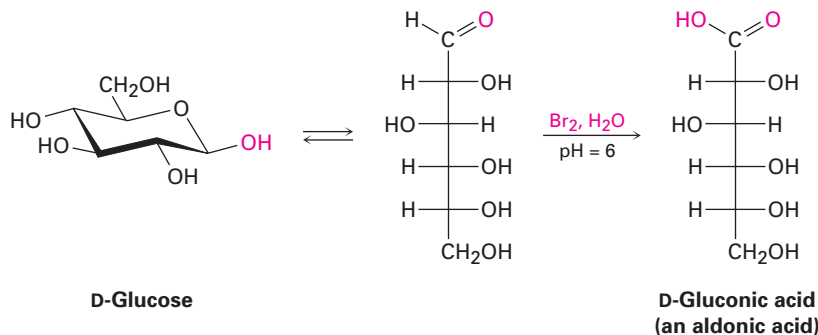
Historically, the oxidation of an aldose with either Ag^+ in aqueous ammonia (*Tollens' reagent*) or Cu^{2+} with aqueous sodium citrate (*Benedict's reagent*) formed the basis of simple tests for what are called **reducing sugars** (*reducing* because the aldose reduces the metal oxidizing agent). Some simple diabetes self-test kits sold in drugstores still use Benedict's reagent to detect glucose in urine, but more modern methods have largely replaced it.

All aldoses are reducing sugars because they contain aldehyde carbonyl groups, but glycosides are nonreducing because the acetal group can't open to an aldehyde under basic conditions.

If warm dilute HNO_3 (nitric acid) is used as the oxidizing agent, an aldose is oxidized to a dicarboxylic acid called an **aldaric acid**. Both the aldehyde carbonyl and the terminal $-CH_2OH$ group are oxidized in this reaction.

D-Glucose　　　　　**D-Glucaric acid (an aldaric acid)**
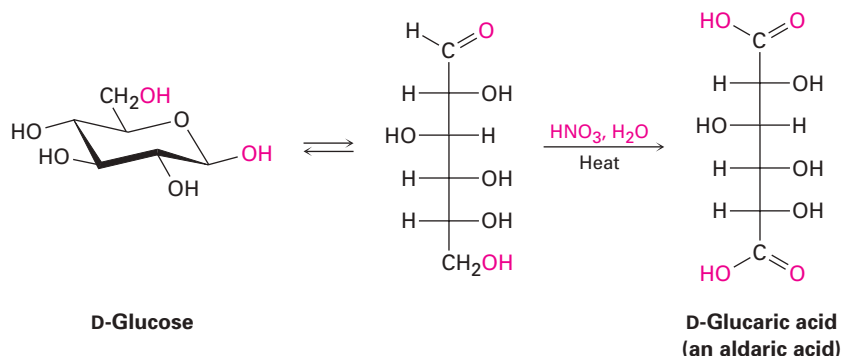
Finally, if only the $-CH_2OH$ end of the aldose is oxidized without affecting the $-CHO$ group, the product is a monocarboxylic acid called a **uronic acid**. The reaction must be done enzymatically; no chemical reagent is known that can accomplish this selective oxidation in the laboratory.

D-Glucose　　　　　**D-Glucuronic acid (a uronic acid)**
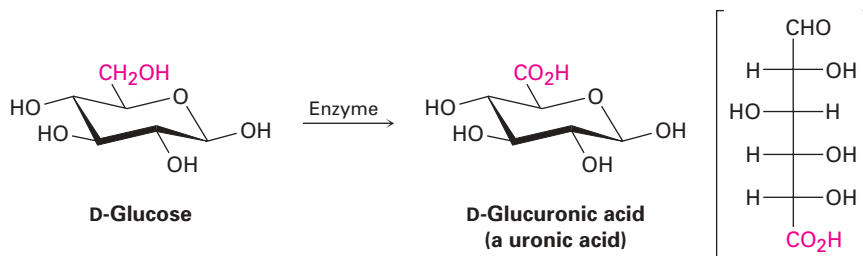
Problem 14.20 D-Glucose yields an optically active aldaric acid on treatment with nitric acid, but D-allose yields an optically inactive aldaric acid. Explain.

Problem 14.21 Which of the other six D aldohexoses yield optically active aldaric acids, and which yield optically inactive aldaric acids? (See Problem 14.20.)

14.8 The Eight Essential Monosaccharides

Humans need to obtain eight monosaccharides for proper functioning. Although all can be biosynthesized in the body from simpler precursors if necessary, it's more energetically efficient to obtain them from the diet. The eight are L-fucose (6-deoxy-L-galactose), D-galactose, D-glucose, D-mannose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine, D-xylose, and *N*-acetyl-D-neuraminic acid

