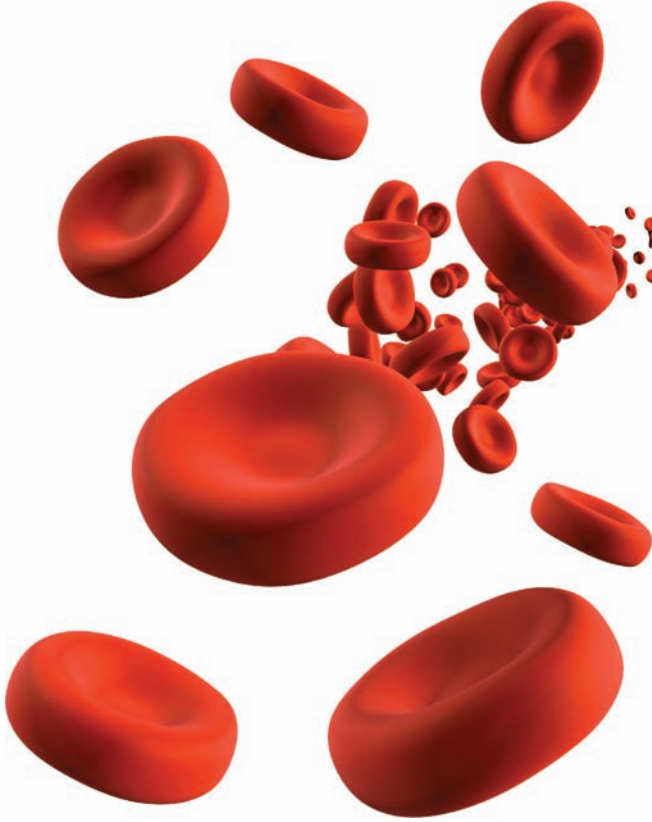


CHAPTER

22

Carbohydrates

Molecules in which most carbon atoms formally have a molecule of water attached in the form of an H and an OH are known as carbohydrates, for hydrated carbon. They are also sometimes called saccharides. But what is most important about this significant group of organic compounds is that they come in many different forms and have an incredible range of properties. Nearly all carbohydrates, such as sucrose (normal table sugar), taste sweet, and are critical to our perception and enjoyment of the foods that we eat. Carbohydrates also serve as stores of chemical energy in our bodies, determine our blood type, and in plants can be united to make important fibers like cellulose and amylose. As we will see later in the chapter, they also can serve as critical molecules in the form of sialyl Lewis^x for the recognition and healing of traumatized tissue. Sometimes, atoms other than oxygen are part of carbohydrates, such as the nitrogen of amines; some of these materials, such as glucosamine, are believed to have the ability to modulate joint pain.

IN THIS CHAPTER WE WILL CONSIDER:

- the structures and properties of different carbohydrates
- reactions by which monosaccharides join to form di- and polysaccharides
- reactions by which carbon atoms are added to or removed from carbohydrates
- the functions of selected carbohydrates

[WHY DO THESE TOPICS MATTER?] At the end of this chapter we will show how chemists have used the structure of a unique glucose-containing natural product to treat diabetes, a disease characterized by having too much glucose in the bloodstream.

22.1 INTRODUCTION

22.1A Classification of Carbohydrates

The group of compounds known as carbohydrates received their general name because of early observations that they often have the formula $C_x(H_2O)_y$—that is, they appear to be "hydrates of carbon" as noted in the chapter opener. They are also characterized by the functional groups that they contain.

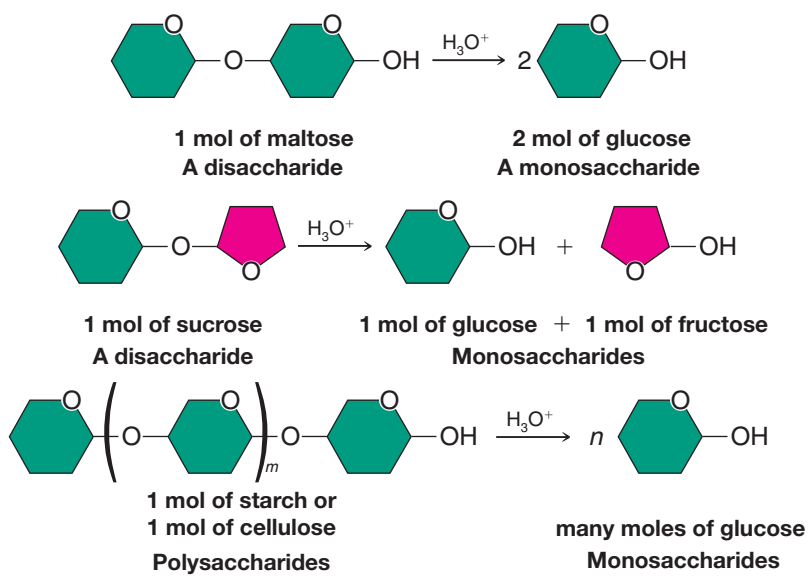
Helpful Hint

You may find it helpful now to review the chemistry of hemiacetals and acetals (Section 16.7).

- **Carbohydrates** are usually defined as polyhydroxy aldehydes and ketones or substances that hydrolyze to yield polyhydroxy aldehydes and ketones. They exist primarily in their hemiacetal or acetal forms (Section 16.7).

The simplest carbohydrates, those that cannot be hydrolyzed into simpler carbohydrates, are called **monosaccharides**. On a molecular basis, carbohydrates that undergo hydrolysis to produce only 2 molecules of monosaccharide are called **disaccharides**; those that yield 3 molecules of monosaccharide are called **trisaccharides**; and so on. (Carbohydrates that hydrolyze to yield 2–10 molecules of monosaccharide are sometimes called **oligosaccharides**.) Carbohydrates that yield a large number of molecules of monosaccharides (>10) are known as **polysaccharides**.

Maltose and sucrose are examples of disaccharides. On hydrolysis, 1 mol of maltose yields 2 mol of the monosaccharide glucose; sucrose undergoes hydrolysis to yield 1 mol of glucose and 1 mol of the monosaccharide fructose. Starch and cellulose are examples of polysaccharides; both are glucose polymers. Hydrolysis of either yields a large number of glucose units. The following shows these hydrolyses in a schematic way:



Carbohydrates are the most abundant organic constituents of plants. They not only serve as an important source of chemical energy for living organisms (sugars and starches are important in this respect), but also in plants and in some animals they serve as important constituents of supporting tissues (this is the primary function of the cellulose found in wood, cotton, and flax, for example).

We encounter carbohydrates at almost every turn of our daily lives. The paper on which this book is printed is largely cellulose; so, too, is the cotton of our clothes and the wood of our houses. The flour from which we make bread is mainly starch, and starch is also a major constituent of many other foodstuffs, such as potatoes, rice, beans, corn, and

peas. Carbohydrates are central to metabolism, and they are important for cell recognition (see the chapter opening vignette and Section 22.16).

Schematic diagram of a chloroplast from corn. (Reprinted with permission of John Wiley & Sons, Inc., from Voet, D. and Voet, J. G., *Biochemistry*, Second Edition. © 1995 Voet, D. and Voet, J. G.)

22.1B Photosynthesis and Carbohydrate Metabolism

Carbohydrates are synthesized in green plants by *photosynthesis*—a process that uses solar energy to reduce, or "fix," carbon dioxide. Photosynthesis in algae and higher plants occurs in cell organelles called chloroplasts. The overall equation for photosynthesis can be written as follows:

$$x\,CO_2 + y\,H_2O + \text{solar energy} \rightarrow \underset{\textbf{Carbohydrate}}{C_x(H_2O)_y} + x\,O_2$$

Many individual enzyme-catalyzed reactions take place in the general photosynthetic process and not all are fully understood. We know, however, that photosynthesis begins with the absorption of light by the important green pigment of plants, chlorophyll (Fig. 22.1). The green color of chlorophyll and, therefore, its ability to absorb sunlight in the visible region are due primarily to its extended conjugated system. As photons of sunlight are trapped by chlorophyll, energy becomes available to the plant in a chemical form that can be used to carry out the reactions that reduce carbon dioxide to carbohydrates and oxidize water to oxygen.

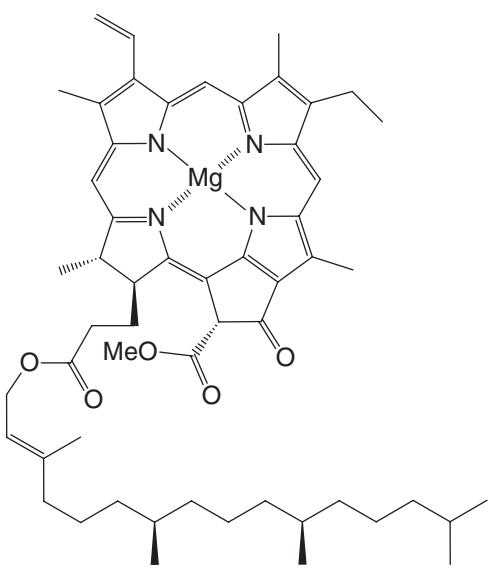


FIGURE 22.1 Chlorophyll a. [The structure of chlorophyll a was established largely through the work of H. Fischer (Munich), R. Willstätter (Munich), and J. B. Conant (Harvard). A synthesis of chlorophyll a from simple organic compounds was achieved by R. B. Woodward (Harvard) in 1960, who won the Nobel prize in 1965 for his outstanding contributions to synthetic organic chemistry.]

Carbohydrates act as a major chemical repository for solar energy. Their energy is released when animals or plants metabolize carbohydrates to carbon dioxide and water:

$$C_x(H_2O)_y + x\,O_2 \rightarrow x\,CO_2 + y\,H_2O + \text{energy}$$

The metabolism of carbohydrates also takes place through a series of enzyme-catalyzed reactions in which each energy-yielding step is an oxidation (or the consequence of an oxidation).

Although some of the energy released in the oxidation of carbohydrates is inevitably converted to heat, much of it is conserved in a new chemical form through reactions that are coupled to the synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate (P_i) (Fig. 22.2). The phosphoric anhydride bond that forms between the terminal phosphate group of ADP and the phosphate ion becomes another repository of chemical energy. Plants and animals can use the conserved energy of ATP (or very similar substances) to carry out all of their energy-requiring processes: the contraction of a muscle, the synthesis of a macromolecule, and so on. When the energy in ATP is used, a coupled reaction takes place in which ATP is hydrolyzed,

$$ATP + H_2O \rightarrow ADP + P_i + \text{energy}$$

or a new anhydride linkage is created,

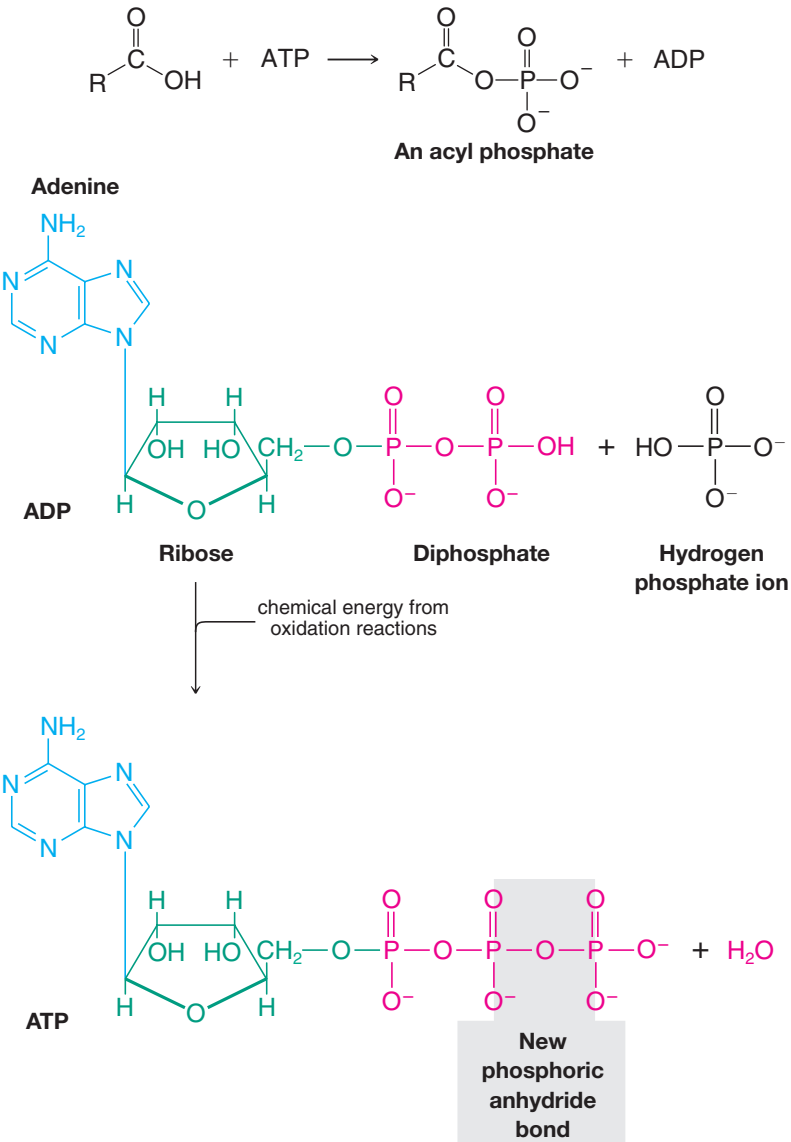
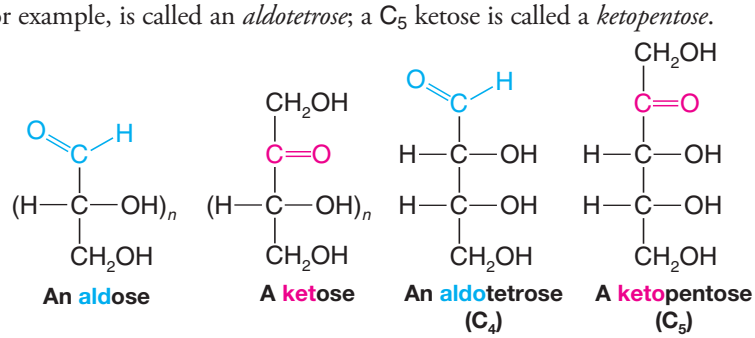


FIGURE 22.2 The synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and hydrogen phosphate ion. This reaction takes place in all living organisms, and adenosine triphosphate is the major compound into which the chemical energy released by biological oxidations is transformed.

