25 Biomolecules: Carbohydrates

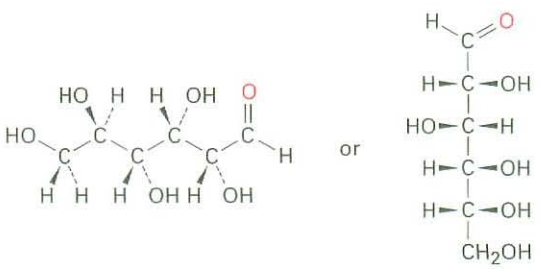
Organic KNOWLEDGE TOOLS

ThomsonNOW™ Throughout this chapter, sign in at **www.thomsonedu.com** for online self-study and interactive tutorials based on your level of understanding.

Online homework for this chapter may be assigned in Organic OWL.

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

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



Glucose (dextrose), a pentahydroxyhexanal

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

Sean Duggan

Thus, carbohydrates act as the chemical intermediaries by which solar energy is stored and used to support life.

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

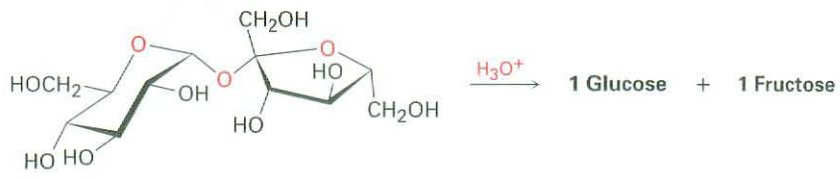
Because humans and most other mammals lack the enzymes needed for digestion of cellulose, they require starch as their dietary source of carbohydrates. Grazing animals such as cows, however, have microorganisms in their first stomach that are able to digest cellulose. The energy stored in cellulose is thus moved up the biological food chain when these ruminant animals eat grass and are then used for food.

WHY THIS CHAPTER?

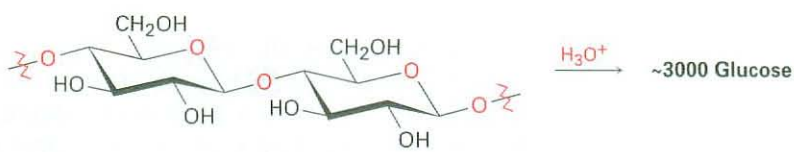
Carbohydrates are the first major class of biomolecules we'll discuss. We'll see in this chapter what the structures and primary biological functions of carbohydrates are, and then in Chapter 29, we'll return to the subject to see how carbohydrates are biosynthesized and degraded in organisms.

25.1 Classification of Carbohydrates

Carbohydrates are generally classed as either *simple* or *complex*. **Simple sugars**, or **monosaccharides**, are carbohydrates like glucose and fructose that can't be converted into smaller sugars by hydrolysis. **Complex carbohydrates** are made of two or more simple sugars linked together by acetal bonds (Section 19.10). Sucrose (table sugar), for example, is a *disaccharide* made up of one glucose linked to one fructose. Similarly, cellulose is a *polysaccharide* made up of several thousand glucose units linked together. Enzyme-catalyzed hydrolysis of a polysaccharide breaks it down into its constituent monosaccharides.

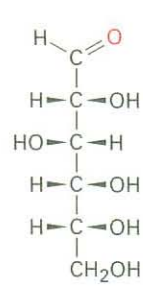


Sucrose
(a disaccharide)

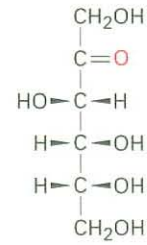


Cellulose
(a polysaccharide)

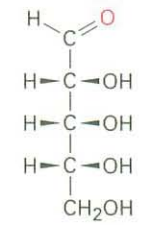
Monosaccharides are further classified as either **aldoses** or **ketoses**. The *-ose* suffix designates a carbohydrate, and the *aldo-* and *keto-* prefixes identify the kind of carbonyl group present in the molecule, whether aldehyde or ketone. The number of carbon atoms in the monosaccharide is indicated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



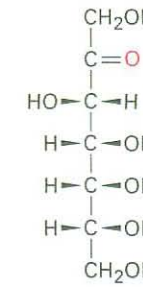
Glucose
(an aldohexose)



Fructose
(a ketohexose)



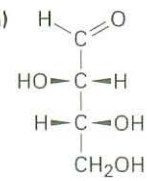
Ribose
(an aldopentose)



Sedoheptulose
(a ketoheptose)

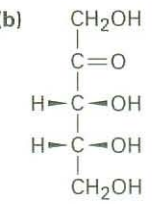
Problem 25.1 Classify each of the following monosaccharides:

(a)



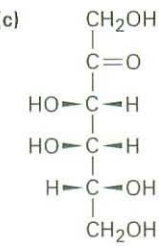
Threose

(b)



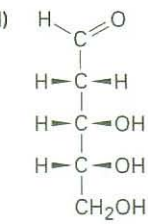
Ribulose

(c)



Tagatose

(d)



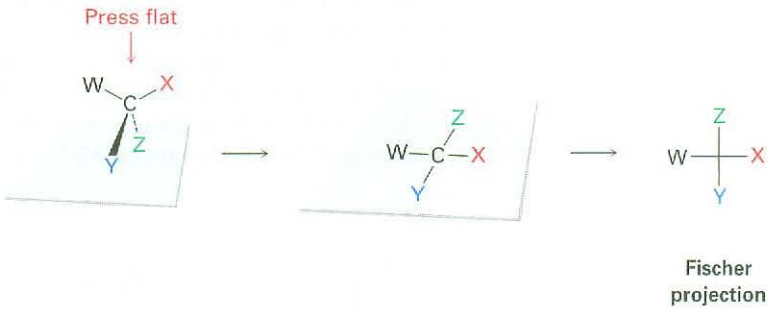
2-Deoxyribose

25.2 Depicting Carbohydrate Stereochemistry: Fischer Projections

ThomsonNOW Click *Organic Interactive* to **learn to draw and interpret Fischer projections of simple monosaccharides.**

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

A tetrahedral carbon atom is represented in a Fischer projection by two crossed lines. The horizontal lines represent bonds coming out of the page, and the vertical lines represent bonds going into the page.



For example, (*R*)-glyceraldehyde, the simplest monosaccharide, can be drawn as in Figure 25.1.

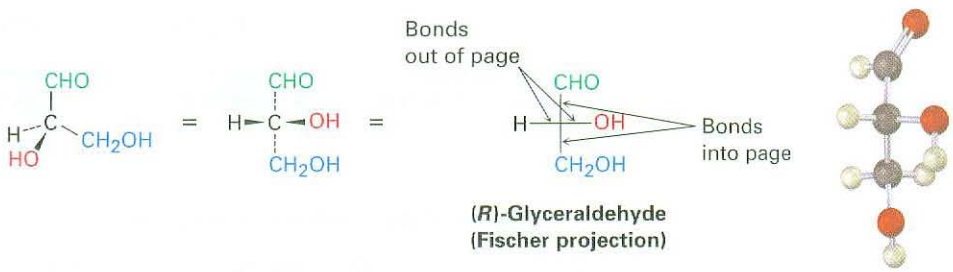
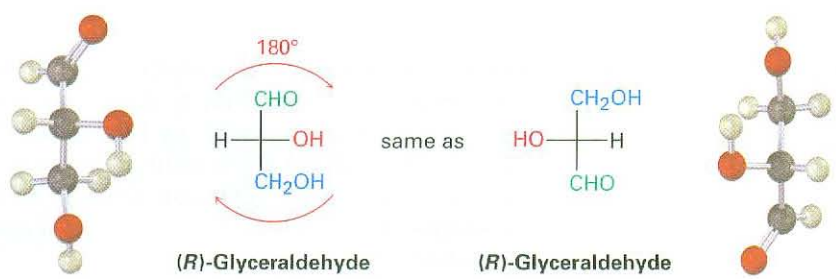


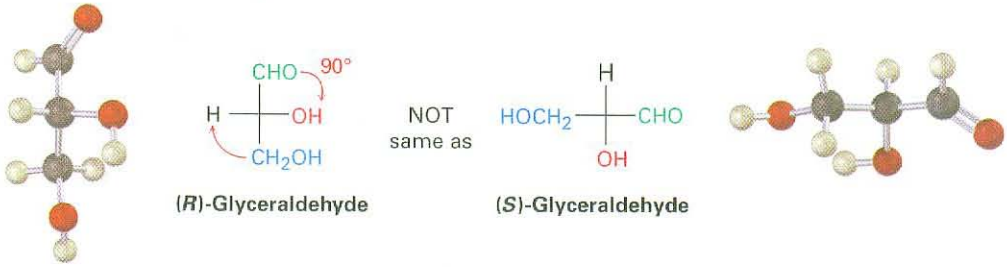
Figure 25.1 A Fischer projection of (*R*)-glyceraldehyde.

Because a given chiral molecule can be drawn in many different ways, it's often necessary to compare two projections to see if they represent the same or different enantiomers. To test for identity, Fischer projections can be moved around on the paper, but only two kinds of motions are allowed; moving a Fischer projection in any other way inverts its meaning.

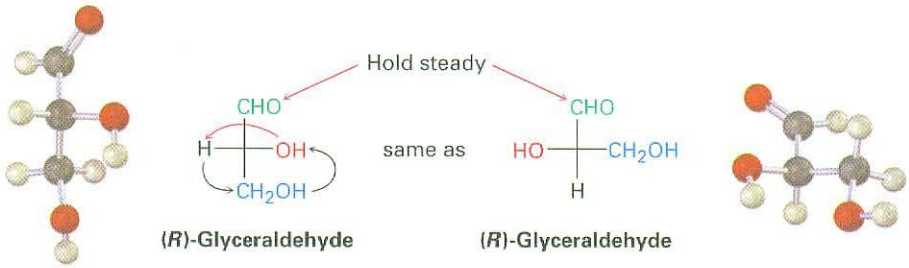
- A Fischer projection can be rotated on the page by 180°, but *not by 90° or 270°*. Only a 180° rotation maintains the Fischer convention by keeping the same substituent groups going into and coming out of the plane. In the following Fischer projection of (*R*)-glyceraldehyde, for example, the −H and −OH groups come out of the plane both before and after a 180° rotation.



A 90° rotation breaks the Fischer convention by exchanging the groups that go into the plane and those that come out. In the following Fischer projections of (*R*)-glyceraldehyde, the −H and −OH groups come out of the plane before rotation but go into the plane after a 90° rotation. As a result, the rotated projection represents (*S*)-glyceraldehyde.



- A Fischer projection can have one group held steady while the other three rotate in either a clockwise or a counterclockwise direction. The effect is simply to rotate around a single bond, which does not change the stereochemistry.



R,*S* stereochemical designations (Section 9.5) can be assigned to the chirality center in a Fischer projection by following three steps, as shown in Worked Example 25.1.

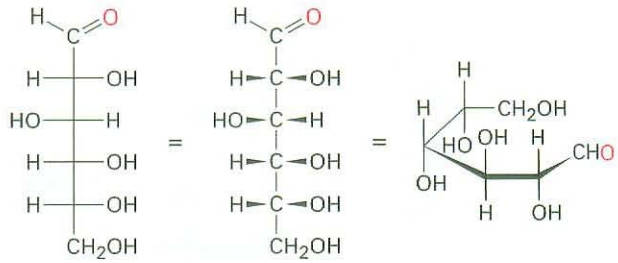
Step 1 Assign priorities to the four substituents in the usual way.

Step 2 Place the group of lowest priority, usually H, at the top of the Fischer projection by using one of the allowed motions. This means that the lowest-priority group is oriented back, away from the viewer, as required for assigning configuration.

Step 3 Determine the direction of rotation 1 → 2 → 3 of the remaining three groups, and assign *R* or *S* configuration.

Carbohydrates with more than one chirality center are shown in Fischer projections by stacking the centers on top of one another. By convention, the carbonyl carbon is always placed either at or near the top. Glucose, for

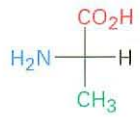
example, has four chirality centers stacked on top of one another in a Fischer projection. Such representations don't, however, give an accurate picture of the true conformation of a molecule, which actually is curled around on itself like a bracelet.



Glucose
(carbonyl group at top)

WORKED EXAMPLE 25.1 *Assigning R or S Configuration to a Fischer Projection*

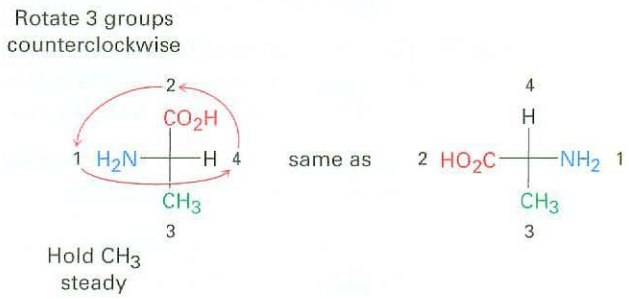
Assign *R* or *S* configuration to the following Fischer projection of alanine:



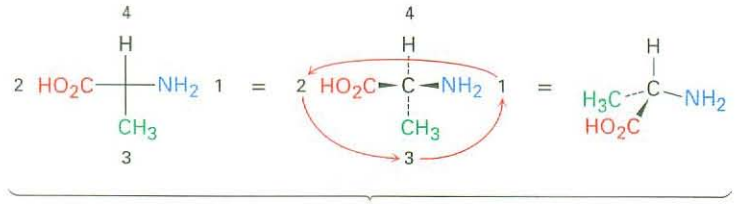
Alanine

Strategy Follow the steps in the text. (1) Assign priorities to the four substituents on the chiral carbon. (2) Manipulate the Fischer projection to place the group of lowest priority at the top by carrying out one of the allowed motions. (3) Determine the direction 1 → 2 → 3 of the remaining three groups.

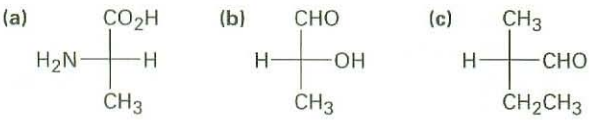
Solution The priorities of the groups are (1) $-NH_2$, (2) $-CO_2H$, (3) $-CH_3$, and (4) $-H$. To bring the group of lowest priority ($-H$) to the top, we might want to hold the $-CH_3$ group steady while rotating the other three groups counterclockwise.



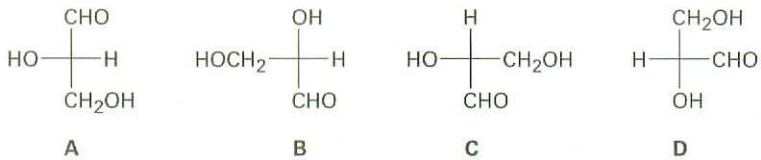
Going from first- to second- to third-highest priority requires a counterclockwise turn, corresponding to *S* stereochemistry.



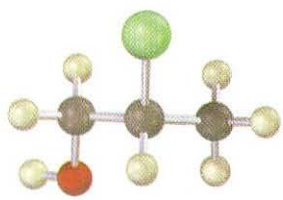
Problem 25.2 Convert the following Fischer projections into tetrahedral representations, and assign *R* or *S* stereochemistry to each:



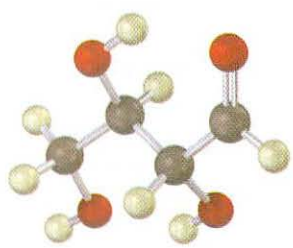
Problem 25.3 Which of the following Fischer projections of glyceraldehyde represent the same enantiomer?



