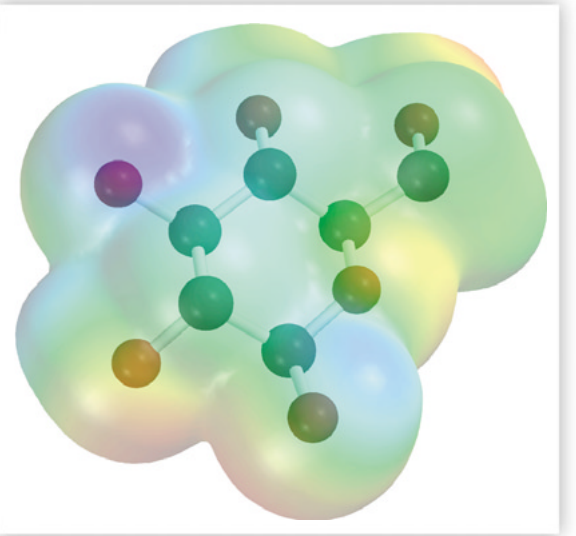


CHAPTER 25

CARBOHYDRATES

The major classes of organic compounds common to living systems are *lipids, proteins, nucleic acids,* and *carbohydrates.* Carbohydrates are very familiar to us—we call many of them "sugars." They make up a substantial portion of the food we eat and provide most of the energy that keeps the human engine running. Carbohydrates are structural components of the walls of plant cells and the wood of trees. Genetic information is stored and transferred by way of nucleic acids, specialized derivatives of carbohydrates, which we'll examine in more detail in Chapter 27.

Historically, carbohydrates were once considered to be "hydrates of carbon" because their molecular formulas in many (but not all) cases correspond to $C_n(H_2O)_m$. It is more realistic to define a carbohydrate as a *polyhydroxy aldehyde* or *polyhydroxy ketone,* a point of view closer to structural reality and more suggestive of chemical reactivity.

This chapter is divided into two parts. The first, and major, portion is devoted to carbohydrate structure. You will see how the principles of stereochemistry and conformational analysis combine to aid our understanding of this complex subject. The remainder of the chapter describes chemical reactions of carbohydrates. Most of these reactions are simply extensions of what you have already learned concerning alcohols, aldehydes, ketones, and acetals.

25.1 CLASSIFICATION OF CARBOHYDRATES

The Latin word for "sugar"* is *saccharum,* and the derived term "saccharide" is the basis of a system of carbohydrate classification. A **monosaccharide** is a simple carbohydrate, one that on attempted hydrolysis is not cleaved to smaller carbohydrates. *Glucose*

*"Sugar" is a combination of the Sanskrit words *su* (sweet) and *gar* (sand). Thus, its literal meaning is "sweet sand."

($C_6H_{12}O_6$), for example, is a monosaccharide. A **disaccharide** on hydrolysis is cleaved to two monosaccharides, which may be the same or different. *Sucrose*—common table sugar—is a disaccharide that yields one molecule of glucose and one of fructose on hydrolysis.

$$\text{Sucrose } (C_{12}H_{22}O_{11}) + H_2O \longrightarrow \text{glucose } (C_6H_{12}O_6) + \text{fructose } (C_6H_{12}O_6)$$

An **oligosaccharide** (*oligos* is a Greek word that in its plural form means "few") yields 3–10 monosaccharide units on hydrolysis. **Polysaccharides** are hydrolyzed to more than 10 monosaccharide units. *Cellulose* is a polysaccharide molecule that gives thousands of glucose molecules when completely hydrolyzed.

Over 200 different monosaccharides are known. They can be grouped according to the number of carbon atoms they contain and whether they are polyhydroxy aldehydes or polyhydroxy ketones. Monosaccharides that are polyhydroxy aldehydes are called **aldoses;** those that are polyhydroxy ketones are **ketoses.** Aldoses and ketoses are further classified according to the number of carbon atoms in the main chain. Table 25.1 lists the terms applied to monosaccharides having four to eight carbon atoms.

25.2 FISCHER PROJECTIONS AND D–L NOTATION

Stereochemistry is the key to understanding carbohydrate structure, a fact that was clearly appreciated by the German chemist Emil Fischer. The projection formulas used by Fischer to represent stereochemistry in chiral molecules are particularly well-suited to studying carbohydrates. Figure 25.1 illustrates their application to the enantiomers of *glyceraldehyde* (2,3-dihydroxypropanal), a fundamental molecule in carbohydrate stereochemistry. When the Fischer projection is oriented as shown in the figure, with the carbon chain vertical and the aldehyde carbon at the top, the C-2 hydroxyl group points to the right in (+)-glyceraldehyde and to the left in (−)-glyceraldehyde.

Fischer determined the structure of glucose in 1900 and won the Nobel Prize in chemistry in 1902.

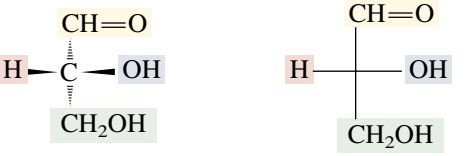
Techniques for determining the absolute configuration of chiral molecules were not developed until the 1950s, and so it was not possible for Fischer and his contemporaries to relate the sign of rotation of any substance to its absolute configuration. A system evolved based on the arbitrary assumption, later shown to be correct, that the enantiomers of glyceraldehyde have the signs of rotation and absolute configurations shown in Figure 25.1. Two stereochemical descriptors were defined: D and L. The absolute configuration of (+)-glyceraldehyde, as depicted in the figure, was said to be D and that of its enantiomer, (−)-glyceraldehyde, L. Compounds that had a spatial arrangement of substituents analogous to D-(+)- and L-(−)-glyceraldehyde were said to have the D and L configurations, respectively.

Adopting the enantiomers of glyceraldehyde as stereochemical reference compounds originated with proposals made in 1906 by M. A. Rosanoff, a chemist at New York University.

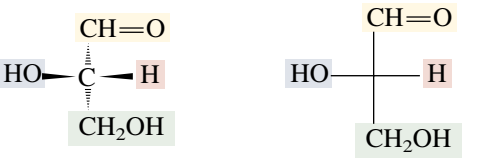
TABLE 25.1 Some Classes of Monosaccharides

Number of carbon atoms	Aldose	Ketose
Four	Aldotetrose	Ketotetrose
Five	Aldopentose	Ketopentose
Six	Aldohexose	Ketohexose
Seven	Aldoheptose	Ketoheptose
Eight	Aldooctose	Ketooctose

FIGURE 25.1 Three-dimensional representations and Fischer projections of the enantiomers of glyceraldehyde.

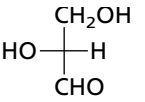


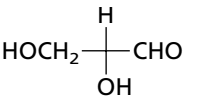
R-(+)-Glyceraldehyde

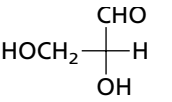


S-(–)-Glyceraldehyde

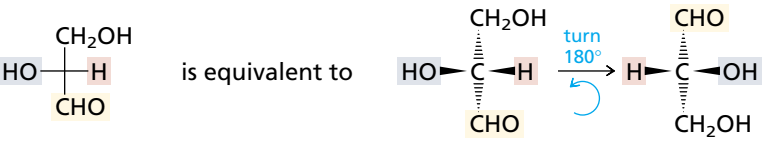
PROBLEM 25.1 Identify each of the following as either D- or L-glyceraldehyde:

(a) 

(b) 

(c) 

SAMPLE SOLUTION (a) Redraw the Fischer projection so as to more clearly show the true spatial orientation of the groups. Next, reorient the molecule so that its relationship to the glyceraldehyde enantiomers in Figure 25.1 is apparent.



The structure is the same as that of (+)-glyceraldehyde in the figure. It is D-glyceraldehyde.

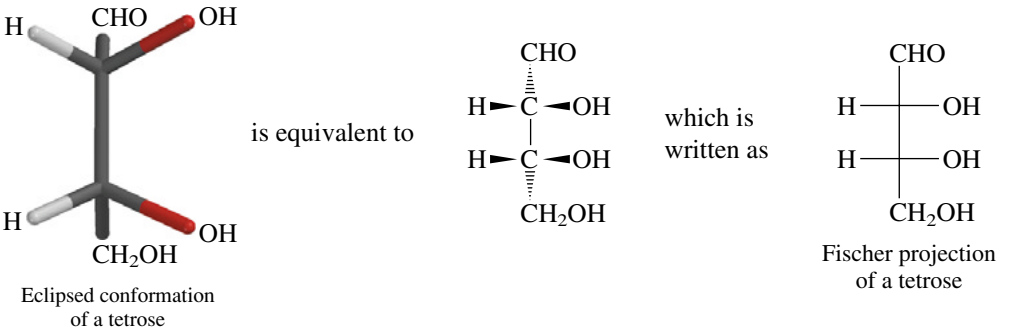
Fischer projections and D–L notation have proved to be so helpful in representing carbohydrate stereochemistry that the chemical and biochemical literature is replete with their use. To read that literature you need to be acquainted with these devices, as well as the more modern Cahn–Ingold–Prelog system.

25.3 THE ALDOTETROSES

Glyceraldehyde can be considered to be the simplest chiral carbohydrate. It is an **aldotriose** and, since it contains one stereogenic center, exists in two stereoisomeric forms: the D and L enantiomers. Moving up the scale in complexity, next come the **aldotetroses.** Examination of their structures illustrates the application of the Fischer system to compounds that contain more than one stereogenic center.

Molecular models of the four stereoisomeric aldotetroses may be viewed on the CD that accompanies this text.

The aldotetroses are the four stereoisomers of 2,3,4-trihydroxybutanal. Fischer projections are constructed by orienting the molecule in an eclipsed conformation with the aldehyde group at what will be the top. The four carbon atoms define the main chain of the Fischer projection and are arranged vertically. Horizontal bonds are directed outward, vertical bonds back.

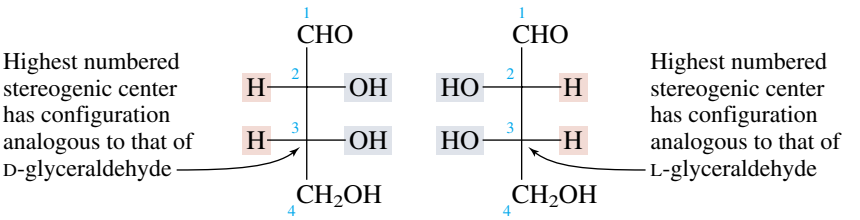


Eclipsed conformation of a tetrose

Fischer projection of a tetrose

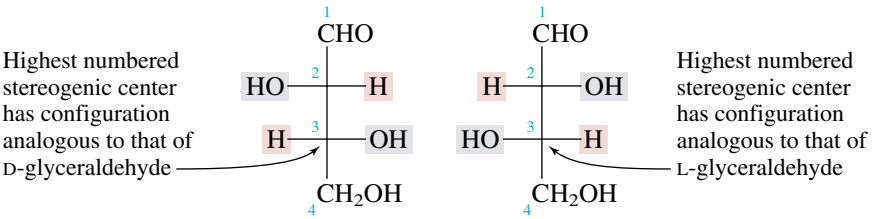
The particular aldotetrose just shown is called D-*erythrose*. The prefix D tells us that the configuration at the *highest numbered stereogenic center* is analogous to that of D-(+)-glyceraldehyde. Its mirror image is L-erythrose.

For a first-person account of the development of systematic carbohydrate nomenclature see C. D. Hurd's article in the December 1989 issue of the *Journal of Chemical Education*, pp. 984–988.



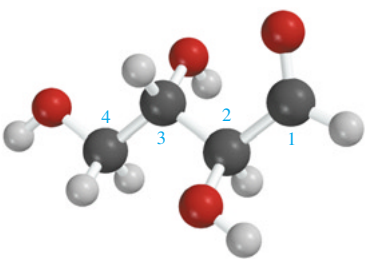
D-Erythrose L-Erythrose

Relative to each other, both hydroxyl groups are on the same side in Fischer projections of the erythrose enantiomers. The remaining two stereoisomers have hydroxyl groups on opposite sides in their Fischer projection. They are diastereomers of D- and L-erythrose and are called D- and L-*threose*. The D and L prefixes again specify the configuration of the highest numbered stereogenic center. D-Threose and L-threose are enantiomers of each other:



D-Threose L-Threose

PROBLEM 25.2 Which aldotetrose is the structure shown? Is it D-erythrose, D-threose, L-erythrose, or L-threose? (Be careful! The conformation given is not the same as that used to generate a Fischer projection.)



As shown for the aldotetroses, an aldose belongs to the D or the L series according to the configuration of the stereogenic center farthest removed from the aldehyde function. Individual names, such as erythrose and threose, specify the particular arrangement of stereogenic centers within the molecule relative to each other. Optical activities cannot be determined directly from the D and L prefixes. As it turns out, both D-erythrose and D-threose are levorotatory, but D-glyceraldehyde is dextrorotatory.

25.4 ALDOPENTOSES AND ALDOHEXOSES

Aldopentoses have three stereogenic centers. The eight stereoisomers are divided into a set of four D-aldopentoses and an enantiomeric set of four L-aldopentoses. The aldopentoses are named *ribose, arabinose, xylose,* and *lyxose.* Fischer projections of the D stereoisomers of the aldopentoses are given in Figure 25.2. Notice that all these diastereomers have the same configuration at C-4 and that this configuration is analogous to that of D-(+)-glyceraldehyde.

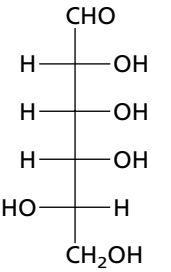
PROBLEM 25.3 L-(+)-Arabinose is a naturally occurring L sugar. It is obtained by acid hydrolysis of the polysaccharide present in mesquite gum. Write a Fischer projection for L-(+)-arabinose.

Among the aldopentoses, D-ribose is a component of many biologically important substances, most notably the ribonucleic acids, and D-xylose is very abundant and is isolated by hydrolysis of the polysaccharides present in corncobs and the wood of trees.

Cellulose is more abundant than glucose, but each cellulose molecule is a polysaccharide composed of thousands of glucose units (Section 25.15). Methane may also be more abundant, but most of the methane comes from glucose.

The aldohexoses include some of the most familiar of the monosaccharides, as well as one of the most abundant organic compounds on earth, D-(+)-glucose. With four stereogenic centers, 16 stereoisomeric aldohexoses are possible; 8 belong to the D series and 8 to the L series. All are known, either as naturally occurring substances or as the products of synthesis. The eight D-aldohexoses are given in Figure 25.2; it is the spatial arrangement at C-5, hydrogen to the left in a Fischer projection and hydroxyl to the right, that identifies them as carbohydrates of the D series.

PROBLEM 25.4 Name the following sugar:



Of all the monosaccharides, D-(+)-*glucose* is the best known, most important, and most abundant. Its formation from carbon dioxide, water, and sunlight is the central theme of photosynthesis. Carbohydrate formation by photosynthesis is estimated to be on the order of 10^{11} tons per year, a source of stored energy utilized, directly or indirectly, by all higher forms of life on the planet. Glucose was isolated from raisins in 1747 and by hydrolysis of starch in 1811. Its structure was determined, in work culminating in 1900, by Emil Fischer.

D-(+)-*Galactose* is a constituent of numerous polysaccharides. It is best obtained by acid hydrolysis of lactose (milk sugar), a disaccharide of D-glucose and D-galactose.

FIGURE 25.2 Configurations of the D series of aldoses containing three through six carbon atoms.

L(−)-Galactose also occurs naturally and can be prepared by hydrolysis of flaxseed gum and agar. The principal source of D-(+)-*mannose* is hydrolysis of the polysaccharide of the ivory nut, a large, nut-like seed obtained from a South American palm.

25.5 A MNEMONIC FOR CARBOHYDRATE CONFIGURATIONS

See, for example, the November 1955 issue of the *Journal of Chemical Education* (p. 584). An article giving references to a variety of chemistry mnemonics appears in the July 1960 issue of the *Journal of Chemical Education* (p. 366).

The task of relating carbohydrate configurations to names requires either a world-class memory or an easily recalled mnemonic. A mnemonic that serves us well here was popularized by the husband–wife team of Louis F. Fieser and Mary Fieser of Harvard University in their 1956 textbook, *Organic Chemistry.* As with many mnemonics, it's not clear who actually invented it, and references to this particular one appeared in the chemical education literature before publication of the Fiesers' text. The mnemonic has two features: (1) a system for setting down all the stereoisomeric D-aldohexoses in a logical order; and (2) a way to assign the correct name to each one.

A systematic way to set down all the D-hexoses (as in Fig. 25.2) is to draw skeletons of the necessary eight Fischer projections, placing the hydroxyl group at C-5 to the right in each so as to guarantee that they all belong to the D series. Working up the carbon chain, place the hydroxyl group at C-4 to the right in the first four structures, and to the left in the next four. In each of these two sets of four, place the C-3 hydroxyl group to the right in the first two and to the left in the next two; in each of the resulting four sets of two, place the C-2 hydroxyl group to the right in the first one and to the left in the second.

Once the eight Fischer projections have been written, they are named in order with the aid of the sentence: All altruists gladly make gum in gallon tanks. The words of the sentence stand for *allose, altrose, glucose, mannose, gulose, idose, galactose, talose.*

An analogous pattern of configurations can be seen in the aldopentoses when they are arranged in the order *ribose, arabinose, xylose, lyxose.* (RAXL is an easily remembered nonsense word that gives the correct sequence.) This pattern is discernible even in the aldotetroses erythrose and threose.