22.2 MONOSACCHARIDES

22.2A Classification of Monosaccharides

Monosaccharides are classified according to (1) the number of carbon atoms present in the molecule and (2) whether they contain an aldehyde or keto group. Thus, a monosaccharide containing three carbon atoms is called a *triose*; one containing four carbon atoms is called a *tetrose*; one containing five carbon atoms is a *pentose*; and one containing six carbon atoms is a *hexose*. A monosaccharide containing an aldehyde group is called an **aldose**; one containing a keto group is called a **ketose**. These two classifications are frequently combined. A C_4 aldose, for example, is called an *aldotetrose*; a C_5 ketose is called a *ketopentose*.



PRACTICE PROBLEM 22.1

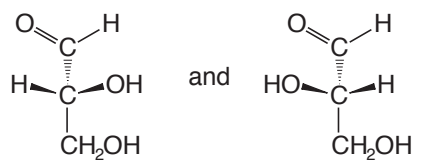
How many chirality centers are contained in **(a)** the aldotetrose and **(b)** the ketopentose just given? **(c)** How many stereoisomers would you expect from each general structure?

22.2B D and L Designations of Monosaccharides

The simplest monosaccharides are the compounds glyceraldehyde and dihydroxyacetone (see the following structures). Of these two compounds, only glyceraldehyde contains a chirality center.

Glyceraldehyde (an aldotriose) **Dihydroxyacetone (a ketotriose)**

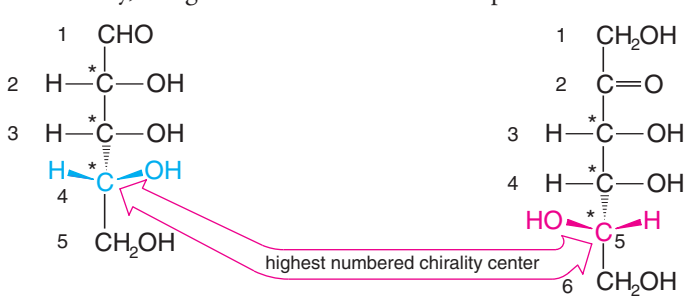
Glyceraldehyde exists, therefore, in two enantiomeric forms that are known to have the absolute configurations shown here:



(+)-Glyceraldehyde **(−)-Glyceraldehyde**

We saw in Section 5.7 that, according to the Cahn–Ingold–Prelog convention, (+)-glyceraldehyde should be designated (*R*)-(+)-glyceraldehyde and (−)-glyceraldehyde should be designated (*S*)-(−)-glyceraldehyde.

Early in the twentieth century, before the absolute configurations of any organic compounds were known, another system of stereochemical designations was introduced. According to this system (first suggested by M. A. Rosanoff of New York University in 1906), (+)-glyceraldehyde is designated D-(+)-glyceraldehyde and (−)-glyceraldehyde is designated L-(−)-glyceraldehyde. These two compounds, moreover, serve as configurational standards for all monosaccharides. A monosaccharide *whose highest numbered chirality center* (the penultimate carbon) has the same configuration as D-(+)-glyceraldehyde is designated as a D sugar; one whose highest numbered chirality center has the same configuration as L-glyceraldehyde is designated as an L sugar. By convention, acyclic forms of monosaccharides are drawn vertically with the aldehyde or keto group at or nearest the top. When drawn in this way, D sugars have the —OH on their penultimate carbon on the right:



A D-aldopentose **An L-ketohexose**

The **D and L nomenclature** designations are like (*R*) and (*S*) designations in that they are not necessarily related to the optical rotations of the sugars to which they are applied. Thus, one may encounter other sugars that are D-(+) or D-(−) and ones that are L-(+) or L-(−).

The D–L system of stereochemical designations is thoroughly entrenched in the literature of carbohydrate chemistry, and even though it has the disadvantage of specifying the configuration of only one chirality center—that of the highest numbered chirality center—we shall employ the D–L system in our designations of carbohydrates.

PRACTICE PROBLEM 22.2 Write three-dimensional formulas for each aldotetrose and ketopentose isomer in Practice Problem 22.1 and designate each as a D or L sugar.

22.2C Structural Formulas for Monosaccharides

Later in this chapter we shall see how the great carbohydrate chemist Emil Fischer* was able to establish the stereochemical configuration of the aldohexose D-(+)-glucose, the most abundant monosaccharide. In the meantime, however, we can use D-(+)-glucose as an example illustrating the various ways of representing the structures of monosaccharides.

Fischer represented the structure of D-(+)-glucose with the cross formulation **(1)** in Fig. 22.3. This type of formulation is now called a **Fischer projection** (Section 5.13) and is

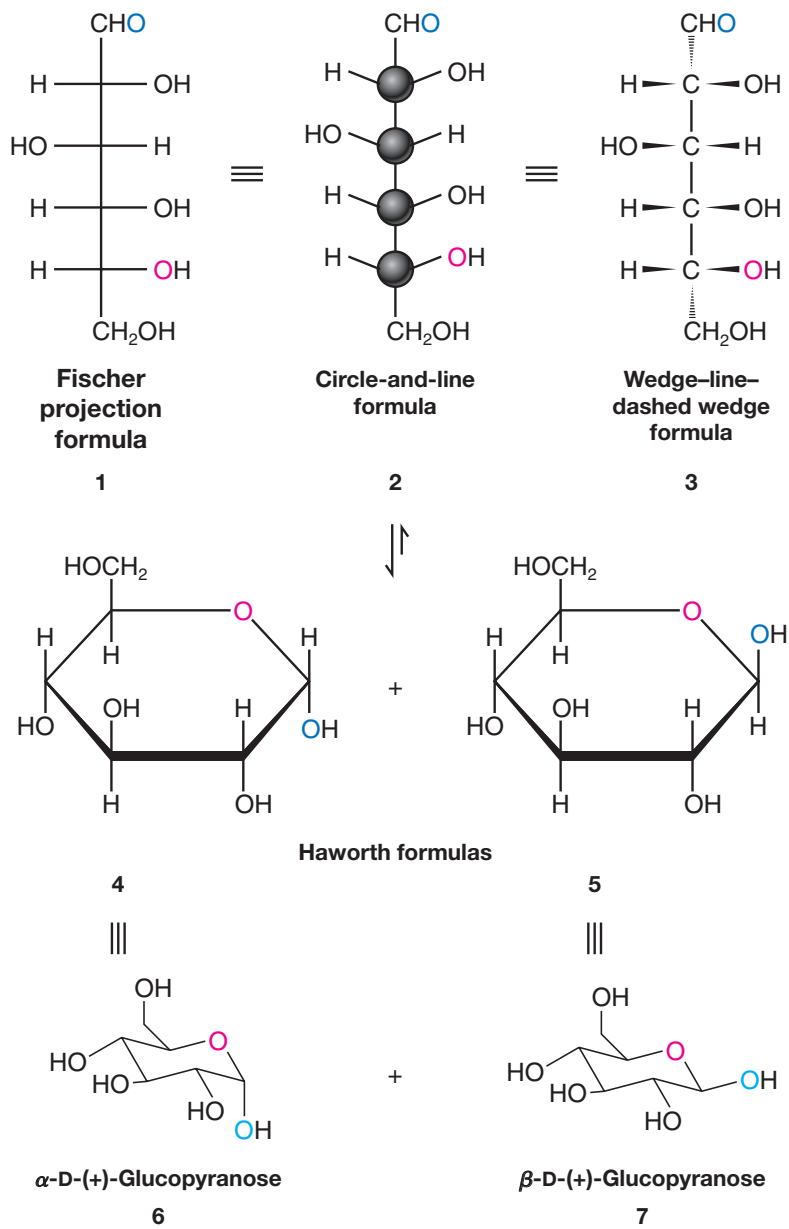


FIGURE 22.3 Formulas 1–3 are used for the open-chain structure of D-(+)-glucose. Formulas 4–7 are used for the two cyclic hemiacetal forms of D-(+)-glucose.

*Emil Fischer (1852–1919) was professor of organic chemistry at the University of Berlin. In addition to monumental work in the field of carbohydrate chemistry, where Fischer and co-workers established the configuration of most of the monosaccharides, Fischer also made important contributions to studies of amino acids, proteins, purines, indoles, and stereochemistry generally. As a graduate student, Fischer discovered phenylhydrazine, a reagent that was highly important in his later work with carbohydrates. Fischer was the second recipient (in 1902) of the Nobel Prize in Chemistry.

still useful for carbohydrates. In Fischer projections, by convention, *horizontal lines project out toward the reader and vertical lines project behind the plane of the page. When we use Fischer projections, however, we must not* (in our mind's eye) *remove them from the plane of the page in order to test their superposability and we must not rotate them by 90°*. In terms of more familiar formulations, the Fischer projection translates into formulas **6** and **7**. In IUPAC nomenclature and with the Cahn–Ingold–Prelog system of stereochemical designations, the open-chain form of D-(+)-glucose is (2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanal.

The meaning of formulas **1**, **2**, and **3** can be seen best through the use of molecular models: we first construct a chain of six carbon atoms with the —CHO group at the top and a —CH_2OH group at the bottom. We then bring the CH_2OH group up behind the chain until it almost touches the —CHO group. Holding this model so that the —CHO and —CH_2OH groups are directed generally away from us, we then begin placing —H and —OH groups on each of the four remaining carbon atoms. The —OH group of C2 is placed on the right; that of C3 on the left; and those of C4 and C5 on the right.

Although many of the properties of D-(+)-glucose can be explained in terms of an open-chain structure (**1**, **2**, or **3**), a considerable body of evidence indicates that the open-chain structure exists, primarily, in equilibrium with two cyclic forms. These can be represented by structures **4** and **5** or **6** and **7**. The cyclic forms of D-(+)-glucose are **hemiacetals** formed by an intramolecular reaction of the —OH group at C5 with the aldehyde group (Fig. 22.4). Cyclization creates a new chirality center at C1, and this chirality center explains how two cyclic forms are possible. These two cyclic forms are *diastereomers* that differ only in the configuration of C1.

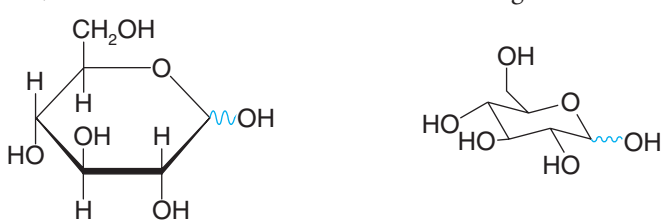
- In carbohydrate chemistry diastereomers differing only at the hemiacetal or acetal carbon are called **anomers**, and the hemiacetal or acetal carbon atom is called the **anomeric carbon atom**.

Structures **4** and **5** for the glucose anomers are called **Haworth formulas*** and, although they do not give an accurate picture of the shape of the six-membered ring, they have many practical uses. Figure 22.4 demonstrates how the representation of each chirality center of the open-chain form can be correlated with its representation in the Haworth formula.

Each glucose anomer is designated as an **α anomer** or a **β anomer** depending on the location of the —OH group of C1. When we draw the cyclic forms of a D sugar in the orientation shown in Figs. 22.3 or 22.4, the α anomer has the —OH trans to the —CH_2OH group and the β anomer has the —OH cis to the —CH_2OH group.

Studies of the structures of the cyclic hemiacetal forms of D-(+)-glucose using X-ray analysis have demonstrated that the actual conformations of the rings are the chair forms represented by conformational formulas **6** and **7** in Fig. 22.3. This shape is exactly what we would expect from our studies of the conformations of cyclohexane (Chapter 4), and it is especially interesting to notice that in the β anomer of D-glucose all of the large substituents, —OH and —CH_2OH, are equatorial. In the α anomer, the only bulky axial substituent is the —OH at C1.

It is convenient at times to represent the cyclic structures of a monosaccharide without specifying whether the configuration of the anomeric carbon atom is α or β. When we do this, we shall use formulas such as the following:



The symbol ∿ indicates α or β (three-dimensional view not specified).

*Haworth formulas are named after the English chemist W. N. Haworth (University of Birmingham), who, in 1926, along with E. L. Hirst, demonstrated that the cyclic form of glucose acetals consists of a six-membered ring. Haworth received the Nobel Prize for his work in carbohydrate chemistry in 1937. For an excellent discussion of Haworth formulas and their relation to open-chain forms, see "The Conversion of Open Chain Structures of Monosaccharides into the Corresponding Haworth Formulas," Wheeler, D. M. S., Wheeler, M. M., and Wheeler, T. S., *J. Chem. Educ.* **1982**, *59*, 969–970.