Problem 25.4 Redraw the following molecule as a Fischer projection, and assign *R* or *S* configuration to the chirality center (yellow-green = Cl):



Problem 25.5 Redraw the following aldotetrose as a Fischer projection, and assign *R* or *S* configuration to each chirality center:



25.3 D,L Sugars

Glyceraldehyde, the simplest aldose, has only one chirality center and thus has two enantiomeric (mirror-image) forms. Only the dextrorotatory enantiomer occurs naturally, however. That is, a sample of naturally occurring glyceraldehyde placed in a polarimeter rotates plane-polarized light in a clockwise direction, denoted (+). Since (+)-glyceraldehyde has been found to have an *R* configuration at C2, it can be represented in a Fischer projection as shown in Figure 25.1. For historical reasons dating back long before the adoption of the *R*,*S* system, (*R*)-(+)-glyceraldehyde is also referred to as D-glyceraldehyde (D for dextrorotatory). The other enantiomer, (*S*)-(−)-glyceraldehyde, is known as L-glyceraldehyde (L for levorotatory).

Because of the way monosaccharides are biosynthesized in nature, glucose, fructose, and most (although not all) other naturally occurring monosaccharides have the same *R* stereochemical configuration as D-glyceraldehyde at the chirality center farthest from the carbonyl group. In Fischer projections, therefore, most naturally occurring sugars have the hydroxyl group at the bottom chirality center pointing to the right (Figure 25.2). All such compounds are referred to as **D sugars**.

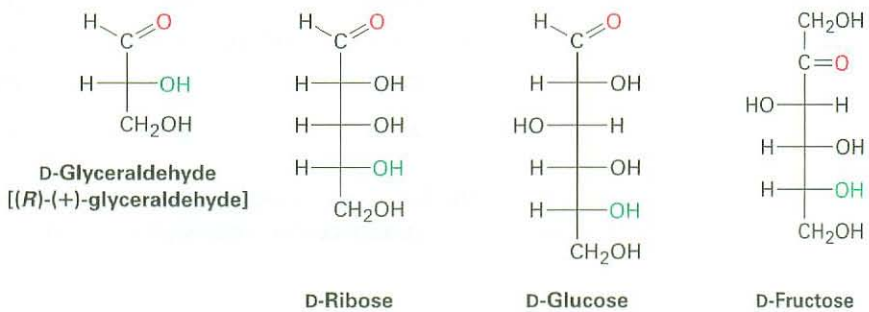
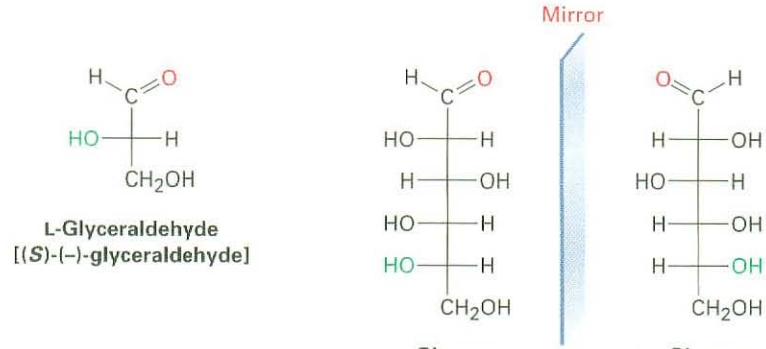
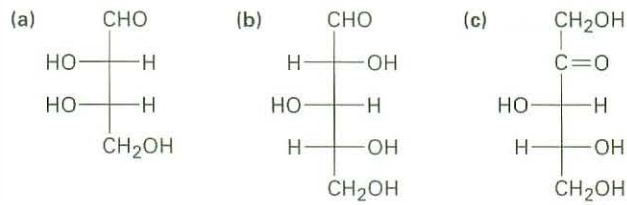


Figure 25.2 Some naturally occurring D sugars. The −OH group at the chirality center farthest from the carbonyl group has the same configuration as (*R*)-(+)-glyceraldehyde and points toward the right in Fischer projections.

In contrast with D sugars, **L sugars** have an *S* configuration at the lowest chirality center, with the bottom −OH group pointing to the *left* in Fischer projections. Thus, an L sugar is the mirror image (enantiomer) of the corresponding D sugar and has the opposite configuration from the D sugar at all chirality centers. Note that the D and L notations have no relation to the direction in which a given sugar rotates plane-polarized light; a D sugar can be either dextrorotatory or levorotatory. The prefix D indicates only that the −OH group at the lowest chirality center has *R* stereochemistry and points to the right when the molecule is drawn in a Fischer projection. Note also that the D,L system of carbohydrate nomenclature describes the configuration at only one chirality center and says nothing about the configuration of other chirality centers that may be present.



Problem 25.6 Assign *R* or *S* configuration to each chirality center in the following monosaccharides, and tell whether each is a D sugar or an L sugar:



Problem 25.7 (+)-Arabinose, an aldopentose that is widely distributed in plants, is systematically named (2*R*,3*S*,4*S*)-2,3,4,5-tetrahydroxypentanal. Draw a Fischer projection of (+)-arabinose, and identify it as a D sugar or an L sugar.

25.4 Configurations of the Aldoses

Louis F. Fieser

Louis F. Fieser (1899–1977) was born in Columbus, Ohio, and received his Ph.D. at Harvard University in 1924 with James B. Conant. He was professor of chemistry at Bryn Mawr College and then at Harvard University from 1930 to 1968. While at Bryn Mawr, he met his future wife, Mary, then a student. In collaboration, the two Fiesers wrote numerous chemistry texts and monographs. Among his scientific contributions, Fieser was known for his work in steroid chemistry and in carrying out the first synthesis of vitamin K. He was also the inventor of jellied gasoline, or napalm, which was developed at Harvard during World War II.

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

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

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

Fischer projections of the four-, five-, and six-carbon D aldoses are shown in Figure 25.3. Starting with D-glyceraldehyde, we can imagine constructing the two D aldotetroses by inserting a new chirality center just below the aldehyde carbon. Each of the two D aldotetroses then leads to two D aldopentoses (four total), and

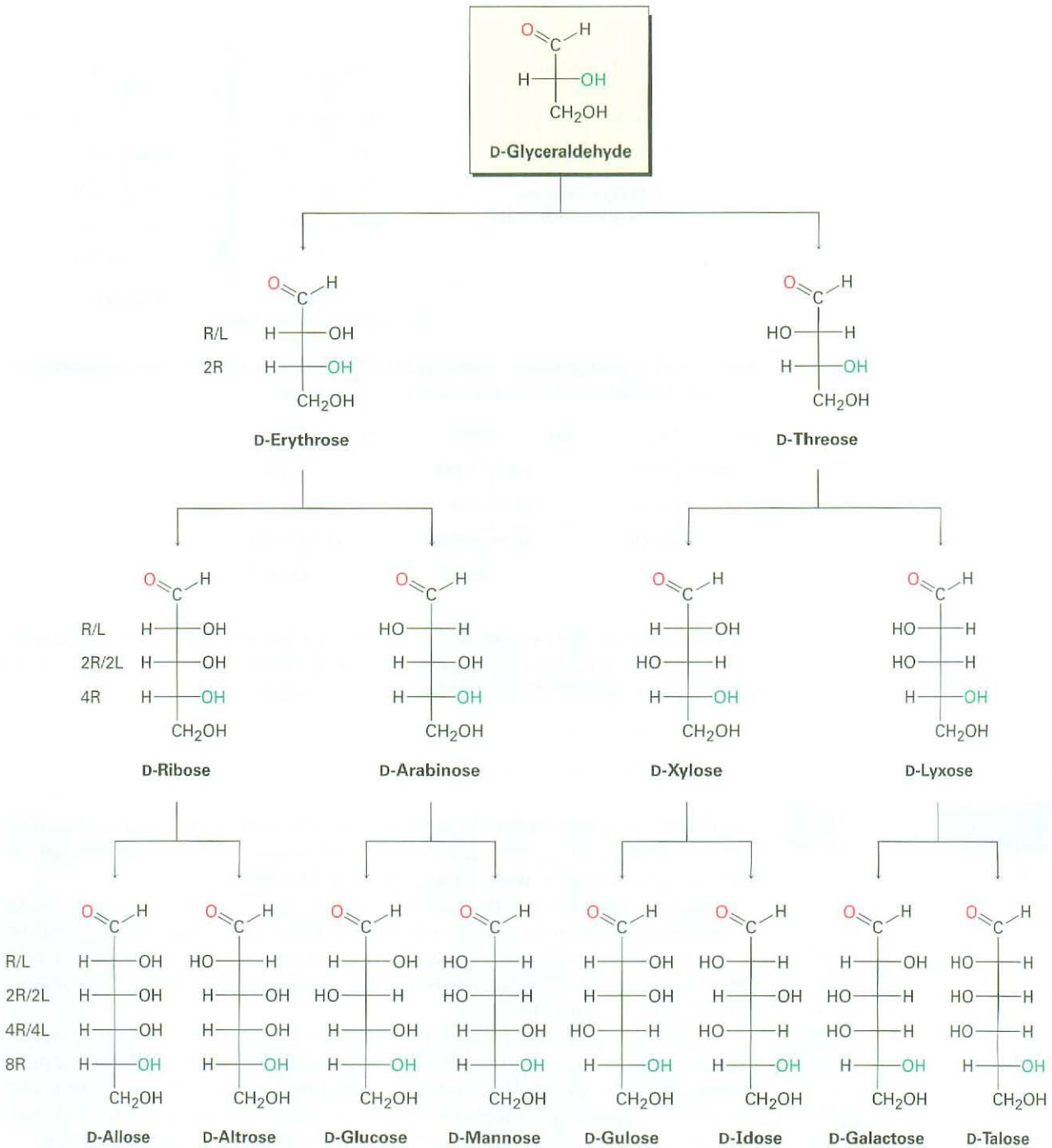


Figure 25.3 Configurations of D aldoses. The structures are arranged from left to right so that the —OH groups on C2 alternate right/left (R/L) in going across a series. Similarly, the —OH groups at C3 alternate two right/two left (2R/2L), the —OH groups at C4 alternate 4R/4L, and the —OH groups at C5 are to the right in all eight (8R). Each D aldose has a corresponding L enantiomer, which is not shown.

each of the four D aldopentoses leads to two D aldohexoses (eight total). In addition, each of the D aldoses in Figure 25.3 has an L enantiomer, which is not shown.

Louis Fieser of Harvard University suggested the following procedure for remembering the names and structures of the eight D aldohexoses:

Step 1 Set up eight Fischer projections with the $-CHO$ group on top and the $-CH_2OH$ group at the bottom.

Step 2 At C5, place all eight $-OH$ groups to the right (D series).

Step 3 At C4, alternate four $-OH$ groups to the right and four to the left.

Step 4 At C3, alternate two $-OH$ groups to the right, two to the left.

Step 5 At C2, alternate $-OH$ groups right, left, right, left.

Step 6 Name the eight isomers using the mnemonic "**All altruists gladly make gum in gallon tanks.**"

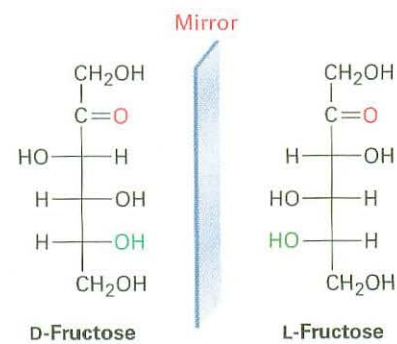
The structures of the four D aldopentoses can be generated in a similar way and named by the mnemonic suggested by a Cornell University undergraduate: "**ribs are extra lean.**"

WORKED EXAMPLE 25.2 ***Drawing a Fischer Projection***

Draw a Fischer projection of L-fructose.

Strategy Because L-fructose is the enantiomer of D-fructose, simply look at the structure of D-fructose and reverse the configuration at each chirality center.

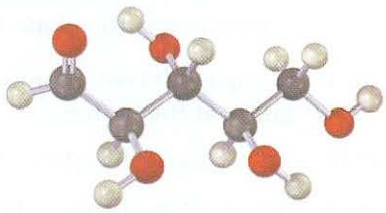
Solution



Problem 25.8 Only the D sugars are shown in Figure 25.3. Draw Fischer projections for the following L sugars:
(a) L-Xylose (b) L-Galactose (c) L-Allose

Problem 25.9 How many aldoheptoses are there? How many are D sugars, and how many are L sugars?

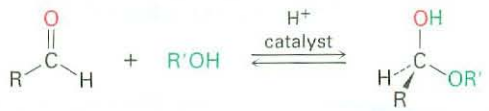
Problem 25.10 The following model is that of an aldopentose. Draw a Fischer projection of the sugar, name it, and identify it as a D sugar or an L sugar.



25.5 Cyclic Structures of Monosaccharides: Anomers

ThomsonNOW Click *Organic Interactive* to **learn to draw cyclic forms of simple monosaccharides.**

We said in Section 19.10 that aldehydes and ketones undergo a rapid and reversible nucleophilic addition reaction with alcohols to form hemiacetals.

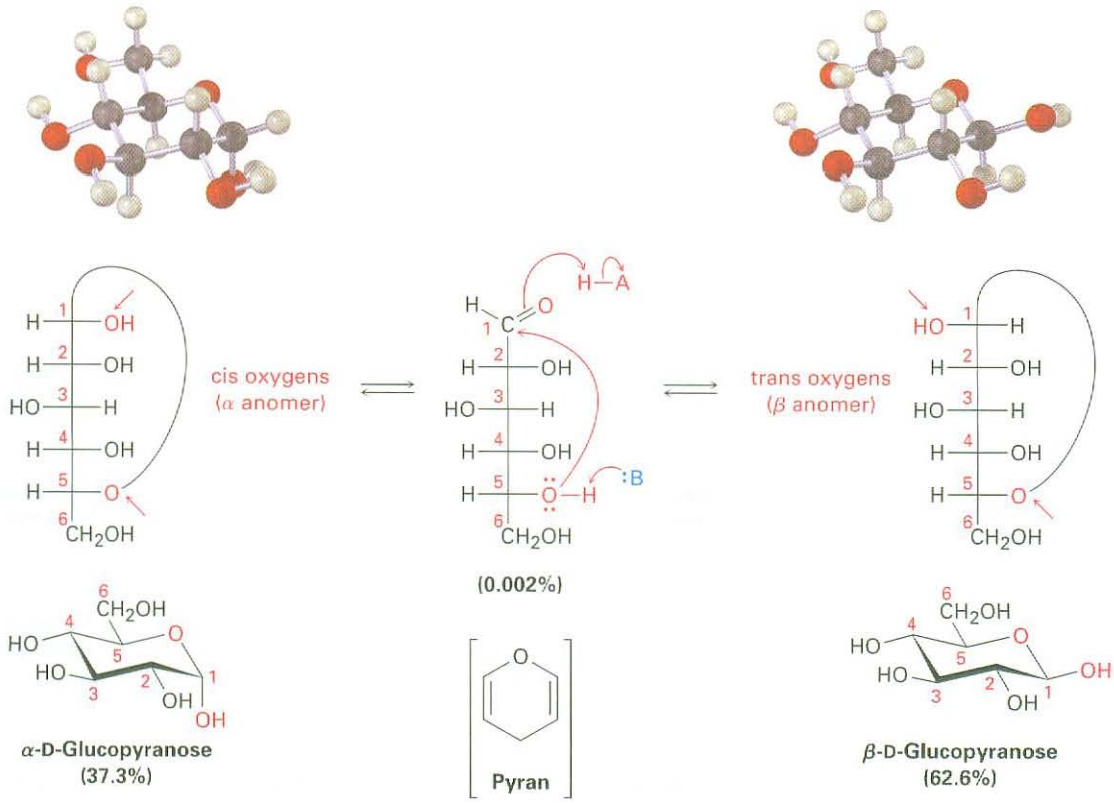


An aldehyde **A hemiacetal**

If the carbonyl and the hydroxyl group are in the same molecule, an intramolecular nucleophilic addition can take place, leading to the formation of a cyclic hemiacetal. Five- and six-membered cyclic hemiacetals are relatively strain-free and particularly stable, and many carbohydrates therefore exist in an equilibrium between open-chain and cyclic forms. Glucose, for instance, exists in aqueous solution primarily in the six-membered, **pyranose** form resulting from intramolecular nucleophilic addition of the −OH group at C5 to the C1 carbonyl group (Figure 25.4). The name *pyranose* is derived from *pyran*, the name of the unsaturated six-membered cyclic ether.