25.6 CYCLIC FORMS OF CARBOHYDRATES: FURANOSE FORMS

Aldoses incorporate two functional groups, C═O and OH, which are capable of reacting with each other. We saw in Section 17.8 that nucleophilic addition of an alcohol function to a carbonyl group gives a hemiacetal. When the hydroxyl and carbonyl groups are part of the same molecule, a *cyclic hemiacetal* results, as illustrated in Figure 25.3.

Cyclic hemiacetal formation is most common when the ring that results is five- or six-membered. Five-membered cyclic hemiacetals of carbohydrates are called **furanose** forms; six-membered ones are called **pyranose** forms. The ring carbon that is derived from the carbonyl group, the one that bears two oxygen substituents, is called the **anomeric** carbon.

Aldoses exist almost exclusively as their cyclic hemiacetals; very little of the open-chain form is present at equilibrium. To understand their structures and chemical reactions, we need to be able to translate Fischer projections of carbohydrates into their cyclic hemiacetal forms. Consider first cyclic hemiacetal formation in D-erythrose. So as to visualize furanose ring formation more clearly, redraw the Fischer projection in a form more suited to cyclization, being careful to maintain the stereochemistry at each stereogenic center.

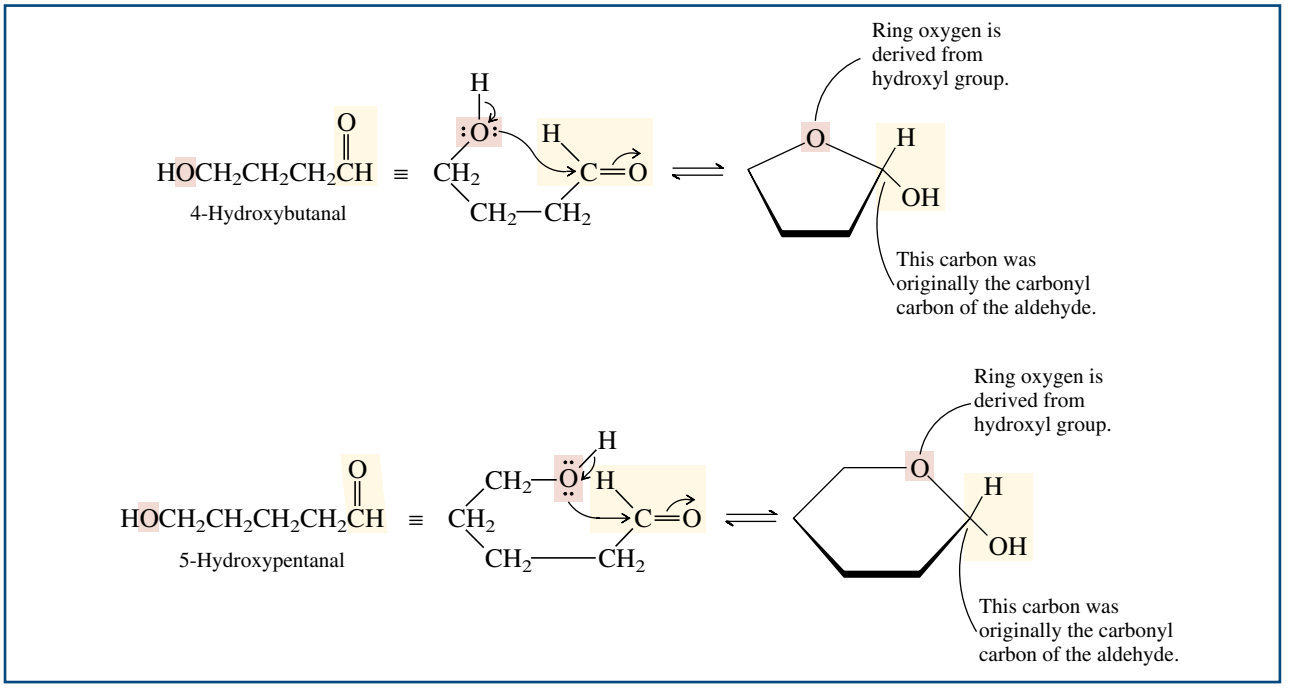
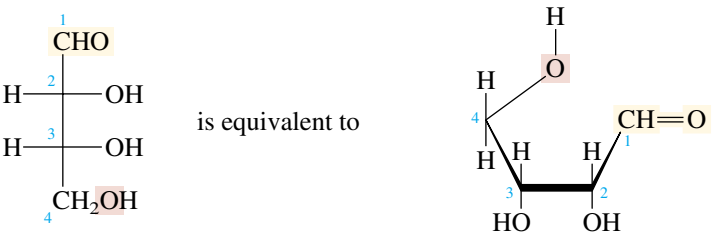


FIGURE 25.3 Cyclic hemiacetal formation in 4-hydroxybutanal and 5-hydroxypentanal.

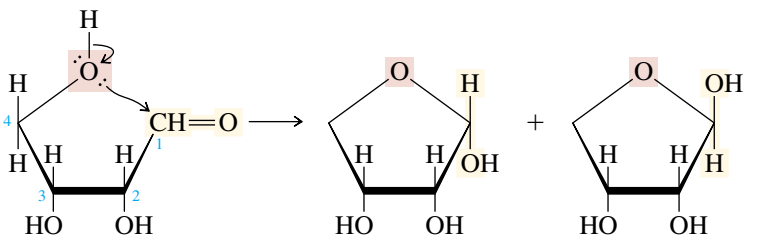

A molecular model can help you to visualize this relationship.



D-Erythrose

Reoriented eclipsed conformation of D-erythrose showing C-4 hydroxyl group in position to add to carbonyl group

Hemiacetal formation between the carbonyl group and the terminal hydroxyl yields the five-membered furanose ring form. The anomeric carbon becomes a new stereogenic center; its hydroxyl group can be either cis or trans to the other hydroxyl groups of the molecule.



D-Erythrose

α-D-Erythrofuranose (hydroxyl group at anomeric carbon is down)

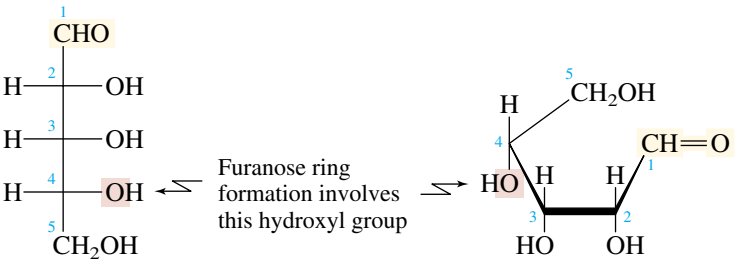
β-D-Erythrofuranose (hydroxyl group at anomeric carbon is up)

Structural drawings of carbohydrates of this type are called **Haworth formulas,** after the British carbohydrate chemist Sir Walter Norman Haworth (St. Andrew's University and the University of Birmingham). Early in his career Haworth contributed to the discovery that sugars exist as cyclic hemiacetals rather than in open-chain forms. Later he collaborated on an efficient synthesis of vitamin C from carbohydrate precursors. This was the first chemical synthesis of a vitamin and provided an inexpensive route to its preparation on a commercial scale. Haworth was a corecipient of the Nobel Prize for chemistry in 1937.

The two stereoisomeric furanose forms of D-erythrose are named α-D-erythrofuranose and β-D-erythrofuranose. The prefixes α and β describe *relative configuration.* The configuration of the anomeric carbon is α when its hydroxyl group is on the same side of a Fischer projection as the hydroxyl group at the highest numbered stereogenic center. When the hydroxyl groups at the anomeric carbon and the highest numbered stereogenic center are on opposite sides of a Fischer projection, the configuration at the anomeric carbon is β.

Substituents that are to the right in a Fischer projection are "down" in the corresponding Haworth formula.

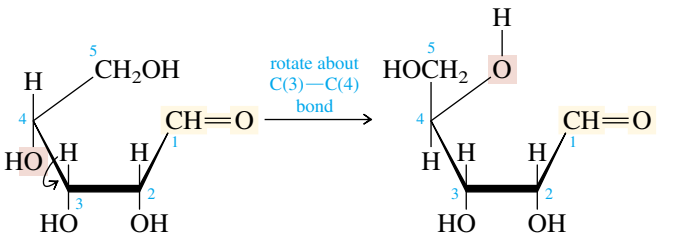
Generating Haworth formulas to show stereochemistry in furanose forms of higher aldoses is slightly more complicated and requires an additional operation. Furanose forms of D-ribose are frequently encountered building blocks in biologically important organic molecules. They result from hemiacetal formation between the aldehyde group and the hydroxyl at C-4:



D-Ribose — Eclipsed conformation of D-ribose

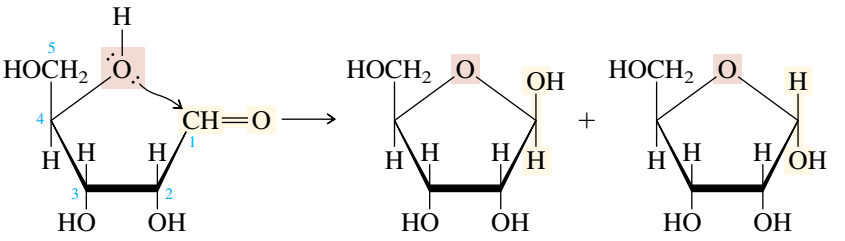
Notice that the eclipsed conformation of D-ribose derived directly from the Fischer projection does not have its C-4 hydroxyl group properly oriented for furanose ring formation. We must redraw it in a conformation that permits the five-membered cyclic hemiacetal to form. This is accomplished by rotation about the C(3)—C(4) bond, taking care that the configuration at C-4 is not changed.

Try using a molecular model to help see this.



Conformation of D-ribose suitable for furanose ring formation

As viewed in the drawing, a 120° anticlockwise rotation of C-4 places its hydroxyl group in the proper position. At the same time, this rotation moves the CH_2OH group to a position such that it will become a substituent that is "up" on the five-membered ring. The hydrogen at C-4 then will be "down" in the furanose form.

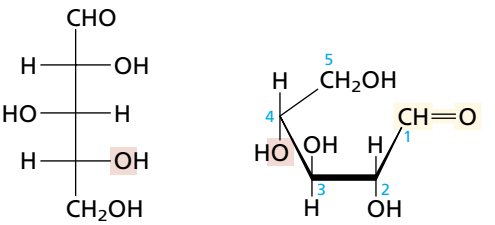


β-D-Ribofuranose α-D-Ribofuranose

PROBLEM 25.5 Write Haworth formulas corresponding to the furanose forms of each of the following carbohydrates:

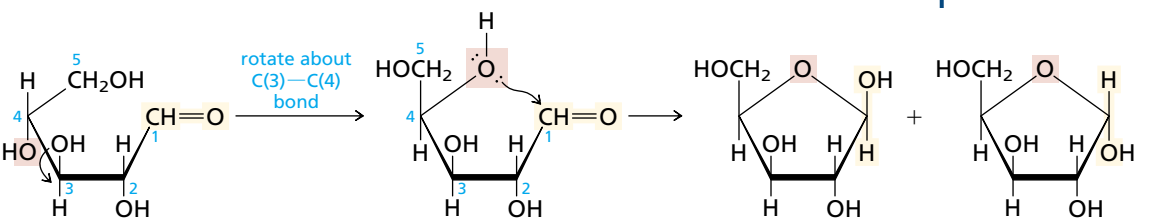
(a) D-Xylose
(b) D-Arabinose
(c) L-Arabinose
(d) D-Threose

SAMPLE SOLUTION (a) The Fischer projection of D-xylose is given in Figure 25.2.



D-Xylose Eclipsed conformation of D-xylose

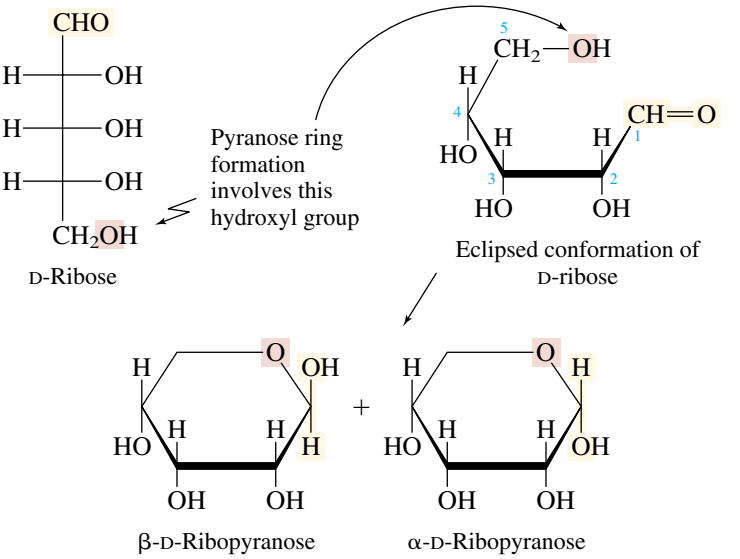
Carbon-4 of D-xylose must be rotated in an anticlockwise sense in order to bring its hydroxyl group into the proper orientation for furanose ring formation.



D-Xylose β-D-Xylofuranose α-D-Xylofuranose

25.7 CYCLIC FORMS OF CARBOHYDRATES: PYRANOSE FORMS

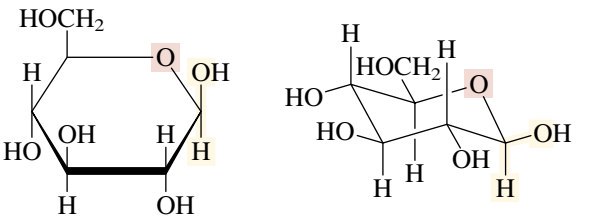
During the discussion of hemiacetal formation in D-ribose in the preceding section, you may have noticed that aldopentoses have the potential of forming a six-membered cyclic hemiacetal via addition of the C-5 hydroxyl to the carbonyl group. This mode of ring closure leads to α- and β-*pyranose* forms:

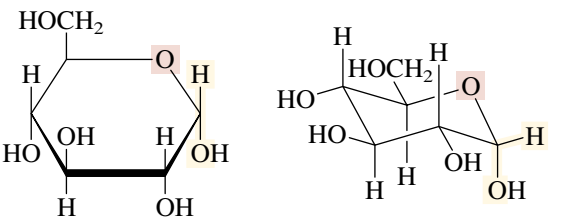


Like aldopentoses, aldohexoses such as D-glucose are capable of forming two furanose forms (α and β) and two pyranose forms (α and β). The Haworth representations of the pyranose forms of D-glucose are constructed as shown in Figure 25.4; each has a CH_2OH group as a substituent on the six-membered ring.

Haworth formulas are satisfactory for representing *configurational* relationships in pyranose forms but are uninformative as to carbohydrate *conformations.* X-ray crystallographic studies of a large number of carbohydrates reveal that the six-membered pyranose ring of D-glucose adopts a chair conformation:

Make a molecular model of the chair conformation of β-D-glucopyranose.





All the ring substituents other than hydrogen in β-D-glucopyranose are equatorial in the most stable chair conformation. Only the anomeric hydroxyl group is axial in the α isomer; all the other substituents are equatorial.

Other aldohexoses behave similarly in adopting chair conformations that permit the CH_2OH substituent to occupy an equatorial orientation. Normally the CH_2OH group is the bulkiest, most conformationally demanding substituent in the pyranose form of a hexose.