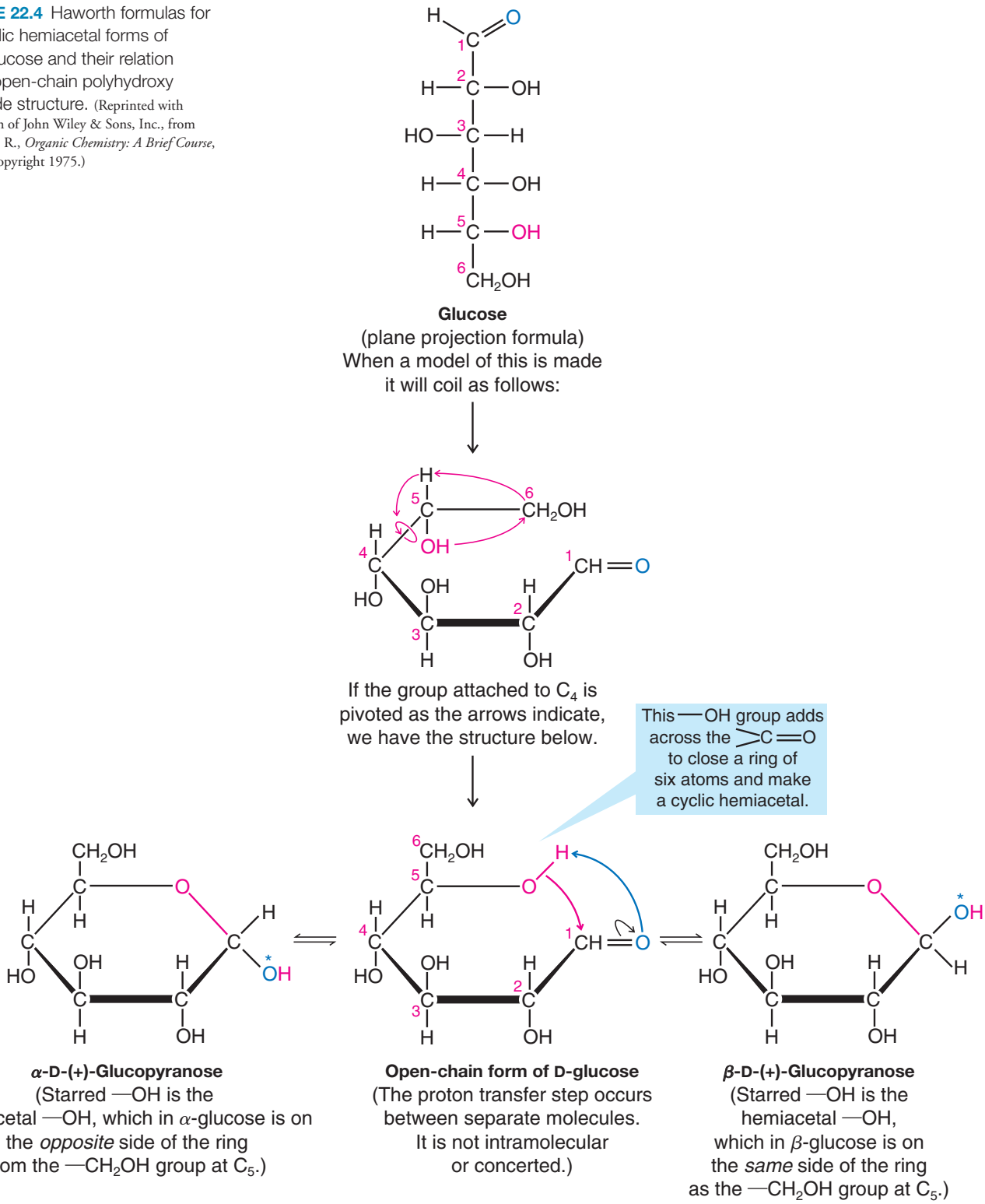
Helpful Hint

Use molecular models to help you learn to interpret Fischer projection formulas.

Helpful Hint

α and β also find common use in steroid nomenclature (Section 23.4A).

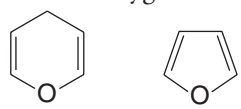
FIGURE 22.4 Haworth formulas for the cyclic hemiacetal forms of D-(+)-glucose and their relation to the open-chain polyhydroxy aldehyde structure. (Reprinted with permission of John Wiley & Sons, Inc., from Holum, J. R., *Organic Chemistry: A Brief Course*, p. 316. Copyright 1975.)



Not all carbohydrates exist in equilibrium with six-membered hemiacetal rings; in several instances the ring is five membered. (Even glucose exists, to a small extent, in equilibrium with five-membered hemiacetal rings.) Because of this variation, a system of nomenclature has been introduced to allow designation of the ring size.

- If the monosaccharide ring is six membered, the compound is called a **pyranose**; if the ring is five membered, the compound is designated as a **furanose**.

These names come from the names of the oxygen heterocycles *pyran* and *furan* + *ose*:



A pyran **Furan**

Thus, the full name of compound **4** (or **6**) is α-D-(+)-glucopyranose, while that of **5** (or **7**) is β-D-(+)-glucopyranose.

PRACTICE PROBLEM 22.3

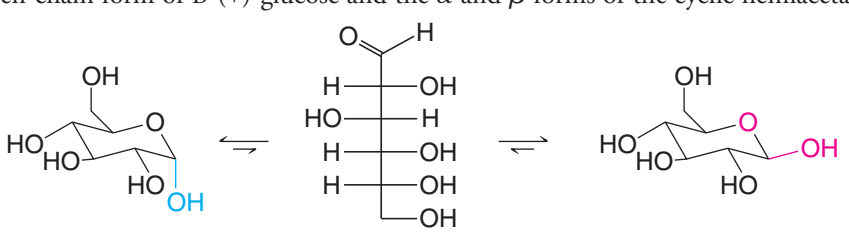
Draw the β-pyranose form of **(a)** in its lowest energy chair conformation, and a Fischer projection for **(b)**.

22.3 MUTAROTATION

Part of the evidence for the cyclic hemiacetal structure for D-(+)-glucose comes from experiments in which both α and β forms have been isolated. Ordinary D-(+)-glucose has a melting point of 146 °C. However, when D-(+)-glucose is crystallized by evaporating an aqueous solution kept above 98 °C, a second form of D-(+)-glucose with a melting point of 150 °C can be obtained. When the optical rotations of these two forms are measured, they are found to be significantly different, but when an aqueous solution of either form is allowed to stand, its rotation changes. The specific rotation of one form decreases and the rotation of the other increases, *until both solutions show the same value*. A solution of ordinary D-(+)-glucose (mp 146 °C) has an initial specific rotation of +112, but, ultimately, the specific rotation of this solution falls to +52.7. A solution of the second form of D-(+)-glucose (mp 150 °C) has an initial specific rotation of +18.7, but, slowly, the specific rotation of this solution rises to +52.7.

- This change in specific rotation toward an equilibrium value is called **mutarotation**.

The explanation for this mutarotation lies in the existence of an equilibrium between the open-chain form of D-(+)-glucose and the α and β forms of the cyclic hemiacetals:



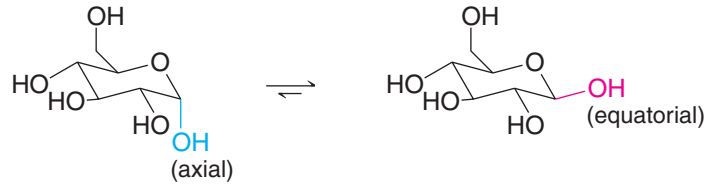
α-D-(+)-Glucopyranose (mp 146 °C; $[\alpha]_D^{25}$ = +112) **Open-chain form of D-(+)-glucose** **β-D-(+)-Glucopyranose (mp 150 °C; $[\alpha]_D^{25}$ = +18.7)**

X-ray analysis has confirmed that ordinary D-(+)-glucose has the α configuration at the anomeric carbon atom and that the higher melting form has the β configuration.

The concentration of open-chain D-(+)-glucose in solution at equilibrium is very small. Solutions of D-(+)-glucose give no observable UV or IR absorption band for a carbonyl group, and solutions of D-(+)-glucose give a negative test with Schiff's reagent—a special reagent that requires a relatively high concentration of a free aldehyde group (rather than a hemiacetal) in order to give a positive test.

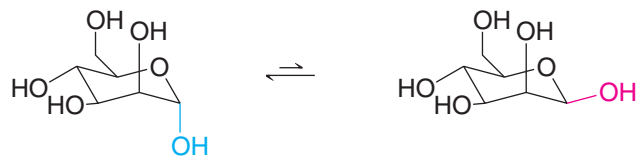
Assuming that the concentration of the open-chain form is negligible, one can, by use of the specific rotations in the preceding figures, calculate the percentages of the α and β anomers present at equilibrium. These percentages, 36% α anomer and 64% β anomer,

are in accord with a greater stability for β-D-(+)-glucopyranose. This preference is what we might expect on the basis of its having only equatorial groups:



α-D-(+)-Glucopyranose (36% at equilibrium) ⇌ **β-D-(+)-Glucopyranose (64% at equilibrium)**

The β anomer of a pyranose is not always the more stable, however. With D-mannose, the equilibrium favors the α anomer, and this result is called an *anomeric effect*:

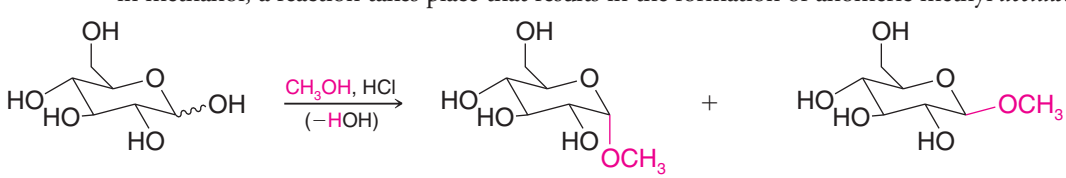


α-D-Mannopyranose (69% at equilibrium) ⇌ **β-D-Mannopyranose (31% at equilibrium)**

The anomeric effect is widely believed to be caused by hyperconjugation. An axially oriented orbital associated with nonbonding electrons of the ring oxygen can overlap with a σ* orbital of the axial exocyclic C—O hemiacetal bond. This effect is similar to that which helps cause the lowest energy conformation of ethane to be the anti conformation (Section 4.8). An anomeric effect will frequently cause an electronegative substituent, such as a hydroxyl or alkoxyl group, to prefer the axial orientation.

22.4 GLYCOSIDE FORMATION

When a small amount of gaseous hydrogen chloride is passed into a solution of D-(+)-glucose in methanol, a reaction takes place that results in the formation of anomeric methyl *acetals*:



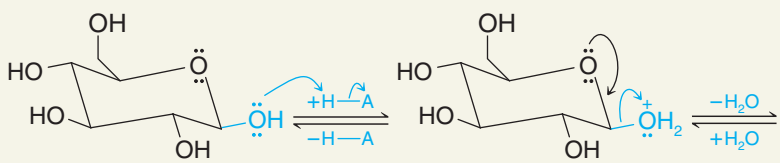
D-(+)-Glucose | **Methyl α-D-glucopyranoside (mp 165 °C; $[\alpha]_D^{25} = +158$)** | **Methyl β-D-glucopyranoside (mp 107 °C; $[\alpha]_D^{25} = -33$)**

- Carbohydrate acetals are generally called **glycosides** (see the following mechanism), and an acetal of glucose is called a *glucoside*. (Acetals of mannose are *mannosides*, acetals of fructose are *fructosides*, and so on.)

The methyl D-glucosides have been shown to have six-membered rings (Section 22.2C) so they are properly named methyl α-D-glucopyranoside and methyl β-D-glucopyranoside.

The mechanism for the formation of the methyl glucosides (starting arbitrarily with β-D-glucopyranose) is as follows:

A MECHANISM FOR THE REACTION — Formation of a Glycoside



β-D-Glucopyranose

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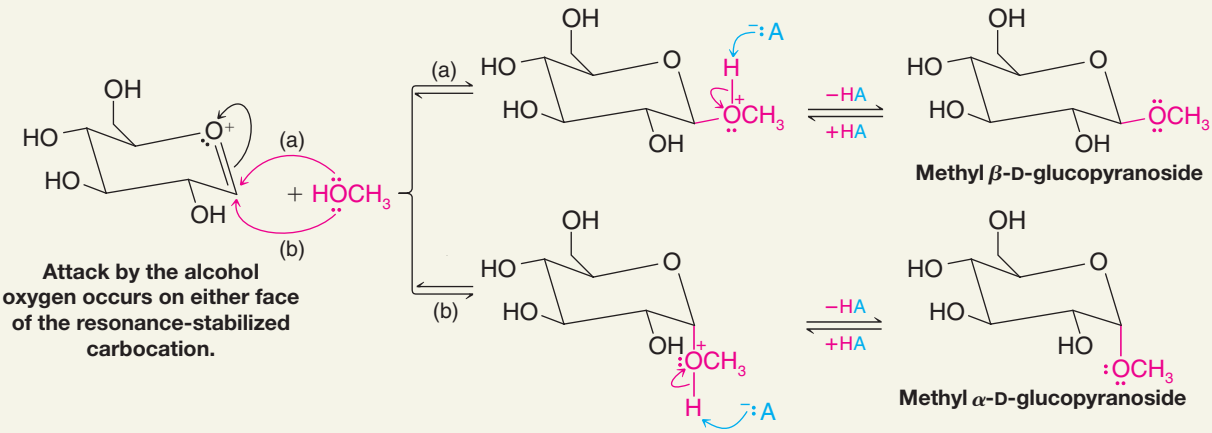
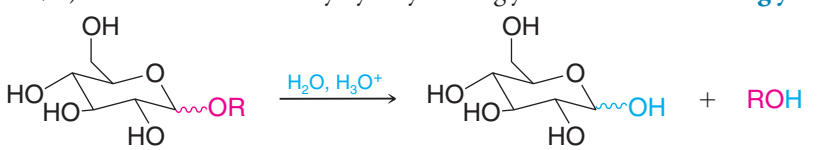