Like cyclohexane rings (Section 4.6), pyranose rings have a chairlike geometry with axial and equatorial substituents. By convention, the rings are usually drawn by placing the hemiacetal oxygen atom at the right rear, as shown in Figure 25.4. Note that an −OH group on the *right* in a Fischer projection is on the *bottom* face of the pyranose ring, and an −OH group on the *left* in a Fischer projection is on the *top* face of the ring. For D sugars, the terminal $-CH_2OH$ group is on the top of the ring, whereas for L sugars, the $-CH_2OH$ group is on the bottom.

When an open-chain monosaccharide cyclizes to a pyranose form, a new chirality center is generated at the former carbonyl carbon and two diastereomers, called **anomers**, are produced. The hemiacetal carbon atom is referred to as the **anomeric center**. For example, glucose cyclizes reversibly in aqueous solution to a 37:63 mixture of two anomers (Figure 25.4). The compound with its newly generated −OH group at C1 *cis* to the −OH at the lowest chirality center in a Fischer projection is called the **α anomer**; its full name is α-D-glucopyranose. The compound with its newly generated −OH group *trans* to the −OH at the lowest chirality center in a Fischer projection is called the **β anomer**; its full name is β-D-glucopyranose. Note that in β-D-glucopyranose, all the



Active Figure 25.4 Glucose in its cyclic pyranose forms. As explained in the text, two anomers are formed by cyclization of glucose. The molecule whose newly formed −OH group at C1 is cis to the oxygen atom on the lowest chirality center (C5) in a Fischer projection is the α anomer. The molecule whose newly formed −OH group is trans to the oxygen atom on the lowest chirality center in a Fischer projection is the β anomer. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

substituents on the ring are equatorial. Thus, β-D-glucopyranose is the least sterically crowded and most stable of the eight D aldohexoses.

Some monosaccharides also exist in a five-membered cyclic hemiacetal form called a **furanose** form. D-Fructose, for instance, exists in water solution as 70% β-pyranose, 2% α-pyranose, 0.7% open-chain, 23% β-furanose, and 5% α-furanose. The pyranose form results from addition of the −OH at C6 to the carbonyl group, while the furanose form results from addition of the −OH at C5 to the carbonyl group (Figure 25.5).

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

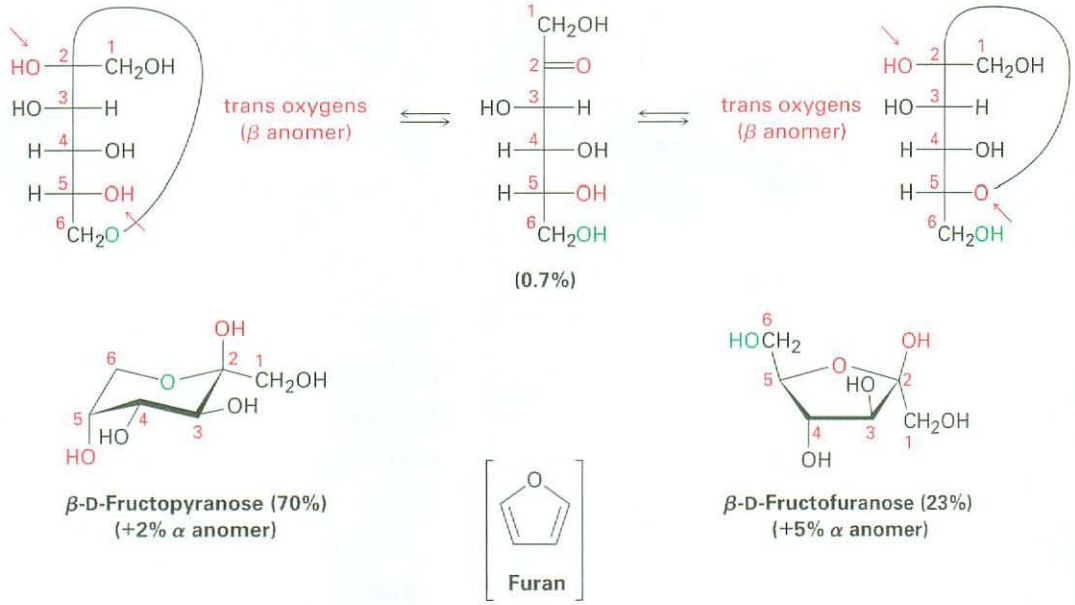


Figure 25.5 Pyranose and furanose forms of fructose in aqueous solution. The two pyranose anomers result from addition of the C6 –OH group to the C2 carbonyl; the two furanose anomers result from addition of the C5 –OH group to the C2 carbonyl.

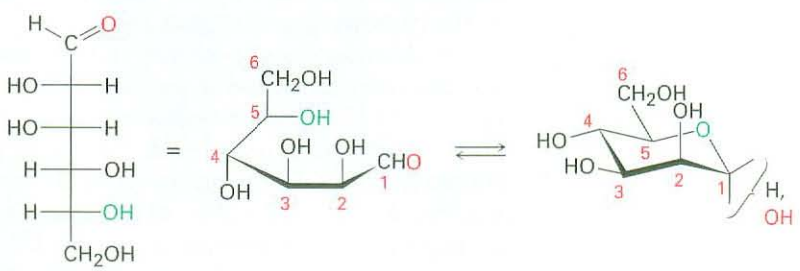
Mutarotation occurs by a reversible ring-opening of each anomer to the open-chain aldehyde, followed by reclosure. Although equilibration is slow at neutral pH, it is catalyzed by both acid and base.

WORKED EXAMPLE 25.3 ***Drawing the Chair Conformation of an Aldohexose***

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

Strategy First draw a Fischer projection of D-mannose. Then lay it on its side, and curl it around so that the –CHO group (C1) is on the right front and the $-CH_2OH$ group (C6) is toward the left rear. Now, connect the –OH at C5 to the C1 carbonyl group to form the pyranose ring. In drawing the chair form, raise the leftmost carbon (C4) up and drop the rightmost carbon (C1) down.

Solution

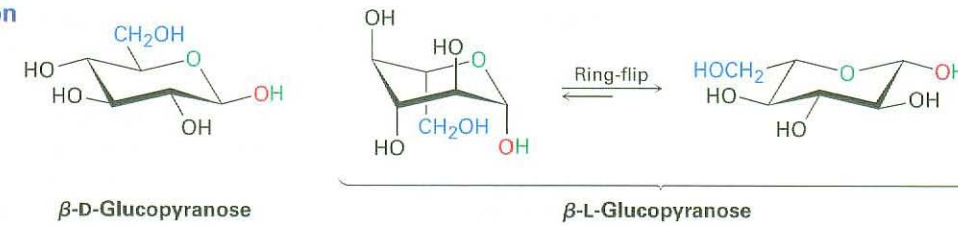


WORKED EXAMPLE 25.4 ***Drawing the Chair Conformation of a Pyranose***

Draw β-L-glucopyranose in its more stable chair conformation.

Strategy It's probably easiest to begin by drawing the chair conformation of β-D-glucopyranose. Then draw its mirror image by changing the stereochemistry at every position on the ring, and carry out a ring-flip to give the more stable chair conformation. Note that the $-CH_2OH$ group is on the bottom face of the ring in the L enantiomer.

Solution



β-D-Glucopyranose β-L-Glucopyranose

Problem 25.11 Ribose exists largely in a furanose form, produced by addition of the C4 −OH group to the C1 aldehyde. Draw D-ribose in its furanose form.

Problem 25.12 Figure 25.5 shows only the β-pyranose and β-furanose anomers of D-fructose. Draw the α-pyranose and α-furanose anomers.

Problem 25.13 Draw β-D-galactopyranose and β-D-mannopyranose in their more stable chair conformations. Label each ring substituent as either axial or equatorial. Which would you expect to be more stable, galactose or mannose?

Problem 25.14 Draw β-L-galactopyranose in its more stable chair conformation, and label the substituents as either axial or equatorial.

Problem 25.15 Identify the following monosaccharide, write its full name, and draw its open-chain form in Fischer projection.

25.6 Reactions of Monosaccharides

ThomsonNOW Click *Organic Interactive* to **predict products from reactions of simple monosaccharides.**

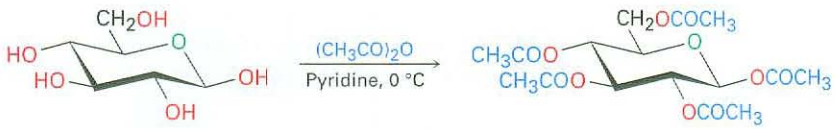
Because monosaccharides contain only two kinds of functional groups, hydroxyls and carbonyls, most of the chemistry of monosaccharides is the familiar chemistry of these two groups. Alcohols can be converted to esters and ethers

and can be oxidized; carbonyl compounds can react with nucleophiles and can be reduced.

Ester and Ether Formation

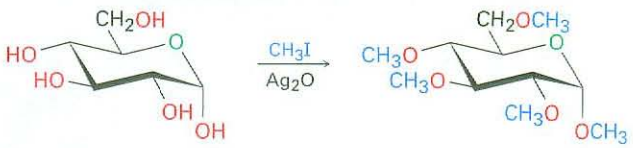
Monosaccharides behave as simple alcohols in much of their chemistry. For example, carbohydrate –OH groups can be converted into esters and ethers, which are often easier to work with than the free sugars. Because of their many hydroxyl groups, monosaccharides are usually soluble in water but insoluble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

Esterification is normally carried out by treating the carbohydrate with an acid chloride or acid anhydride in the presence of a base (Sections 21.4 and 21.5). All the –OH groups react, including the anomeric one. For example, β-D-glucopyranose is converted into its pentaacetate by treatment with acetic anhydride in pyridine solution.



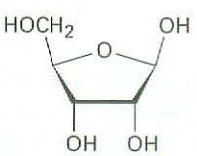
β-D-Glucopyranose — **Penta-*O*-acetyl-β-D-glucopyranose (91%)**

Carbohydrates are converted into ethers by treatment with an alkyl halide in the presence of base—the Williamson ether synthesis (Section 18.2). Standard Williamson conditions using a strong base tend to degrade sensitive sugar molecules, but silver oxide works well as a mild base and gives high yields of ethers. For example, α-D-glucopyranose is converted into its pentamethyl ether in 85% yield on reaction with iodomethane and Ag_2O.



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

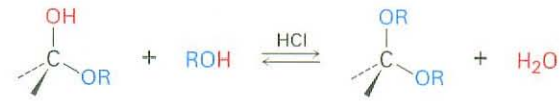
Problem 25.16 Draw the products you would obtain by reaction of β-D-ribofuranose with:
(a) CH_3I, Ag_2O (b) $(CH_3CO)_2O$, pyridine



β-D-Ribofuranose

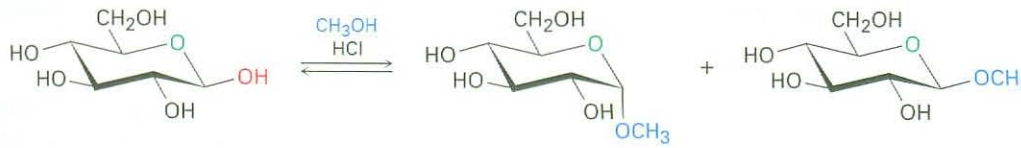
Glycoside Formation

We saw in Section 19.10 that treatment of a hemiacetal with an alcohol and an acid catalyst yields an acetal.



A hemiacetal **An acetal**

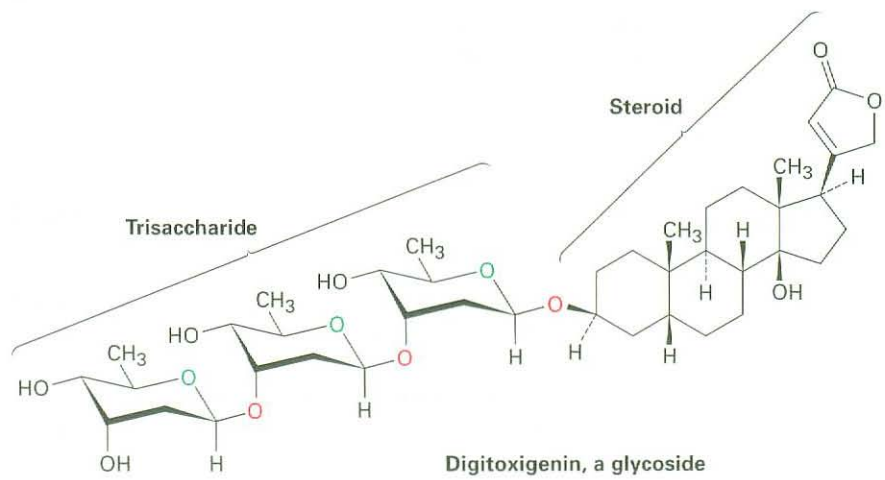
In the same way, treatment of a monosaccharide hemiacetal with an alcohol and an acid catalyst yields an acetal called a **glycoside**, in which the anomeric −OH has been replaced by an −OR group. For example, reaction of β-D-glucopyranose with methanol gives a mixture of α and β methyl D-glucopyranosides. (Note that a *glyc*oside is the functional group name for any sugar, whereas a *gluc*oside is a glycoside formed specifically from glucose.)



β-D-Glucopyranose (a cyclic hemiacetal) **Methyl α-D-glucopyranoside (66%)** **Methyl β-D-glucopyranoside (33%)**

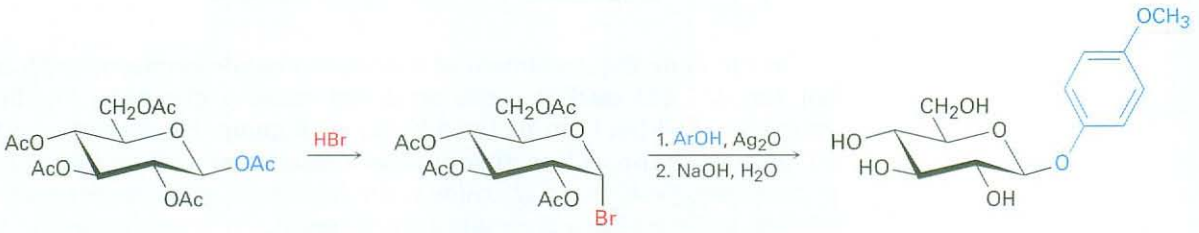
Glycosides are named by first citing the alkyl group and then replacing the *-ose* ending of the sugar with *-oside*. Like all acetals, glycosides are stable to neutral water. They aren't in equilibrium with an open-chain form, and they don't show mutarotation. They can, however, be converted back to the free monosaccharide by hydrolysis with aqueous acid (Section 19.10).

Glycosides are abundant in nature, and many biologically important molecules contain glycosidic linkages. For example, digitoxin, the active component of the digitalis preparations used for treatment of heart disease, is a glycoside consisting of a steroid alcohol linked to a trisaccharide. Note also that the three sugars are linked to one another by glycoside bonds.