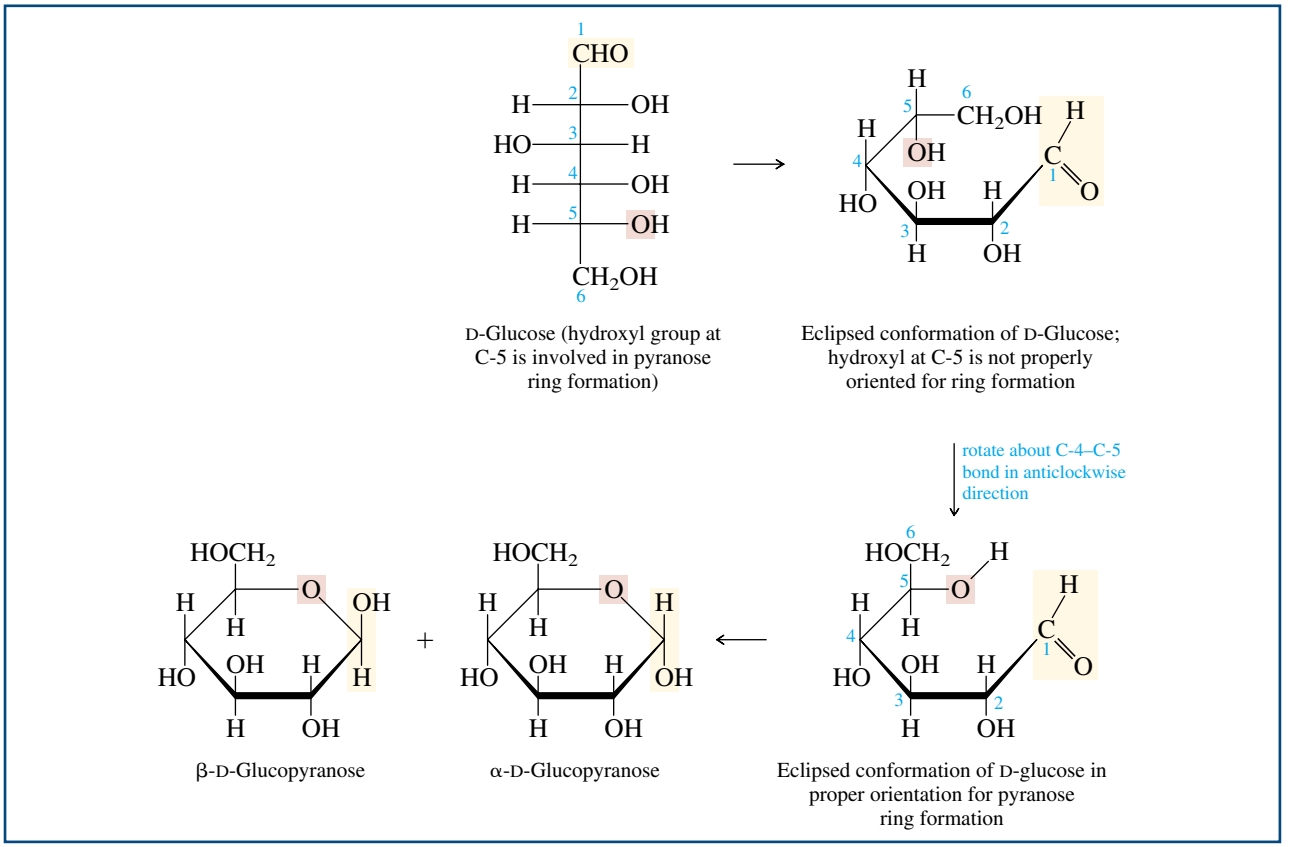
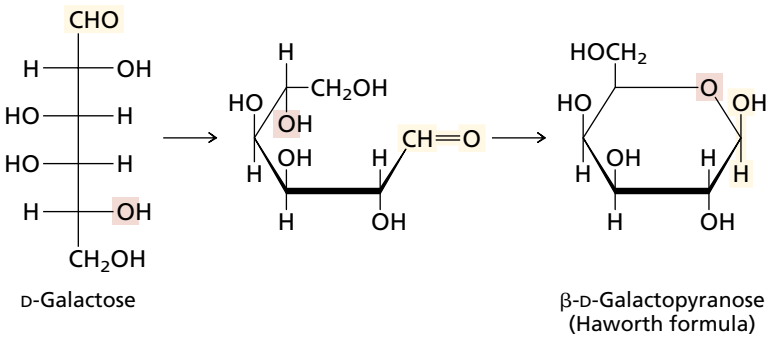


FIGURE 25.4 Haworth formulas for α- and β-pyranose forms of D-glucose.

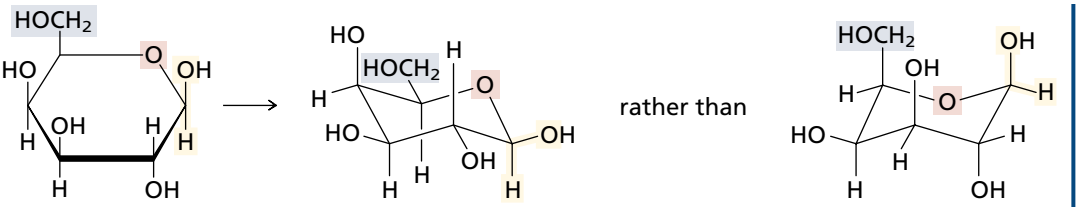
PROBLEM 25.6 Clearly represent the most stable conformation of the β-pyranose form of each of the following sugars:

(a) D-Galactose
(b) D-Mannose
(c) L-Mannose
(d) L-Ribose

SAMPLE SOLUTION (a) By analogy with the procedure outlined for D-glucose in Figure 25.4, first generate a Haworth formula for β-D-galactopyranose:



Next, redraw the planar Haworth formula more realistically as a chair conformation, choosing the one that has the CH_2OH group equatorial.



Galactose differs from glucose in configuration at C-4. The C-4 hydroxyl is axial in β-D-galactopyranose, but it is equatorial in β-D-glucopyranose.

Since six-membered rings are normally less strained than five-membered ones, pyranose forms are usually present in greater amounts than furanose forms at equilibrium, and the concentration of the open-chain form is quite small. The distribution of carbohydrates among their various hemiacetal forms has been examined by using ^{1}H and ^{13}C NMR spectroscopy. In aqueous solution, for example, D-ribose is found to contain the various α and β-furanose and pyranose forms in the amounts shown in Figure 25.5. The concentration of the open-chain form at equilibrium is too small to measure directly. Nevertheless, it occupies a central position, in that interconversions of α and β anomers and furanose and pyranose forms take place by way of the open-chain form as an intermediate. As will be seen later, certain chemical reactions also proceed by way of the open-chain form.

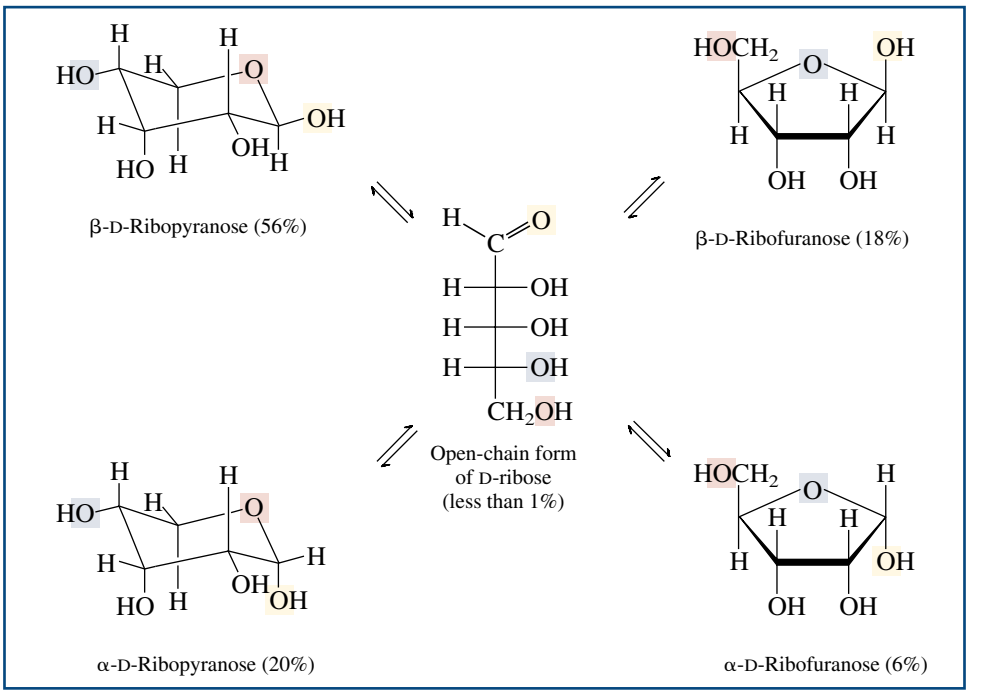
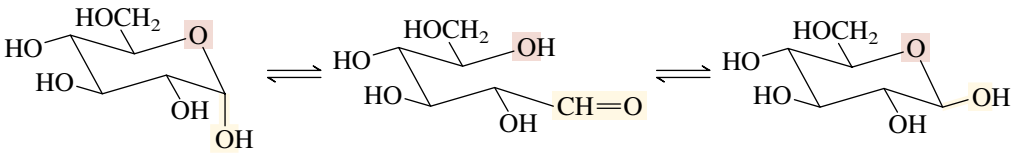


FIGURE 25.5 Distribution of furanose, pyranose, and open-chain forms of D-ribose in aqueous solution as measured by ^{1}H and ^{13}C NMR spectroscopy.

25.8 MUTAROTATION

In spite of their easy interconversion in solution, α and β forms of carbohydrates are capable of independent existence, and many have been isolated in pure form as crystalline solids. When crystallized from ethanol, D-glucose yields α-D-glucopyranose, mp 146°C, $[\alpha]_D$ +112.2°. Crystallization from a water–ethanol mixture produces β-D-glucopyranose, mp 148–155°C, $[\alpha]_D$ +18.7°. In the solid state the two forms do not interconvert and are stable indefinitely. Their structures have been unambiguously confirmed by X-ray crystallography.

The optical rotations just cited for each isomer are those measured immediately after each one is dissolved in water. On standing, the rotation of the solution containing the α isomer decreases from +112.2° to +52.5°; the rotation of the solution of the β isomer increases from +18.7° to the same value of +52.5°. This phenomenon is called **mutarotation.** What is happening is that each solution, initially containing only one anomeric form, undergoes equilibration to the same mixture of α- and β-pyranose forms. The open-chain form is an intermediate in the process.



α-D-Glucopyranose (mp 146°C; $[\alpha]_D$ +112.2°) ⇌ Open-chain form of D-glucose ⇌ β-D-Glucopyranose (mp 148–155°C; $[\alpha]_D$ +18.7°)

The distribution between the α and β anomeric forms at equilibrium is readily calculated from the optical rotations of the pure isomers and the final optical rotation of the solution, and is determined to be 36% α to 64% β. Independent measurements have established that only the pyranose forms of D-glucose are present in significant quantities at equilibrium.

A ^{13}C NMR study of D-glucose in water detected five species: the α-pyranose (38.8%), β-pyranose (60.9%), α-furanose (0.14%), and β-furanose (0.15%) forms, and the hydrate of the open-chain form (0.0045%).

PROBLEM 25.7 The specific optical rotations of pure α- and β-D-mannopyranose are +29.3° and −17.0°, respectively. When either form is dissolved in water, mutarotation occurs, and the observed rotation of the solution changes until a final rotation of +14.2° is observed. Assuming that only α- and β-pyranose forms are present, calculate the percent of each isomer at equilibrium.

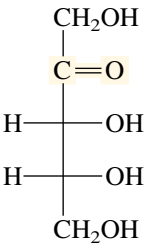
It's not possible to tell by inspection whether the α- or β-pyranose form of a particular carbohydrate predominates at equilibrium. As just described, the β-pyranose form is the major species present in an aqueous solution of D-glucose, whereas the α-pyranose form predominates in a solution of D-mannose (Problem 25.7). The relative abundance of α-and β-pyranose forms in solution is a complicated issue and depends on several factors. One is solvation of the anomeric hydroxyl group. An equatorial OH is less crowded and better solvated by water than an axial one. This effect stabilizes the β-pyranose form in aqueous solution. A second factor, called the **anomeric effect,** involves an electronic interaction between the ring oxygen and the anomeric substituent and preferentially stabilizes the axial OH of the α-pyranose form. Because the two effects

The anomeric effect is best explained by a molecular orbital analysis that is beyond the scope of this text.

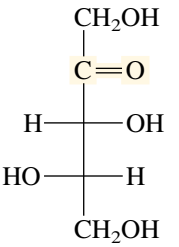
operate in different directions but are comparable in magnitude in aqueous solution, the α-pyranose form is more abundant for some carbohydrates and the β-pyranose form for others.

25.9 KETOSES

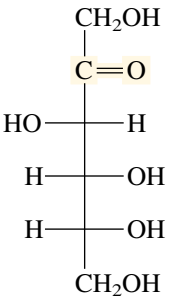
Up to this point all our attention has been directed toward aldoses, carbohydrates having an aldehyde function in their open-chain form. Aldoses are more common than ketoses, and their role in biological processes has been more thoroughly studied. Nevertheless, a large number of ketoses are known, and several of them are pivotal intermediates in carbohydrate biosynthesis and metabolism. Examples of some ketoses include D-*ribulose,* L-*xylulose,* and D-*fructose:*



D-Ribulose
(a 2-ketopentose that is a key compound in photosynthesis)



L-Xylulose
(a 2-ketopentose excreted in excessive amounts in the urine of persons afflicted with the mild genetic disorder pentosuria)

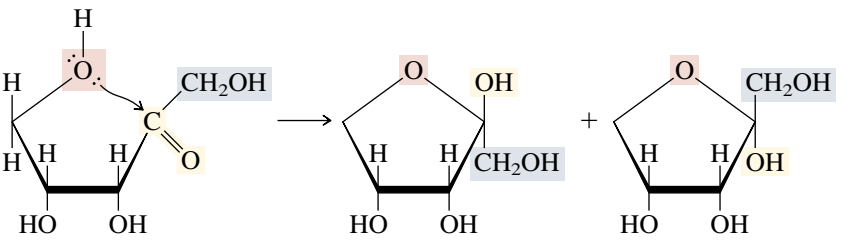


D-Fructose
(a 2-ketohexose also known as *levulose;* it is found in honey and is signficantly sweeter than table sugar)

In these three examples the carbonyl group is located at C-2, which is the most common location for the carbonyl function in naturally occurring ketoses.

PROBLEM 25.8 How many ketotetroses are possible? Write Fischer projections for each.

Ketoses, like aldoses, exist mainly as cyclic hemiacetals. In the case of D-ribulose, furanose forms result from addition of the C-5 hydroxyl to the carbonyl group.



Eclipsed conformation of D-ribulose

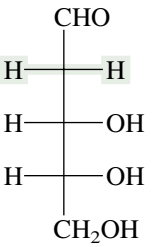
β-D-Ribulofuranose

α-D-Ribulofuranose

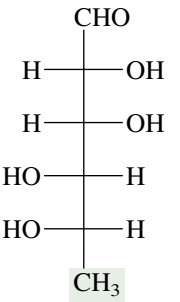
The anomeric carbon of a furanose or pyranose form of a ketose bears both a hydroxyl group and a carbon substituent. In the case of 2-ketoses, this substituent is a CH_2OH group. As with aldoses, the anomeric carbon of a cyclic hemiacetal is readily identifiable because it is bonded to two oxygens.

25.10 DEOXY SUGARS

A commonplace variation on the general pattern seen in carbohydrate structure is the replacement of one or more of the hydroxyl substituents by some other atom or group. In **deoxy sugars** the hydroxyl group is replaced by hydrogen. Two examples of deoxy sugars are 2-deoxy-D-ribose and L-rhamnose:



2-Deoxy-D-ribose



L-Rhamnose
(6-deoxy-L-mannose)

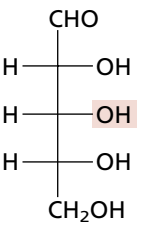
The hydroxyl at C-2 in D-ribose is absent in 2-deoxy-D-ribose. In Chapter 27 we shall see how derivatives of 2-deoxy-D-ribose, called *deoxyribonucleotides,* are the fundamental building blocks of deoxyribonucleic acid (DNA), the material responsible for storing genetic information. L-Rhamnose is a compound isolated from a number of plants. Its carbon chain terminates in a methyl rather than a CH_2OH group.

PROBLEM 25.9 Write Fischer projections of

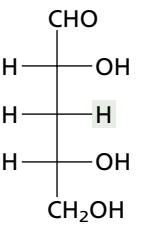
(a) *Cordycepose* (3-deoxy-D-ribose): a deoxy sugar isolated by hydrolysis of the antibiotic substance *cordycepin*

(b) L-*Fucose* (6-deoxy-L-galactose): obtained from seaweed

SAMPLE SOLUTION (a) The hydroxyl group at C-3 in D-ribose is replaced by hydrogen in 3-deoxy-D-ribose.



D-Ribose
(from Figure 25.2)

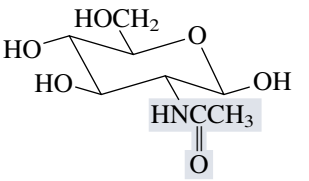


3-Deoxy-D-ribose
(cordycepose)

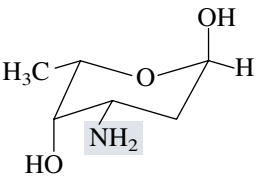
25.11 AMINO SUGARS

For a review of the isolation of chitin from natural sources and some of its uses, see the November 1990 issue of the *Journal of Chemical Education* (pp. 938–942).

Another structural variation is the replacement of a hydroxyl group in a carbohydrate by an amino group to give an **amino sugar.** The most abundant amino sugar is one of the oldest and most abundant organic compounds on earth. *N*-Acetyl-D-glucosamine is the main component of the polysaccharide in *chitin,* the substance that makes up the tough outer skeleton of arthropods and insects. Chitin has been isolated from a 25-million-year-old beetle fossil, and more than 10^{11} tons of chitin is produced in the biosphere each year. Lobster shells, for example, are mainly chitin. More than 60 amino sugars are known, many of them having been isolated and identified only recently as components of antibiotics. The anticancer drug doxorubicin hydrochloride (Adriamycin), for example, contains the amino sugar L-daunosamine as one of its structural units.