(Figure 14.7). All are used for the synthesis of the glycoconjugate components of cell walls, and glucose is also the body's primary source of energy.
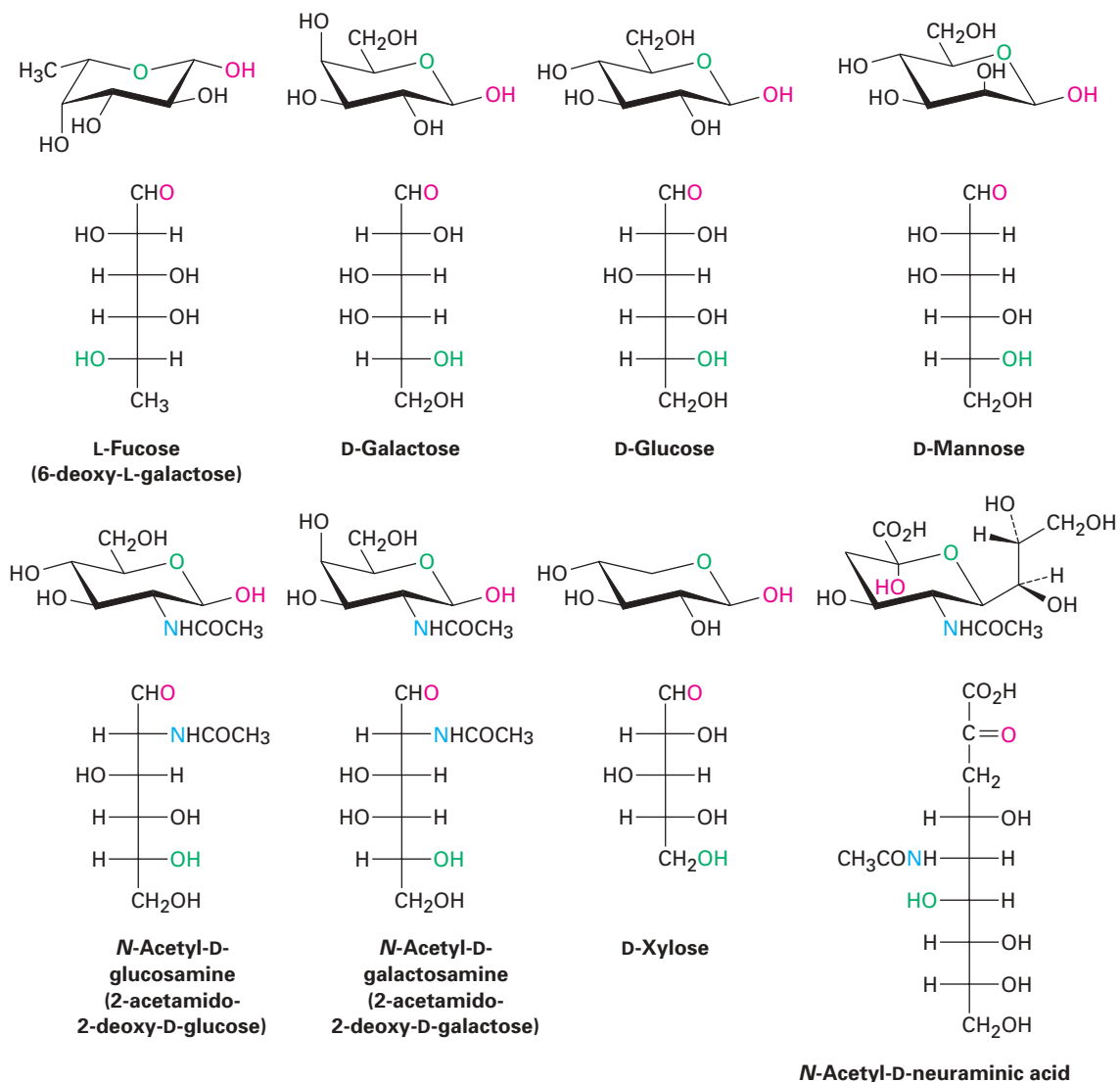

Figure 14.7 Structures of the eight monosaccharides essential to humans.

Of the eight essential monosaccharides, galactose, glucose, and mannose are simple aldohexoses, while xylose is an aldopentose. Fucose is a **deoxy sugar**, meaning that it has an oxygen atom "missing." That is, an −OH group (the one at C6) is replaced by an −H. N-Acetylglucosamine and N-acetylgalactosamine are amide derivatives of **amino sugars** in which an −OH (the one at C2) is replaced by an −NH₂ group. N-Acetylneuraminic acid is the parent compound of the *sialic acids,* a group of more than 30 substances with different modifications, including various oxidations, acetylations, sulfations, and methylations. All the essential monosaccharides are biosynthesized from glucose.

14.9 | Disaccharides

We saw in Section 14.7 that reaction of a monosaccharide hemiacetal with an alcohol yields a glycoside in which the anomeric −OH group is replaced by an −OR. If the alcohol is itself a sugar, the glycoside product is a *disaccharide*.

Maltose and Cellobiose

Disaccharides contain a glycoside acetal bond between the anomeric carbon of one sugar and an −OH group at any position on the other sugar. A glycoside link between C1 of the first sugar and C4 of the second sugar is particularly common. Such a bond is called a **1→4 link**.

A glycoside bond to the anomeric carbon can be either α or β. Maltose, the disaccharide obtained by enzyme-catalyzed hydrolysis of starch, consists of two α-D-glucopyranose units joined by a 1→4-α-glycoside bond. Cellobiose, the disaccharide obtained by partial hydrolysis of cellulose, consists of two β-D-glucopyranose units joined by a 1→4-β-glycoside bond.
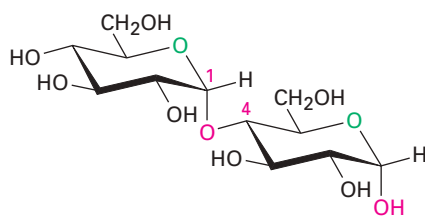
Maltose, a 1→4-α-glycoside
[4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranose]
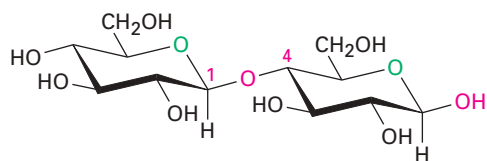
Cellobiose, a 1→4-β-glycoside
[4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose]
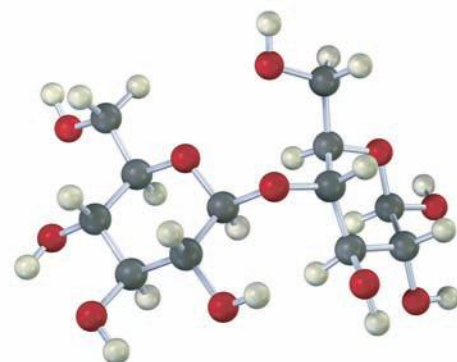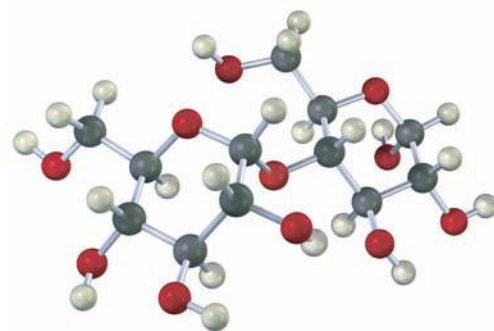
Maltose and cellobiose are both reducing sugars because the anomeric carbons on the right-hand glucopyranose units have hemiacetal groups and are in equilibrium with aldehyde forms. For a similar reason, both maltose and cellobiose show mutarotation of α and β anomers of the glucopyranose unit on the right.