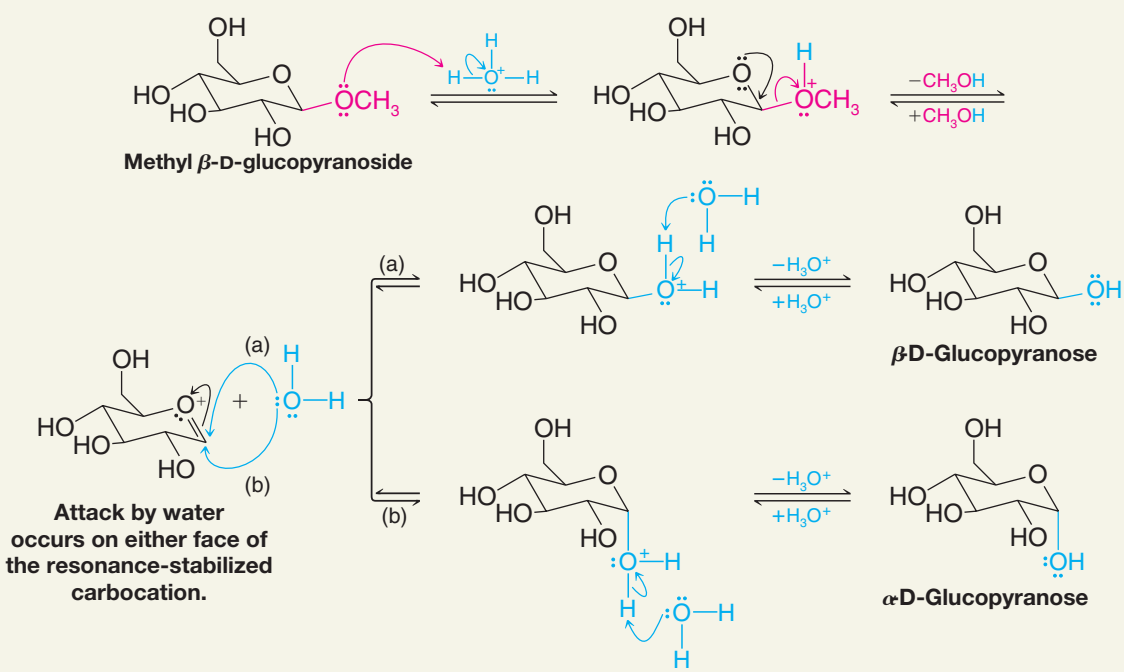
You should review the mechanism for acetal formation given in Section 16.7B and compare it with the steps given here. Notice, again, the important role played by the electron pair of the adjacent oxygen atom in stabilizing the carbocation that forms in the second step.

Glycosides are stable in basic solutions because they are acetals. In acidic solutions, however, glycosides undergo hydrolysis to produce a sugar and an alcohol (again, because they are acetals, Section 16.7B). The alcohol obtained by hydrolysis of a glycoside is known as an **aglycone**:

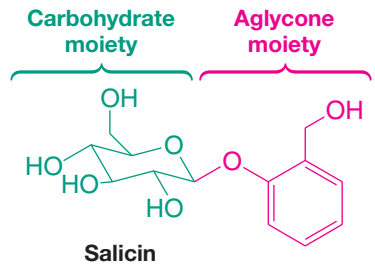


For example, when an aqueous solution of methyl β-D-glucopyranoside is made acidic, the glycoside undergoes hydrolysis to produce D-glucose as a mixture of the two pyranose forms (in equilibrium with a small amount of the open-chain form).

A MECHANISM FOR THE REACTION — Hydrolysis of a Glycoside



Glycosides may be as simple as the methyl glucosides that we have just studied or they may be considerably more complex. Many naturally occurring compounds are glycosides. An example is *salicin*, a compound found in the bark of willow trees:



Salicin

As early as the time of the ancient Greeks, preparations made from willow bark were used in relieving pain. Eventually, chemists isolated salicin from other plant materials and were able to show that it was responsible for the analgesic effect of the willow bark preparations. Salicin can be converted to salicylic acid, which in turn can be converted into the most widely used modern analgesic, *aspirin* (Section 21.8).

SOLVED PROBLEM 22.1

In neutral or basic solutions, glycosides do not show mutarotation. However, if the solutions are made acidic, glycosides show mutarotation. Explain.

ANSWER: Because glycosides are acetals, they undergo hydrolysis in aqueous acid to form cyclic hemiacetals that then undergo mutarotation. Acetals are stable to base, and therefore in basic solution they do not show mutarotation.

PRACTICE PROBLEM 22.4 **(a)** What products would be formed if salicin were treated with dilute aqueous HCl? **(b)** Outline a mechanism for the reactions involved in their formation.

PRACTICE PROBLEM 22.5 How would you convert D-glucose to a mixture of ethyl α-D-glucopyranoside and ethyl β-D-glucopyranoside? Show all steps in the mechanism for their formation.

22.5 OTHER REACTIONS OF MONOSACCHARIDES

22.5A Enolization, Tautomerization, and Isomerization

Dissolving monosaccharides in aqueous base causes them to undergo a series of enolizations and keto–enol tautomerizations that lead to isomerizations. For example, if a solution of D-glucose containing calcium hydroxide is allowed to stand for several days, a number of products can be isolated, including D-fructose and D-mannose (Fig. 22.5). This type of reaction is called the **Lobry de Bruyn–Alberda van Ekenstein transformation** after the two Dutch chemists who discovered it in 1895.

When carrying out reactions with monosaccharides, it is usually important to prevent these isomerizations and thereby to preserve the stereochemistry at all of the chirality centers. One way to do this is to convert the monosaccharide to the methyl glycoside first. We can then safely carry out reactions in basic media because the aldehyde group has been converted to an acetal and acetals are stable in aqueous base. Preparation of the methyl glycoside serves to "protect" the monosaccharide from undesired reactions that could occur with the anomeric carbon in its hemiacetal form.

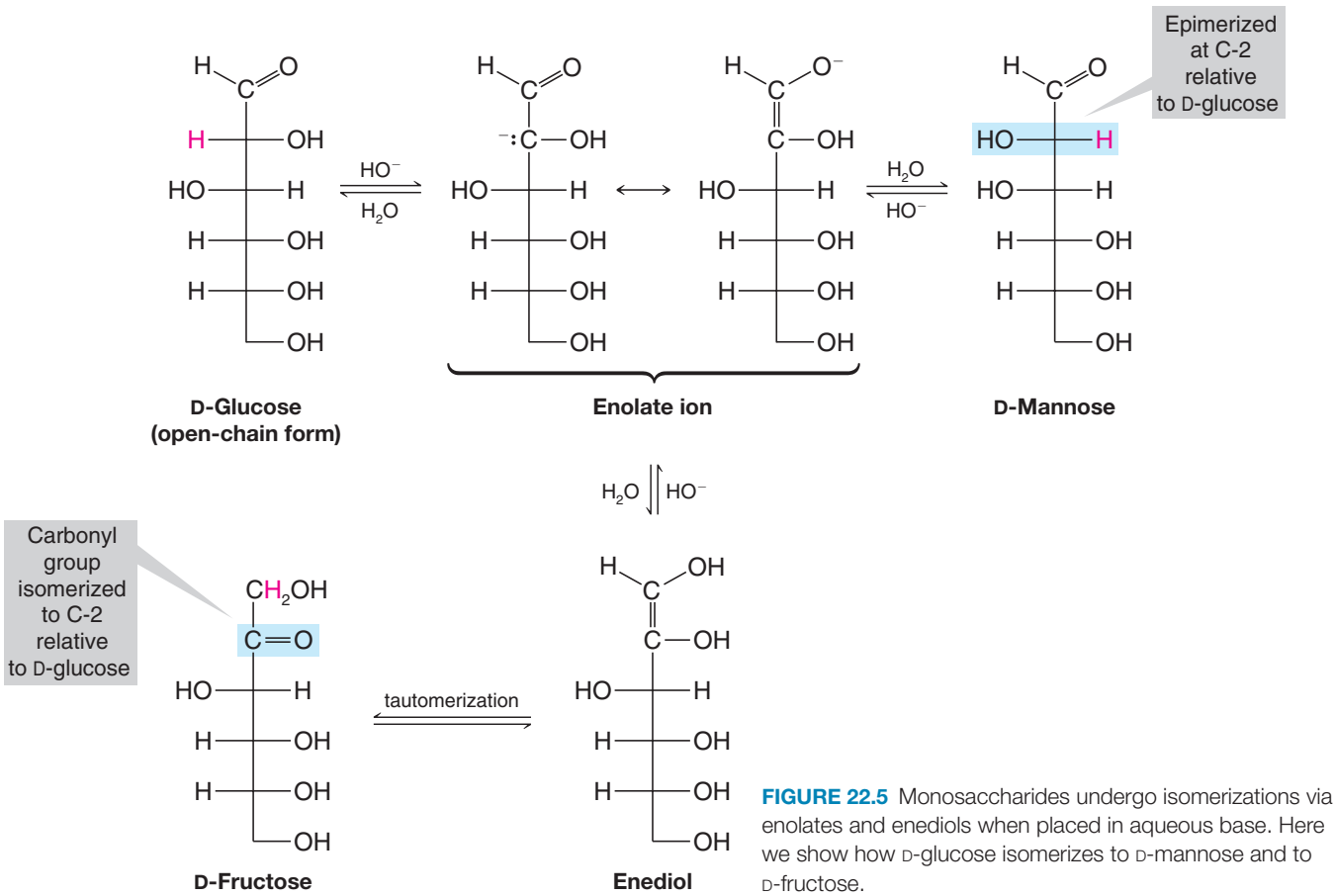


FIGURE 22.5 Monosaccharides undergo isomerizations via enolates and enediols when placed in aqueous base. Here we show how D-glucose isomerizes to D-mannose and to D-fructose.

22.5B Use of Protecting Groups in Carbohydrate Synthesis

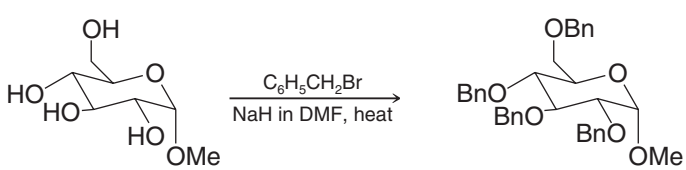
Protecting groups are functional groups introduced selectively to block the reactivity of certain sites in a molecule while desired transformations are carried on elsewhere. After the desired transformations are accomplished, the protecting groups are removed. Laboratory reactions involving carbohydrates often require the use of protecting groups due to the multiple sites of reactivity present in carbohydrates. As we have just seen, formation of a glycoside (an acetal) can be used to prevent undesired reactions that would involve the anomeric carbon in its hemiacetal form. Common protecting groups for the alcohol functional groups in carbohydrates include ethers, esters, and acetals.

22.5C Formation of Ethers

- Hydroxyl groups of sugars can be converted to ethers using a base and an alkyl halide by a version of the Williamson ether synthesis (Section 11.11B).

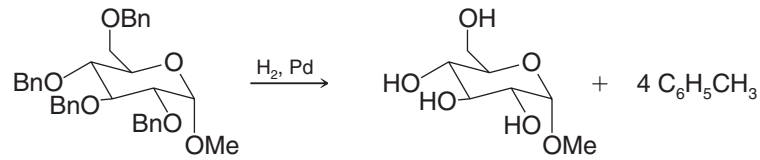
Benzyl ethers are commonly used to protect hydroxyl groups in sugars. Benzyl halides are easily introduced because they are highly reactive in S_N2 reactions. Sodium or potassium hydride is typically used as the base in an aprotic solvent such as DMF or DMSO. The benzyl groups can later be easily removed by hydrogenolysis using a palladium catalyst.

Benzyl Ether Formation

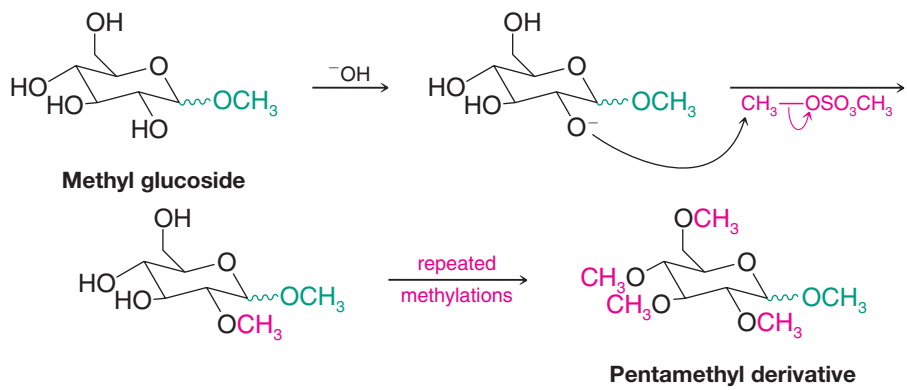


Bn = $C_6H_5CH_2$

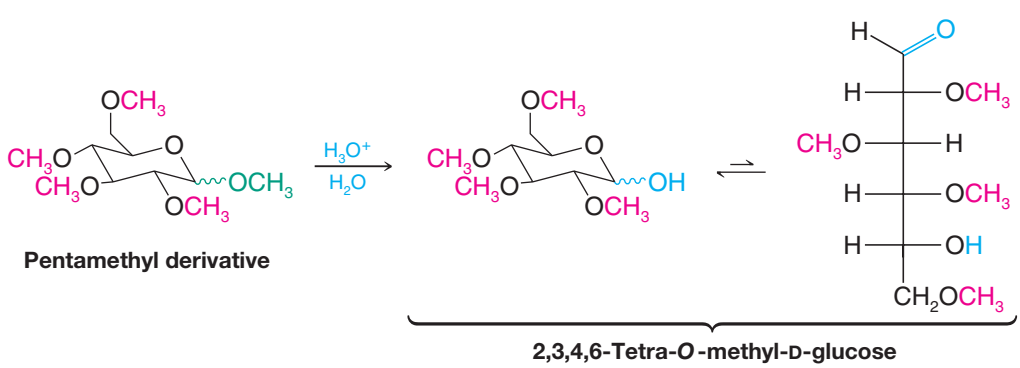
Benzyl Ether Cleavage



Methyl ethers can also be prepared. The pentamethyl derivative of glucopyranose, for example, can be synthesized by treating methyl glucoside with excess dimethyl sulfate in aqueous sodium hydroxide. Sodium hydroxide is a competent base in this case because the hydroxyl groups of monosaccharides are more acidic than those of ordinary alcohols due to the many electronegative atoms in the sugar, all of which exert electron-withdrawing inductive effects on nearby hydroxyl groups. In aqueous NaOH the hydroxyl groups are all converted to alkoxide ions, and each of these, in turn, reacts with dimethyl sulfate in an S_N2 reaction to yield a methyl ether. The process is called *exhaustive methylation*:

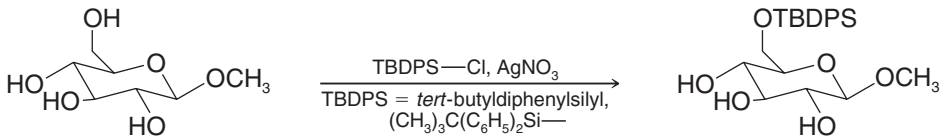


Although not often used as protecting groups for alcohols in carbohydrates, methyl ethers have been useful in the structure elucidation of sugars. For example, evidence for the pyranose form of glucose can be obtained by exhaustive methylation followed by aqueous hydrolysis of the acetal linkage. Because the C2, C3, C4, and C6 methoxy groups of the pentamethyl derivative are ethers, they are not affected by aqueous hydrolysis. (To cleave them requires heating with concentrated HBr or HI, Section 11.12.) The methoxyl group at C1, however, is part of an acetal linkage, and so it is labile under the conditions of aqueous hydrolysis. Hydrolysis of the pentamethyl derivative of glucose gives evidence that the C5 oxygen was the one involved in the cyclic hemiacetal form because in the open-chain form of the product (which is in equilibrium with the cyclic hemiacetal) it is the C5 oxygen that is not methylated:

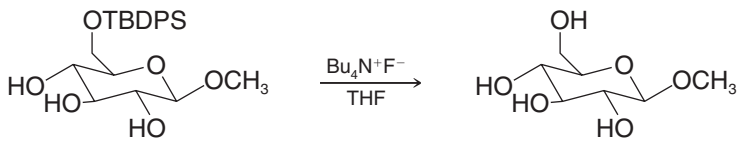


Silyl ethers, including *tert*-butyldimethylsilyl (TBS) ethers (Section 11.11E) and phenyl-substituted ethers, are also used as protecting groups in carbohydrate synthesis. *tert*-Butyldiphenylsilyl (TBDPS) ethers show excellent regioselectivity for primary hydroxyl groups in sugars, such as at C6 in a hexopyranose.

Regioselective TBDPS Ether Formation

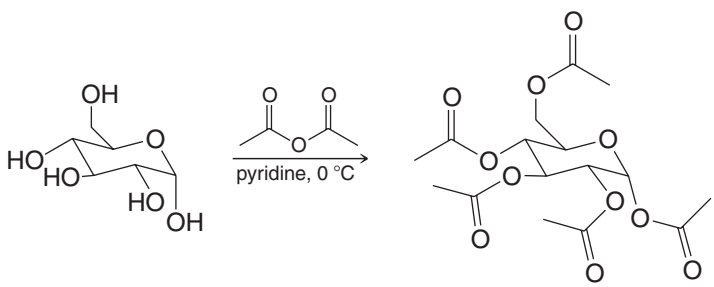


TBDPS Ether Cleavage



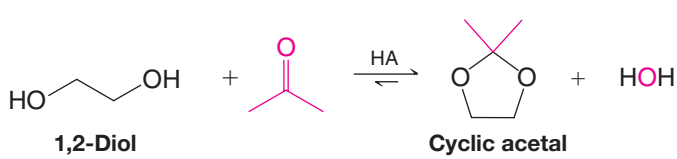
22.5D Conversion to Esters

Treating a monosaccharide with excess acetic anhydride and a weak base (such as pyridine or sodium acetate) converts all of the hydroxyl groups, including the anomeric hydroxyl, to ester groups. If the reaction is carried out at a low temperature (e.g., 0 °C), the reaction occurs stereospecifically; the α anomer gives the α-acetate and the β anomer gives the β-acetate. Acetate esters are common protecting groups for carbohydrate hydroxyls.

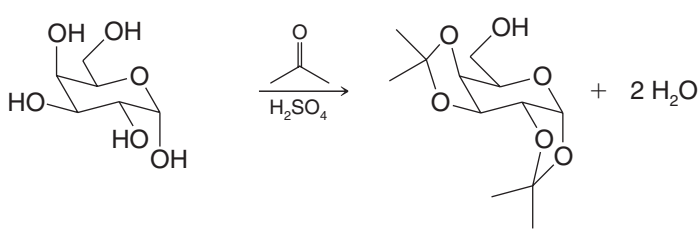


22.5E Conversion to Cyclic Acetals

In Section 16.7B we learned that aldehydes and ketones react with open-chain 1,2-diols to produce **cyclic acetals**:



If the 1,2-diol is attached to a ring, as in a monosaccharide, **formation of the cyclic acetals occurs only when the vicinal hydroxyl groups are cis to each other**. For example, α-D-galactopyranose reacts with acetone in the following way:



Cyclic acetals are commonly used to protect vicinal cis hydroxyl groups of a sugar while reactions are carried out on other parts of the molecule. When acetals such as these are formed from acetone, they are called **acetonides**.

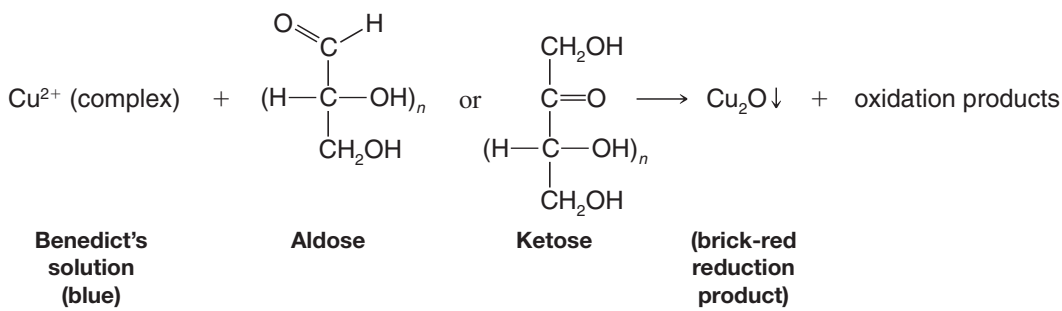
22.6 OXIDATION REACTIONS OF MONOSACCHARIDES

A number of oxidizing agents are used to identify functional groups of carbohydrates, in elucidating their structures, and for syntheses. The most important are (1) Benedict's or Tollens' reagents, (2) bromine water, (3) nitric acid, and (4) periodic acid. Each of these reagents produces a different and usually specific effect when it is allowed to react with a monosaccharide. We shall now examine what these effects are.

22.6A Benedict's or Tollens' Reagents: Reducing Sugars

Benedict's reagent (an alkaline solution containing a cupric citrate complex ion) and Tollens' solution $[Ag^+(NH_3)_2\bar{O}H]$ oxidize and thus give positive tests with *aldoses and ketoses*. The tests are positive even though aldoses and ketoses exist primarily as cyclic hemiacetals.

We studied the use of Tollens' silver mirror test in Section 16.13B. Benedict's solution and the related Fehling's solution (which contains a cupric tartrate complex ion) give brick-red precipitates of Cu_2O when they oxidize an aldose. [In alkaline solution ketoses are converted to aldoses (Section 22.5A), which are then oxidized by the cupric complexes.] Since the solutions of cupric tartrates and citrates are blue, the appearance of a brick-red precipitate is a vivid and unmistakable indication of a positive test.

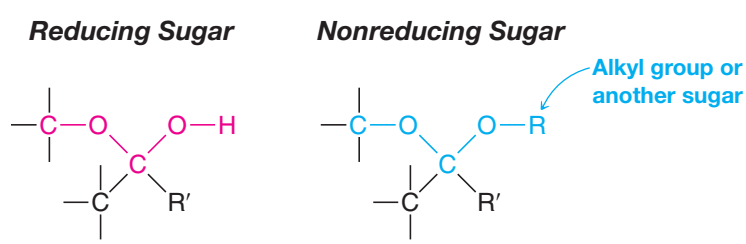


- Sugars that give positive tests with Tollens' or Benedict's solutions are known as **reducing sugars**, and all carbohydrates that contain a *hemiacetal group* give positive tests.

In aqueous solution the hemiacetal form of sugars exists in equilibrium with relatively small, but not insignificant, concentrations of noncyclic aldehydes or α-hydroxy ketones. It is the latter two that undergo the oxidation, perturbing the equilibrium to produce more aldehyde or α-hydroxy ketone, which then undergoes oxidation until one reactant is exhausted.

- Carbohydrates that contain only acetal groups do not give positive tests with Benedict's or Tollens' solutions, and they are called *nonreducing sugars*.

Acetals do not exist in equilibrium with aldehydes or α-hydroxy ketones in the basic aqueous media of the test reagents.



PRACTICE PROBLEM 22.6

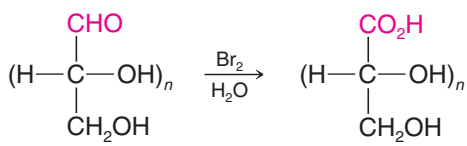
How might you distinguish between α-D-glucopyranose (i.e., D-glucose) and methyl α-D-glucopyranoside?

Although Benedict's and Tollens' reagents have some use as diagnostic tools [Benedict's solution can be used in quantitative determinations of reducing sugars (reported as glucose) in blood or urine], neither of these reagents is useful as a preparative reagent in carbohydrate oxidations. Oxidations with both reagents take place in alkaline solution, *and in alkaline solutions sugars undergo a complex series of reactions that lead to isomerizations* (Section 22.5A).

22.6B Bromine Water: The Synthesis of Aldonic Acids

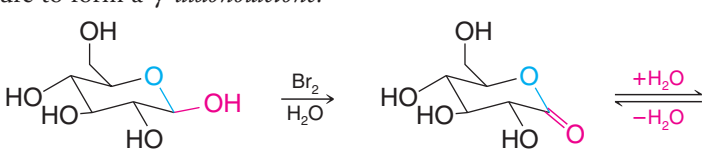
Monosaccharides do not undergo isomerization and fragmentation reactions in mildly acidic solution. Thus, a useful oxidizing reagent for preparative purposes is bromine in water (pH 6.0).

- Bromine water is a general reagent that selectively oxidizes the —CHO group to a —CO_2H group, thus converting an aldose to an **aldonic acid**:

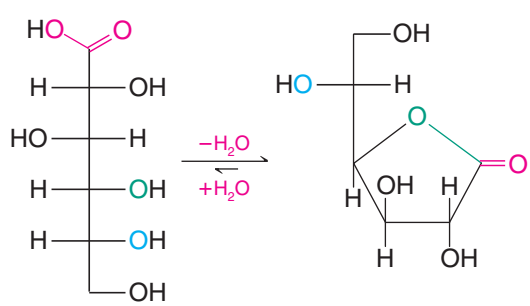


Aldose **Aldonic acid**

Experiments with aldopyranoses have shown that the actual course of the reaction is somewhat more complex than we have indicated. Bromine water specifically oxidizes the β anomer, and the initial product that forms is a δ-*aldonolactone*. This compound may then hydrolyze to an aldonic acid, and the aldonic acid may undergo a subsequent ring closure to form a γ-*aldonolactone:*



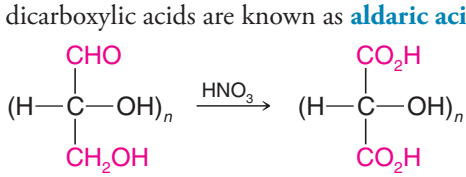
β-D-Glucopyranose **D-Glucono-δ-lactone**



D-Gluconic acid **D-Gluconic-γ-lactone**

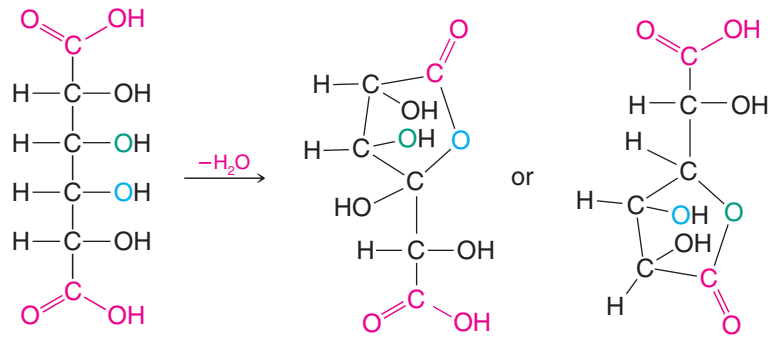
22.6C Nitric Acid Oxidation: Aldaric Acids

- Dilute nitric acid—a stronger oxidizing agent than bromine water—oxidizes both the —CHO group and the terminal —CH_2OH group of an aldose to —CO_2H groups, forming dicarboxylic acids are known as **aldaric acids**:



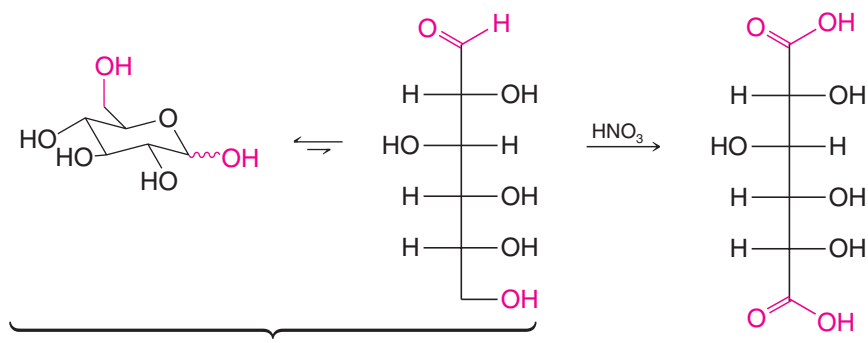
Aldose **Aldaric acid**

It is not known whether a lactone is an intermediate in the oxidation of an aldose to an aldaric acid; however, aldaric acids form γ- and δ-lactones readily:



Aldaric acid (from an aldohexose) **γ-Lactones of an aldaric acid**

The aldaric acid obtained from D-glucose is called D-glucaric acid*:



D-Glucose **D-Glucaric acid**

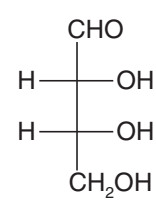
PRACTICE PROBLEM 22.7

(a) Would you expect D-glucaric acid to be optically active?