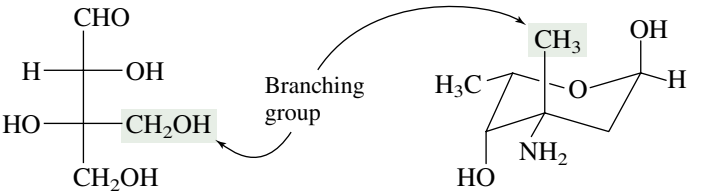
N-Acetyl-D-glucosamine



L-Daunosamine

25.12 BRANCHED-CHAIN CARBOHYDRATES

Carbohydrates that have a carbon substituent attached to the main chain are said to have a **branched chain.** D-Apiose and L-vancosamine are representative branched-chain carbohydrates:

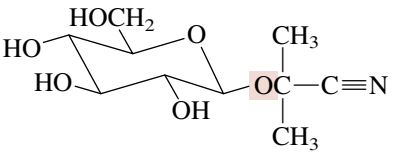


D-Apiose L-Vancosamine

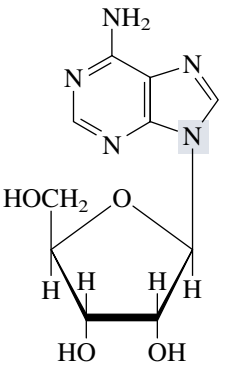
D-Apiose can be isolated from parsley and is a component of the cell wall polysaccharide of various marine plants. Among its novel structural features is the presence of only a single stereogenic center. L-Vancosamine is but one portion of vancomycin, a powerful antibiotic that is reserved for treating only the most stubborn infections. L-Vancosamine is not only a branched-chain carbohydrate, it is a deoxy sugar and an amino sugar as well.

25.13 GLYCOSIDES

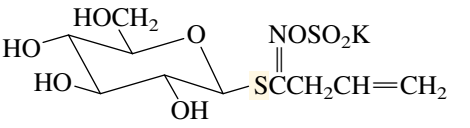
Glycosides are a large and very important class of carbohydrate derivatives characterized by the replacement of the anomeric hydroxyl group by some other substituent. Glycosides are termed *O*-glycosides, *N*-glycosides, *S*-glycosides, and so on, according to the atom attached to the anomeric carbon.



Linamarin
(an *O*-glycoside: obtained from manioc, a type of yam widely distributed in southeast Asia)



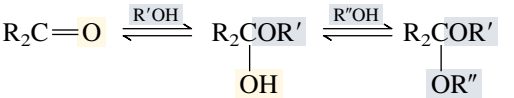
Adenosine
(an *N*-glycoside: also known as a nucleoside; adenosine is one of the fundamental molecules of biochemistry)



Sinigrin
(an *S*-glycoside: contributes to the characteristic flavor of mustard and horseradish)

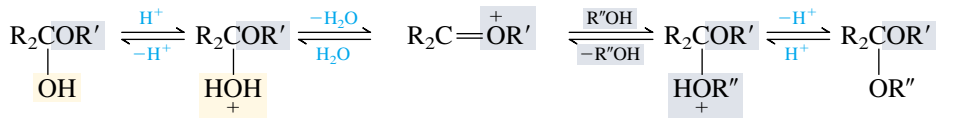
Usually, the term "glycoside" without a prefix is taken to mean an *O*-glycoside and will be used that way in this chapter. Glycosides are classified as α or β in the customary way, according to the configuration at the anomeric carbon. All three of the glycosides just shown are β-glycosides. Linamarin and sinigrin are glycosides of D-glucose; adenosine is a glycoside of D-ribose.

Structurally, *O*-glycosides are mixed acetals that involve the anomeric position of furanose and pyranose forms of carbohydrates. Recall the sequence of intermediates in acetal formation (Section 17.8):



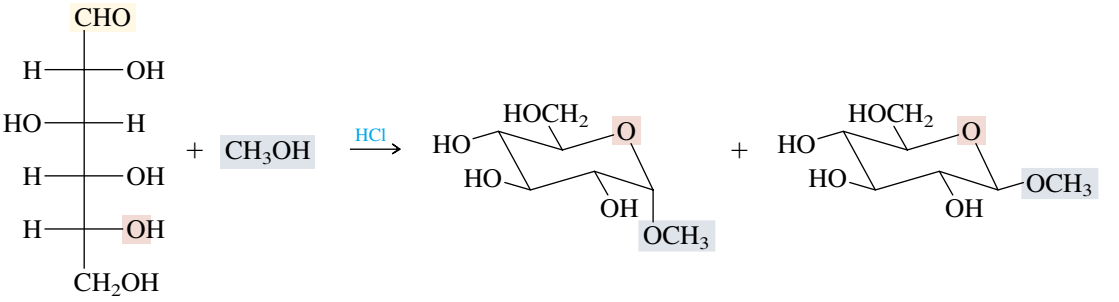
Aldehyde or ketone — Hemiacetal — Acetal

When this sequence is applied to carbohydrates, the first step takes place *intramolecularly* and spontaneously to yield a cyclic hemiacetal. The second step is *intermolecular,* requires an alcohol R″OH as a reactant, and proceeds readily only in the presence of an acid catalyst. An oxygen-stabilized carbocation is an intermediate.



Hemiacetal — Oxygen-stabilized carbocation — Mixed acetal

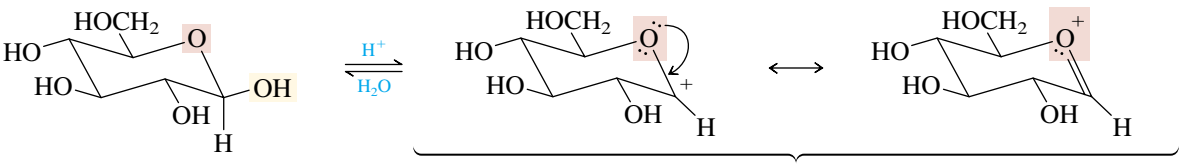
The preparation of glycosides in the laboratory is carried out by simply allowing a carbohydrate to react with an alcohol in the presence of an acid catalyst:



D-Glucose | Methanol | Methyl α-D-glucopyranoside (major product; isolated in 49% yield) | Methyl β-D-glucopyranoside (minor product)

PROBLEM 25.10 Write structural formulas for the α- and β-methyl pyranosides formed by reaction of D-galactose with methanol in the presence of hydrogen chloride.

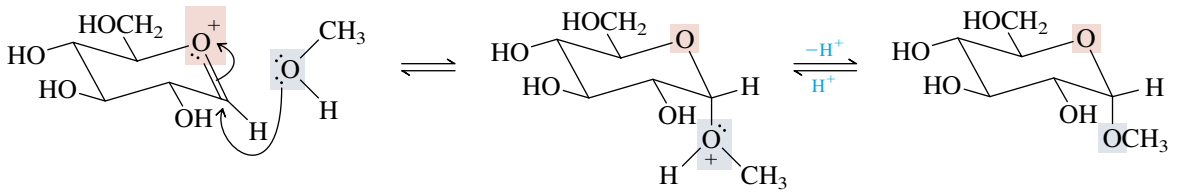
A point to be emphasized about glycoside formation is that, despite the presence of a number of other hydroxyl groups in the carbohydrate, *only the anomeric hydroxyl group is replaced.* This is because a carbocation at the anomeric position is stabilized by the ring oxygen and is the only one capable of being formed under the reaction conditions.



D-Glucose (shown in β-pyranose form) | Electron pair on ring oxygen can stabilize carbocation at anomeric position only.

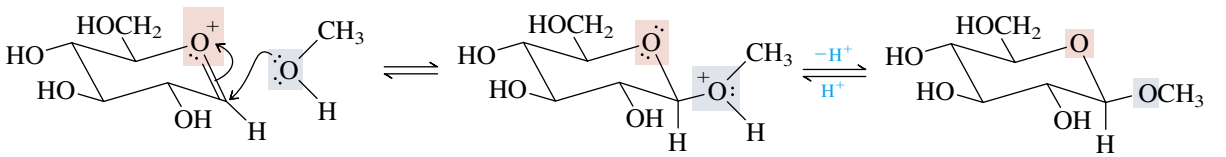
Once the carbocation is formed, it is captured by the alcohol acting as a nucleophile. Attack can occur at either the α or β face of the carbocation.

Attack at the α face gives methyl α-D-glucopyranoside:



Carbocation intermediate + Methanol | Methyl α-D-glucopyranoside

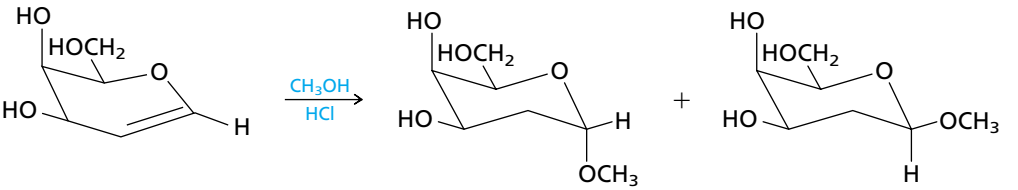
Attack at the β face gives methyl β-D-glucopyranoside:



Carbocation intermediate + Methanol | Methyl β-D-glucopyranoside

All of the reactions, from D-glucose to the methyl glycosides via the carbocation, are reversible. The overall reaction is *thermodynamically controlled* and gives the same mixture of glycosides irrespective of which stereoisomeric pyranose form of D-glucose we start with. Nor does it matter whether we start with a pyranose form or a furanose form of D-glucose. Glucopyranosides are more stable than glucofuranosides and predominate at equilibrium.

PROBLEM 25.11 Methyl glycosides of 2-deoxy sugars have been prepared by the acid-catalyzed addition of methanol to unsaturated sugars known as *glycals.*



Galactal

Methyl 2-deoxy-α-D-lyxohexopyranoside (38%)

Methyl 2-deoxy-β-D-lyxohexopyranoside (36%)

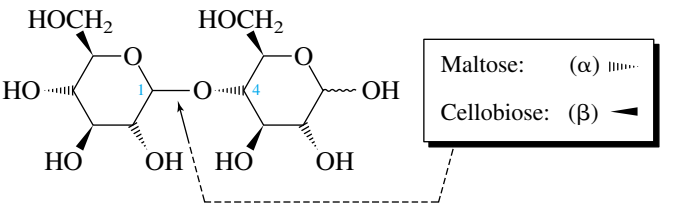
Suggest a reasonable mechanism for this reaction.

Under neutral or basic conditions glycosides are configurationally stable; unlike the free sugars from which they are derived, glycosides do not exhibit mutarotation. Converting the anomeric hydroxyl group to an ether function (hemiacetal → acetal) prevents its reversion to the open-chain form in neutral or basic media. In aqueous acid, acetal formation can be reversed and the glycoside hydrolyzed to an alcohol and the free sugar.

25.14 DISACCHARIDES

Disaccharides are carbohydrates that yield two monosaccharide molecules on hydrolysis. Structurally, disaccharides are *glycosides* in which the alkoxy group attached to the anomeric carbon is derived from a second sugar molecule.

Maltose, obtained by the hydrolysis of starch, and *cellobiose,* by the hydrolysis of cellulose, are isomeric disaccharides. In both maltose and cellobiose two D-glucopyranose units are joined by a glycosidic bond between C-1 of one unit and C-4 of the other. The two are diastereomers, differing only in the stereochemistry at the anomeric carbon of the glycoside bond; maltose is an α-glycoside, cellobiose is a β-glycoside.



You can view molecular models of maltose and cellobiose on *Learning By Modeling.*

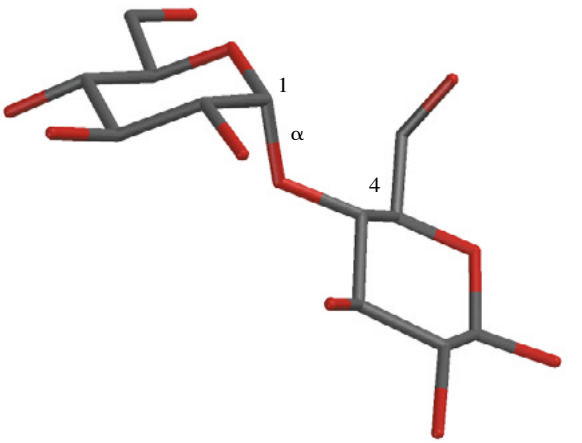
The stereochemistry and points of connection of glycosidic bonds are commonly designated by symbols such as α(1,4) for maltose and β(1,4) for cellobiose; α and β designate the stereochemistry at the anomeric position; the numerals specify the ring carbons involved.

The free anomeric hydroxyl group is the one shown at the far right of the preceding structural formula. The symbol ∿∿∿ is used to represent a bond of variable stereochemistry.

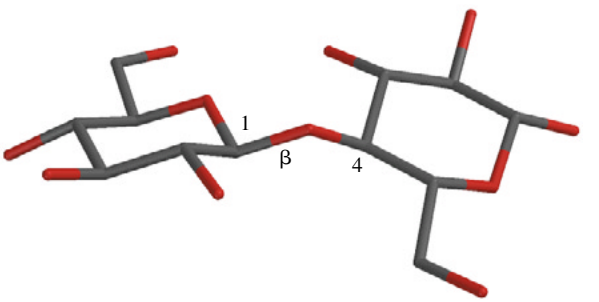
Both maltose and cellobiose have a free anomeric hydroxyl group that is not involved in a glycoside bond. The configuration at the free anomeric center is variable and may be either α or β. Indeed, two stereoisomeric forms of maltose have been isolated: one has its anomeric hydroxyl group in an equatorial orientation; the other has an axial anomeric hydroxyl.

PROBLEM 25.12 The two stereoisomeric forms of maltose just mentioned undergo mutarotation when dissolved in water. What is the structure of the key intermediate in this process?

The single difference in their structures, the stereochemistry of the glycosidic bond, causes maltose and cellobiose to differ significantly in their three-dimensional shape, as the molecular models of Figure 25.6 illustrate. This difference in shape affects the way in which maltose and cellobiose interact with other chiral molecules such as proteins, and they behave much differently toward enzyme-catalyzed hydrolysis. An enzyme known as *maltase* catalyzes the hydrolytic cleavage of the α-glycosidic bond of maltose but is without effect in promoting the hydrolysis of the β-glycosidic bond of cellobiose. A different enzyme, *emulsin,* produces the opposite result: emulsin catalyzes the hydrolysis of cellobiose but not of maltose. The behavior of each enzyme is general for glucosides (glycosides of glucose). Maltase catalyzes the hydrolysis of α-glucosides and is



Maltose



Cellobiose

FIGURE 25.6 Molecular models of the disaccharides maltose and cellobiose. Two D-glucopyranose units are connected by a glycoside linkage between C-1 and C-4. The glycosidic bond has the α orientation in maltose and is β in cellobiose. Maltose and cellobiose are diastereomers.

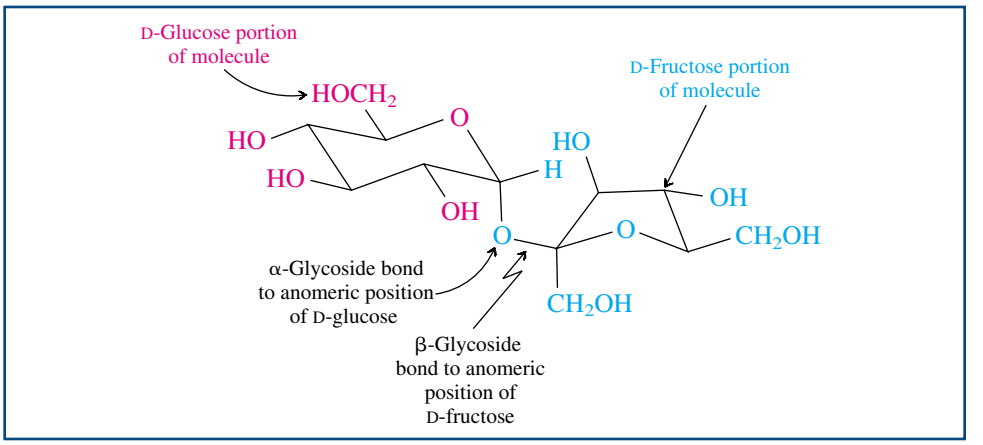
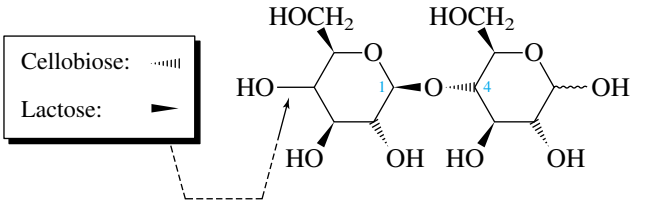


FIGURE 25.7 The structure of sucrose.

also known as α-*glucosidase,* whereas emulsin catalyzes the hydrolysis of β-glucosides and is known as β-*glucosidase.* The specificity of these enzymes offers a useful tool for structure determination because it allows the stereochemistry of glycosidic linkages to be assigned.

Lactose is a disaccharide constituting 2–6% of milk and is known as *milk sugar.* It differs from maltose and cellobiose in that only one of its monosaccharide units is D-glucose. The other monosaccharide unit, the one that contributes its anomeric carbon to the glycoside bond, is D-galactose. Like cellobiose, lactose is a β-glycoside.



You can view molecular models of cellobiose and lactose on *Learning By Modeling.*

Digestion of lactose is facilitated by the β-glycosidase *lactase.* A deficiency of this enzyme makes it difficult to digest lactose and causes abdominal discomfort. Lactose intolerance is a genetic trait; it is treatable through over-the-counter formulations of lactase and by limiting the amount of milk in the diet.