Despite the similarities of their structures, cellobiose and maltose have dramatically different biological properties. Cellobiose can't be digested by humans and can't be fermented by yeast. Maltose, however, is digested without difficulty and is fermented readily.

**Problem 14.22**   Draw the structures of the products obtained from reaction of cellobiose with the following:
**(a)** $NaBH_4$ **(b)** Br_2, H_2O

Sucrose

Sucrose, or ordinary table sugar, is probably the most abundant pure organic chemical in the world. Whether from sugar cane (20% by weight) or from sugar beets (15% by weight), and whether raw or refined, all table sugar is sucrose.

Sucrose is a disaccharide that yields 1 equivalent of glucose and 1 equivalent of fructose on hydrolysis. This 1:1 mixture of glucose and fructose is often referred to as *invert sugar* because the sign of optical rotation changes, or inverts, during the hydrolysis of sucrose ($[\alpha]_D = +66.5$) to a glucose/fructose mixture ($[\alpha]_D = -22.0$). Some insects, such as honeybees, have enzymes called *invertases* that catalyze the hydrolysis of sucrose. Honey, in fact, is primarily a mixture of glucose, fructose, and sucrose.

Unlike most other disaccharides, sucrose is not a reducing sugar and does not exhibit mutarotation. These observations imply that sucrose has no hemiacetal group and that glucose and fructose must *both* be glycosides. This can happen only if the two sugars are joined by a glycoside link between the anomeric carbons of both sugars, C1 of glucose and C2 of fructose.
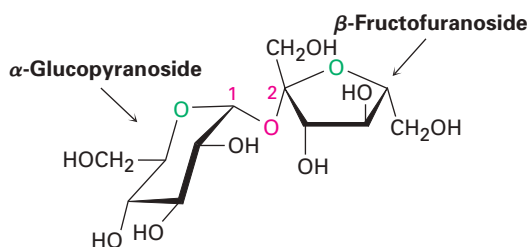
Sucrose, a 1→2-glycoside
[2-*O*-(α-D-glucopyranosyl)-β-D-fructofuranoside]
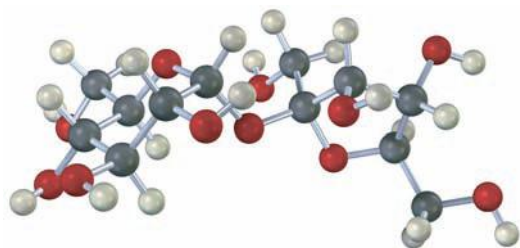
14.10 Polysaccharides

Polysaccharides are complex carbohydrates in which tens, hundreds, or even thousands of simple sugars are linked together through glycoside bonds. Because they have only the one free anomeric –OH group at the end of a very long chain, polysaccharides are not reducing sugars and don't show noticeable mutarotation. Cellulose and starch are the two most widely occurring polysaccharides.

Cellulose

Cellulose consists of several thousand D-glucose units linked by 1→4-β-glycoside bonds like those in cellobiose. Different cellulose molecules then interact to form a large aggregate structure held together by hydrogen bonds.
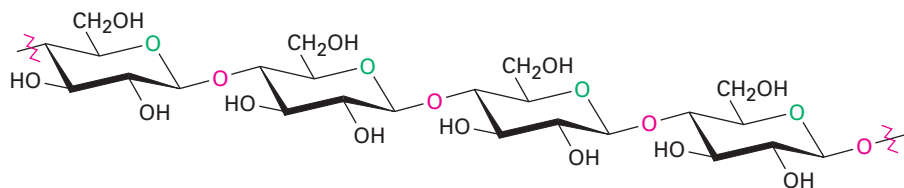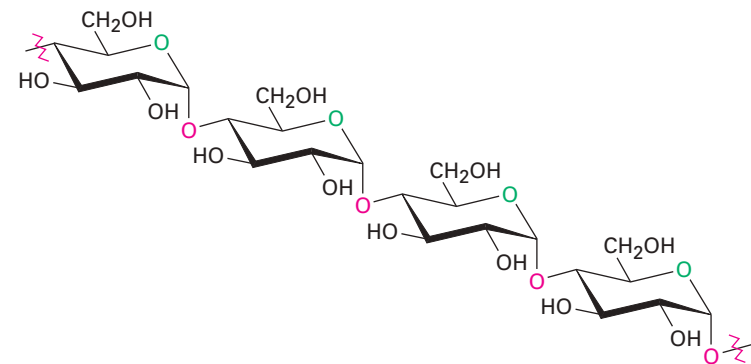

Cellulose, a 1→4-*O*-(β-D-glucopyranoside) polymer

Nature uses cellulose primarily as a structural material to impart strength and rigidity to plants. Leaves, grasses, and cotton are primarily cellulose. Cellulose also serves as a raw material for the manufacture of cellulose acetate, known commercially as *acetate rayon,* and cellulose nitrate, known as *guncotton.* Guncotton is the major ingredient in smokeless powder, the explosive propellant used in artillery shells and ammunition for firearms.

Starch and Glycogen

Potatoes, corn, and cereal grains contain large amounts of *starch,* a polymer of glucose in which the monosaccharide units are linked by 1→4-α-glycoside bonds like those in maltose. Starch can be separated into two fractions: *amylose* and *amylopectin*. Amylose accounts for about 20% by weight of starch and consists of several hundred glucose molecules linked together by 1→4-α-glycoside bonds.