(b) Write the open-chain structure for the aldaric acid (mannaric acid) that would be obtained by nitric acid oxidation of D-mannose.

(c) Would you expect mannaric acid to be optically active?

(d) What aldaric acid would you expect to obtain from D-erythrose?



D-Erythrose

(e) Would the aldaric acid in (d) show optical activity?

(f) D-Threose, a diastereomer of D-erythrose, yields an optically active aldaric acid when it is subjected to nitric acid oxidation. Write Fischer projection formulas for D-threose and its nitric acid oxidation product.

(g) What are the names of the aldaric acids obtained from D-erythrose and D-threose?

PRACTICE PROBLEM 22.8

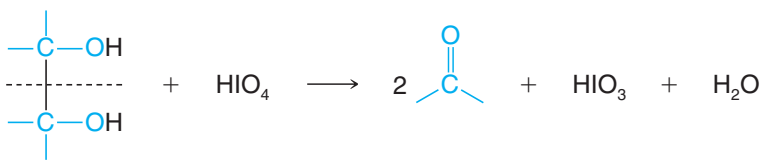
D-Glucaric acid undergoes lactonization to yield two different γ-lactones. What are their structures?

*Older terms for an aldaric acid are a *glycaric* acid or a *saccharic* acid.

22.6D Periodate Oxidations: Oxidative Cleavage of Polyhydroxy Compounds

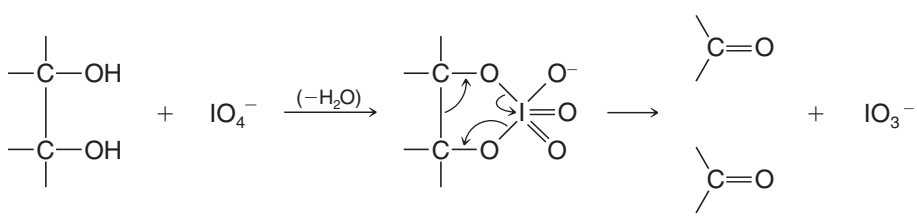
- Compounds that have hydroxyl groups on adjacent atoms undergo oxidative cleavage when they are treated with aqueous periodic acid (HIO_4). The reaction breaks carbon–carbon bonds and produces carbonyl compounds (aldehydes, ketones, or acids).

The stoichiometry of oxidative cleavage by periodic acid is



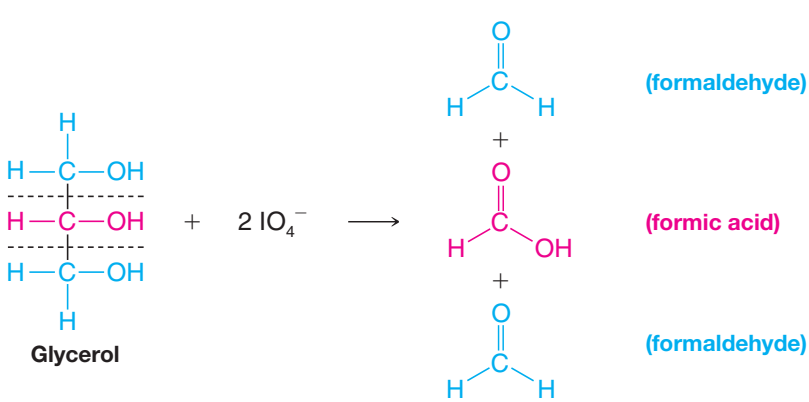
Since the reaction usually takes place in quantitative yield, valuable information can often be gained by measuring the number of molar equivalents of periodic acid consumed in the reaction as well as by identifying the carbonyl products.

Periodate oxidations are thought to take place through a cyclic intermediate:



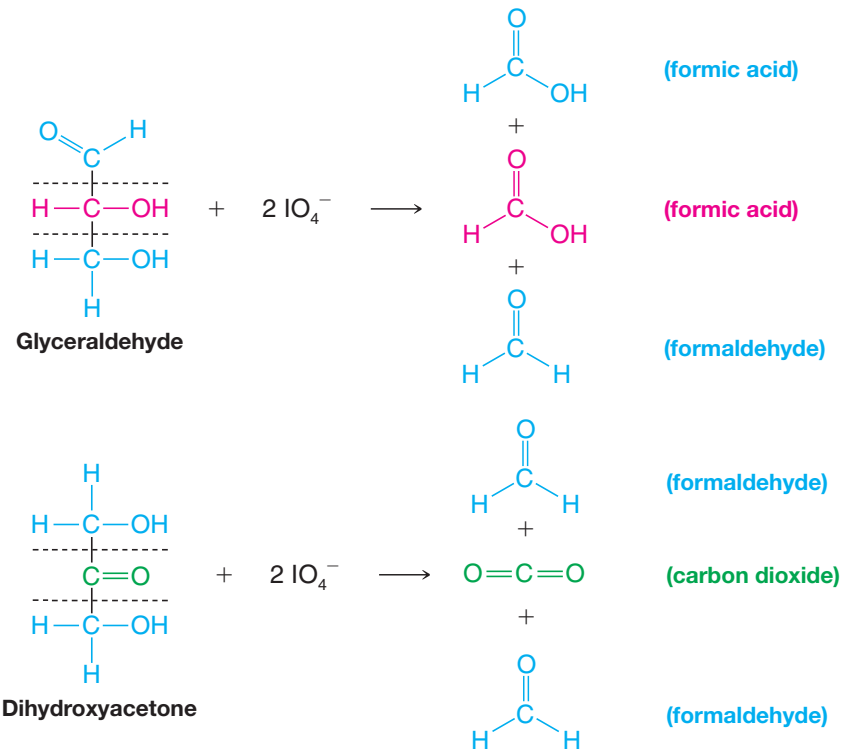
Before we discuss the use of periodic acid in carbohydrate chemistry, we should illustrate the course of the reaction with several simple examples. Notice in these periodate oxidations that *for every C—C bond broken, a C—O bond is formed at each carbon*.

1. When three or more —CHOH groups are contiguous, the internal ones are obtained as *formic acid*. Periodate oxidation of glycerol, for example, gives two molar equivalents of formaldehyde and one molar equivalent of formic acid:

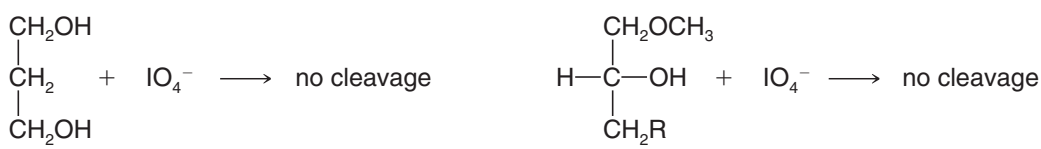


2. Oxidative cleavage also takes place when an —OH group is adjacent to the carbonyl group of an aldehyde or ketone (but not that of an acid or an ester). Glyceraldehyde yields two molar equivalents of formic acid and one molar equivalent of formaldehyde,

while dihydroxyacetone gives two molar equivalents of formaldehyde and one molar equivalent of carbon dioxide:



3. Periodic acid does not cleave compounds in which the hydroxyl groups are separated by an intervening $-CH_2-$ group, nor those in which a hydroxyl group is adjacent to an ether or acetal function:

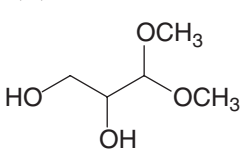


PRACTICE PROBLEM 22.9 What products would you expect to be formed when each of the following compounds is treated with an appropriate amount of periodic acid? How many molar equivalents of HIO_4 would be consumed in each case?

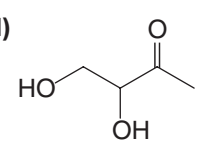
(a) 2,3-Butanediol

(b) 1,2,3-Butanetriol

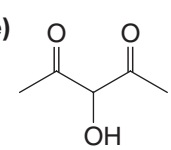
(c)



(d)

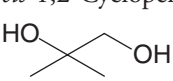


(e)



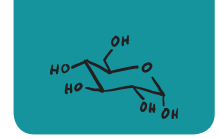
(f) *cis*-1,2-Cyclopentanediol

(g)



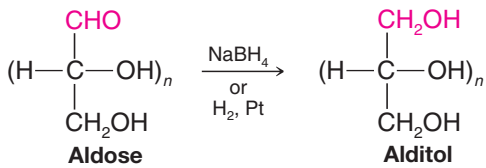
(h) D-Erythrose

PRACTICE PROBLEM 22.10 Show how periodic acid could be used to distinguish between an aldohexose and a ketohexose. What products would you obtain from each, and how many molar equivalents of HIO_4 would be consumed?

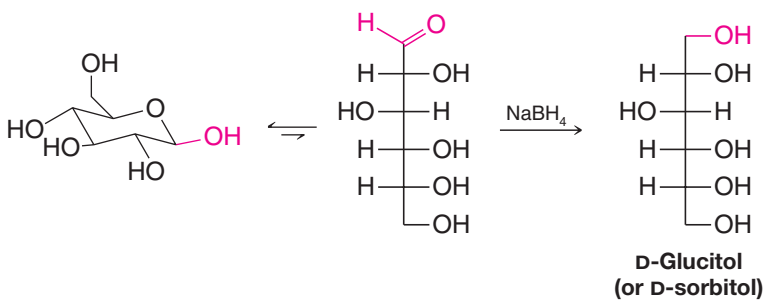


22.7 REDUCTION OF MONOSACCHARIDES: ALDITOLS

- Aldoses (and ketoses) can be reduced with sodium borohydride to give compounds called **alditols**:



Reduction of D-glucose, for example, yields D-glucitol:

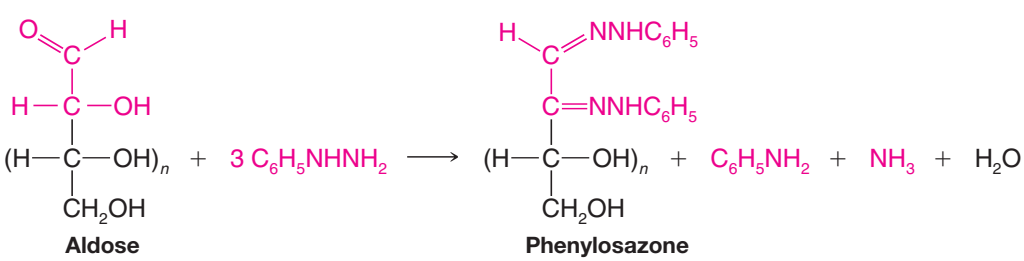


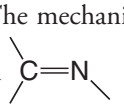
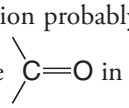
PRACTICE PROBLEM 22.11

(a) Would you expect D-glucitol to be optically active? **(b)** Write Fischer projection formulas for all of the D-aldohexoses that would yield *optically inactive alditols*.

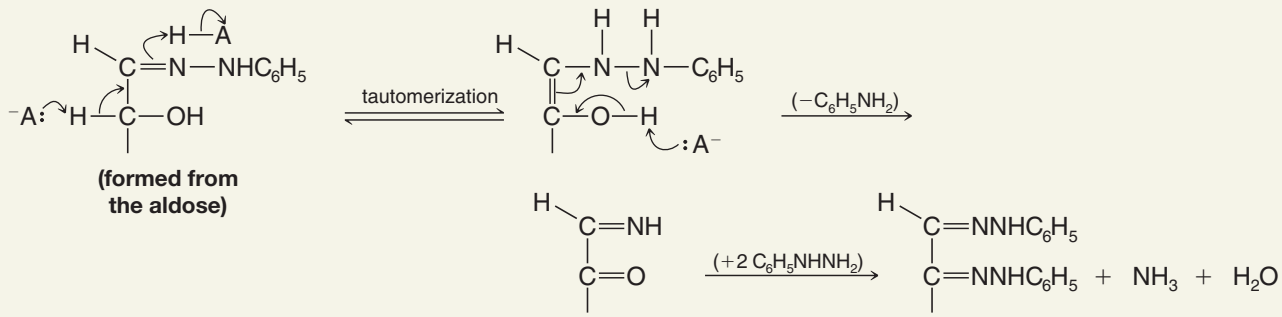
22.8 REACTIONS OF MONOSACCHARIDES WITH PHENYLHYDRAZINE: OSAZONES

The aldehyde group of an aldose reacts with such carbonyl reagents as hydroxylamine and phenylhydrazine (Section 16.8B). With hydroxylamine, the product is the expected oxime. With enough phenylhydrazine, however, three molar equivalents of phenylhydrazine are consumed and a second phenylhydrazone group is introduced at C2. The product is called a *phenylosazone*. Phenylosazones crystallize readily (unlike sugars) and are useful derivatives for identifying sugars.