The most familiar of all the carbohydrates is *sucrose*—common table sugar. Sucrose is a disaccharide in which D-glucose and D-fructose are joined at their anomeric carbons by a glycosidic bond (Figure 25.7). Its chemical composition is the same irrespective of its source; sucrose from cane and sucrose from sugar beets are chemically identical. Since sucrose does not have a free anomeric hydroxyl group, it does not undergo mutarotation.

25.15 POLYSACCHARIDES

Cellulose is the principal structural component of vegetable matter. Wood is 30–40% cellulose, cotton over 90%. Photosynthesis in plants is responsible for the formation of 10^9 tons per year of cellulose. Structurally, cellulose is a polysaccharide composed of several thousand D-glucose units joined by β(1,4)-glycosidic linkages (Figure 25.8). Complete hydrolysis of all the glycosidic bonds of cellulose yields D-glucose. The disaccharide fraction that results from partial hydrolysis is cellobiose.

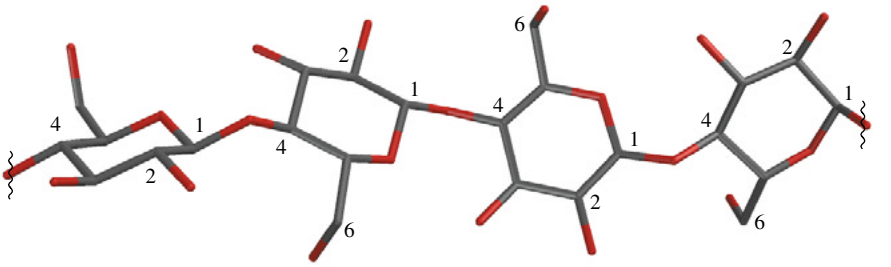


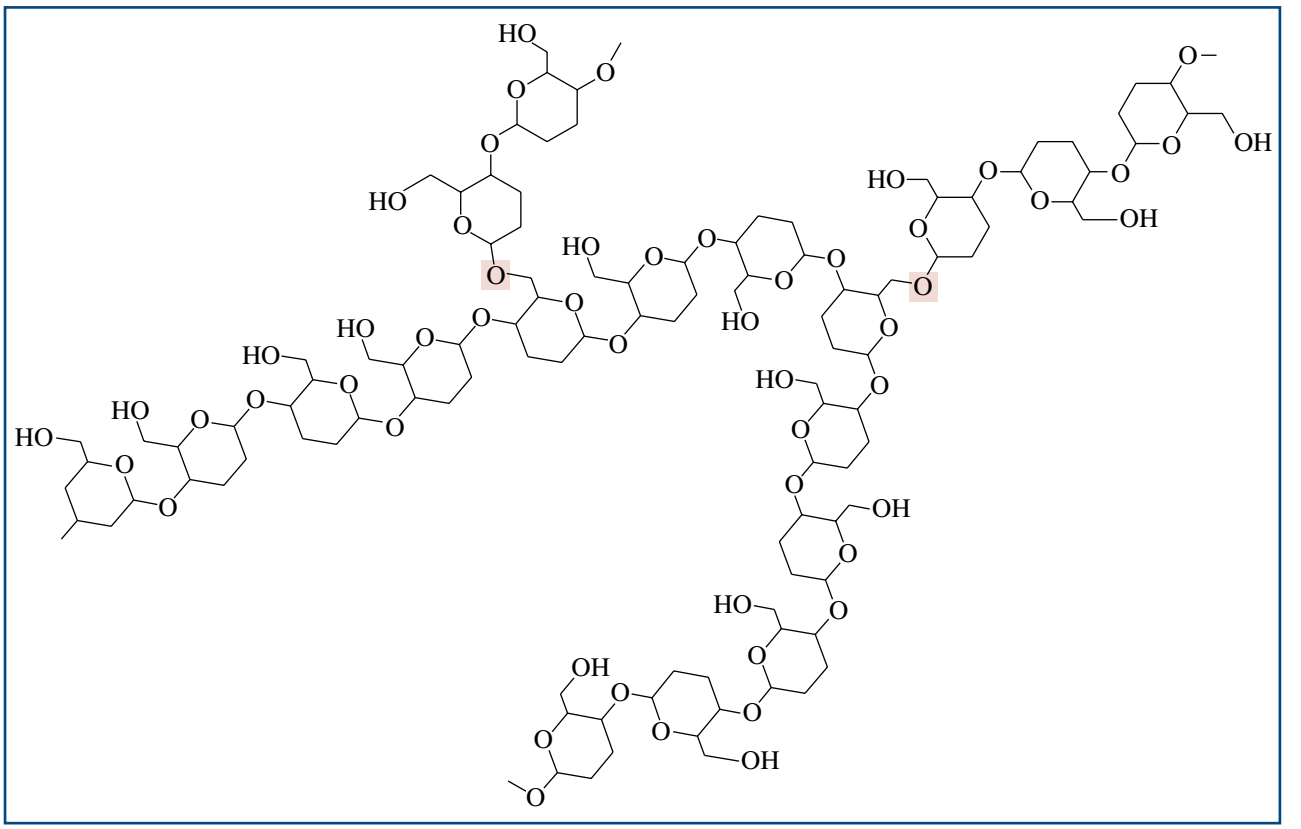
FIGURE 25.8 Cellulose is a polysaccharide in which D-glucose units are connected by β(1,4)-glycoside linkages analogous to cellobiose. Hydrogen bonding, especially between the C-2 and C-6 hydroxyl groups, causes adjacent glucose units to be turned at an angle of 180° with each other.

Animals lack the enzymes necessary to catalyze the hydrolysis of cellulose and so can't digest it. Cattle and other ruminants use cellulose as a food source in an indirect way. Colonies of microorganisms that live in their digestive tract consume cellulose and in the process convert it to other substances that the animal can digest.

A more direct source of energy for animals is provided by the starches found in many foods. Starch is a mixture of a water-dispersible fraction called *amylose* and a second component, *amylopectin.* Amylose is a polysaccharide made up of about 100 to several thousand D-glucose units joined by α(1,4)-glycosidic bonds (Figure 25.9).

Like amylose, amylopectin is a polysaccharide of α(1,4)-linked D-glucose units. Instead of being a continuous length of α(1,4) units, however, amylopectin is branched. Attached to C-6 at various points on the main chain are short polysaccharide branches of 24–30 glucose units joined by α(1,4)-glycosidic bonds.

FIGURE 25.9 Amylose is a polysaccharide in which D-glucose units are connected by α(1,4)-glycoside linkages analogous to maltose.



Starch is a plant's way of storing glucose to meet its energy needs. Animals can tap that source by eating starchy foods and, with the aid of their α-glycosidase enzymes, hydrolyze the starch to glucose. When more glucose is available than is needed as fuel, animals store it as glycogen. *Glycogen* is similar to amylopectin in that it is a branched polysaccharide of α(1,4)-linked D-glucose units with subunits connected to C-6 of the main chain.

25.16 CELL-SURFACE GLYCOPROTEINS

That carbohydrates play an informational role in biological interactions is a recent revelation of great importance. *Glycoproteins,* protein molecules covalently bound to carbohydrates, are often the principal species involved. When a cell is attacked by a virus or bacterium or when it interacts with another cell, the drama begins when the foreign particle attaches itself to the surface of the host cell. The invader recognizes the host by the glycoproteins on the cell surface. More specifically, it recognizes particular carbohydrate sequences at the end of the glycoprotein. For example, the receptor on the cell surface to which an influenza virus attaches itself has been identified as a glycoprotein terminating in a disaccharide of *N*-acetylgalactosamine and *N*-acetylneuraminic acid (Figure 25.10). Since attachment of the invader to the surface of the host cell is the first step in infection, one approach to disease prevention is to selectively inhibit this "host–guest" interaction. Identifying the precise nature of the interaction is the first step in the rational design of drugs that prevent it.

Human blood group substances offer another example of the informational role played by carbohydrates. The structure of the glycoproteins attached to the surface of blood cells determines whether blood is type A, B, AB, or O. Differences between the carbohydrate components of the various glycoproteins have been identified and are shown in Figure 25.11. Compatibility of blood types is dictated by *antigen–antibody* interactions. The cell-surface glycoproteins are *antigens. Antibodies* present in certain blood types can cause the blood cells of certain other types to clump together, and thus set practical limitations on transfusion procedures. The antibodies "recognize" the antigens they act on by their terminal saccharide units.

Antigen–antibody interactions are the fundamental basis by which the immune system functions. These interactions are chemical in nature and often involve associations between glycoproteins of an antigen and complementary glycoproteins of the antibody. The precise chemical nature of antigen–antibody association is an area of active investigation, with significant implications for chemistry, biochemistry, and physiology.

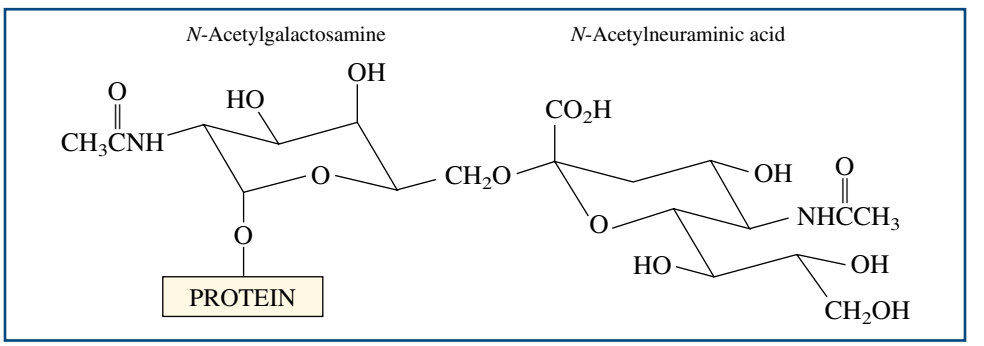


FIGURE 25.10 Diagram of a cell-surface glycoprotein, showing the disaccharide unit that is recognized by an invading influenza virus.

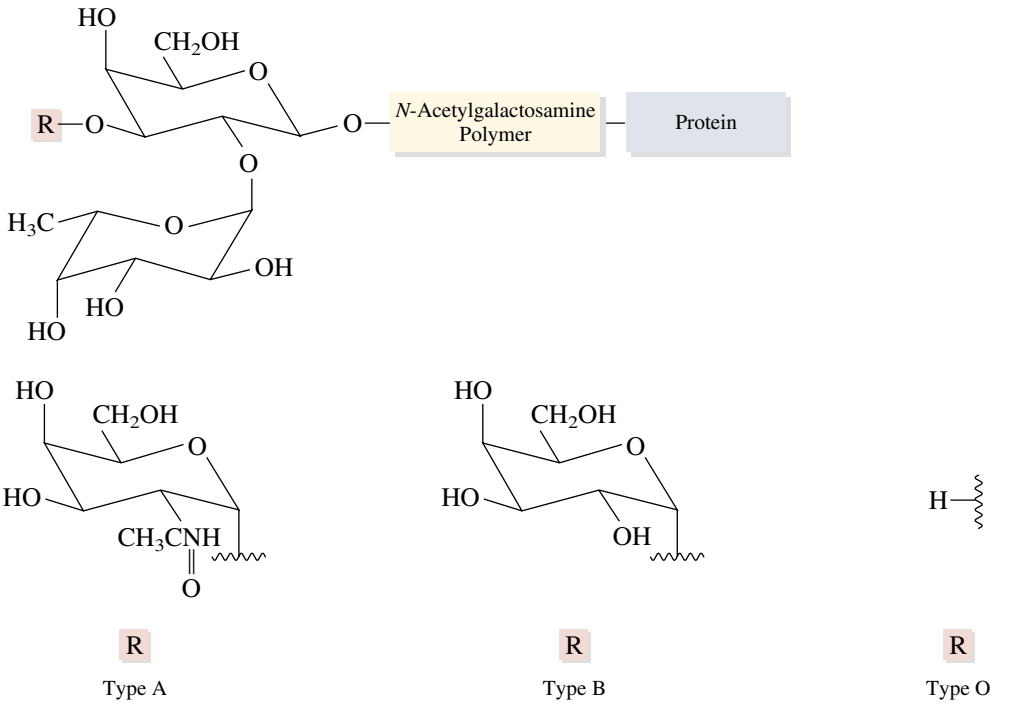


FIGURE 25.11 Terminal carbohydrate units of human blood-group glycoproteins. The structural difference between the type A, type B, and type O glycoproteins lies in the group designated R.

25.17 CARBOHYDRATE STRUCTURE DETERMINATION

Present-day techniques for structure determination in carbohydrate chemistry are substantially the same as those for any other type of compound. The full range of modern instrumental methods, including mass spectrometry and infrared and nuclear magnetic resonance spectroscopy, is brought to bear on the problem. If the unknown substance is crystalline, X-ray diffraction can provide precise structural information that in the best cases is equivalent to taking a three-dimensional photograph of the molecule.

The classical approach to structure determination in carbohydrate chemistry is best exemplified by Fischer's work with D-glucose. A detailed account of this study appears in the August 1941 issue of the *Journal of Chemical Education* (pp. 353–357).

Before the widespread availability of instrumental methods, the major approach to structure determination relied on a battery of chemical reactions and tests. The response of an unknown substance to various reagents and procedures provided a body of data from which the structure could be deduced. Some of these procedures are still used to supplement the information obtained by instrumental methods. To better understand the scope and limitations of these tests, a brief survey of the chemical reactions of carbohydrates is in order. In many cases these reactions are simply applications of chemistry you have already learned. Certain of the transformations, however, are unique to carbohydrates.

25.18 REDUCTION OF CARBOHYDRATES

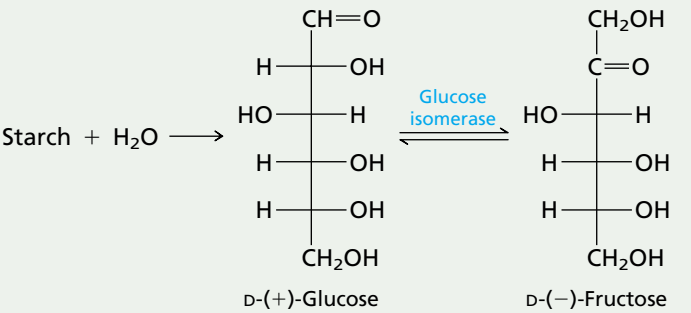
Although carbohydrates exist almost entirely as cyclic hemiacetals in aqueous solution, they are in rapid equilibrium with their open-chain forms, and most of the reagents that react with simple aldehydes and ketones react in an analogous way with the carbonyl functional groups of carbohydrates.

The carbonyl group of carbohydrates can be reduced to an alcohol function. Typical procedures include catalytic hydrogenation and sodium borohydride reduction. Lithium aluminum hydride is not suitable, because it is not compatible with the solvents (water,

HOW SWEET IT IS!

How sweet is it?

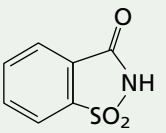
There is no shortage of compounds, natural or synthetic, that taste sweet. The most familiar are naturally occurring sugars, especially sucrose, glucose, and fructose. All occur naturally, with worldwide production of sucrose from cane and sugar beets exceeding 100 million tons per year. Glucose is prepared by the enzymatic hydrolysis of starch, and fructose is made by the isomerization of glucose.

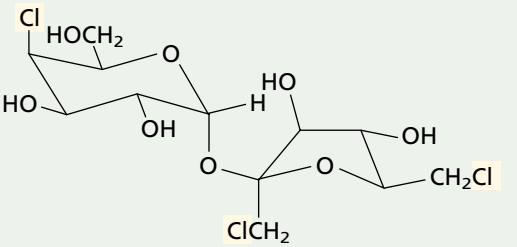


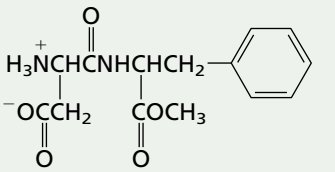
Among sucrose, glucose, and fructose, fructose is the sweetest. Honey is sweeter than table sugar because it contains fructose formed by the isomerization of glucose as shown in the equation.

You may have noticed that most soft drinks contain "high-fructose corn syrup." Corn starch is hydrolyzed to glucose, which is then treated with glucose isomerase to produce a fructose-rich mixture. The enhanced sweetness permits less to be used, reducing the cost of production. Using less carbohydrate-based sweetener also reduces the number of calories.

Artificial sweeteners are a billion-dollar-per-year industry. The primary goal is, of course, to maximize sweetness and minimize calories. We'll look at the following three sweeteners to give us an overview of the field.


Saccharin


Sucralose


Aspartame

All three of these are hundreds of times sweeter than sucrose and variously described as "low-calorie" or "nonnutritive" sweeteners.

Saccharin was discovered at Johns Hopkins University in 1879 in the course of research on coal-tar derivatives and is the oldest artificial sweetener. In spite of its name, which comes from the Latin word for sugar, saccharin bears no structural relationship to any sugar. Nor is saccharin itself very soluble in water. The proton bonded to nitrogen, however, is fairly acidic and saccharin is normally marketed as its water-soluble sodium or calcium salt. Its earliest applications were not in weight control, but as a replacement for sugar in the diet of diabetics before insulin became widely available.

Sucralose has the structure most similar to sucrose. Galactose replaces the glucose unit of sucrose, and chlorines replace three of the hydroxyl groups. Sucralose is the newest artificial sweetener, having been approved by the U.S. Food and Drug Administration in 1998. The three chlorine substituents do not diminish sweetness, but do interfere with the ability of the body to metabolize sucralose. It, therefore, has no food value and is "noncaloric."