Amylose, a 1→4-*O*-(α-D-glucopyranoside) polymer

Amylopectin accounts for the remaining 80% of starch and is more complex in structure than amylose. Unlike cellulose and amylose, which are linear

polymers, amylopectin contains 1→6-α-glycoside branches approximately every 25 glucose units.
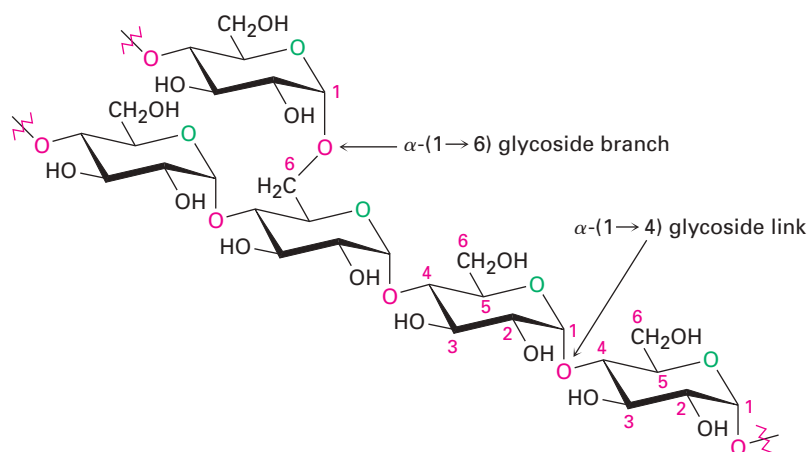
Amylopectin: α-(1→4) links
with α-(1→6) branches

Starch is digested in the mouth and stomach by α-glycosidases, which catalyze the hydrolysis of glycoside bonds and release individual molecules of glucose. Like most enzymes, α-glycosidases are highly selective in their action. They hydrolyze only the α-glycoside links in starch and leave the β-glycoside links in cellulose untouched. Thus, humans can digest potatoes and grains but not grass and leaves.

Glycogen is a polysaccharide that serves the same energy storage function in animals that starch serves in plants. Dietary carbohydrates not needed for immediate energy are converted by the body to glycogen for long-term storage. Like the amylopectin found in starch, glycogen contains a complex branching structure with both 1→4 and 1→6 links (Figure 14.8). Glycogen molecules are larger than those of amylopectin—up to 100,000 glucose units—and contain even more branches.

Figure 14.8 A representation of the structure of glycogen. The hexagons represent glucose units linked by 1→4 and 1→6 glycoside bonds.
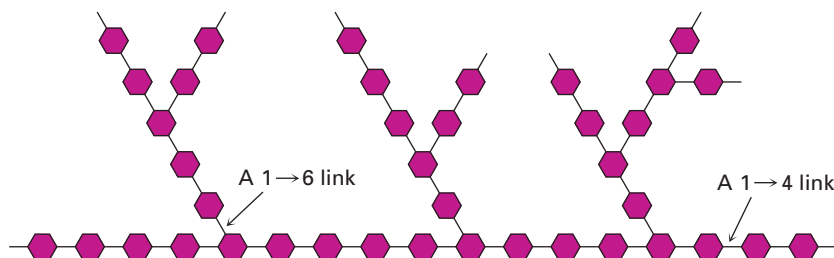
14.11 / Cell-Surface Carbohydrates and Carbohydrate Vaccines

It was once thought that carbohydrates were useful in nature only as structural materials and energy sources. Although carbohydrates do indeed serve these purposes, they have many other important biochemical functions as

well. As noted previously, for instance, glycoconjugates are centrally involved in cell–cell recognition, the critical process by which one type of cell distinguishes another. Small polysaccharide chains, covalently bound by glycosidic links to −OH or −NH$_2$ groups on proteins, act as biochemical markers on cell surfaces, as illustrated by the human blood group antigens.

It has been known for more than a century that human blood can be classified into four blood group types (A, B, AB, and O) and that blood from a donor of one type can't be transfused into a recipient with another type unless the two types are compatible (Table 14.1). If an incompatible mix is made, the red blood cells clump together, or *agglutinate*.

Table **14.1**	**Human Blood Group Compatibilities**			
Donor blood type	**A**	**B**	**AB**	**O**
A	o	x	o	x
B	x	o	o	x
AB	x	x	o	x
O	o	o	o	o

The agglutination of incompatible red blood cells, which indicates that the body's immune system has recognized the presence of foreign cells in the body and has formed antibodies against them, results from the presence of polysaccharide markers on the surface of the cells. Types A, B, and O red blood cells each have their own unique markers, called *antigenic determinants;* type AB cells have both type A and type B markers. The structures of all three blood group determinants are shown in Figure 14.9. Note that the monosaccharide constituents of each marker are among the eight essential sugars shown previously in Figure 14.7.