Digitoxigenin, a glycoside

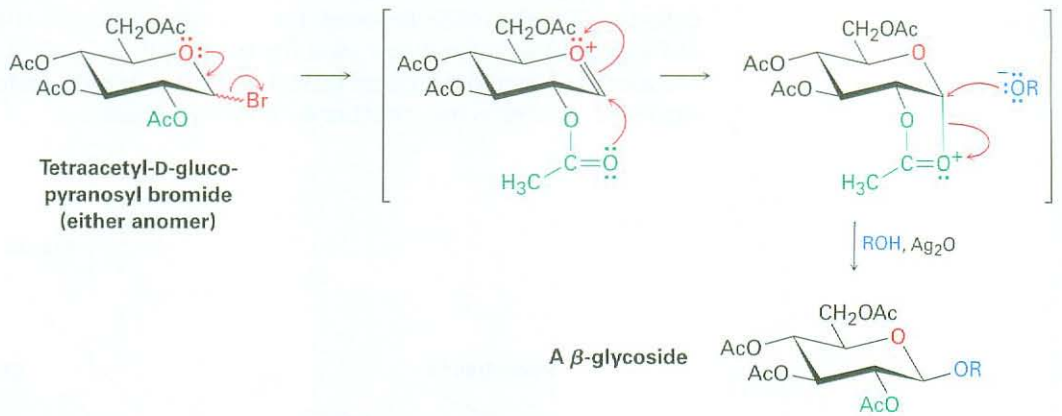
The laboratory synthesis of glycosides can be difficult because of the numerous −OH groups on the sugar molecule. One method that is particularly suitable for preparing glucose β-glycosides involves treatment of glucose pentaacetate with HBr, followed by addition of the appropriate alcohol in the presence of silver oxide. Called the *Koenigs–Knorr reaction,* the sequence involves formation of a pyranosyl bromide, followed by nucleophilic substitution. For example, methylarbutin, a glycoside found in pears, has been prepared by reaction of tetraacetyl-α-D-glucopyranosyl bromide with *p*-methoxyphenol.



Pentaacetyl-β-D-glucopyranose **Tetraacetyl-β-D-glucopyranosyl bromide** **Methylarbutin**

Although the Koenigs–Knorr reaction appears to involve a simple backside S_N2 displacement of bromide ion by alkoxide ion, the situation is actually more complex. Both α and β anomers of tetraacetyl-D-glucopyranosyl bromide give the same β-glycoside product, implying that they react by a common pathway.

The results can be understood by assuming that tetraacetyl-D-glucopyranosyl bromide (either α or β anomer) undergoes a spontaneous S_N1-like loss of Br^-, followed by internal reaction with the ester group at C2 to form an oxonium ion. Since the acetate at C2 is on the bottom of the glucose ring, the C−O bond also forms from the bottom. Backside S_N2 displacement of the oxonium ion then occurs with the usual inversion of configuration, yielding a β-glycoside and regenerating the acetate at C2 (Figure 25.6).



Tetraacetyl-D-glucopyranosyl bromide (either anomer) **A β-glycoside**

Figure 25.6 Mechanism of the Koenigs–Knorr reaction, showing the neighboring-group effect of a nearby acetate.

The participation shown by the nearby acetate group in the Koenigs–Knorr reaction is referred to as a *neighboring-group effect* and is a common occurrence

in organic chemistry. Neighboring-group effects are usually noticeable only because they affect the rate or stereochemistry of a reaction; the nearby group itself does not undergo any evident change during the reaction.

Biological Ester Formation: Phosphorylation

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

Glycoconjugate formation occurs by reaction of the lipid or protein with a glycosyl nucleoside diphosphate, itself formed by initial phosphorylation of a monosaccharide with ATP to give a glycosyl phosphate. The glycosyl phosphate then reacts with a second nucleoside triphosphate, usually uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. The purpose of the phosphorylation is to activate the anomeric –OH group of the sugar and make it a better leaving group in a nucleophilic substitution reaction by a protein or lipid (Figure 25.7).

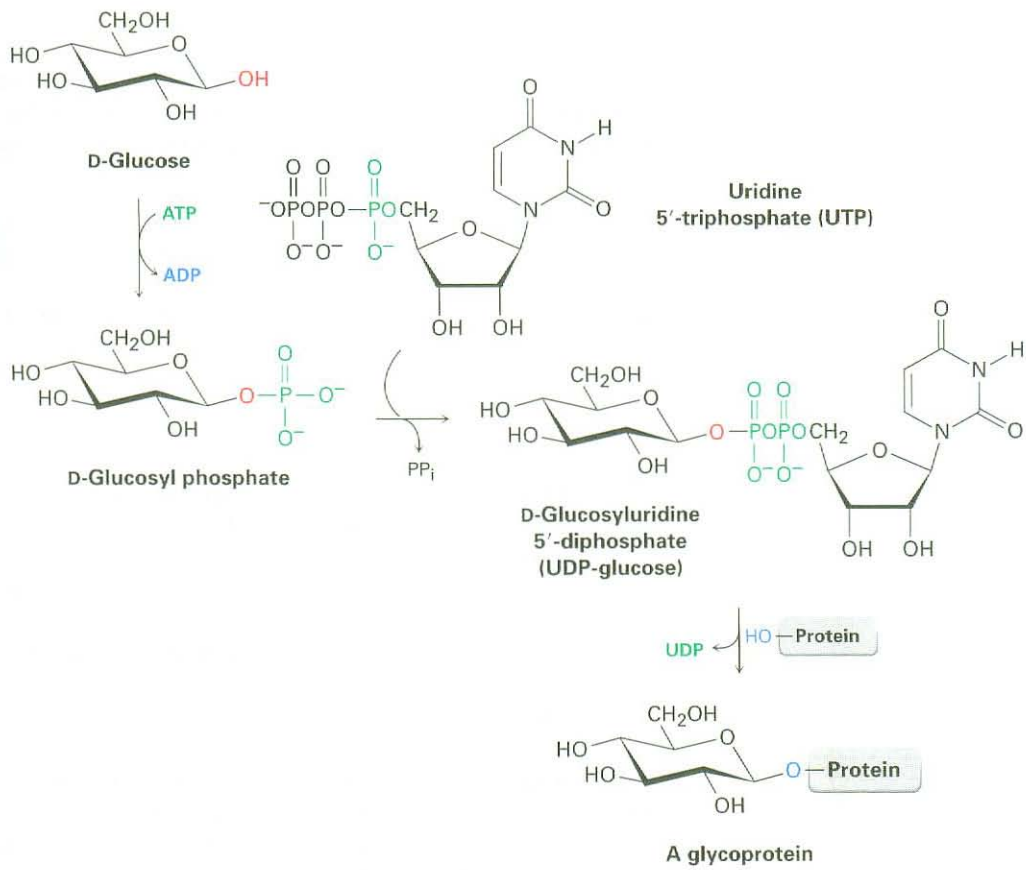
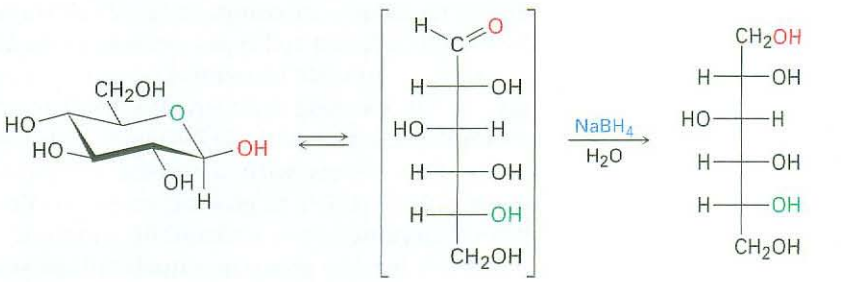


Figure 25.7 Glycoprotein formation occurs by initial phosphorylation of the starting carbohydrate to a glycosyl phosphate, followed by reaction with UTP to form a glycosyl uridine 5′-diphosphate. Nucleophilic substitution by an –OH (or $-NH_2$) group on a protein then gives the glycoprotein.

Reduction of Monosaccharides

Treatment of an aldose or ketose with $NaBH_4$ reduces it to a polyalcohol called an **alditol**. The reduction occurs by reaction of the open-chain form present in the aldehyde/ketone ⇄ hemiacetal equilibrium. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced, more is produced by opening of the pyranose form, that additional amount is reduced, and so on, until the entire sample has undergone reaction.



β-D-Glucopyranose | D-Glucose | D-Glucitol (D-sorbitol), an alditol

D-Glucitol, the alditol produced by reduction of D-glucose, is itself a naturally occurring substance present in many fruits and berries. It is used under its alternative name, D-sorbitol, as a sweetener and sugar substitute in foods.

Problem 25.17 Reduction of D-glucose leads to an optically active alditol (D-glucitol), whereas reduction of D-galactose leads to an optically inactive alditol. Explain.

Problem 25.18 Reduction of L-gulose with $NaBH_4$ leads to the same alditol (D-glucitol) as reduction of D-glucose. Explain.

Oxidation of Monosaccharides

Like other aldehydes, an aldose is easily oxidized to yield the corresponding carboxylic acid, called an **aldonic acid**. Many specialized reagents whose names you may have run across will oxidizes aldoses, including *Tollens' reagent* (Ag^+ in aqueous NH_3), *Fehling's reagent* (Cu^{2+} in aqueous sodium tartrate), and *Benedict's reagent* (Cu^{2+} in aqueous sodium citrate). All three reactions serve as simple chemical tests for what are called **reducing sugars**—*reducing* because the sugar reduces the metal oxidizing reagent.

If Tollens' reagent is used, metallic silver is produced as a shiny mirror on the walls of the reaction flask or test tube. In fact, the reaction is used commercially for manufacturing specialty mirrors. If Fehling's or Benedict's reagent is used, a reddish precipitate of Cu_2O signals a positive result. Some simple diabetes self-test kits sold in drugstores still use the Benedict test, although more modern methods have largely replaced the chemical test.

All aldoses are reducing sugars because they contain an aldehyde group, but some ketoses are reducing sugars as well. Fructose reduces Tollens' reagent, for example, even though it contains no aldehyde group. Reduction occurs because fructose is readily isomerized to an aldose in basic solution by a series

of keto–enol tautomeric shifts (Figure 25.8). Glycosides, however, are nonreducing because the acetal group is not hydrolyzed to an aldehyde under basic conditions.

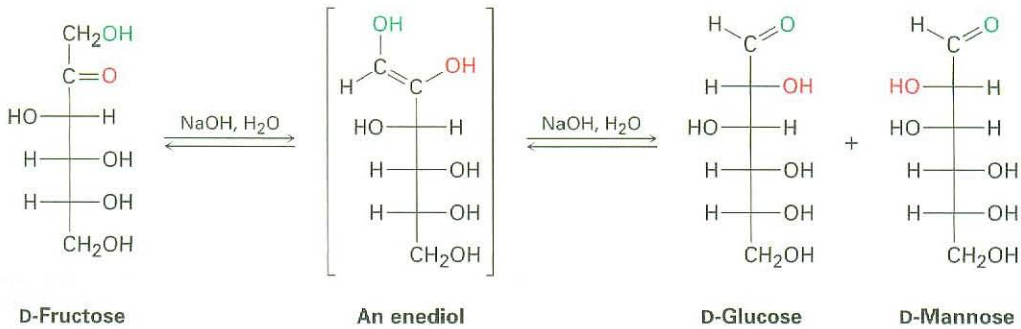
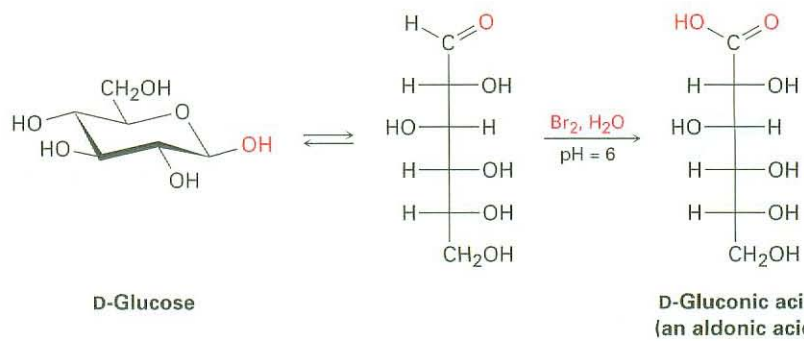
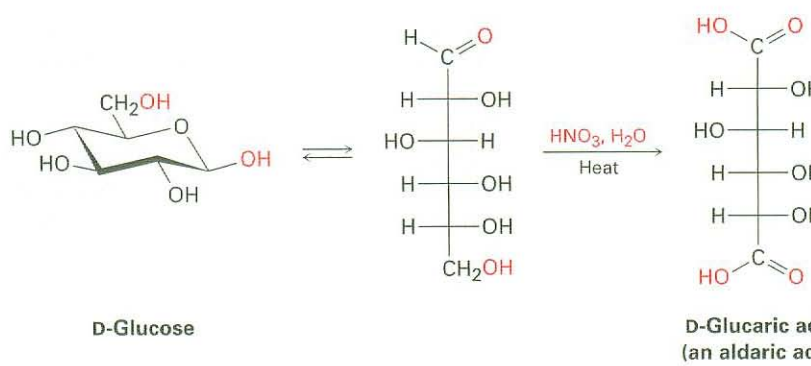


Figure 25.8 Fructose, a ketose, is a reducing sugar because it undergoes two base-catalyzed keto–enol tautomerizations that result in conversion to an aldose.

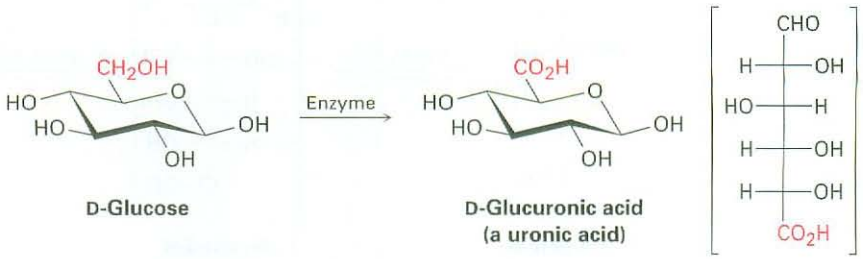
Although the Tollens reaction is a useful test for reducing sugars, it doesn't give good yields of aldonic acid products because the alkaline conditions cause decomposition of the carbohydrate. For preparative purposes, a buffered solution of aqueous Br_2 is a better oxidant. The reaction is specific for aldoses; ketoses are not oxidized by aqueous Br_2.



If a more powerful oxidizing agent such as warm dilute HNO_3 is used, an aldose is oxidized to a dicarboxylic acid, called an **aldaric acid**. Both the $-CHO$ group at C1 and the terminal $-CH_2OH$ group are oxidized in this reaction.



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



D-Glucose

D-Glucuronic acid (a uronic acid)

Problem 25.19 D-Glucose yields an optically active aldaric acid on treatment with HNO_3, but D-allose yields an optically inactive aldaric acid. Explain.

Problem 25.20 Which of the other six D aldohexoses yield optically active aldaric acids on oxidation, and which yield optically inactive (meso) aldaric acids? (See Problem 25.19.)