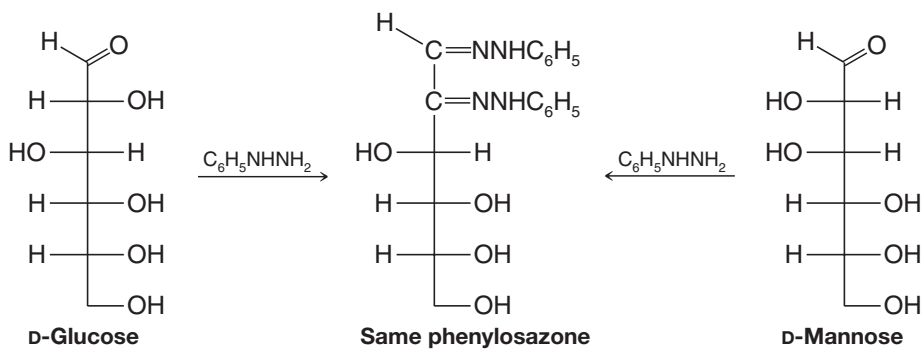


The mechanism for osazone formation probably depends on a series of reactions in which  behaves very much like  in giving a nitrogen version of an enol.

A MECHANISM FOR THE REACTION — Phenylosazone Formation



Osazone formation results in a loss of the chirality center at C2 but does not affect other chirality centers; D-glucose and D-mannose, for example, yield the same phenylosazone:



This experiment, first done by Emil Fischer, established that D-glucose and D-mannose have the same configurations about C3, C4, and C5. Diastereomeric aldoses that differ in configuration at only one carbon (such as D-glucose and D-mannose) are called epimers. In general, any pair of diastereomers that differ in configuration at only a single tetrahedral chirality center can be called **epimers**.

PRACTICE PROBLEM 22.12 Although D-fructose is not an epimer of D-glucose or D-mannose (D-fructose is a ketohexose), all three yield the same phenylosazone. **(a)** Using Fischer projection formulas, write an equation for the reaction of fructose with phenylhydrazine. **(b)** What information about the stereochemistry of D-fructose does this experiment yield?

22.9 SYNTHESIS AND DEGRADATION OF MONOSACCHARIDES

22.9A Kiliani–Fischer Synthesis

In 1885, Heinrich Kiliani (Freiburg, Germany) discovered that an aldose can be converted to the epimeric aldonic acids having one additional carbon through the addition of hydrogen cyanide and subsequent hydrolysis of the epimeric cyanohydrins. Fischer later extended this method by showing that aldonolactones obtained from the aldonic acids can be reduced to aldoses. Today, this method for lengthening the carbon chain of an aldose is called the Kiliani–Fischer synthesis.

We can illustrate the Kiliani–Fischer synthesis with the synthesis of D-threose and D-erythrose (aldotetroses) from D-glyceraldehyde (an aldotriose) in Fig. 22.6.

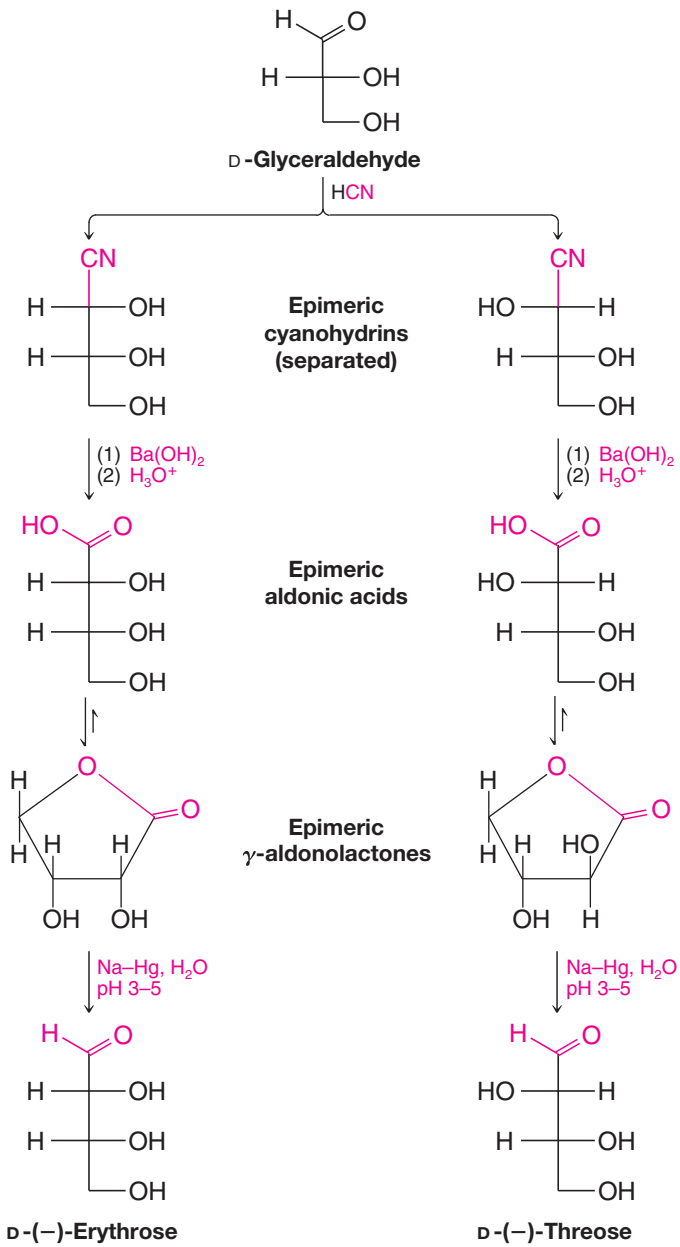


FIGURE 22.6 A Kiliani–Fischer synthesis of D-(−)-erythrose and D-(−)-threose from D-glyceraldehyde.

Addition of hydrogen cyanide to glyceraldehyde produces two epimeric cyanohydrins because the reaction creates a new chirality center. The cyanohydrins can be separated easily (since they are diastereomers), and each can be converted to an aldose through hydrolysis, acidification, lactonization, and reduction with Na–Hg at pH 3–5. One cyanohydrin ultimately yields D-(−)-erythrose and the other yields D-(−)-threose.

We can be sure that the aldotetroses that we obtain from this Kiliani–Fischer synthesis are both D sugars because the starting compound is D-glyceraldehyde and its chirality center is unaffected by the synthesis. On the basis of the Kiliani–Fischer synthesis, we cannot know just which aldotetrose has both —OH groups on the right and which has the top —OH on the left in the Fischer projection. However, if we oxidize both aldotetroses to aldaric acids, one [D-(−)-erythrose] will yield an *optically inactive* (meso) product while the other [D-(−)-threose] will yield a product that is *optically active* (see Practice Problem 22.7).

PRACTICE PROBLEM 22.13

(a) What are the structures of L-(+)-threose and L-(+)-erythrose? **(b)** What aldotriose would you use to prepare them in a Kiliani–Fischer synthesis?

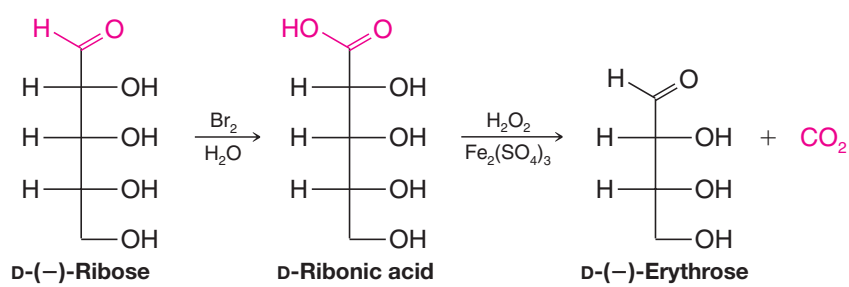
PRACTICE PROBLEM 22.14 **(a)** Outline a Kiliani–Fischer synthesis of epimeric aldopentoses starting with D-(−)-erythrose (use Fischer projections). **(b)** The two epimeric aldopentoses that one obtains are D-(−)-arabinose and D-(−)-ribose. Nitric acid oxidation of D-(−)-ribose yields an optically inactive aldaric acid, whereas similar oxidation of D-(−)-arabinose yields an optically active product. On the basis of this information alone, which Fischer projection represents D-(−)-arabinose and which represents D-(−)-ribose?

PRACTICE PROBLEM 22.15 Subjecting D-(−)-threose to a Kiliani–Fischer synthesis yields two other epimeric aldopentoses, D-(+)-xylose and D-(−)-lyxose. D-(+)-Xylose can be oxidized (with nitric acid) to an optically inactive aldaric acid, while similar oxidation of D-(−)-lyxose gives an optically active product. What are the structures of D-(+)-xylose and D-(−)-lyxose?

PRACTICE PROBLEM 22.16 There are eight aldopentoses. In Practice Problems 22.14 and 22.15 you have arrived at the structures of four. What are the names and structures of the four that remain?

22.9B The Ruff Degradation

Just as the Kiliani–Fischer synthesis can be used to lengthen the chain of an aldose by one carbon atom, the Ruff degradation* can be used to shorten the chain by a similar unit. The Ruff degradation involves (1) oxidation of the aldose to an aldonic acid using bromine water and (2) oxidative decarboxylation of the aldonic acid to the next lower aldose using hydrogen peroxide and ferric sulfate. D-(−)-Ribose, for example, can be degraded to D-(−)-erythrose:



D-(−)-Ribose D-Ribonic acid D-(−)-Erythrose

PRACTICE PROBLEM 22.17 The aldohexose D-(+)-galactose can be obtained by hydrolysis of *lactose*, a disaccharide found in milk. When D-(+)-galactose is treated with nitric acid, it yields an optically inactive aldaric acid. When D-(+)-galactose is subjected to Ruff degradation, it yields D-(−)-lyxose (see Practice Problem 22.15). Using only these data, write the Fischer projection formula for D-(+)-galactose.

22.10 THE D FAMILY OF ALDOSES

The Ruff degradation and the Kiliani–Fischer synthesis allow us to place all of the aldoses into families or "family trees" based on their relation to D- or L-glyceraldehyde. Such a tree is constructed in Fig. 22.7 and includes the structures of the D-aldohexoses, **1–8**.

- Most, but not all, of the naturally occurring aldoses belong to the D family, with D-(+)-glucose being by far the most common.

*Developed by Otto Ruff, 1871–1939, a German chemist.

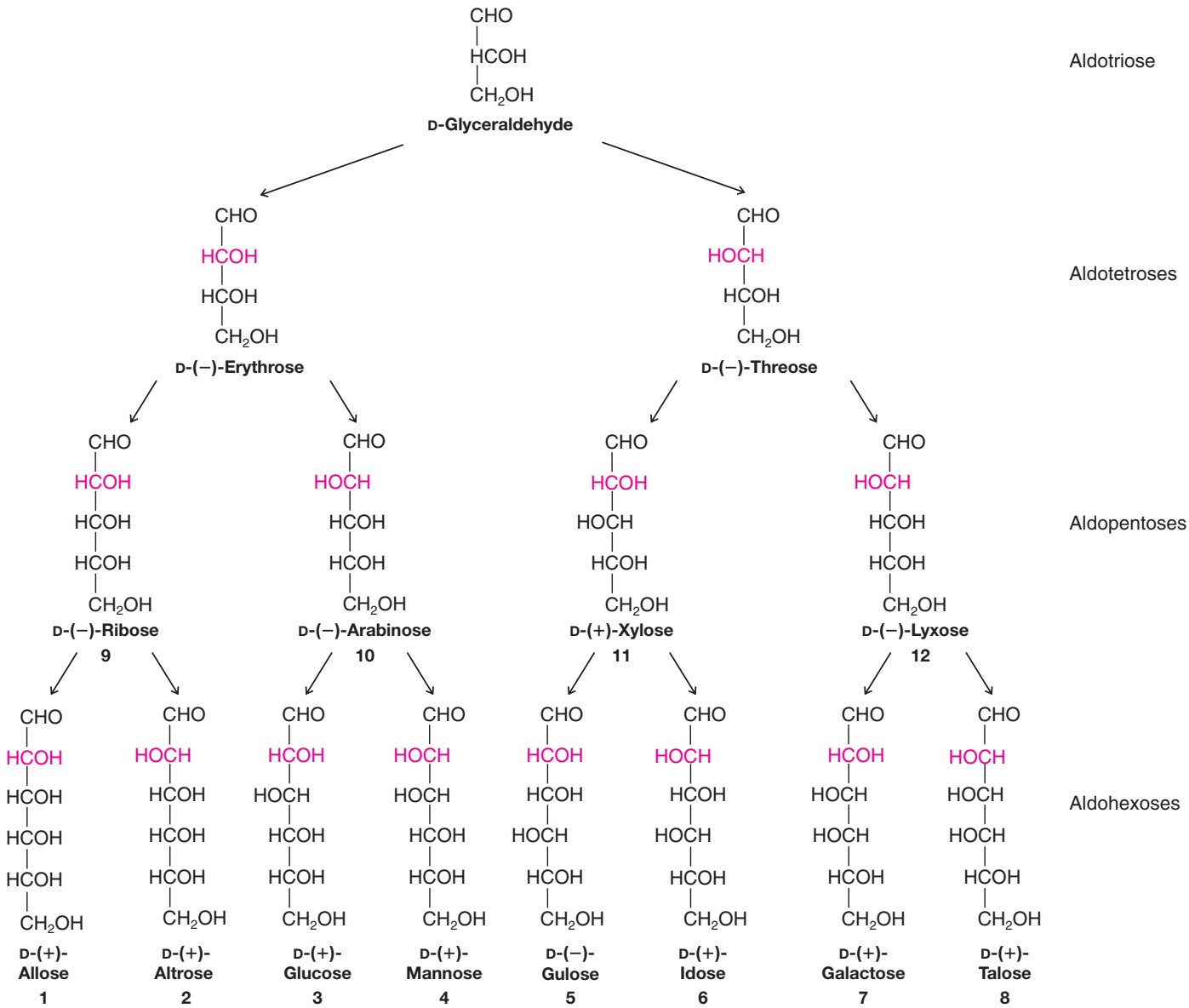


FIGURE 22.7 The D family of aldohexoses.