Figure 14.9 Structures of the A, B, and O blood group antigenic determinants.
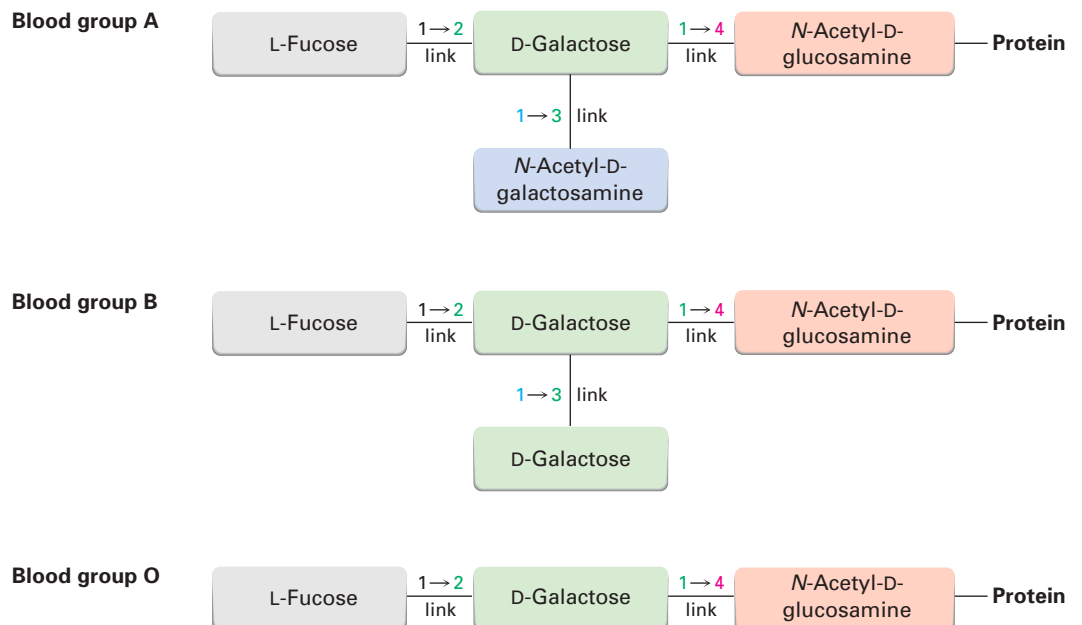
All three blood group antigenic determinants contain *N*-acetylamino sugars as well as the unusual monosaccharide L-fucose.

β-D-*N*-Acetylglucosamine   **β-D-*N*-Acetylgalactosamine**   **α-L-Fucose**
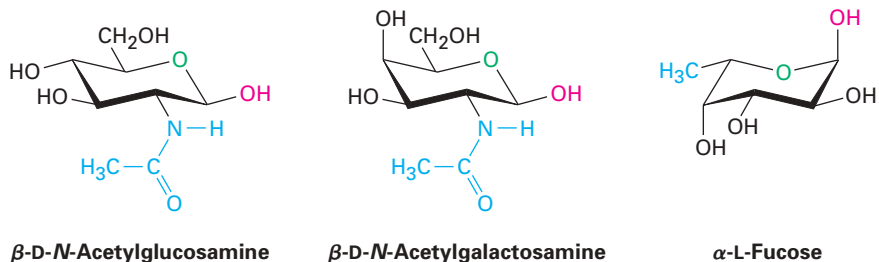
Elucidation of the role of carbohydrates in cell recognition is a vigorous area of current research that offers hope of breakthroughs in treating a wide range of diseases from bacterial infections to cancer. Particularly exciting is the possibility of developing carbohydrate-based vaccines to help mobilize the body's immune system. Diseases currently being studied for vaccine development include pneumonia, malaria, several cancers, and AIDS.

INTERLUDE

Sweetness

"Dietary disaster!"

ay the word *sugar* and most people immediately think of sweet-tasting candies, desserts, and such. In fact, most simple carbohydrates *do* taste sweet, but the degree of sweetness varies greatly from one sugar to another. With sucrose (table sugar) as a reference point, fructose is nearly twice as sweet, but lactose is only about one-sixth as sweet. Comparisons are difficult, though, because perceived sweetness varies depending on the concentration of the solution being tasted and on personal opinion. Nevertheless, the ordering in Table 14.2 is generally accepted.

| Table **14.2**	Sweetness of Some Sugars and Sugar Substitutes	
Name	**Type**	**Sweetness**
Lactose	Disaccharide	0.16
Glucose	Monosaccharide	0.75
Sucrose	**Disaccharide**	**1.00**
Fructose	Monosaccharide	1.75
Aspartame	Synthetic	180
Acesulfame-K	Synthetic	200
Saccharin	Synthetic	350
Sucralose	Semisynthetic	600
Alitame	Semisynthetic	2000

⊛ **INTERLUDE**

The desire of many people to cut their caloric intake has led to the development of synthetic sweeteners such as saccharin, aspartame, acesulfame, and sucralose. All are far sweeter than natural sugars, so the choice of one or another depends on personal taste, government regulations, and (for baked goods) heat stability. Saccharin, the oldest synthetic sweetener, has been used for more than a century, although it has a somewhat metallic aftertaste. Doubts about its safety and potential carcinogenicity were raised in the early 1970s, but it has now been cleared of suspicion.

Acesulfame potassium, one of the most recently approved sweeteners, is proving to be extremely popular in soft drinks because it has little aftertaste. Sucralose, another recently approved sweetener, is particularly useful in baked goods because of its stability at high temperatures. Alitame, marketed in some countries under the name Aclame, is not approved for sale in the United States. It is some 2000 times as sweet as sucrose and, like acesufame-K, has no aftertaste. Of the five synthetic sweeteners listed in Table 14.2, only sucralose has clear structural resemblance to a carbohydrate, although it differs dramatically in containing three chlorine atoms. Aspartame and alitame are both dipeptides.
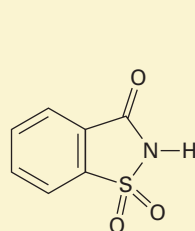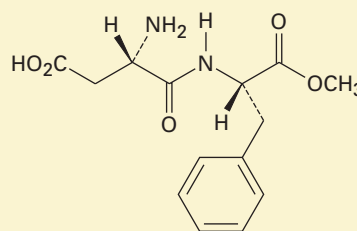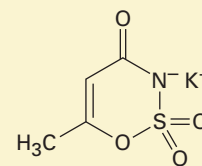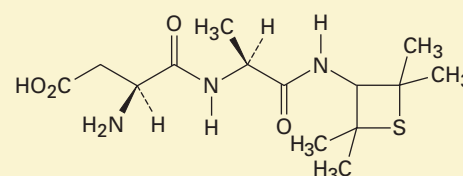
Saccharin   **Aspartame**   **Acesulfame potassium**
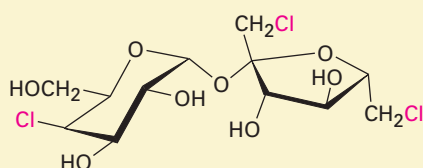
Sucralose   **Alitame**

Summary and Key Words

Now that we've now seen all the common functional groups and reaction types, our focus has changed to looking at the major classes of biological molecules. **Carbohydrates** are polyhydroxy aldehydes and ketones. They are classified according to the number of carbon atoms and the kind of carbonyl group they contain. Glucose, for example, is an aldohexose, a six-carbon aldehydo sugar. **Monosaccharides** are further classified as either **D** or **L sugars**, depending on the stereochemistry of the chirality center farthest from the carbonyl group. Carbohydrate stereochemistry is frequently shown

using **Fischer projections**, which represent a chirality center as the intersection of two crossed lines.