Chain Lengthening: The Kiliani–Fischer Synthesis

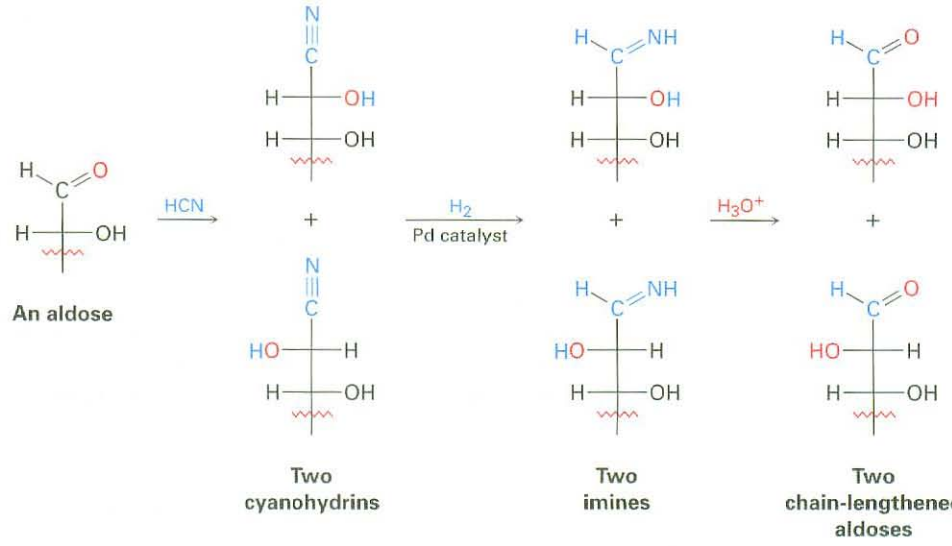
Heinrich Kiliani

Heinrich Kiliani (1855–1945) was born in Würzburg, Germany, and received a Ph.D. at the University of Munich with Emil Erlenmeyer. He was professor of chemistry at the University of Freiburg, where he worked on the chemistry of the heart stimulant drug digitoxin.

Much early activity in carbohydrate chemistry was devoted to unraveling the stereochemical relationships among monosaccharides. One of the most important methods used was the *Kiliani–Fischer synthesis,* which results in the lengthening of an aldose chain by one carbon atom. The C1 aldehyde group of the starting sugar becomes C2 of the chain-lengthened sugar, and a new C1 carbon is added. For example, an aldo*pent*ose is converted by the Kiliani–Fischer synthesis into two aldo*hex*oses.

Discovery of the chain-lengthening sequence was initiated by the observation of Heinrich Kiliani in 1886 that aldoses react with HCN to form cyanohydrins (Section 19.6). Emil Fischer immediately realized the importance of Kiliani's discovery and devised a method for converting the cyanohydrin nitrile group into an aldehyde.

Fischer's original method for conversion of the nitrile into an aldehyde involved hydrolysis to a carboxylic acid, ring closure to a cyclic ester (lactone), and subsequent reduction. A modern improvement is to reduce the nitrile over a palladium catalyst, yielding an imine intermediate that is hydrolyzed to an aldehyde. Note that the cyanohydrin is formed as a mixture of stereoisomers at the new chirality center, so two new aldoses, differing only in their stereochemistry at C2, result from Kiliani–Fischer synthesis. Chain extension of D-arabinose, for example, yields a mixture of D-glucose and D-mannose.



Problem 25.21 What product(s) would you expect from Kiliani–Fischer reaction of D-ribose?

Problem 25.22 What aldopentose would give a mixture of L-gulose and L-idose on Kiliani–Fischer chain extension?

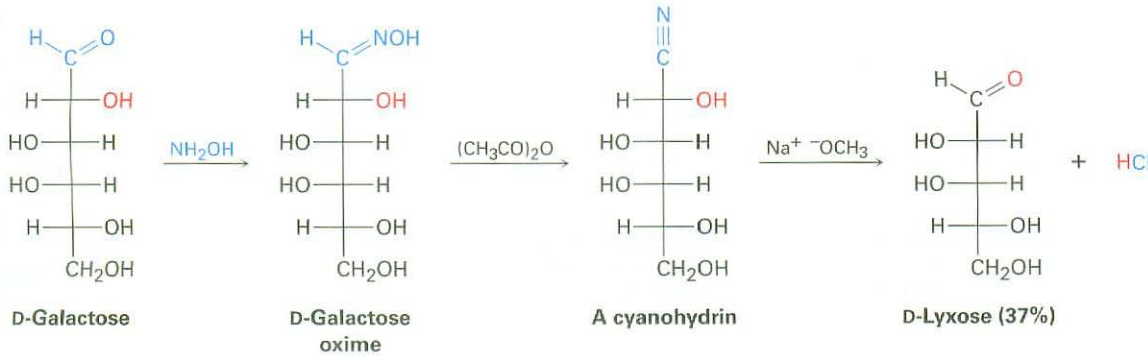
Chain Shortening: The Wohl Degradation

Alfred Wohl

Alfred Wohl (1863–1933) was born in Graudenz, West Prussia, now part of Poland. He received his Ph.D. at the University of Berlin in 1886 with August von Hofmann and became professor of chemistry at the Technical University of Danzig.

Just as the Kiliani–Fischer synthesis lengthens an aldose chain by one carbon, the *Wohl degradation* shortens an aldose chain by one carbon. The Wohl degradation is almost the exact opposite of the Kiliani–Fischer sequence. That is, the aldose aldehyde carbonyl group is first converted into a nitrile, and the resulting cyanohydrin loses HCN under basic conditions—the reverse of a nucleophilic addition reaction.

Conversion of the aldehyde into a nitrile is accomplished by treatment of an aldose with hydroxylamine to give an *oxime* (Section 19.8), followed by dehydration of the oxime with acetic anhydride. The Wohl degradation does not give particularly high yields of chain-shortened aldoses, but the reaction is general for all aldopentoses and aldohexoses. For example, D-galactose is converted by Wohl degradation into D-lyxose.



Problem 25.23 Two of the four D aldopentoses yield D-threose on Wohl degradation. What are their structures?

25.7 The Eight Essential Monosaccharides

Our bodies need to obtain eight monosaccharides for proper functioning. Although all can be biosynthesized from simpler precursors if necessary, it's more energetically efficient to obtain them from the diet. The eight are L-fucose (6-deoxy-L-galactose), D-galactose, D-glucose, D-mannose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine, D-xylose, and *N*-acetyl-D-neuraminic acid (Figure 25.9). All are used for the synthesis of the glycoconjugate components of cell walls.

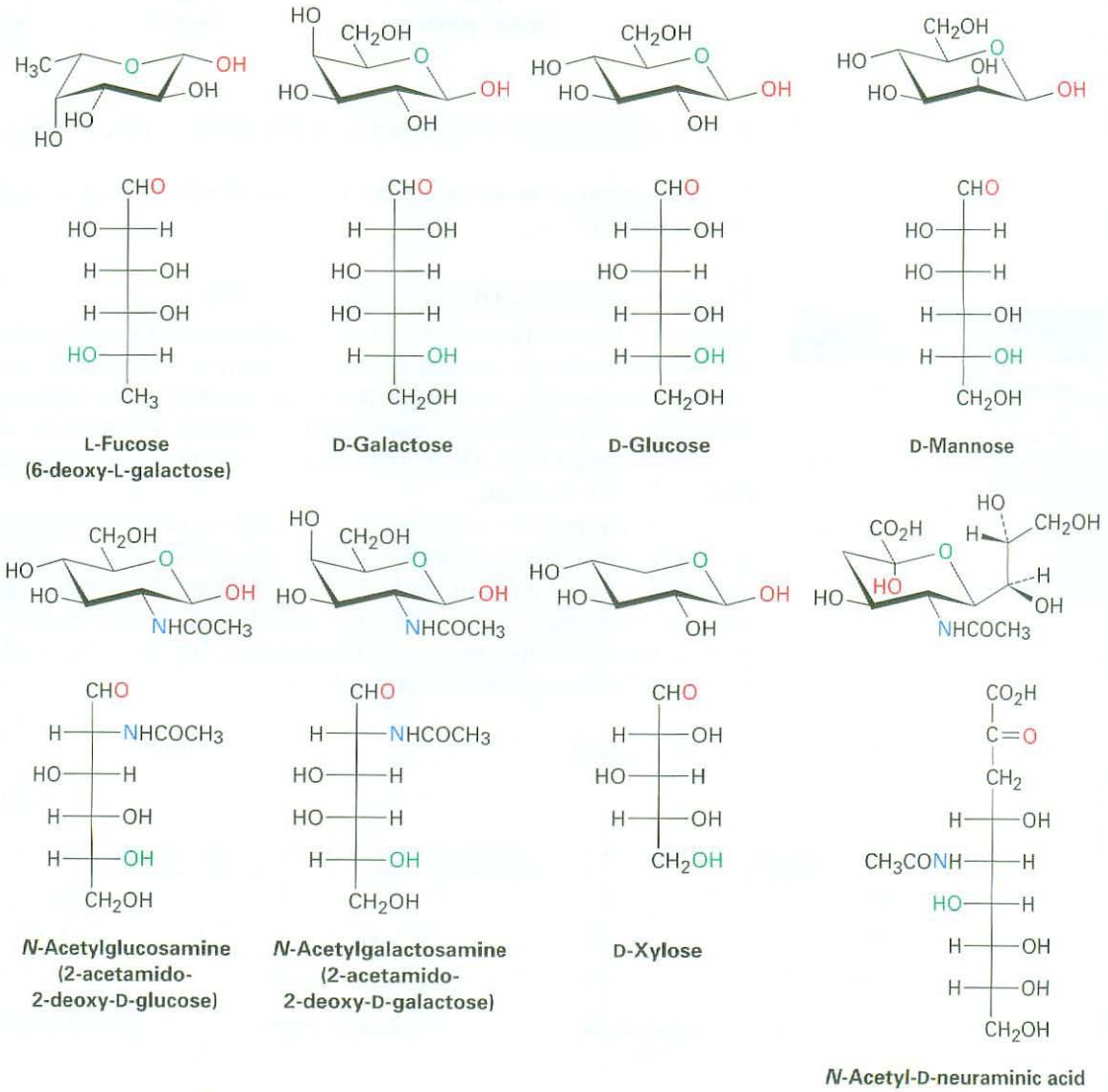


Figure 25.9 Structures of the eight monosaccharides essential to humans.

Of the eight essential monosaccharides, galactose, glucose, and mannose are simple aldohexoses, while xylose is an aldopentose. Fucose is a **deoxy sugar**, meaning that it has an oxygen atom "missing." That is, an −OH group (the one at C6) is replaced by an −H. *N*-Acetylglucosamine and *N*-acetylgalactosamine are amide derivatives of **amino sugars** in which an −OH (the one at C2) is replaced by an $-NH_2$ group. *N*-Acetylneuraminic acid is the parent compound of the *sialic acids*, a group of more than 30 compounds with different modifications, including various oxidations, acetylations, sulfations, and methylations. Note that neuraminic acid has nine carbons and is an aldol reaction product of *N*-acetylmannosamine with pyruvate ($CH_3COCO_2^-$).

All the essential monosaccharides arise from glucose, by the conversions summarized in Figure 25.10. We'll not look specifically at these conversions, but might note that end-of-chapter Problems 25.55 through 25.57 lead you through several of the biosynthetic pathways.

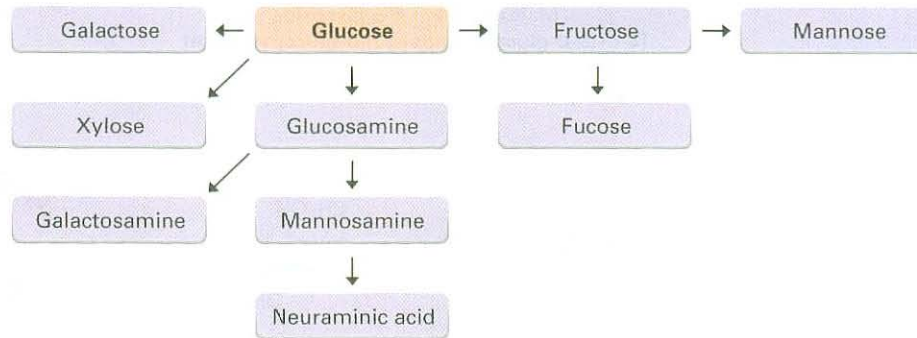
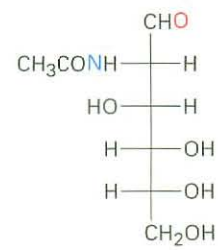


Figure 25.10 An overview of biosynthetic pathways for the eight essential monosaccharides.

Problem 25.24 Show how neuraminic acid can arise by an aldol reaction of *N*-acetylmannosamine with pyruvate ($CH_3COCO_2^-$).



***N*-Acetylmannosamine**

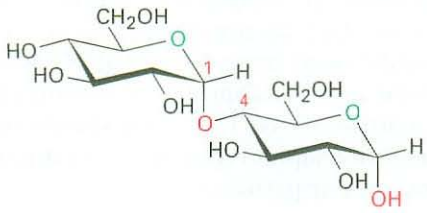
25.8 Disaccharides

We saw in Section 25.6 that reaction of a monosaccharide with an alcohol yields a glycoside in which the anomeric −OH group is replaced by an −OR substituent. If the alcohol is itself a sugar, the glycosidic product is a **disaccharide**.

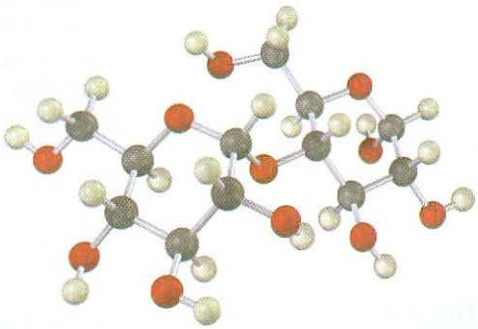
Cellobiose and Maltose

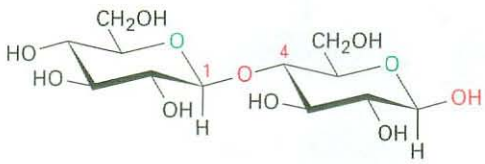
Disaccharides contain a glycosidic acetal bond between the anomeric carbon of one sugar and an −OH group at any position on the other sugar. A glycosidic bond between C1 of the first sugar and the −OH at C4 of the second sugar is particularly common. Such a bond is called a *1→4 link*.

The glycosidic bond to an anomeric carbon can be either α or β. Maltose, the disaccharide obtained by enzyme-catalyzed hydrolysis of starch, consists of two α-D-glucopyranose units joined by a 1→4-α-glycoside bond. Cellobiose, the disaccharide obtained by partial hydrolysis of cellulose, consists of two β-D-glucopyranose units joined by a 1→4-β-glycoside bond.

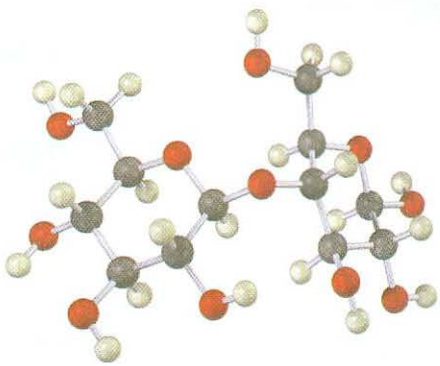


Maltose, a 1→4-α-glycoside
[4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranose]

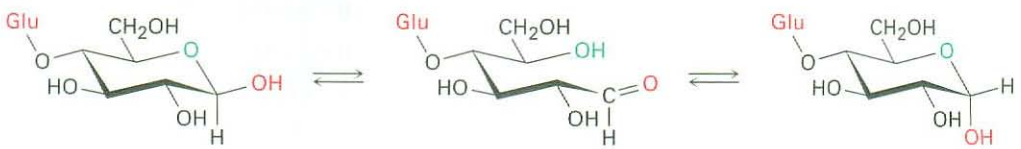




Cellobiose, a 1→4-β-glycoside
[4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose]



Maltose and cellobiose are both reducing sugars because the anomeric carbons on the right-hand glucopyranose units have hemiacetal groups and are in equilibrium with aldehyde forms. For a similar reason, both maltose and cellobiose exhibit mutarotation of α and β anomers of the glucopyranose unit on the right.