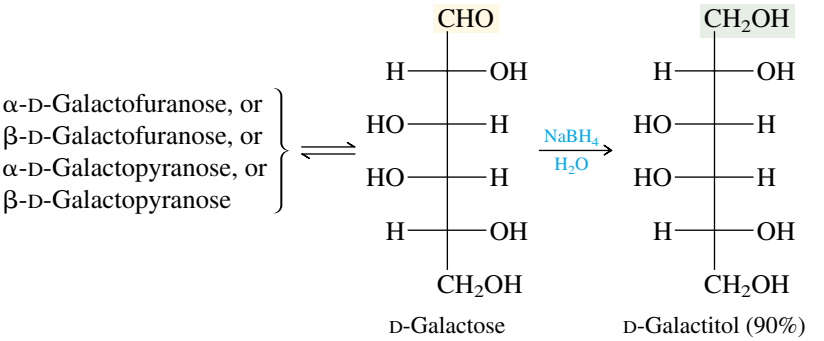
—Cont.

Aspartame is the market leader among artificial sweeteners. It is a methyl ester of a dipeptide, unrelated to any carbohydrate. It was discovered in the course of research directed toward developing drugs to relieve indigestion.

Saccharin, sucralose, and aspartame illustrate the diversity of structural types that taste sweet, and the vitality and continuing development of the industry of which they are a part.*

*For more information, including theories of structure–taste relationships, see the symposium "Sweeteners and Sweetness Theory" in the August, 1995 issue of the *Journal of Chemical Education,* pp. 671–683.

alcohols) that are required to dissolve carbohydrates. The products of carbohydrate reduction are called **alditols.** Since these alditols lack a carbonyl group, they are, of course, incapable of forming cyclic hemiacetals and exist exclusively in noncyclic forms.

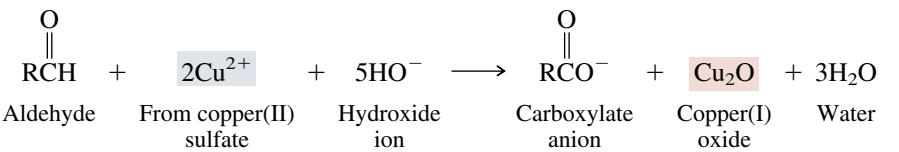


PROBLEM 25.13 Does sodium borohydride reduction of D-ribose yield an optically active product? Explain.

Another name for glucitol, obtained by reduction of D-glucose, is *sorbitol;* it is used as a sweetener, especially in special diets required to be low in sugar. Reduction of D-fructose yields a mixture of glucitol and mannitol, corresponding to the two possible configurations at the newly generated stereogenic center at C-2.

25.19 OXIDATION OF CARBOHYDRATES

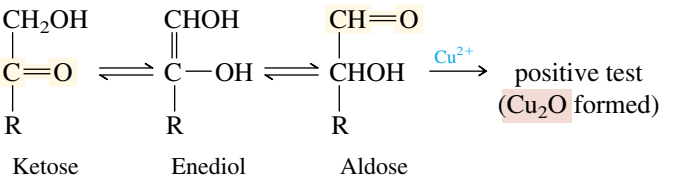
A characteristic property of an aldehyde function is its sensitivity to oxidation. A solution of copper(II) sulfate as its citrate complex **(Benedict's reagent)** is capable of oxidizing aliphatic aldehydes to the corresponding carboxylic acid.



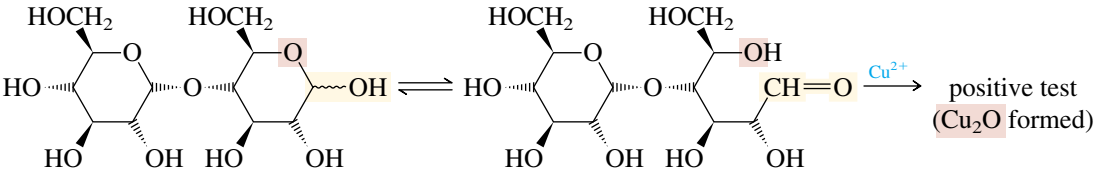
Benedict's reagent is the key material in a test kit available from drugstores that permits individuals to monitor the glucose levels in their urine.

The formation of a red precipitate of copper(I) oxide by reduction of Cu(II) is taken as a positive test for an aldehyde. Carbohydrates that give positive tests with Benedict's reagent are termed **reducing sugars.**

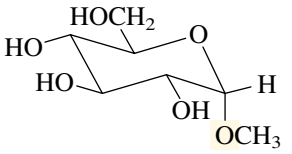
Aldoses are reducing sugars, since they possess an aldehyde function in their open-chain form. Ketoses are also reducing sugars. Under the conditions of the test, ketoses equilibrate with aldoses by way of *enediol intermediates,* and the aldoses are oxidized by the reagent.

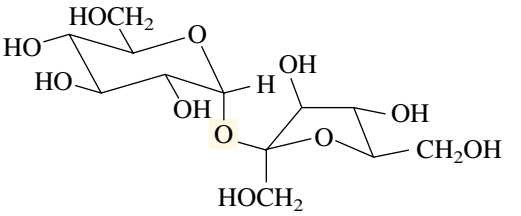


The same kind of equilibrium is available to α-hydroxy ketones generally; such compounds give a positive test with Benedict's reagent. Any carbohydrate that contains a free hemiacetal function is a reducing sugar. The free hemiacetal is in equilibrium with the open-chain form and through it is susceptible to oxidation. Maltose, for example, gives a positive test with Benedict's reagent.



Glycosides, in which the anomeric carbon is part of an acetal function, are not reducing sugars and do not give a positive test.

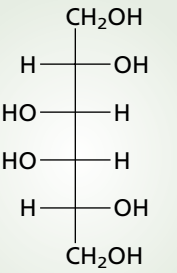

Methyl α-D-glucopyranoside: not a reducing sugar


Sucrose: not a reducing sugar

PROBLEM 25.14 Which of the following would be expected to give a positive test with Benedict's reagent? Why?

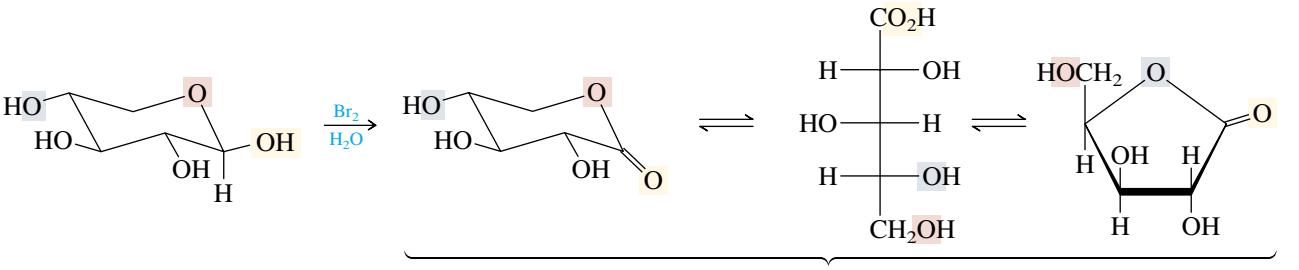
(a) D-Galactitol (see structure in margin)
(b) L-Arabinose
(c) 1,3-Dihydroxyacetone
(d) D-Fructose
(e) Lactose
(f) Amylose

SAMPLE SOLUTION (a) D-Galactitol lacks an aldehyde, an α-hydroxy ketone, or a hemiacetal function, so cannot be oxidized by Cu^{2+} and will not give a positive test with Benedict's reagent.


D-Galactitol

Fehling's solution, a tartrate complex of copper(II) sulfate, has also been used as a test for reducing sugars.

Derivatives of aldoses in which the terminal aldehyde function is oxidized to a carboxylic acid are called **aldonic acids.** Aldonic acids are named by replacing the *-ose* ending of the aldose by *-onic acid.* Oxidation of aldoses with bromine is the most commonly used method for the preparation of aldonic acids and involves the furanose or pyranose form of the carbohydrate.

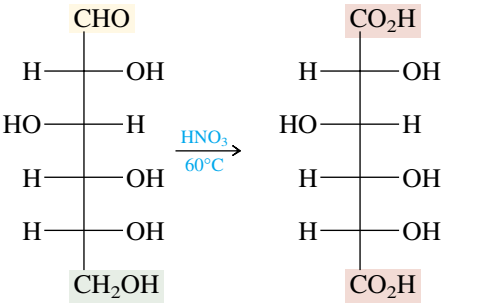


β-D-Xylopyranose

D-Xylonic acid (90%)

Aldonic acids exist in equilibrium with their five- or six-membered lactones. They can be isolated as carboxylate salts of their open-chain forms on treatment with base.

The reaction of aldoses with nitric acid leads to the formation of **aldaric acids** by oxidation of both the aldehyde and the terminal primary alcohol function to carboxylic acid groups. Aldaric acids are also known as *saccharic acids* and are named by substituting *-aric acid* for the *-ose* ending of the corresponding carbohydrate.



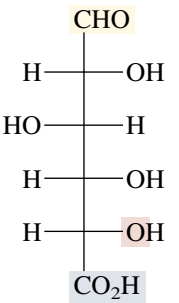
D-Glucose

D-Glucaric acid (41%)

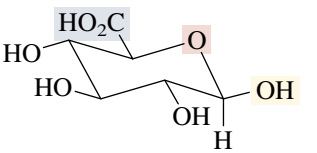
Like aldonic acids, aldaric acids exist mainly as lactones.

PROBLEM 25.15 Another hexose gives the same aldaric acid on oxidation as does D-glucose. Which one?

Uronic acids occupy an oxidation state between aldonic and aldaric acids. They have an aldehyde function at one end of their carbon chain and a carboxylic acid group at the other.



Fischer projection of D-glucuronic acid

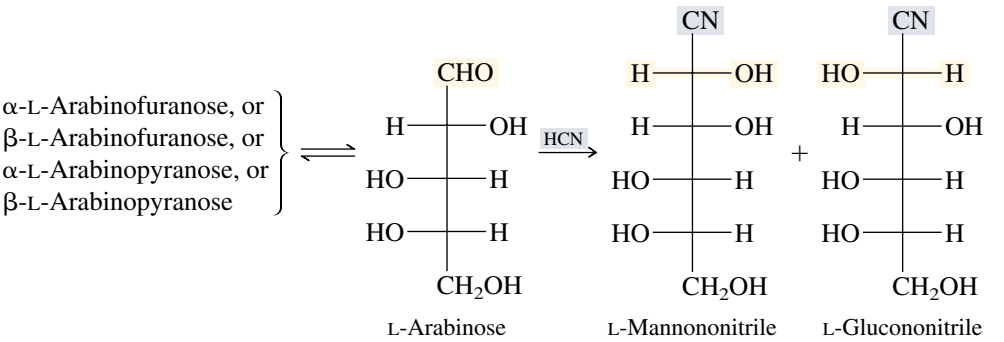


β-Pyranose form of D-glucuronic acid

Uronic acids are biosynthetic intermediates in various metabolic processes; ascorbic acid (vitamin C), for example, is biosynthesized by way of glucuronic acid. Many metabolic waste products are excreted in the urine as their glucuronate salts.

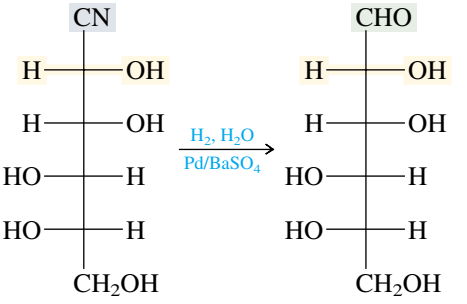
25.20 CYANOHYDRIN FORMATION AND CARBOHYDRATE CHAIN EXTENSION

The presence of an aldehyde function in their open-chain forms makes aldoses reactive toward nucleophilic addition of hydrogen cyanide. Addition yields a mixture of diastereomeric cyanohydrins.



L-Arabinose L-Mannononitrile L-Gluconononitrile

The reaction is used for the chain extension of aldoses in the synthesis of new or unusual sugars. In this case, the starting material, L-arabinose, is an abundant natural product and possesses the correct configurations at its three stereogenic centers for elaboration to the relatively rare L-enantiomers of glucose and mannose. After cyanohydrin formation, the cyano groups are converted to aldehyde functions by hydrogenation in aqueous solution. Under these conditions, —C≡N is reduced to —CH=NH and hydrolyzes rapidly to —CH=O. Use of a poisoned palladium-on-barium sulfate catalyst prevents further reduction to the alditols.



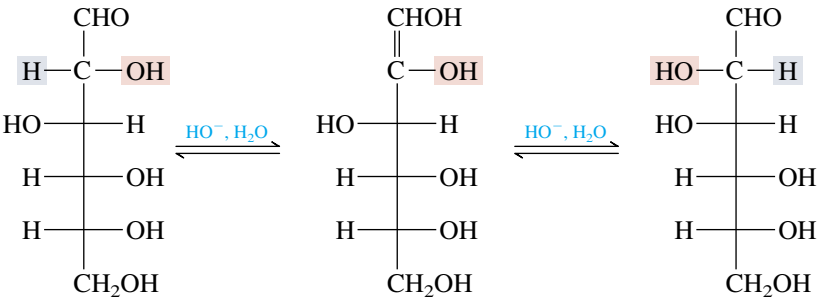
L-Mannononitrile L-Mannose (56% yield from L-arabinose)

(Similarly, L-gluconononitrile has been reduced to L-glucose; its yield was 26% from L-arabinose.)

An older version of this sequence is called the **Kiliani-Fischer synthesis.** It, too, proceeds through a cyanohydrin, but it uses a less efficient method for converting the cyano group to the required aldehyde.

25.21 EPIMERIZATION, ISOMERIZATION, AND RETRO-ALDOL CLEAVAGE REACTIONS OF CARBOHYDRATES

Carbohydrates undergo a number of isomerization and degradation reactions under both laboratory and physiological conditions. For example, a mixture of glucose, fructose, and mannose results when any one of them is treated with aqueous base. This reaction can be understood by examining the consequences of enolization of glucose:

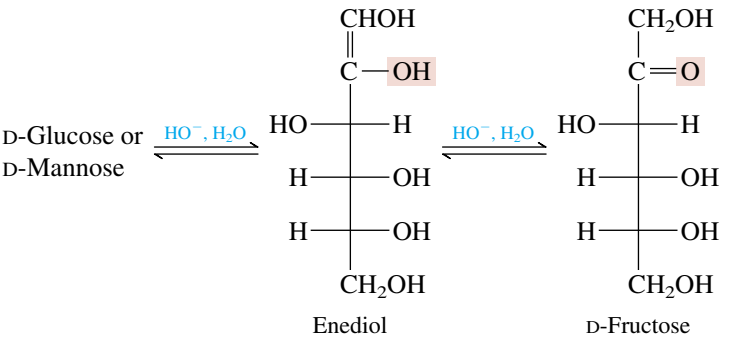


D-Glucose (*R* configuration at C-2) | Enediol (C-2 not a stereogenic center) | D-Mannose (*S* configuration at C-2)

Because the configuration at C-2 is lost on enolization, the enediol intermediate can revert either to D-glucose or to D-mannose. Two stereoisomers that have multiple stereogenic centers but differ in configuration at only one of them are referred to as **epimers.** Glucose and mannose are epimeric at C-2. Under these conditions epimerization occurs only at C-2 because it alone is α to the carbonyl group.

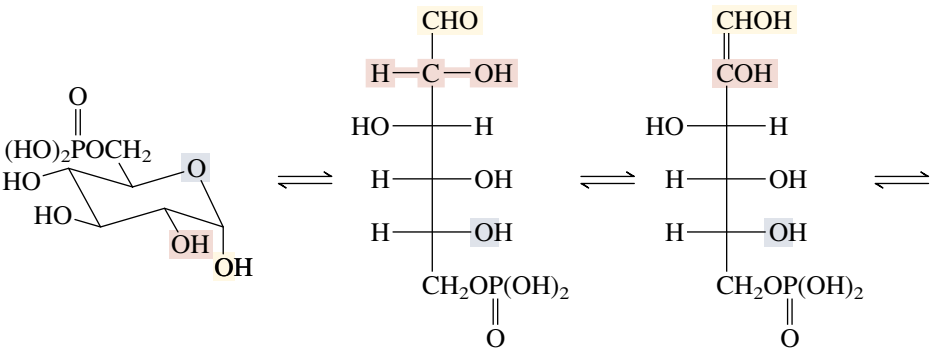
There is another reaction available to the enediol intermediate. Proton transfer from water to C-1 converts the enediol not to an aldose but to the ketose D-fructose:

See the boxed essay "How Sweet It Is!" for more on this process.