Monosaccharides normally exist as cyclic hemiacetals rather than as open-chain aldehydes or ketones. The hemiacetal linkage results from reaction of the carbonyl group with an –OH group three or four carbon atoms away. A five-membered cyclic hemiacetal is a **furanose**, and a six-membered cyclic hemiacetal is a **pyranose**. Cyclization leads to the formation of a new chirality center called the **anomeric center** and the production of two diastereomeric hemiacetals called **alpha (α)** and **beta (β) anomers**.

Much of the chemistry of monosaccharides is the familiar chemistry of alcohol and carbonyl functional groups. Thus, the –OH groups of carbohydrates form esters and ethers. The carbonyl group of a monosaccharide can be reduced with $NaBH_4$ to yield an **alditol**, oxidized with aqueous Br_2 to yield an **aldonic acid**, oxidized with warm HNO_3 to yield an **aldaric acid**, oxidized enzymatically to form a **uronic acid**, or treated with an alcohol in the presence of acid to form a **glycoside**.

Disaccharides are complex carbohydrates in which two simple sugars are linked by a glycoside bond between the anomeric carbon of one unit and an –OH of the second unit. The two sugars can be the same, as in maltose and cellobiose, or different, as in sucrose. The glycoside bond can be either α (maltose) or β (cellobiose) and can involve any –OH of the second sugar. A 1→4 link is most common (cellobiose, maltose), but other links, such as 1→2 (sucrose), also occur. Polysaccharides, such as cellulose, starch, and glycogen, are used in nature both as structural materials and for long-term energy storage.
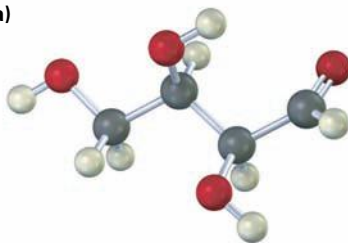
Exercises

Visualizing Chemistry

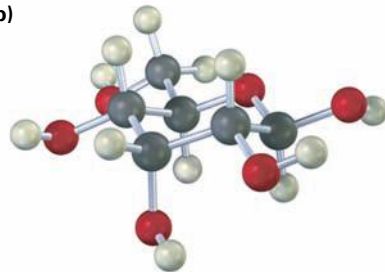(Problems 14.1–14.22 appear
within the chapter.)

♡WL

Interactive versions of these
problems are assignable in OWL.

14.23 Identify the following aldoses (see Figure 14.3), and indicate whether each is a D or L sugar.
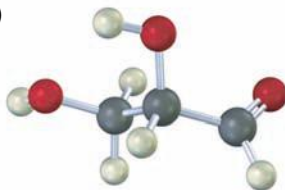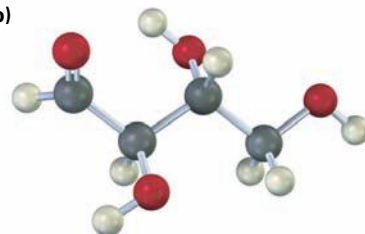
(a)

(b)

14.24 Draw Fischer projections of the following molecules, placing the carbonyl group at the top in the usual way. Identify each as a D or L sugar.
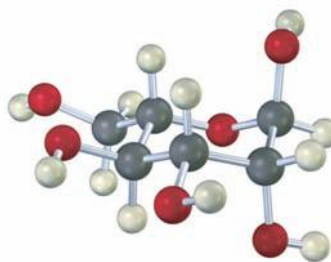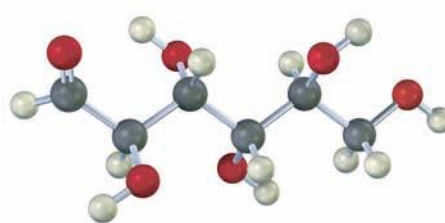
(a)

(b)

14.25 The following structure is that of an L aldohexose in its pyranose form. Identify it (see Figure 14.3).

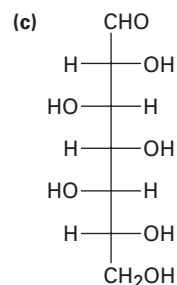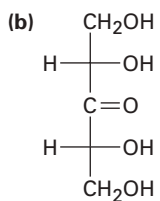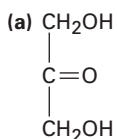**14.26** The following model is that of an aldohexose:

  (a) Draw Fischer projections of the sugar, its enantiomer, and a diastereomer.
  (b) Is this a D sugar or an L sugar? Explain.
  (c) Draw the β anomer of the sugar in its furanose form.