Maltose or cellobiose (β anomers) ⇌ **Maltose or cellobiose (aldehydes)** ⇌ **Maltose or cellobiose (α anomers)**

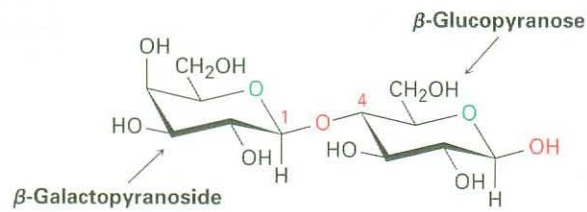
Despite the similarities of their structures, cellobiose and maltose have dramatically different biological properties. Cellobiose can't be digested by humans and can't be fermented by yeast. Maltose, however, is digested without difficulty and is fermented readily.

Problem 25.25 Show the product you would obtain from the reaction of cellobiose with the following reagents:

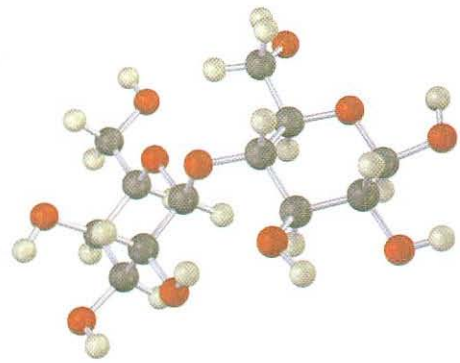
(a) $NaBH_4$ (b) Br_2, H_2O (c) CH_3COCl, pyridine

Lactose

Lactose is a disaccharide that occurs naturally in both human and cow's milk. It is widely used in baking and in commercial milk formulas for infants. Like cellobiose and maltose, lactose is a reducing sugar. It exhibits mutarotation and is a 1→4-β-linked glycoside. Unlike cellobiose and maltose, however, lactose contains two different monosaccharides—D-glucose and D-galactose—joined by a β-glycosidic bond between C1 of galactose and C4 of glucose.



Lactose, a 1→4-β-glycoside
[4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranose]

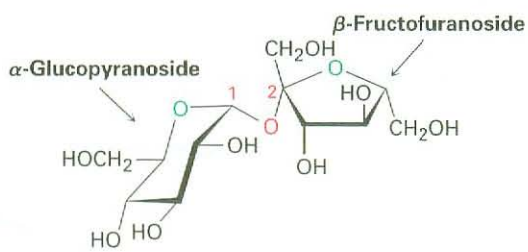


Sucrose

Sucrose, or ordinary table sugar, is among the most abundant pure organic chemicals in the world and is the one most widely known to nonchemists. Whether from sugar cane (20% by weight) or sugar beets (15% by weight) and whether raw or refined, all table sugar is sucrose.

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

Unlike most other disaccharides, sucrose is not a reducing sugar and does not undergo mutarotation. These observations imply that sucrose is not a hemiacetal and suggest that glucose and fructose must both be glycosides. This can happen only if the two sugars are joined by a glycoside link between the anomeric carbons of both sugars—C1 of glucose and C2 of fructose.



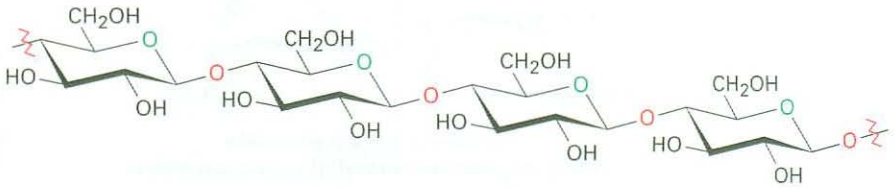
Sucrose, a 1→2-glycoside
[2-*O*-(α-D-glucopyranosyl)-β-D-fructofuranoside]

25.9 Polysaccharides and Their Synthesis

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

Cellulose

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

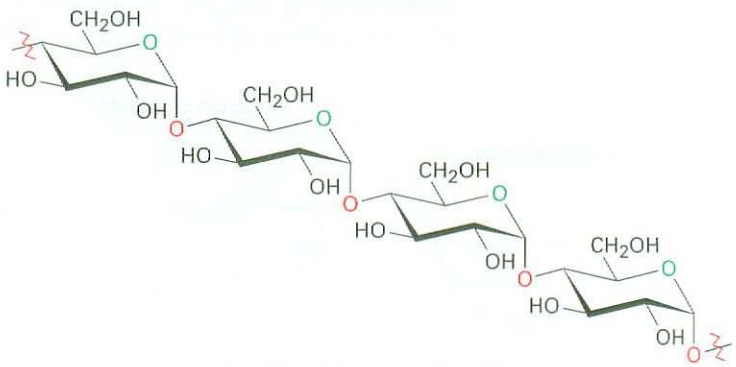


Cellulose, a 1→4-*O*-(β-D-glucopyranoside) polymer

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

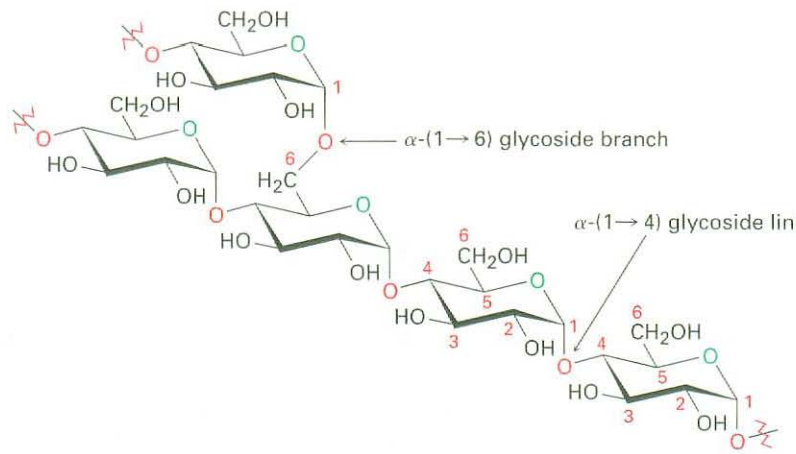
Starch and Glycogen

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



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

Amylopectin accounts for the remaining 80% of starch and is more complex in structure than amylose. Unlike cellulose and amylose, which are linear polymers, amylopectin contains 1→6-α-glycoside branches approximately every 25 glucose units.



Amylopectin: α-(1→4) links with α-(1→6) branches

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

Glycogen is a polysaccharide that serves the same energy storage function in animals that starch serves in plants. Dietary carbohydrates not needed for immediate energy are converted by the body to glycogen for long-term storage. Like the amylopectin found in starch, glycogen contains a complex branching structure with both 1→4 and 1→6 links (Figure 25.11). Glycogen molecules are larger than those of amylopectin—up to 100,000 glucose units—and contain even more branches.

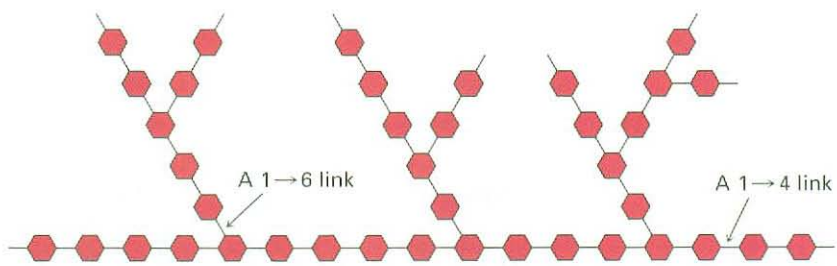


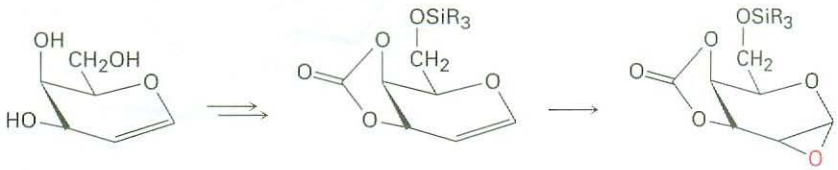
Figure 25.11 A representation of the structure of glycogen. The hexagons represent glucose units linked by 1→4 and 1→6 glycoside bonds.

Polysaccharide Synthesis

With numerous −OH groups of similar reactivity, polysaccharides are so structurally complex that their laboratory synthesis has been a particularly difficult problem. Several methods have recently been devised, however, that have

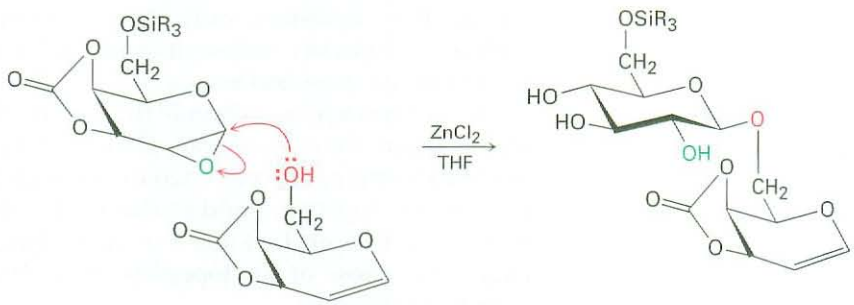
greatly simplified the problem. Among these new approaches is the *glycal assembly method,* developed by Samuel Danishefsky at Columbia University.

Easily prepared from the appropriate monosaccharide, a *glycal* is an unsaturated sugar with a C1–C2 double bond. To ready it for use in polysaccharide synthesis, the primary —OH group of the glycal is first protected at its primary —OH group by formation of a silyl ether (Section 17.8) and at its two adjacent secondary —OH groups by formation of a cyclic carbonate ester. Then, the protected glycal is epoxidized.



A glycal **A protected glycal** **An epoxide**

Treatment of the protected glycal epoxide in the presence of $ZnCl_2$ with a *second* glycal having a free —OH group causes acid-catalyzed opening of the epoxide ring by backside attack (Section 18.6) and yields a disaccharide. The disaccharide is itself a glycal, so it can be epoxidized and coupled again to yield a trisaccharide, and so on. Using the appropriate sugars at each step, a great variety of polysaccharides can be prepared. After the appropriate sugars are linked, the silyl ethers and cyclic carbonate protecting groups are removed by hydrolysis.

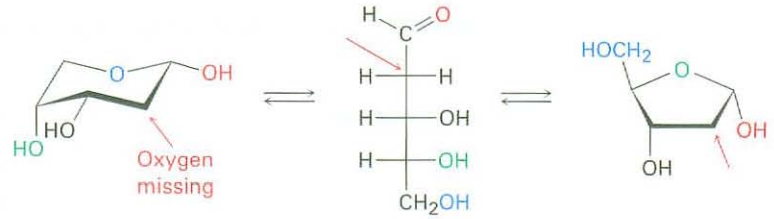


A disaccharide glycal

25.10 Some Other Important Carbohydrates

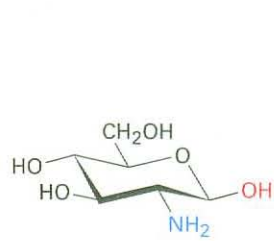
In addition to the common carbohydrates mentioned in previous sections, there are a variety of important carbohydrate-derived materials. Their structural resemblance to sugars is clear, but they aren't simple aldoses or ketoses.

Deoxy sugars, as we saw in Section 25.7, have an oxygen atom "missing." That is, an —OH group is replaced by an —H. The most common deoxy sugar is 2-deoxyribose, a monosaccharide found in DNA (deoxyribonucleic acid). Note that 2-deoxyribose exists in water solution as a complex equilibrium mixture of both furanose and pyranose forms.

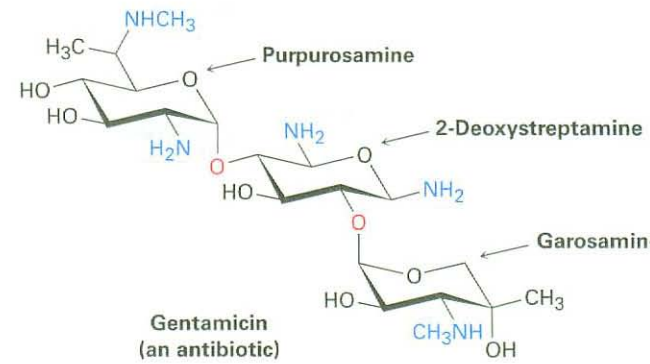


α-D-2-Deoxyribopyranose (40%) (+ 35% β anomer) (0.7%) α-D-2-Deoxyribofuranose (13%) (+ 12% β anomer)

Amino sugars, such as D-glucosamine, have an −OH group replaced by an $-NH_2$. The *N*-acetyl amide derived from D-glucosamine is the monosaccharide unit from which *chitin,* the hard crust that protects insects and shellfish, is made. Still other amino sugars are found in antibiotics such as streptomycin and gentamicin.



β-D-Glucosamine



Gentamicin (an antibiotic)

25.11 Cell-Surface Carbohydrates and Carbohydrate Vaccines

It was once thought that carbohydrates were useful in nature only as structural materials and energy sources. Although carbohydrates do indeed serve these purposes, they have many other important biochemical functions as well. As noted in Section 25.6, for instance, glycoconjugates are centrally involved in cell–cell recognition, the critical process by which one type of cell distinguishes another. Small polysaccharide chains, covalently bound by glycosidic links to −OH or $-NH_2$ groups on proteins, act as biochemical markers on cell surfaces, as illustrated by the human blood-group antigens.

It has been known for more than a century that human blood can be classified into four blood-group types (A, B, AB, and O) and that blood from a donor of one type can't be transfused into a recipient with another type unless the two types are compatible (Table 25.1). Should an incompatible mix be made, the red blood cells clump together, or *agglutinate.*

The agglutination of incompatible red blood cells, which indicates that the body's immune system has recognized the presence of foreign cells in the body and has formed antibodies against them, results from the presence of polysaccharide markers on the surface of the cells. Types A, B, and O red blood cells

Table 25.1 Human Blood-Group Compatibilities

	Acceptor blood type			
Donor blood type	**A**	**B**	**AB**	**O**
A	O	X	O	X
B	X	O	O	X
AB	X	X	O	X
O	O	O	O	O

each have their own unique markers, or *antigenic determinants;* type AB cells have both type A and type B markers. The structures of all three blood-group determinants are shown in Figure 25.12. Note that the monosaccharide constituents of each marker are among the eight essential sugars shown previously in Figure 25.9.