Enediol | D-Fructose

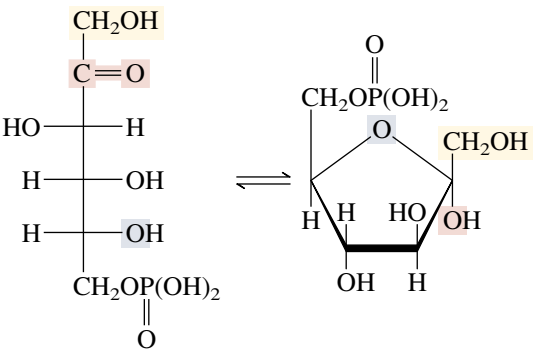
The isomerization of D-glucose to D-fructose by way of an enediol intermediate is an important step in **glycolysis,** a complex process (11 steps) by which an organism converts glucose to chemical energy. The substrate is not glucose itself but its 6-phosphate ester. The enzyme that catalyzes the isomerization is called *phosphoglucose isomerase.*



D-Glucose 6-phosphate

Open-chain form of D-glucose 6-phosphate

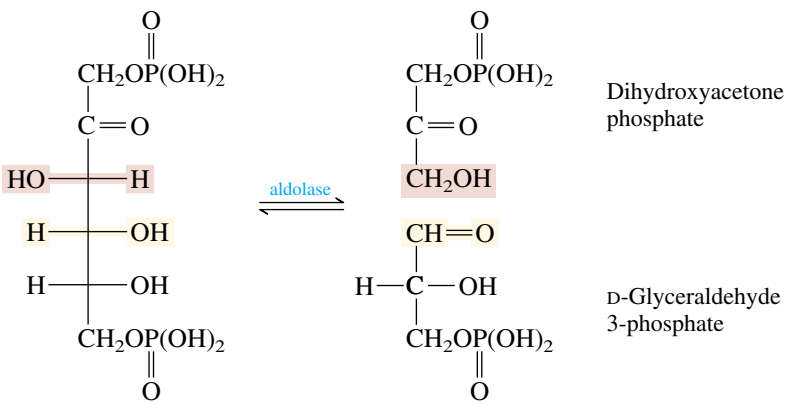
Enediol



Open-chain form of D-Fructose 6-phosphate

D-Fructose 6-phosphate

Following its formation, D-fructose 6-phosphate is converted to its corresponding 1,6-phosphate diester, which is then cleaved to two 3-carbon fragments under the influence of the enzyme *aldolase:*



Dihydroxyacetone phosphate

D-Glyceraldehyde 3-phosphate

D-Fructose 1,6-diphosphate

This cleavage is a *retro-aldol* reaction. It is the reverse of the process by which D-fructose 1,6-diphosphate would be formed by addition of the enolate of dihydroxyacetone phosphate to D-glyceraldehyde 3-phosphate. The enzyme aldolase catalyzes both the

aldol condensation of the two components and, in glycolysis, the retro-aldol cleavage of D-fructose 1,6-diphosphate.

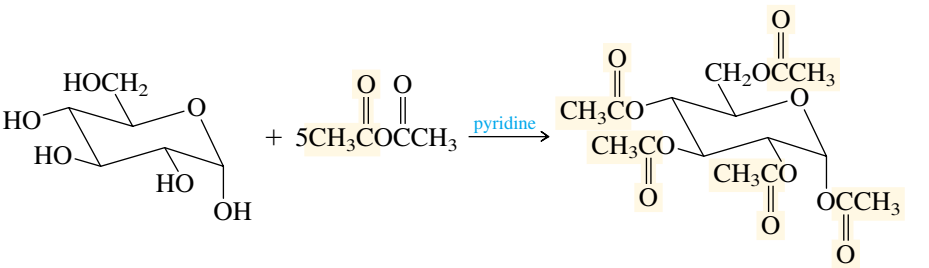
Further steps in glycolysis use the D-glyceraldehyde 3-phosphate formed in the aldolase-catalyzed cleavage reaction as a substrate. Its coproduct, dihydroxyacetone phosphate, is not wasted, however. The enzyme *triose phosphate isomerase* converts dihydroxyacetone phosphate to D-glyceraldehyde 3-phosphate, which enters the glycolysis pathway for further transformations.

PROBLEM 25.16 Suggest a reasonable structure for the intermediate in the conversion of dihydroxyacetone phosphate to D-glyceraldehyde 3-phosphate.

Cleavage reactions of carbohydrates also occur on treatment with aqueous base for prolonged periods as a consequence of base-catalyzed retro-aldol reactions. As pointed out in Section 18.9, aldol addition is a reversible process, and β-hydroxy carbonyl compounds can be cleaved to an enolate and either an aldehyde or a ketone.

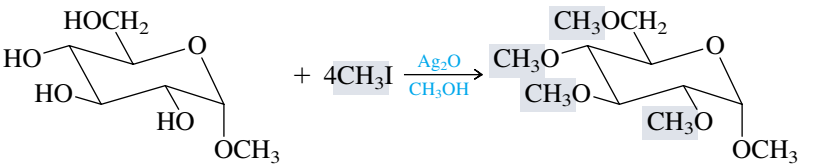
25.22 ACYLATION AND ALKYLATION OF HYDROXYL GROUPS IN CARBOHYDRATES

The alcohol groups of carbohydrates undergo chemical reactions typical of hydroxyl functions. They are converted to esters by reaction with acyl chlorides and carboxylic acid anhydrides.



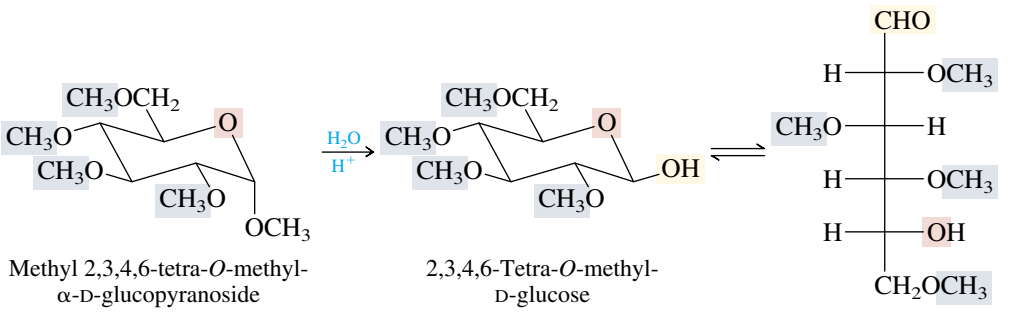
α-D-Glucopyranose | Acetic anhydride | 1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranose (88%)

Ethers are formed under conditions of the Williamson ether synthesis. Methyl ethers of carbohydrates are efficiently prepared by alkylation with methyl iodide in the presence of silver oxide.



Methyl α-D-glucopyranoside | Methyl iodide | Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (97%)

This reaction has been used in an imaginative way to determine the ring size of glycosides. Once all the free hydroxyl groups of a glycoside have been methylated, the glycoside is subjected to acid-catalyzed hydrolysis. Only the anomeric methoxy group is hydrolyzed under these conditions—another example of the ease of carbocation formation at the anomeric position.



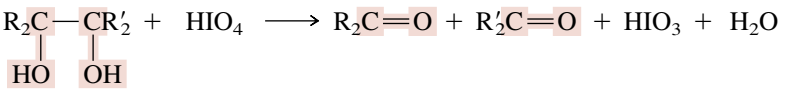
Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside

2,3,4,6-Tetra-*O*-methyl-D-glucose

Notice that all the hydroxyl groups in the free sugar except C-5 are methylated. Carbon-5 is not methylated, because it was originally the site of the ring oxygen in the methyl glycoside. Once the position of the hydroxyl group in the free sugar has been determined, either by spectroscopy or by converting the sugar to a known compound, the ring size stands revealed.

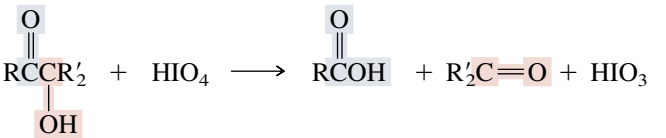
25.23 PERIODIC ACID OXIDATION OF CARBOHYDRATES

Periodic acid oxidation (Section 15.12) finds extensive use as an analytical method in carbohydrate chemistry. Structural information is obtained by measuring the number of equivalents of periodic acid that react with a given compound and by identifying the reaction products. A vicinal diol consumes one equivalent of periodate and is cleaved to two carbonyl compounds:



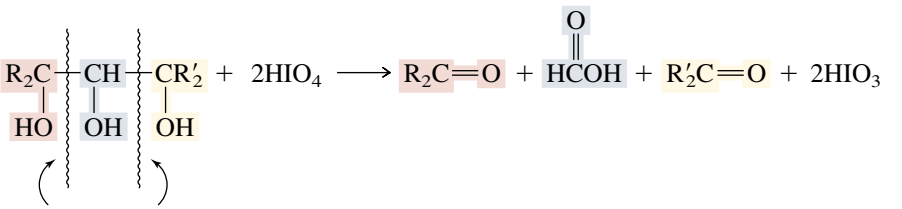
Vicinal diol | Periodic acid | Two carbonyl compounds | Iodic acid | Water

α-Hydroxy carbonyl compounds are cleaved to a carboxylic acid and a carbonyl compound:



α-Hydroxy carbonyl compound | Periodic acid | Carboxylic acid | Carbonyl compound | Iodic acid

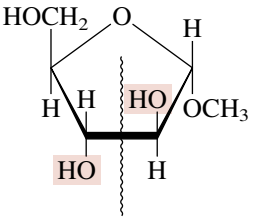
When three contiguous carbons bear hydroxyl groups, two moles of periodate are consumed per mole of carbohydrate and the central carbon is oxidized to a molecule of formic acid:



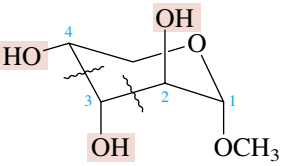
Points at which cleavage occurs | Periodic acid | Carbonyl compound | Formic acid | Carbonyl compound | Iodic acid

Ether and acetal functions are not affected by the reagent.

The use of periodic acid oxidation in structure determination can be illustrated by a case in which a previously unknown methyl glycoside was obtained by the reaction of D-arabinose with methanol and hydrogen chloride. The size of the ring was identified as five-membered because only one mole of periodic acid was consumed per mole of glycoside and no formic acid was produced. Were the ring six-membered, two moles of periodic acid would be required per mole of glycoside and one mole of formic acid would be produced.



Only one site for periodic acid cleavage in methyl α-D-arabinofuranoside

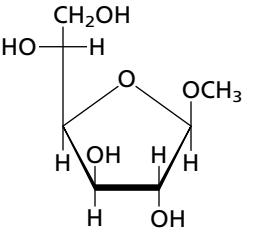


Two sites of periodic acid cleavage in methyl α-D-arabinopyranoside, C-3 lost as formic acid

PROBLEM 25.17 Give the products of periodic acid oxidation of each of the following. How many moles of reagent will be consumed per mole of substrate in each case?

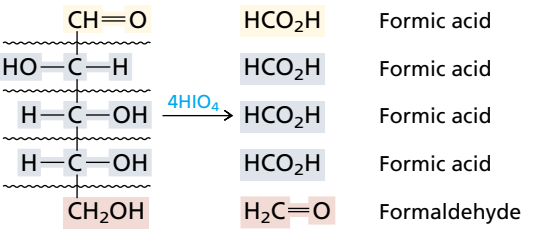
(a) D-Arabinose
(b) D-Ribose
(c) Methyl β-D-glucopyranoside

(d)



SAMPLE SOLUTION (a) The α-hydroxy aldehyde unit at the end of the sugar chain is cleaved, as well as all the vicinal diol functions. Four moles of periodic acid are required per mole of D-arabinose. Four moles of formic acid and one mole of formaldehyde are produced.

D-Arabinose, showing points of cleavage by periodic acid; each cleavage requires one equivalent of HIO_4.



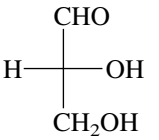
25.24 SUMMARY

Section 25.1 Carbohydrates are marvelous molecules! In most of them, every carbon bears a functional group, and the nature of the functional groups changes as the molecule interconverts between open-chain and cyclic hemiacetal

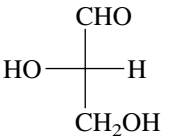
forms. Any approach to understanding carbohydrates must begin with structure.

Carbohydrates are polyhydroxy aldehydes and ketones. Those derived from aldehydes are classified as **aldoses;** those derived from ketones are **ketoses.**

Section 25.2 Fischer projections and D–L notation are commonly used to describe carbohydrate stereochemistry. The standards are the enantiomers of glyceraldehyde.



D-(+)-Glyceraldehyde



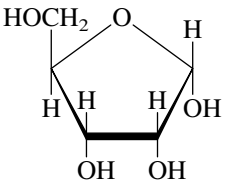
L-(−)-Glyceraldehyde

Section 25.3 Aldotetroses have two stereogenic centers, so four stereoisomers are possible. They are assigned to the D or the L series according to whether the configuration at their highest numbered stereogenic center is analogous to D- or L-glyceraldehyde, respectively. Both hydroxyl groups are on the same side of the Fischer projection in erythrose, but on opposite sides in threose. The Fischer projections of D-erythrose and D-threose are shown in Figure 25.2.

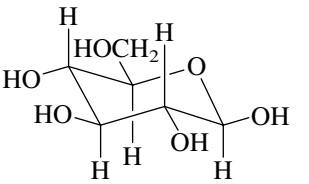
Section 25.4 Of the eight stereoisomeric aldopentoses, Figure 25.2 shows the Fischer projections of the D-enantiomers (D-ribose, D-arabinose, D-xylose, and D-lyxose). Likewise, Figure 25.2 gives the Fischer projections of the eight D-aldohexoses.

Section 25.5 The aldohexoses are allose, altrose, glucose, mannose, gulose, idose, galactose, and talose. The mnemonic "All altruists gladly make gum in gallon tanks" is helpful in writing the correct Fischer projection for each one.

Sections 25.6–25.7 Most carbohydrates exist as cyclic hemiacetals. Cyclic acetals with five-membered rings are called **furanose** forms; those with six-membered rings are called **pyranose** forms.



α-D-Ribofuranose



β-D-Glucopyranose

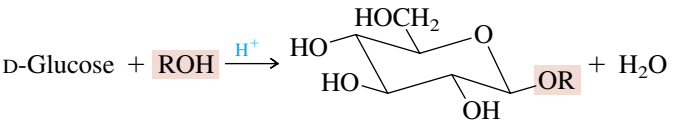
The **anomeric carbon** in a cyclic acetal is the one attached to *two* oxygens. It is the carbon that corresponds to the carbonyl carbon in the open-chain form. The symbols α and β refer to the configuration at the anomeric carbon.

Section 25.8 A particular carbohydrate can interconvert between furanose and pyranose forms and between the α and β configuration of each form. The change from one form to an equilibrium mixture of all the possible hemiacetals causes a change in optical rotation called **mutarotation.**

Section 25.9 Ketoses are characterized by the ending *-ulose* in their name. Most naturally occurring ketoses have their carbonyl group located at C-2. Like aldoses, ketoses cyclize to hemiacetals and exist as furanose or pyranose forms.

Sections 25.10–25.12 Structurally modified carbohydrates include **deoxy sugars, amino sugars,** and **branched-chain carbohydrates.**

Section 25.13 Glycosides are acetals, compounds in which the anomeric hydroxyl group has been replaced by an alkoxy group. Glycosides are easily prepared by allowing a carbohydrate and an alcohol to stand in the presence of an acid catalyst.



A glycoside

Sections 25.14–25.15 **Disaccharides** are carbohydrates in which two monosaccharides are joined by a glycoside bond. **Polysaccharides** have many monosaccharide units connected through glycosidic linkages. Complete hydrolysis of disaccharides and polysaccharides cleaves the glycoside bonds, yielding the free monosaccharide components.

Section 25.16 Carbohydrates and proteins that are connected by a chemical bond are called **glycoproteins** and often occur on the surfaces of cells. They play an important role in the recognition events connected with the immune response.

Sections 25.17–25.24 Carbohydrates undergo chemical reactions characteristic of aldehydes and ketones, alcohols, diols, and other classes of compounds, depending on their structure. A review of the reactions described in this chapter is presented in Table 25.2. Although some of the reactions have synthetic value, many of them are used in analysis and structure determination.