Additional Problems

CLASSIFYING MONOSACCHARIDES

14.27 Classify the following sugars by type (for example, glucose is an aldohexose):

(a) CH₂OH
      |
      C=O
      |
      CH₂OH

(b) CH₂OH
    H——OH
      C=O
    H——OH
      CH₂OH

(c) CHO
    H——OH
    HO——H
    H——OH
   HO——H
    H——OH
      CH₂OH

14.28 Write open-chain structures for a ketotetrose and a ketopentose.

14.29 Write an open-chain structure for a deoxyaldohexose.

**14.30** Write an open-chain structure for a five-carbon amino sugar.

14.31 Define the following terms, and give an example of each:
  (a) Monosaccharide   **(b)** Anomeric center   **(c)** Fischer projection
  (d) Glycoside   **(e)** Reducing sugar   **(f)** Pyranose form
  (g) 1→4 Link   **(h)** D-Sugar

CARBOHYDRATE STRUCTURES

14.32 The structure of ascorbic acid (vitamin C) is shown. Does ascorbic acid have a D or L configuration?
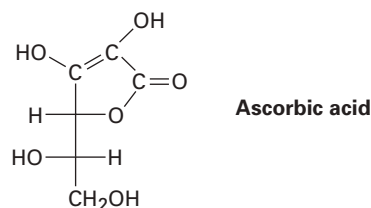

Ascorbic acid

14.33 Assign R or S stereochemistry to each chirality center in ascorbic acid (Problem 14.32).

14.34 The following cyclic structure is that of allose. Is this a furanose or pyranose form? Is it an α or β anomer? Is it a D sugar or L sugar?
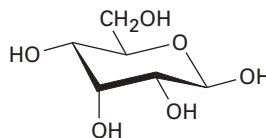
14.35 Uncoil allose (see Problem 14.34), and write it in its open-chain form.

14.36 Write the following monosaccharides in their open-chain forms:
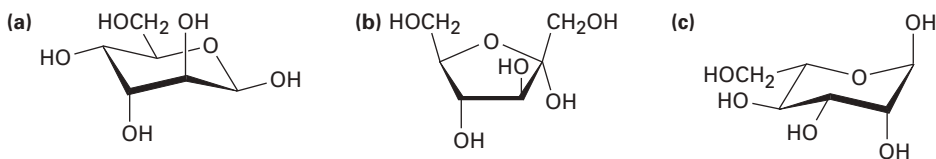
14.37 Draw D-ribulose in its five-membered cyclic β hemiacetal form.

Ribulose
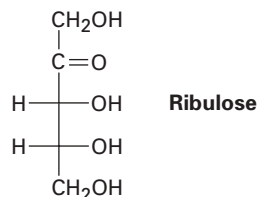
14.38 Look up the structures of maltose and sucrose in Section 14.9, and explain why maltose is reduced by $NaBH_4$ but sucrose is not.

14.39 Look up the structure of D-talose in Figure 14.3, and draw the β anomer in its pyranose form. Identify the ring substituents as axial or equatorial.

14.40 What is the stereochemical relationship of D-allose to L-allose? What generalizations can you make about the following properties of the two sugars?
(a) Melting point   (b) Solubility in water
(c) Specific rotation   (d) Density

14.41 What is the stereochemical relationship of D-ribose to L-xylose? What generalizations can you make about the following properties of the two sugars?
(a) Melting point   (b) Solubility in water
(c) Specific rotation   (d) Density

14.42 How many D-2-ketohexoses are there? Draw them.

CARBOHYDRATE REACTIONS

14.43 Draw structures for the products you would expect to obtain from the reaction of β-D-talopyranose (see Problem 14.39) with each of the following reagents:
(a) $NaBH_4$ (b) Warm dilute HNO_3
(c) aqueous Br_2 (d) CH_3CH_2OH, H^+
(e) CH_3I, Ag_2O (f) $(CH_3CO)_2O$, pyridine

14.44 One of the D-2-ketohexoses (see Problem 14.42) is called *sorbose.* On treatment with $NaBH_4$, sorbose yields a mixture of gulitol and iditol. What is the structure of D-sorbose? (Gulitol and iditol are the alditols obtained by reduction of gulose and idose.)

14.45 Another D-2-ketohexose, *psicose,* yields a mixture of allitol and altritol when reduced with $NaBH_4$ (see Problem 14.44). What is the structure of psicose?

GENERAL PROBLEMS

14.46 Draw Fischer projections of the following substances:
(a) (*R*)-2-Methylbutanoic acid   (b) (*S*)-3-Methylpentan-2-one

14.47 Convert the following Fischer projections into tetrahedral representations:

(a)   Br   (b) CH_3

    H——————OCH_3 H——————NH_2

         CH_3 CH_2CH_3

14.48 Which of the eight D aldohexoses yield optically inactive (meso) alditols on reduction with $NaBH_4$?

14.49 What other D aldohexose gives the same alditol as D-talose? (See Problem 14.48.)

14.50 Which of the eight D aldohexoses give the same aldaric acids as their L enantiomers?

14.51 Which of the other three D aldopentoses gives the same aldaric acid as D-lyxose?

14.52 The *Ruff degradation* is a method used to shorten an aldose chain by one carbon atom. The original C1 carbon atom is cut off, and the original C2 carbon atom becomes the aldehyde of the chain-shortened aldose. For example, D-glucose, an aldohexose, is converted by Ruff degradation into D-arabinose, an aldopentose. What other D aldohexose would also yield D-arabinose on Ruff degradation?

14.53 D-Galactose and D-talose yield the same aldopentose on Ruff degradation (Problem 14.52). What does this tell you about the stereochemistry of galactose and talose? Which D aldopentose is obtained?

14.54 The aldaric acid obtained by nitric acid oxidation of D-erythrose, one of the D aldotetroses, is optically inactive. The aldaric acid obtained from oxidation of the other D aldotetrose, D-threose, however, is optically active. How does this information allow you to assign structures to the two D aldotetroses?