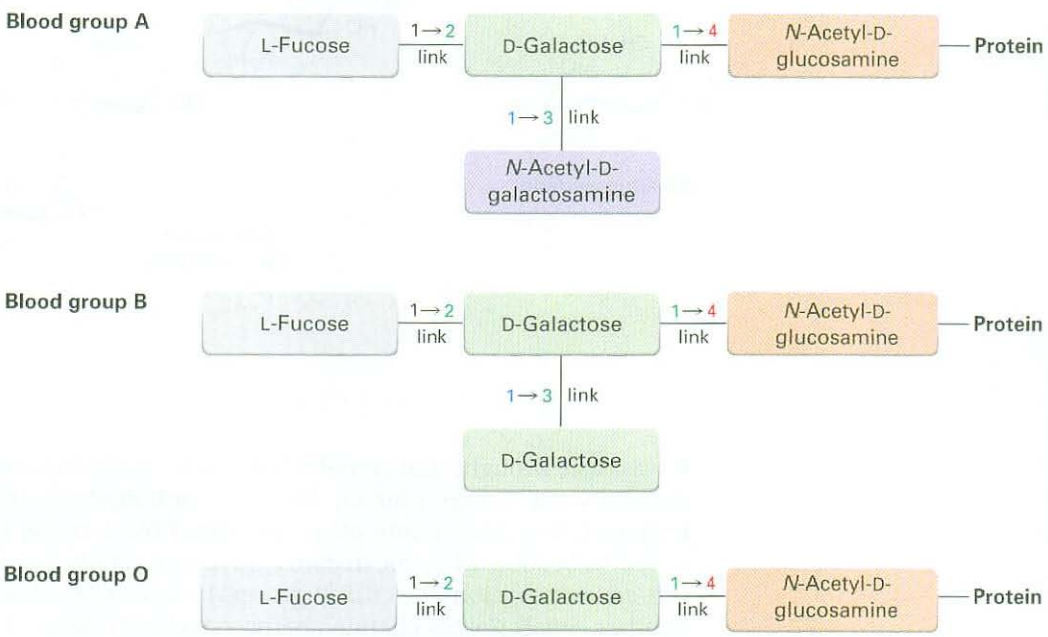
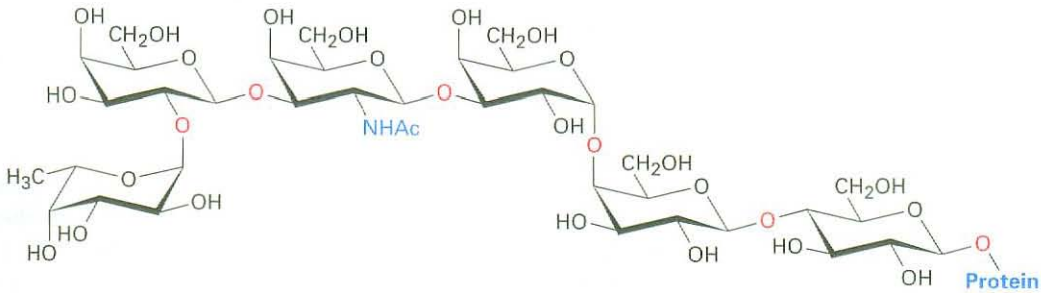


Figure 25.12 Structures of the A, B, and O blood-group antigenic determinants.

Elucidation of the role of carbohydrates in cell recognition is a vigorous area of current research that offers hope of breakthroughs in the understanding of a wide range of diseases from bacterial infections to cancer. Particularly exciting is the possibility of developing useful anticancer vaccines to help mobilize the body's immune system against tumor cells. Recent advances along these lines have included a laboratory synthesis of the so-called globo H hexasaccharide, found on the surface of human breast, prostate, colon, and pancreatic cancer cells. Preliminary studies have shown that patients treated with the synthetic globo H hexasaccharide linked to a carrier protein develop

antibodies that recognize and kill tumor cells. Clinical trials against breast cancer are in progress.



Globo H hexasaccharide

Focus On . . .

Sweetness

© Lawrence Worcester/Getty Images

The real thing comes from cane fields like this one.

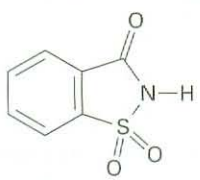
Say the word *sugar* and most people immediately think of sweet-tasting candies, desserts, and such. In fact, most simple carbohydrates *do* taste sweet, but the degree of sweetness varies greatly from one sugar to another. With sucrose (table sugar) as a reference point, fructose is nearly twice as sweet, but lactose is only about one-sixth as sweet. Comparisons are difficult, though, because perceived sweetness varies depending on the concentration of the solution being tasted. Nevertheless, the ordering in Table 25.2 is generally accepted.

Table 25.2 Sweetness of Some Sugars and Sugar Substitutes

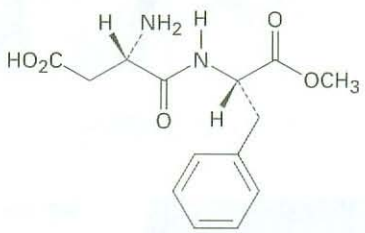
Name	Type	Sweetness
Lactose	Disaccharide	0.16
Glucose	Monosaccharide	0.75
Sucrose	Disaccharide	1.00
Fructose	Monosaccharide	1.75
Aspartame	Synthetic	180
Acesulfame-K	Synthetic	200
Saccharin	Synthetic	350
Sucralose	Semisynthetic	600
Alitame	Semisynthetic	2000

(continued)

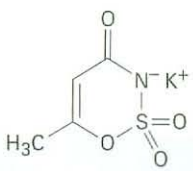
The desire of many people to cut their caloric intake has led to the development of synthetic sweeteners such as saccharin, aspartame, acesulfame, and sucralose. All are far sweeter than natural sugars, so the choice of one or another depends on personal taste, government regulations, and (for baked goods) heat stability. Saccharin, the oldest synthetic sweetener has been used for more than a century, although it has a somewhat metallic aftertaste. Doubts about its safety and potential carcinogenicity were raised in the early 1970s, but it has now been cleared of suspicion. Acesulfame potassium, one of the most recently approved sweeteners, is proving to be extremely popular in soft drinks because it has little aftertaste. Sucralose, another recently approved sweetener, is particularly useful in baked goods because of its stability at high temperatures. Alitame, not yet approved for sale in the United States but likely to be so soon, is claimed to be 2000 times as sweet as sucrose! Of the five synthetic sweeteners listed in Table 25.2, only sucralose has clear structural resemblance to a carbohydrate, but it differs dramatically in containing three chlorine atoms.



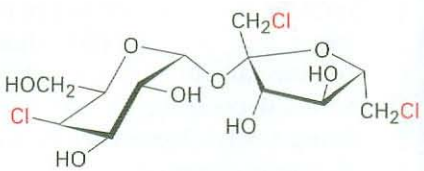
Saccharin



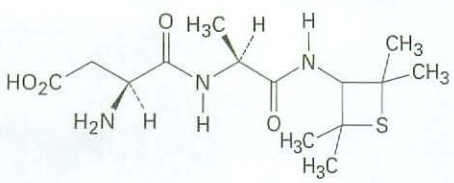
Aspartame



Acesulfame potassium



Sucralose



Alitame

SUMMARY AND KEY WORDS

aldaric acid, 993
alditol, 992
aldonic acid, 992
aldose, 975
amino sugar, 997
α anomer, β anomer, 984
anomeric center, 984
carbohydrate, 973

Carbohydrates are polyhydroxy aldehydes and ketones. They are classified according to the number of carbon atoms and the kind of carbonyl group they contain. Glucose, for example, is an aldohexose, a six-carbon aldehydo sugar. **Monosaccharides** are further classified as either **D sugars** or **L sugars**, depending on the stereochemistry of the chirality center farthest from the carbonyl group. Carbohydrate stereochemistry is frequently depicted using **Fischer projections**, which represent a chirality center as the intersection of two crossed lines.

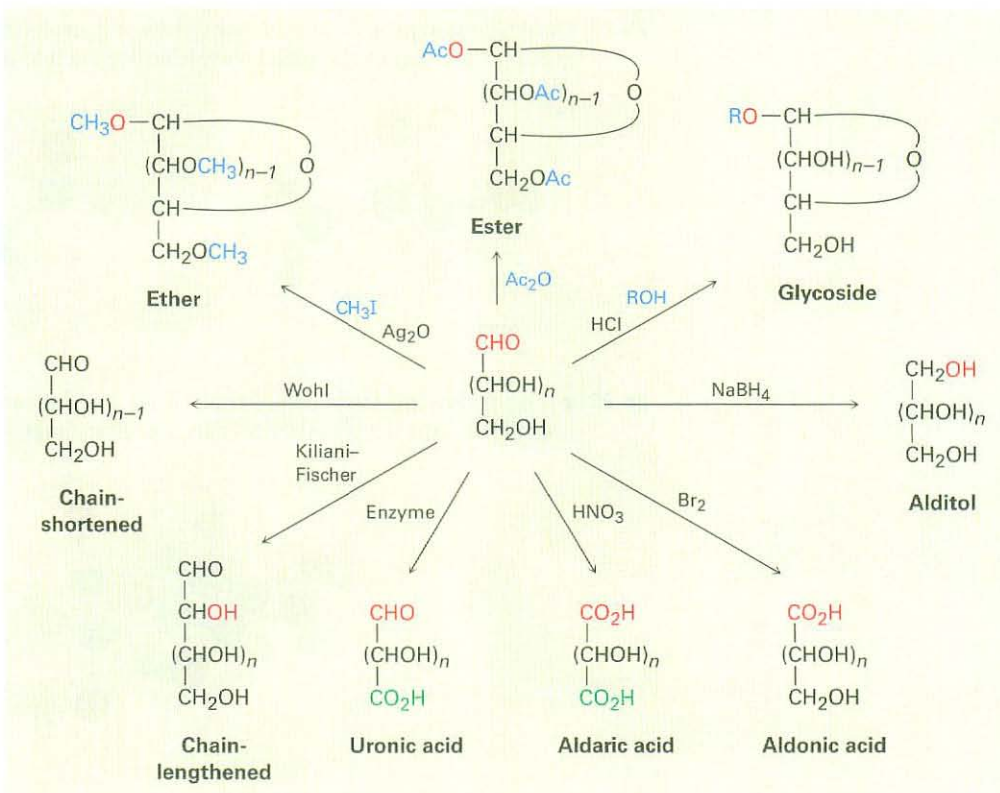
Monosaccharides normally exist as cyclic hemiacetals rather than as open-chain aldehydes or ketones. The hemiacetal linkage results from reaction of the carbonyl group with an —OH group three or four carbon atoms away. A

five-membered cyclic hemiacetal is called a **furanose**, and a six-membered cyclic hemiacetal is called a **pyranose**. Cyclization leads to the formation of a new chirality center and production of two diastereomeric hemiacetals, called α and β **anomers**.

Much of the chemistry of monosaccharides is the familiar chemistry of alcohols and aldehydes/ketones. Thus, the hydroxyl groups of carbohydrates form esters and ethers. The carbonyl group of a monosaccharide can be reduced with $NaBH_4$ to form an **alditol**, oxidized with aqueous Br_2 to form an **aldonic acid**, oxidized with HNO_3 to form an **aldaric acid**, oxidized enzymatically to form a **uronic acid**, or treated with an alcohol in the presence of acid to form a **glycoside**. Monosaccharides can also be chain-lengthened by the multistep **Kiliani–Fischer synthesis** and can be chain-shortened by the **Wohl degradation**.

Disaccharides are complex carbohydrates in which simple sugars are linked by a glycoside bond between the **anomeric center** of one unit and a hydroxyl of the second unit. The sugars can be the same, as in maltose and cellobiose, or different, as in lactose and sucrose. The glycosidic bond can be either α (maltose) or β (cellobiose, lactose) and can involve any hydroxyl of the second sugar. A 1→4 link is most common (cellobiose, maltose), but others such as 1→2 (sucrose) are also known. **Polysaccharides**, such as cellulose, starch, and glycogen, are used in nature as structural materials, as a means of long-term energy storage, and as cell-surface markers.

SUMMARY OF REACTIONS



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

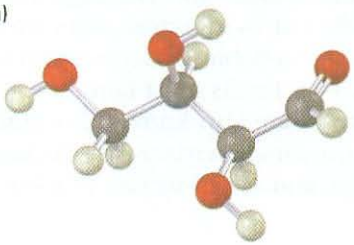
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

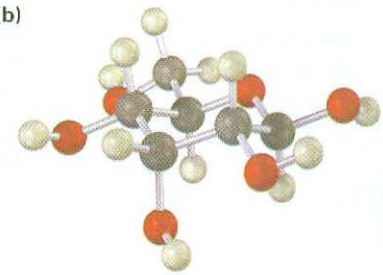
(Problems 25.1–25.25 appear within the chapter.)

25.26 ■ Identify the following aldoses, and tell whether each is a D or L sugar:

(a)

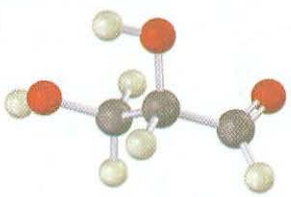


(b)

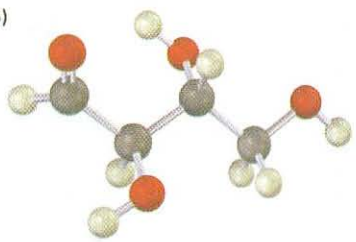


25.27 Draw Fischer projections of the following molecules, placing the carbonyl group at the top in the usual way. Identify each as a D or L sugar.

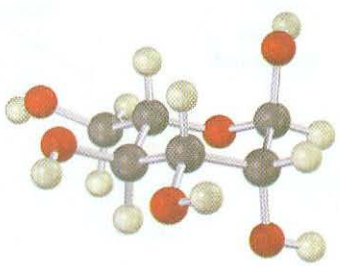
(a)



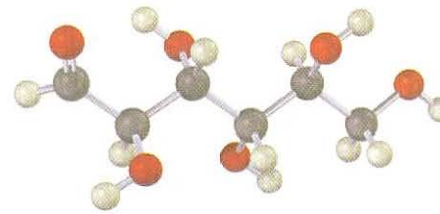
(b)



25.28 ■ The following structure is that of an L aldohexose in its pyranose form. Identify it, and tell whether it is an α or β anomer.



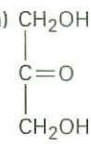
25.29 ■ The following model is that of an aldohexose:

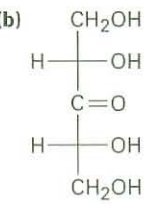


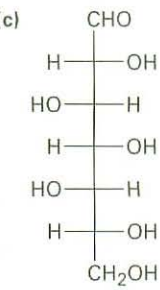
(a) Draw Fischer projections of the sugar, its enantiomer, and a diastereomer.
(b) Is this a D sugar or an L sugar? Explain.
(c) Draw the β anomer of the sugar in its furanose form.

ADDITIONAL PROBLEMS

25.30 ■ Classify each of the following sugars. (For example, glucose is an aldohexose.)

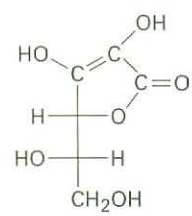
(a)


(b)


(c)


25.31 Write open-chain structures for the following:
(a) A ketotetrose
(b) A ketopentose
(c) A deoxyaldohexose
(d) A five-carbon amino sugar

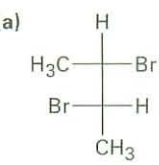
25.32 Does ascorbic acid (vitamin C) have a D or L configuration?

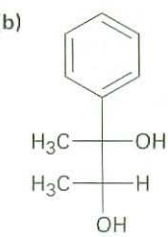


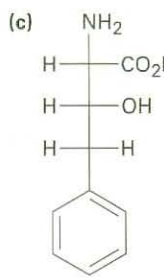
Ascorbic acid

25.33 Draw the three-dimensional furanose form of ascorbic acid (Problem 25.32), and assign *R* or *S* stereochemistry to each chirality center.

25.34 ■ Assign *R* or *S* configuration to each chirality center in the following molecules:

(a)


(b)


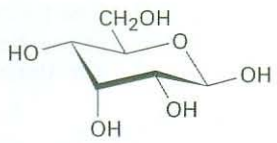
(c)


■ Assignable in OWL

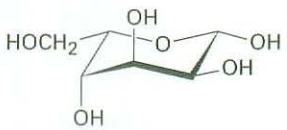
25.35 Draw Fischer projections of the following molecules:
(a) The *S* enantiomer of 2-bromobutane
(b) The *R* enantiomer of alanine, $CH_3CH(NH_2)COOH$
(c) The *R* enantiomer of 2-hydroxypropanoic acid
(d) The *S* enantiomer of 3-methylhexane

25.36 Draw Fischer projections for the two D aldoheptoses whose stereochemistry at C3, C4, C5, and C6 is the same as that of D-glucose at C2, C3, C4, and C5.

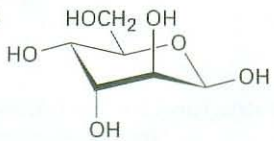
25.37 ■ The following cyclic structure is that of allose. Is this a furanose or pyranose form? Is it an α or β anomer? Is it a D or L sugar?