PROBLEMS

25.18 Refer to the Fischer projection of D-(+)-xylose in Figure 25.2 (Section 25.4) and give structural formulas for

(a) (−)-Xylose (Fischer projection)

(b) D-Xylitol

(c) β-D-Xylopyranose

(d) α-L-Xylofuranose

(e) Methyl α-L-xylofuranoside

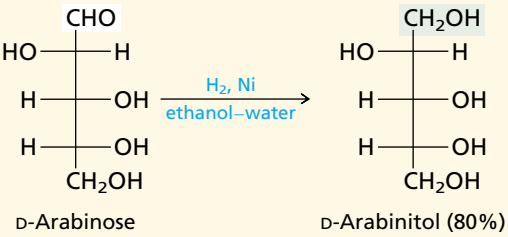
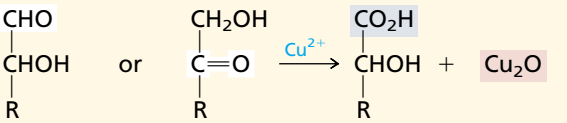
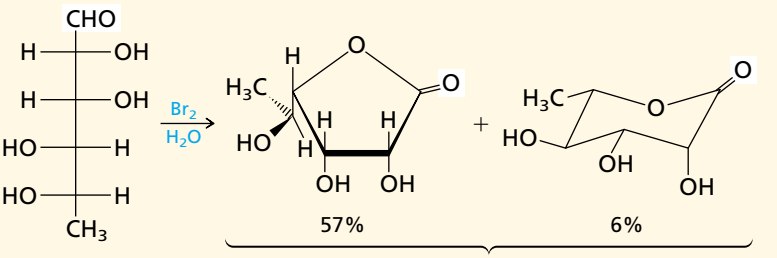
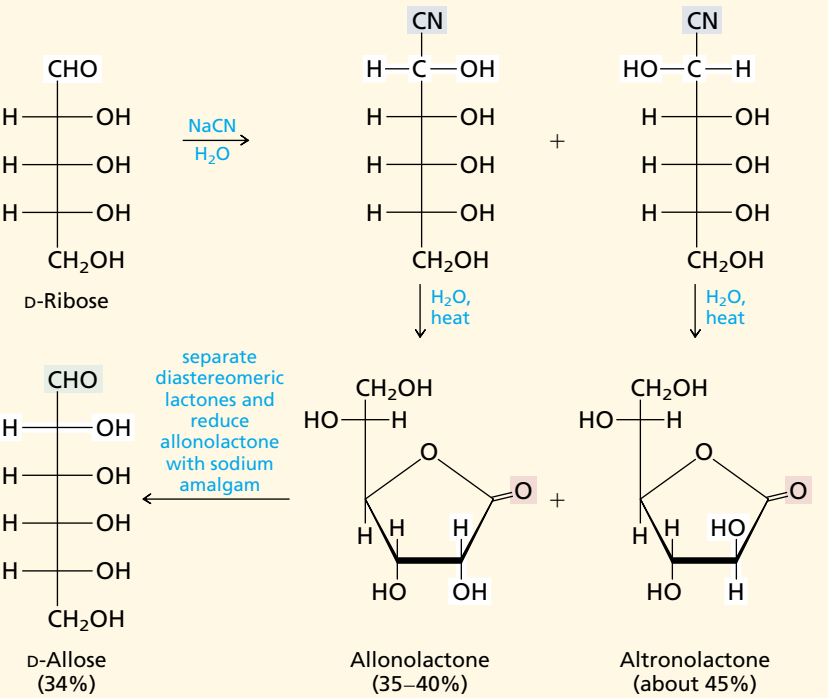
(f) D-Xylonic acid (open-chain Fischer projection)

(g) δ-Lactone of D-xylonic acid

(h) γ-Lactone of D-xylonic acid

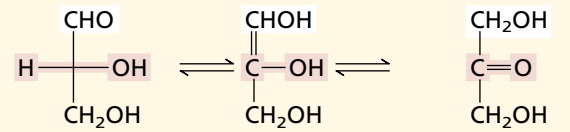
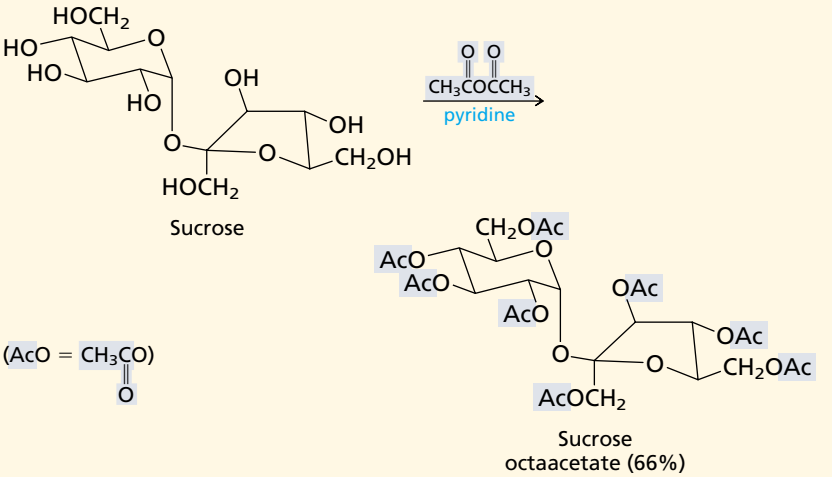
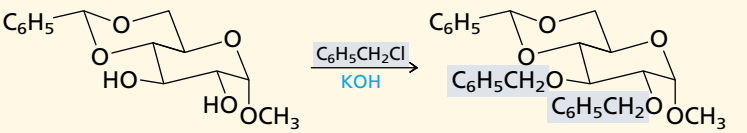
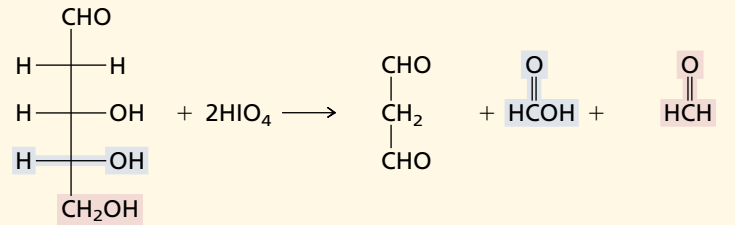
(i) D-Xylaric acid (open-chain Fischer projection)

TABLE 25.2 Summary of Reactions of Carbohydrates

Reaction (section) and comments	Example
Transformations of the carbonyl group	
Reduction (Section 25.18) The carbonyl group of aldoses and ketoses is reduced by sodium borohydride or by catalytic hydrogenation. The products are called *alditols*.	 D-Arabinose → D-Arabinitol (80%)
Oxidation with Benedict's reagent (Section 25.19) Sugars that contain a free hemiacetal function are called reducing sugars. They react with copper(II) sulfate in a sodium citrate/sodium carbonate buffer (Benedict's reagent) to form a red precipitate of copper(I) oxide. Used as a qualitative test for reducing sugars.	 Aldose; Ketose → Aldonic acid + Copper(I) oxide
Oxidation with bromine (Section 25.19) When a preparative method for an aldonic acid is required, bromine oxidation is used. The aldonic acid is formed as its lactone. More properly described as a reaction of the anomeric hydroxyl group than of a free aldehyde.	 L-Rhamnose → L-Rhamnonolactone
Chain extension by way of cyanohydrin formation (Section 25.20) The Kiliani–Fischer synthesis proceeds by nucleophilic addition of HCN to an aldose, followed by conversion of the cyano group to an aldehyde. A mixture of stereoisomers results; the two aldoses are epimeric at C-2. Section 25.20 describes the modern version of the Kiliani–Fischer synthesis. The example at the right illustrates the classical version.	 D-Ribose → D-Allose (34%) + Allonolactone (35–40%) + Altronolactone (about 45%)

(Continued)

TABLE 25.2 Summary of Reactions of Carbohydrates *(Continued)*

Reaction (section) and comments	Example
Enediol formation (Section 25.21) Enolization of an aldose or a ketose gives an enediol. Enediols can revert to aldoses or ketoses with loss of stereochemical integrity at the α-carbon atom.	 D-Glyceraldehyde ⇌ Enediol ⇌ 1,3-Dihydroxyacetone
Reactions of the hydroxyl group	
Acylation (Section 25.22) Esterification of the available hydroxyl groups occurs when carbohydrates are treated with acylating agents.	 Sucrose → Sucrose octaacetate (66%)
Alkylation (Section 25.22) Alkyl halides react with carbohydrates to form ethers at the available hydroxyl groups. An application of the Williamson ether synthesis to carbohydrates.	 Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside → Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (92%)
Periodic acid oxidation (Section 25.23) Vicinal diol and α-hydroxy carbonyl functions in carbohydrates are cleaved by periodic acid. Used analytically as a tool for structure determination.	 2-Deoxy-D-ribose → Propanedial + Formic acid + Formaldehyde

25.19 From among the carbohydrates shown in Figure 25.2, choose the D-aldohexoses that yield

(a) An optically inactive product on reduction with sodium borohydride

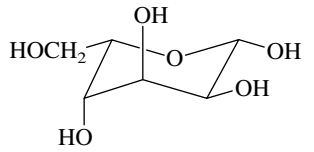
(b) An optically inactive product on oxidation with bromine

(c) An optically inactive product on oxidation with nitric acid

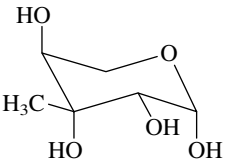
(d) The same enediol

25.20 Write the Fischer projection of the open-chain form of each of the following:

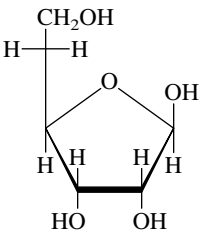
(a)



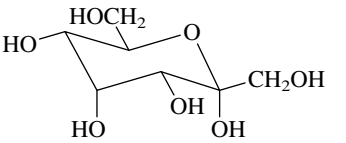
(c)



(b)



(d)



25.21 What are the *R,S* configurations of the three stereogenic centers in D-ribose? (A molecular model will be helpful here.)

25.22 From among the carbohydrates shown in Problem 25.20 choose the one(s) that

(a) Belong to the L series

(b) Are deoxy sugars

(c) Are branched-chain sugars

(d) Are ketoses

(e) Are furanose forms

(f) Have the α configuration at their anomeric carbon

25.23 How many pentuloses are possible? Write their Fischer projections.

25.24 The Fischer projection of the branched-chain carbohydrate D-apiose has been presented in Section 25.12.

(a) How many stereogenic centers are in the open-chain form of D-apiose?

(b) Does D-apiose form an optically active alditol on reduction?

(c) How many stereogenic centers are in the furanose forms of D-apiose?

(d) How many stereoisomeric furanose forms of D-apiose are possible? Write their Haworth formulas.

25.25 Treatment of D-mannose with methanol in the presence of an acid catalyst yields four isomeric products having the molecular formula $C_7H_{14}O_6$. What are these four products?

25.26 Maltose and cellobiose (Section 25.14) are examples of disaccharides derived from D-glucopyranosyl units.

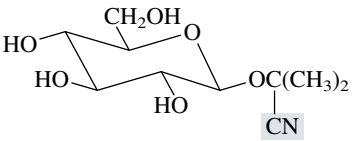
(a) How many other disaccharides are possible that meet this structural requirement?

(b) How many of these are reducing sugars?

25.27 Gentiobiose has the molecular formula $C_{12}H_{22}O_{11}$ and has been isolated from gentian root and by hydrolysis of amygdalin. Gentiobiose exists in two different forms, one melting at 86°C and the other at 190°C. The lower melting form is dextrorotatory ($[\alpha]_D^{22}$ +16°), the higher melting one is levorotatory ($[\alpha]_D^{22}$ −6°). The rotation of an aqueous solution of either form, however, gradually changes until a final value of $[\alpha]_D^{22}$ +9.6° is observed. Hydrolysis of gentiobiose is efficiently catalyzed by emulsin and produces two moles of D-glucose per mole of gentiobiose. Gentiobiose forms an octamethyl ether, which on hydrolysis in dilute acid yields 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-D-glucose. What is the structure of gentiobiose?

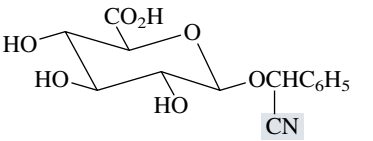
25.28 *Cyanogenic glycosides* are potentially toxic because they liberate hydrogen cyanide on enzyme-catalyzed or acidic hydrolysis. Give a mechanistic explanation for this behavior for the specific cases of

(a)



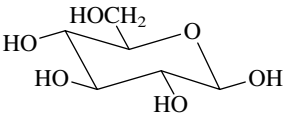
Linamarin

(b)

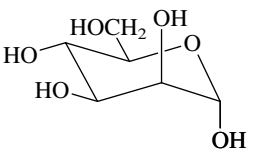


Laetrile

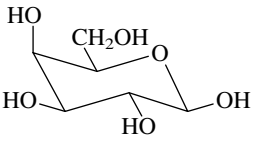
25.29 The following are the more stable anomers of the pyranose forms of D-glucose, D-mannose, and D-galactose:



β-D-Glucopyranose
(64% at equilibrium)



α-D-Mannopyranose
(68% at equilibrium)

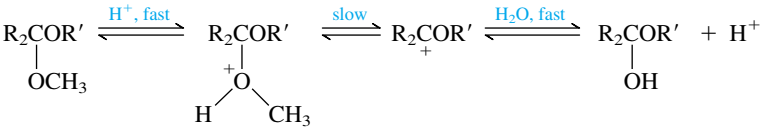


β-D-Galactopyranose
(64% at equilibrium)

On the basis of these empirical observations and your own knowledge of steric effects in six-membered rings, predict the preferred form (α- or β-pyranose) at equilibrium in aqueous solution for each of the following:

(a) D-Gulose
(b) D-Talose
(c) D-Xylose
(d) D-Lyxose

25.30 Basing your answers on the general mechanism for the first stage of acid-catalyzed acetal hydrolysis

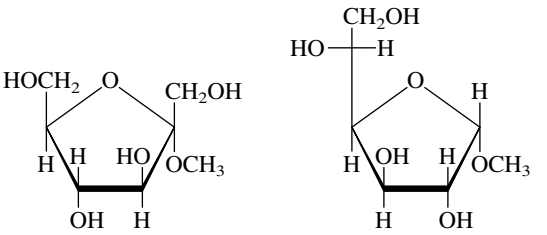


Acetal

Hemiacetal

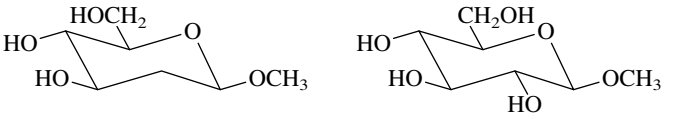
suggest reasonable explanations for the following observations:

(a) Methyl α-D-fructofuranoside (compound A) undergoes acid-catalyzed hydrolysis some 10^5 times faster than methyl α-D-glucofuranoside (compound B).



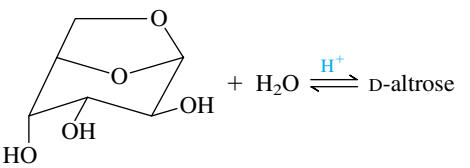
Compound A Compound B

(b) The β-methyl glucopyranoside of 2-deoxy-D-glucose (compound C) undergoes hydrolysis several thousand times faster than that of D-glucose (compound D).



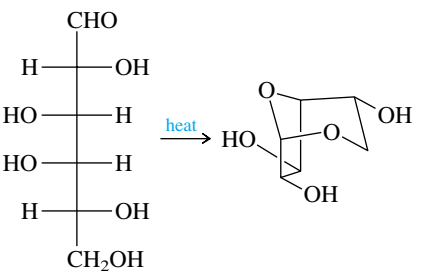
Compound C Compound D

25.31 D-Altrosan is converted to D-altrose by dilute aqueous acid. Suggest a reasonable mechanism for this reaction.



D-Altrosan

25.32 When D-galactose was heated at 165°C, a small amount of compound A was isolated:



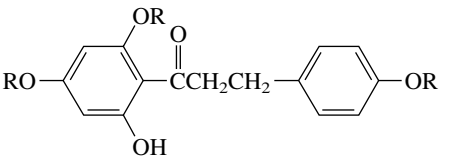
D-Galactose Compound A

The structure of compound A was established, in part, by converting it to known compounds. Treatment of A with excess methyl iodide in the presence of silver oxide, followed by hydrolysis with dilute hydrochloric acid, gave a trimethyl ether of D-galactose. Comparing this trimethyl ether with known trimethyl ethers of D-galactose allowed the structure of compound A to be deduced.

How many trimethyl ethers of D-galactose are there? Which one is the same as the product derived from compound A?

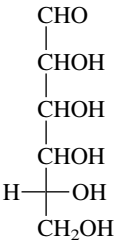
25.33 Phlorizin is obtained from the root bark of apple, pear, cherry, and plum trees. It has the molecular formula $C_{21}H_{24}O_{10}$ and yields a compound A and D-glucose on hydrolysis in the presence of emulsin. When phlorizin is treated with excess methyl iodide in the presence of potassium

carbonate and then subjected to acid-catalyzed hydrolysis, a compound B is obtained. Deduce the structure of phlorizin from this information.



Compound A: R = H
Compound B: R = CH_3

25.34 Emil Fischer's determination of the structure of glucose was carried out as the nineteenth century ended and the twentieth began. The structure of no other sugar was known at that time, and none of the spectroscopic techniques that aid organic analysis were then available. All Fischer had was information from chemical transformations, polarimetry, and his own intellect. Fischer realized that (+)-glucose could be represented by 16 possible stereostructures. By arbitrarily assigning a particular configuration to the stereogenic center at C-5, the configurations of C-2, C-3, and C-4 could be determined relative to it. This reduces the number of structural possibilities to eight. Thus, he started with a structural representation shown as follows, in which C-5 of (+)-glucose has what is now known as the D configuration.



Eventually, Fischer's arbitrary assumption proved to be correct, and the structure he proposed for (+)-glucose is correct in an absolute as well as a relative sense. The following exercise uses information available to Fischer and leads you through a reasoning process similar to that employed in his determination of the structure of (+)-glucose. See if you can work out the configuration of (+)-glucose from the information provided, assuming the configuration of C-5 as shown here.

1. Chain extension of the aldopentose (−)-arabinose by way of the derived cyanohydrin gave a mixture of (+)-glucose and (+)-mannose.
2. Oxidation of (−)-arabinose with warm nitric acid gave an optically active aldaric acid.
3. Both (+)-glucose and (+)-mannose were oxidized to optically active aldaric acids with nitric acid.
4. There is another sugar, (+)-gulose, that gives the same aldaric acid on oxidation as does (+)-glucose.