14.55 D-Fructose and D-glucose are interconverted on treatment with dilute acid or base. Propose a mechanism for this interconversion. (See Section 11.1.)
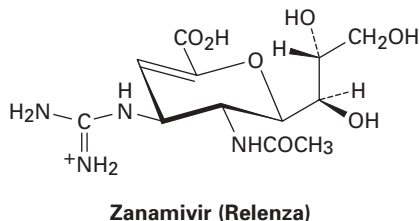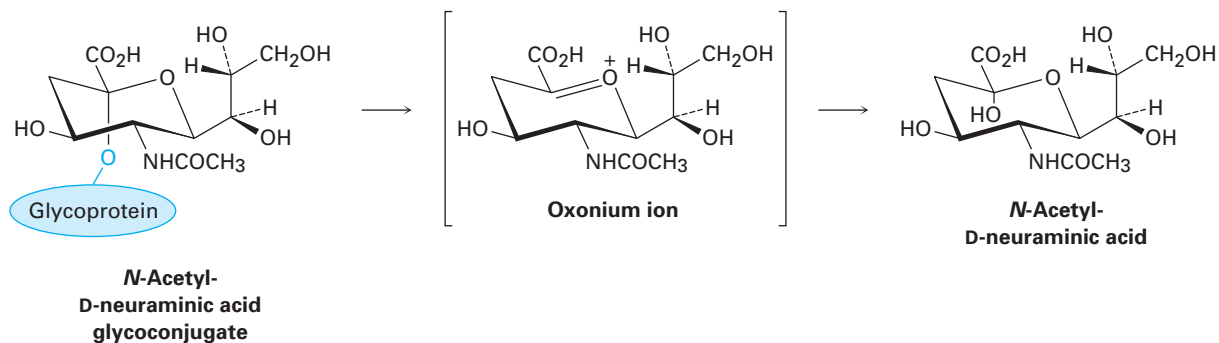

D-Fructose   **D-Glucose**
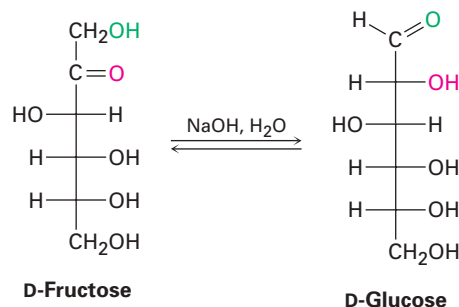
14.56 What other aldohexose besides glucose is likely to be interconvertible with fructose when treated with dilute aqueous base? (See Problem 14.55.)

14.57 Mannose, one of the eight essential monosaccharides (Section 14.8), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate in three steps. The initial step is hemiacetal ring-opening, the second step is keto–enol equilibration, and the third step is hemiacetal formation. Propose a mechanism. (See Problem 14.55.)


Fructose   **Mannose**
6-phosphate   **6-phosphate**
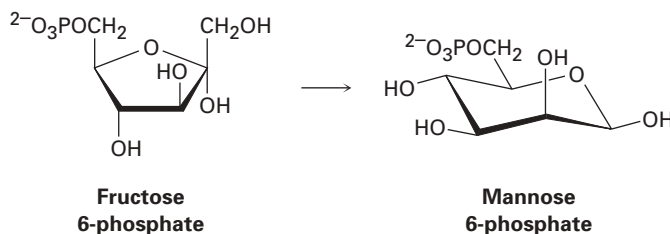
14.58 Gentiobiose is a rare disaccharide found in saffron and gentian. It is a reducing sugar and forms only glucose on hydrolysis with aqueous acid. If gentiobiose contains a 1→6-β-glycoside link, what is its structure?

14.59 Raffinose, a trisaccharide found in sugar beets, is formed by a 1→6 α linkage of D-galactose to the glucose unit of sucrose. Draw the structure of raffinose.

14.60 Is raffinose (see Problem 14.59) a reducing sugar? Explain.

IN THE MEDICINE CABINET   **14.61** Zanamivir, sold under the trade name Relenza, is one of the very few compounds active against the H5N1 avian flu virus. The virus attacks cells by recognizing a terminal sialic acid on a cell-surface glycoprotein and hydrolyzing it from the cell surface. Zanamivir is able to prevent the hydrolysis by mimicking the oxonium ion intermediate in the hydrolysis and blocking the enzyme necessary for removal. Why is Relenza a good mimic of the intermediate oxonium ion?

**N-Acetyl-
D-neuraminic acid
glycoconjugate**

Oxonium ion

**N-Acetyl-
D-neuraminic acid**

Zanamivir (Relenza)

14.62 *N*-Acetylneuraminic acid, one of the eight essential monosaccharides and the simplest sialic acid (Problem 14.61), is biosynthesized by reaction of *N*-acetylmannosamine with pyruvate, $CH_3COCO_2^-$. What kind of reaction takes place? Show the mechanism.
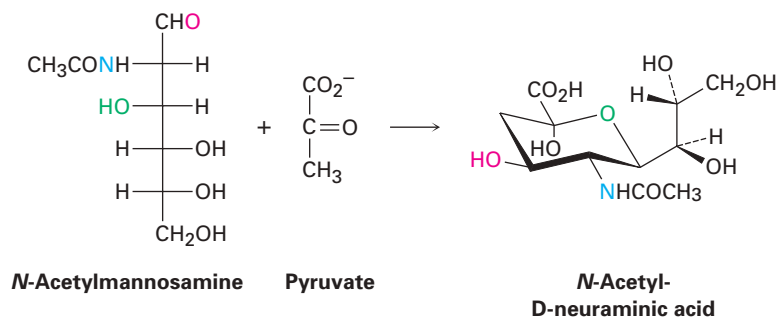
N-Acetylmannosamine   **Pyruvate**   **N-Acetyl-
D-neuraminic acid**

14.63 Betulinic acid is found in the bark of the white birch tree and is useful against melanomas, dangerous forms of skin cancer.
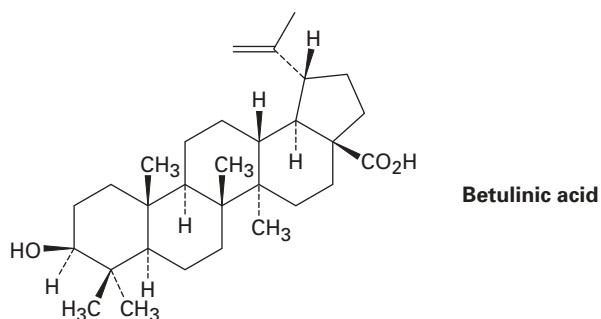
Betulinic acid

(a) How many chirality centers are in betulinic acid?

(b) To increase the solubility of betulinic acid, it can be converted into a glycoside by letting it react with a carbohydrate. Draw a mechanism for the formation of a glycoside bond between betulinic acid and glucose.