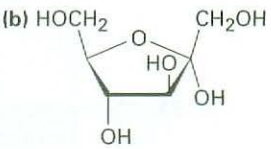


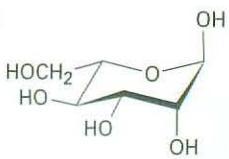
25.38 ■ What is the complete name of the following sugar?



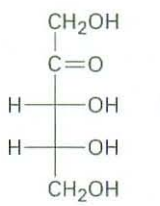
25.39 ■ Write the following sugars in their open-chain forms:

(a)


(b)


(c)


25.40 ■ Draw D-ribulose in its five-membered cyclic β-hemiacetal form.



Ribulose

25.41 Look up the structure of D-talose in Figure 25.3, and draw the β anomer in its pyranose form. Identify the ring substituents as axial or equatorial.

25.42 ■ Draw structures for the products you would expect to obtain from reaction of β-D-talopyranose with each of the following reagents:
(a) $NaBH_4$ in H_2O (b) Warm dilute HNO_3 (c) Br_2, H_2O
(d) CH_3CH_2OH, HCl (e) CH_3I, Ag_2O (f) $(CH_3CO)_2O$, pyridine

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

■ Assignable in OWL

25.44 All aldoses exhibit mutarotation. For example, α-D-galactopyranose has $[\alpha]_D = +150.7$, and β-D-galactopyranose has $[\alpha]_D = +52.8$. If either anomer is dissolved in water and allowed to reach equilibrium, the specific rotation of the solution is +80.2. What are the percentages of each anomer at equilibrium? Draw the pyranose forms of both anomers.

25.45 How many D-2-ketohexoses are possible? Draw them.

25.46 One of the D-2-ketohexoses is called *sorbose*. On treatment with $NaBH_4$, sorbose yields a mixture of gulitol and iditol. What is the structure of sorbose?

25.47 Another D-2-ketohexose, *psicose*, yields a mixture of allitol and altritol when reduced with $NaBH_4$. What is the structure of psicose?

25.48 L-Gulose can be prepared from D-glucose by a route that begins with oxidation to D-glucaric acid, which cyclizes to form two six-membered-ring lactones. Separating the lactones and reducing them with sodium amalgam gives D-glucose and L-gulose. What are the structures of the two lactones, and which one is reduced to L-gulose?

25.49 ■ What other D aldohexose gives the same alditol as D-talose?

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

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

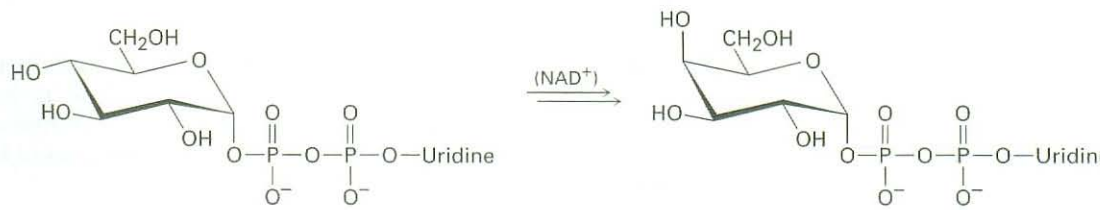
25.52 Draw the structure of L-galactose, and then answer the following questions:

(a) Which other aldohexose gives the same aldaric acid as L-galactose on oxidation with warm HNO_3?

(b) Is this other aldohexose a D sugar or an L sugar?

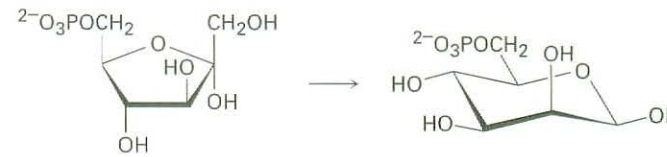
(c) Draw this other aldohexose in its most stable pyranose conformation.

25.53 Galactose, one of the eight essential monosaccharides (Section 25.7), is biosynthesized from UDP-glucose by galactose 4-epimerase, where UDP = uridylyl diphosphate (a ribonucleotide diphosphate; Section 28.1). The enzyme requires NAD^+ for activity (Section 17.7), but it is not a stoichiometric reactant, and NADH is not a final reaction product. Propose a mechanism.



UDP-Glucose **UDP-Galactose**

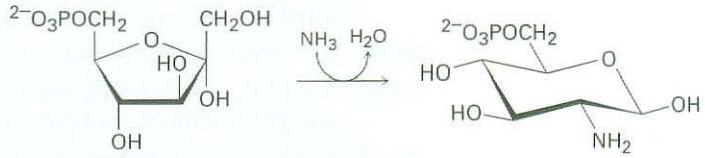
25.54 Mannose, one of the eight essential monosaccharides (Section 25.7), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate. No enzyme cofactor is required. Propose a mechanism.



Fructose 6-phosphate **Mannose 6-phosphate**

■ Assignable in OWL

25.55 Glucosamine, one of the eight essential monosaccharides (Section 25.7), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate by reaction with ammonia. Propose a mechanism.



Fructose 6-phosphate **Glucosamine 6-phosphate**

25.56 ■ Gentiobiose, a rare disaccharide found in saffron and gentian, is a reducing sugar and forms only D-glucose on hydrolysis with aqueous acid. Reaction of gentiobiose with iodomethane and Ag_2O yields an octamethyl derivative, which can be hydrolyzed with aqueous acid to give 1 equivalent of 2,3,4,6-tetra-*O*-methyl-D-glucopyranose and 1 equivalent of 2,3,4-tri-*O*-methyl-D-glucopyranose. If gentiobiose contains a β-glycoside link, what is its structure?

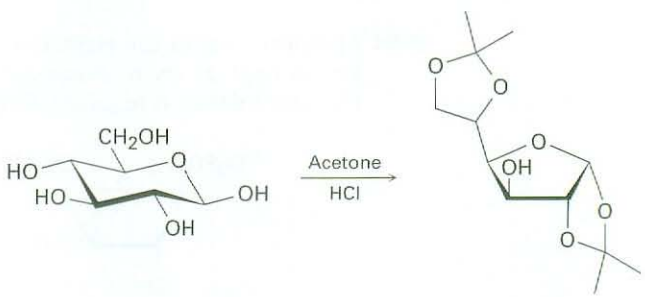
25.57 Amygdalin, or laetrile, is a cyanogenic glycoside isolated in 1830 from almond and apricot seeds. Acidic hydrolysis of amygdalin liberates HCN, along with benzaldehyde and 2 equivalents of D-glucose. If amygdalin is a β-glycoside of benzaldehyde cyanohydrin with gentiobiose (Problem 21.56), what is its structure?

25.58 Trehalose is a nonreducing disaccharide that is hydrolyzed by aqueous acid to yield 2 equivalents of D-glucose. Methylation followed by hydrolysis yields 2 equivalents of 2,3,4,6-tetra-*O*-methylglucose. How many structures are possible for trehalose?

25.59 Trehalose (Problem 25.58) is cleaved by enzymes that hydrolyze α-glycosides but not by enzymes that hydrolyze β-glycosides. What is the structure and systematic name of trehalose?

25.60 Isotrehalose and neotrehalose are chemically similar to trehalose (Problems 25.58 and 25.59) except that neotrehalose is hydrolyzed only by β-glycosidase enzymes, whereas isotrehalose is hydrolyzed by both α- and β-glycosidase enzymes. What are the structures of isotrehalose and neotrehalose?

25.61 D-Glucose reacts with acetone in the presence of acid to yield the nonreducing 1,2:5,6-diisopropylidene-D-glucofuranose. Propose a mechanism.



1,2:5,6-Diisopropylidene-D-glucofuranose

■ Assignable in OWL

25.62 D-Mannose reacts with acetone to give a diisopropylidene derivative (Problem 25.61) that is still reducing toward Tollens' reagent. Propose a likely structure for this derivative.

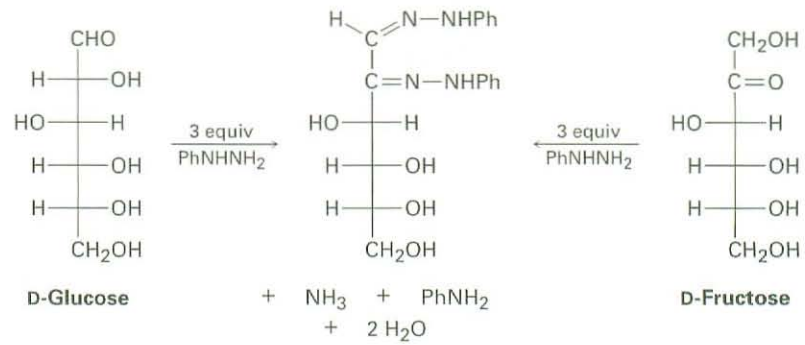
25.63 ■ Glucose and mannose can be interconverted (in low yield) by treatment with dilute aqueous NaOH. Propose a mechanism.

25.64 Propose a mechanism to account for the fact that D-gluconic acid and D-mannonic acid are interconverted when either is heated in pyridine solvent.

25.65 The *cyclitols* are a group of carbocyclic sugar derivatives having the general formulation 1,2,3,4,5,6-cyclohexanehexol. How many stereoisomeric cyclitols are possible? Draw them in their chair forms.

25.66 Compound **A** is a D aldopentose that can be oxidized to an optically inactive aldaric acid **B**. On Kiliani–Fischer chain extension, **A** is converted into **C** and **D**; **C** can be oxidized to an optically active aldaric acid **E**, but **D** is oxidized to an optically inactive aldaric acid **F**. What are the structures of **A**–**F**?

25.67 Simple sugars undergo reaction with phenylhydrazine, $PhNHNH_2$, to yield crystalline derivatives called *osazones*. The reaction is a bit complex, however, as shown by the fact that glucose and fructose yield the same osazone.



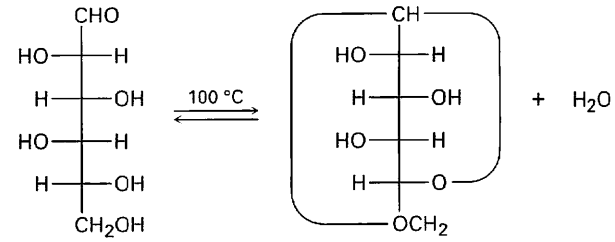
(a) Draw the structure of a third sugar that yields the same osazone as glucose and fructose.

(b) Using glucose as the example, the first step in osazone formation is reaction of the sugar with phenylhydrazine to yield an imine called a *phenylhydrazone*. Draw the structure of the product.

(c) The second and third steps in osazone formation are tautomerization of the phenylhydrazone to give an enol, followed by elimination of aniline to give a keto imine. Draw the structures of both the enol tautomer and the keto imine.

(d) The final step is reaction of the keto imine with 2 equivalents of phenylhydrazine to yield the osazone plus ammonia. Propose a mechanism for this step.

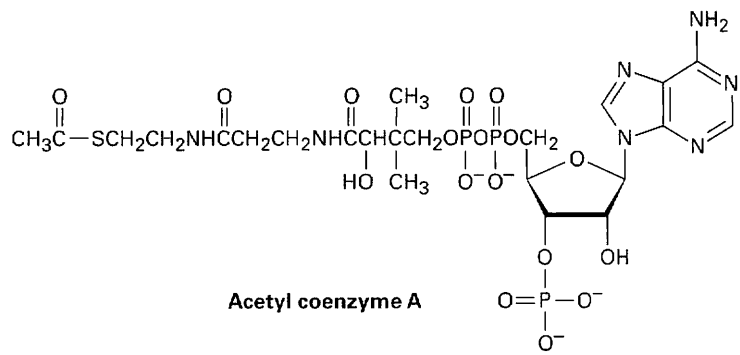
25.68 When heated to 100 °C, D-idose undergoes a reversible loss of water and exists primarily as 1,6-anhydro-D-idopyranose.



D-Idose **1,6-Anhydro-D-idopyranose**

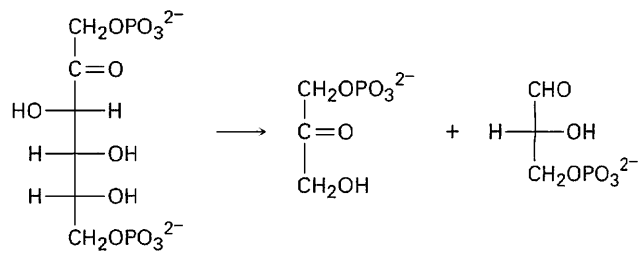
(a) Draw D-idose in its pyranose form, showing the more stable chair conformation of the ring.
(b) Which is more stable, α-D-idopyranose or β-D-idopyranose? Explain.
(c) Draw 1,6-anhydro-D-idopyranose in its most stable conformation.
(d) When heated to 100 °C under the same conditions as those used for D-idose, D-glucose does not lose water and does not exist in a 1,6-anhydro form. Explain.

25.69 Acetyl coenzyme A (acetyl CoA) is the key intermediate in food metabolism. What sugar is present in acetyl CoA?



Acetyl coenzyme A

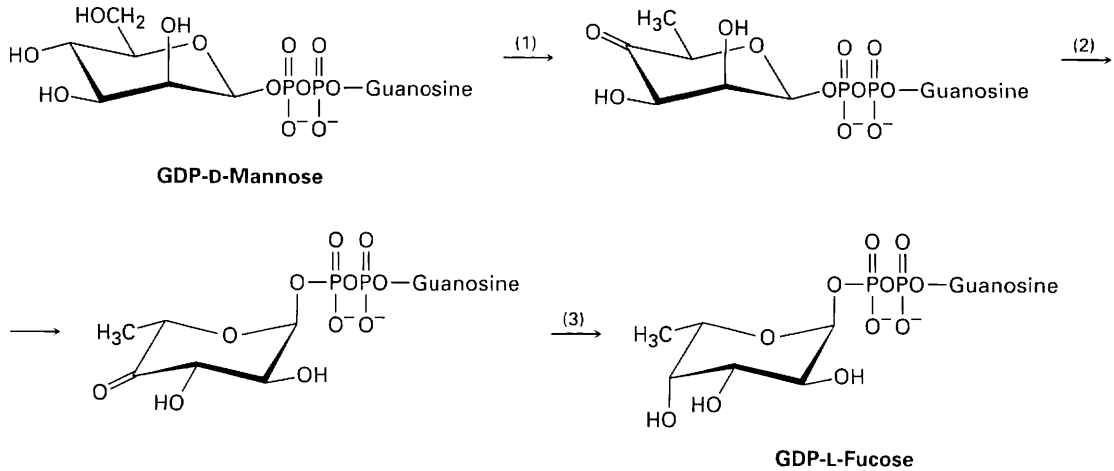
25.70 One of the steps in the biological pathway for carbohydrate metabolism is the conversion of fructose 1,6-bisphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. Propose a mechanism for the transformation.



Fructose 1,6-bisphosphate **Dihydroxyacetone phosphate** **Glyceraldehyde 3-phosphate**

■ Assignable in OWL

25.71 L-Fucose, one of the eight essential monosaccharides (Section 25.7), is biosynthesized from GDP-D-mannose by the following three-step reaction sequence, where GDP = guanosine diphosphate (a ribonucleoside diphosphate: Section 28.1):



(a) Step 1 involves an oxidation to a ketone, a dehydration to an enone, and a conjugate reduction. The step requires $NADP^+$, but no NADPH is formed as a final reaction product. Propose a mechanism.

(b) Step 2 accomplishes two epimerizations and utilizes acidic and basic sites in the enzyme but does not require a coenzyme. Propose a mechanism.

(c) Step 3 requires NADPH as coenzyme. Show the mechanism.