D-(+)-Galactose can be obtained from milk sugar (lactose), but L-(−)-galactose occurs in a polysaccharide obtained from the vineyard snail, *Helix pomatia*. L-(+)-Arabinose is found widely, but D-(−)-arabinose is scarce, being found only in certain bacteria and sponges. Threose, lyxose, gulose, and allose do not occur naturally, but one or both forms (D or L) of each have been synthesized.

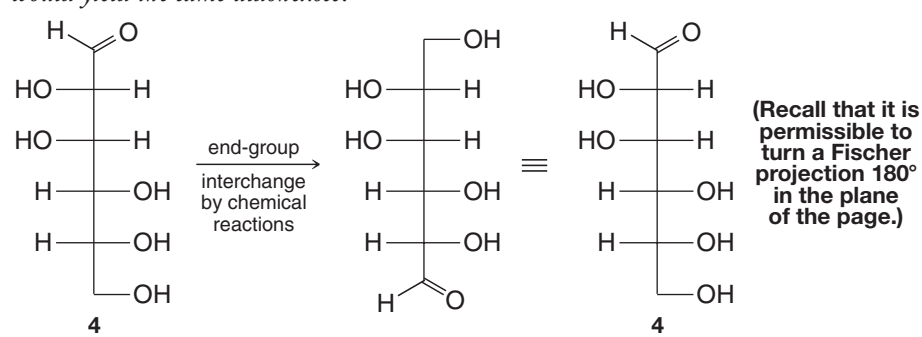
22.11 FISCHER'S PROOF OF THE CONFIGURATION OF D-(+)-GLUCOSE

Emil Fischer began his work on the stereochemistry of (+)-glucose in 1888, only 12 years after van't Hoff and Le Bel had made their proposal concerning the tetrahedral structure of carbon. Only a small body of data was available to Fischer at the beginning. Only a few monosaccharides were known, including (+)-glucose, (+)-arabinose, and (+)-mannose. [(+)-Mannose had just been synthesized by Fischer.] The sugars (+)-glucose and (+)-mannose were known to be aldohexoses; (+)-arabinose was known to be an aldopentose.

Since an aldohexose has four chirality centers, 2^4 (or 16) stereoisomers are possible—*one of which is* (+)-*glucose*. Fischer arbitrarily decided to limit his attention to the eight structures with the D configuration given in Fig. 22.7 (structures **1–8**). Fischer realized that he would be unable to differentiate between enantiomeric configurations because methods for determining the absolute configuration of organic compounds had not been developed. It was not until 1951, when Bijvoet (Section 5.15A) determined the absolute configuration of L-(+)-tartaric acid [and, hence, D-(+)-glyceraldehyde], that Fischer's arbitrary assignment of (+)-glucose to the family we call the D family was known to be correct.

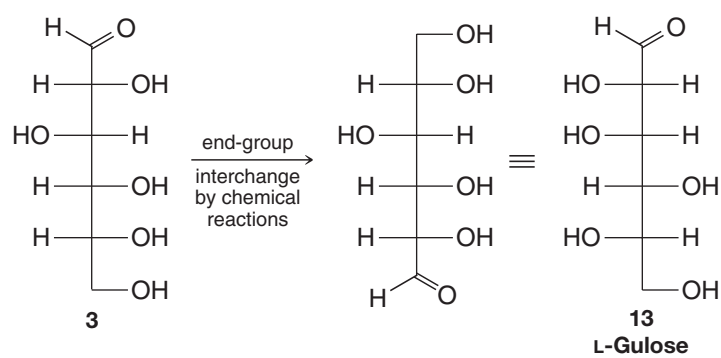
Fischer's assignment of structure **3** to (+)-glucose was based on the following reasoning:

1. Nitric acid oxidation of (+)-glucose gives an optically active aldaric acid. This eliminates structures **1** and **7** from consideration because both compounds would yield *meso*-aldaric acids.
2. *Degradation of* (+)-*glucose gives* (−)-*arabinose, and nitric acid oxidation of* (−)-*arabinose gives an optically active aldaric acid*. This means that (−)-arabinose cannot have configuration **9** or **11** and must have either structure **10** or **12**. It also establishes that (+)-glucose cannot have configuration **2**, **5**, or **6**. This leaves structures **3**, **4**, and **8** as possibilities for (+)-glucose.
3. Kiliani–Fischer synthesis beginning with (−)-arabinose gives (+)-glucose and (+)-mannose; nitric acid oxidation of (+)-mannose gives an optically active aldaric acid. This, together with the fact that (+)-glucose yields a different but also optically active aldaric acid, establishes **10** as the structure of (−)-arabinose and eliminates **8** as a possible structure for (+)-glucose. Had (−)-arabinose been represented by structure **12**, a Kiliani–Fischer synthesis would have given the two aldohexoses, **7** and **8**, one of which (**7**) would yield an optically inactive aldaric acid on nitric acid oxidation.
4. Two structures now remain, **3** and **4**; one structure represents (+)-glucose and one represents (+)-mannose. Fischer realized that (+)-glucose and (+)-mannose were epimeric (at C2), but a decision as to which compound was represented by which structure was most difficult.
5. Fischer had already developed a method for effectively *interchanging the two end groups* (aldehyde and primary alcohol) *of an aldose chain*. And, with brilliant logic, Fischer realized that if (+)-glucose had structure **4**, an interchange of end groups *would yield the same aldohexose*:



4 4

On the other hand, if (+)-glucose has structure **3**, *an end-group interchange will yield a different aldohexose*, **13**:

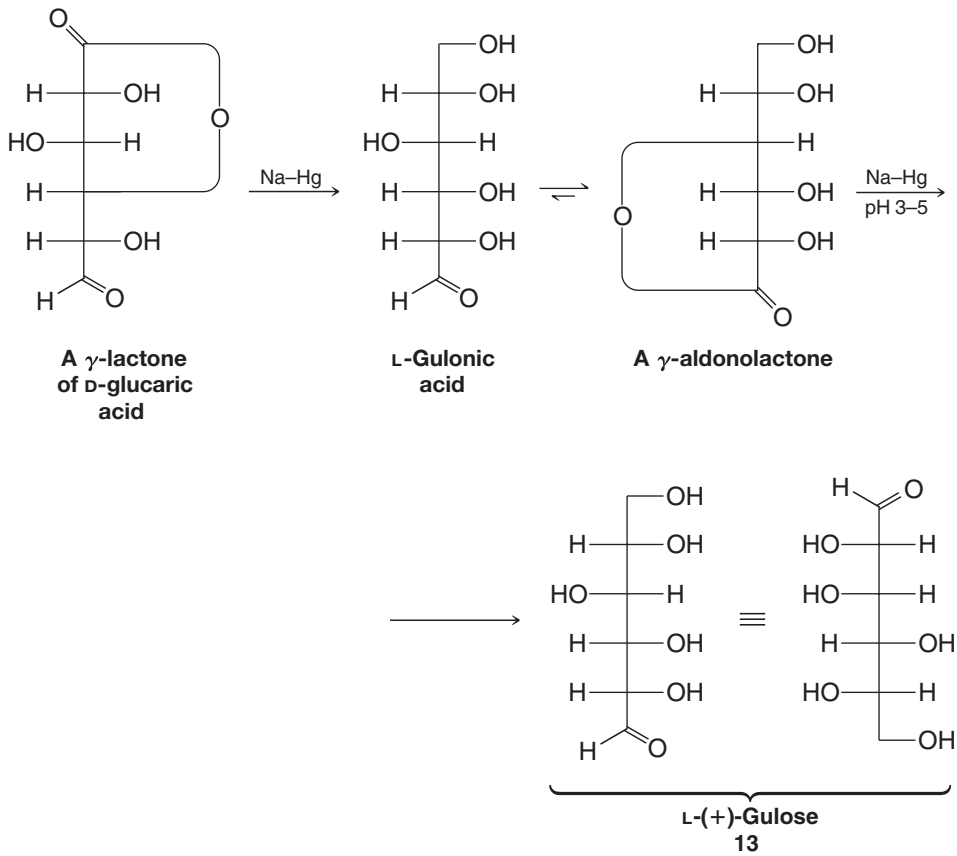


3 13
L-Gulose

This new aldohexose, if it were formed, would be an L sugar and it would be the mirror reflection of D-gulose. Thus its name would be L-gulose.

Fischer carried out the end-group interchange starting with (+)-glucose and *the product was the new aldohexose* **13**. This outcome proved that (+)-glucose has structure **3**. It also established **4** as the structure for (+)-mannose, and it proved the structure of L-(+)-gulose as **13**.

The procedure Fischer used for interchanging the ends of the (+)-glucose chain began with one of the γ-lactones of D-glucaric acid (see Practice Problem 22.8) and was carried out as follows:



Helpful Hint

See *WileyPLUS* for "The Chemistry of . . . Stereoselective Synthesis of all the L-Aldohexoses."

Notice in this synthesis that the second reduction with Na–Hg is carried out at pH 3–5. Under these conditions, reduction of the lactone yields an aldehyde and not a primary alcohol.

PRACTICE PROBLEM 22.18

Fischer actually had to subject both γ-lactones of D-glucaric acid (Practice Problem 22.8) to the procedure just outlined. What product does the other γ-lactone yield?

22.12 DISACCHARIDES

22.12A Sucrose

Ordinary table **sugar** is a **disaccharide** called *sucrose*. Sucrose, the most widely occurring disaccharide, is found in all photosynthetic plants and is obtained commercially from sugarcane or sugar beets. Sucrose has the structure shown in Fig. 22.8.

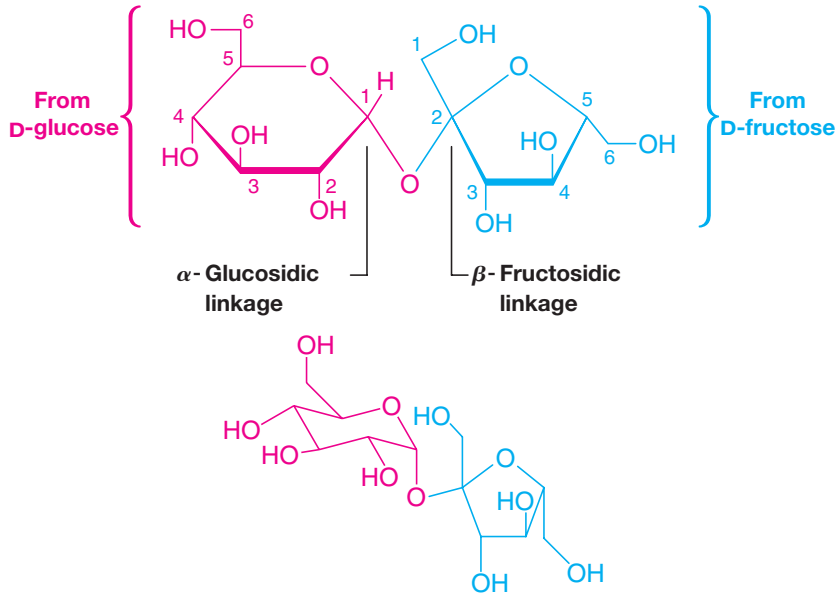
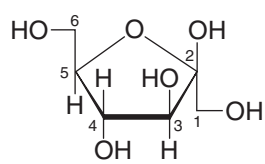


FIGURE 22.8 Two representations of the formula for (+)-sucrose (α-D-glucopyranosyl β-D-fructofuranoside).

The structure of sucrose is based on the following evidence:

1. Sucrose has the molecular formula $C_{12}H_{22}O_{11}$.
2. Acid-catalyzed hydrolysis of 1 mol of sucrose yields 1 mol of D-glucose and 1 mol of D-fructose.



Fructose (as a β-furanose)

3. Sucrose is a nonreducing sugar; it gives negative tests with Benedict's and Tollens' solutions. Sucrose does not form an osazone and does not undergo mutarotation. These facts mean that neither the glucose nor the fructose portion of sucrose has a hemiacetal group. Thus, the two hexoses must have a glycosidic linkage that involves C1 of glucose and C2 of fructose, for only in this way will both carbonyl groups be present as full acetals (i.e., as glycosides).
4. The stereochemistry of the glycosidic linkages can be inferred from experiments done with enzymes. Sucrose is hydrolyzed by an *α-glucosidase* obtained from yeast but not by β-glucosidase enzymes. This hydrolysis indicates *an α configuration at the glucoside portion*. Sucrose is also hydrolyzed by *sucrase*, an enzyme known to hydrolyze β-fructofuranosides but not α-fructofuranosides. This hydrolysis indicates a β *configuration at the fructoside portion*.
5. Methylation of sucrose gives an octamethyl derivative that, on hydrolysis, gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 1,3,4,6-tetra-*O*-methyl-D-fructose. The identities of these two products demonstrate that the glucose portion is a *pyranoside* and that the fructose portion is a *furanoside*.

The structure of sucrose has been confirmed by X-ray analysis and by an unambiguous synthesis.

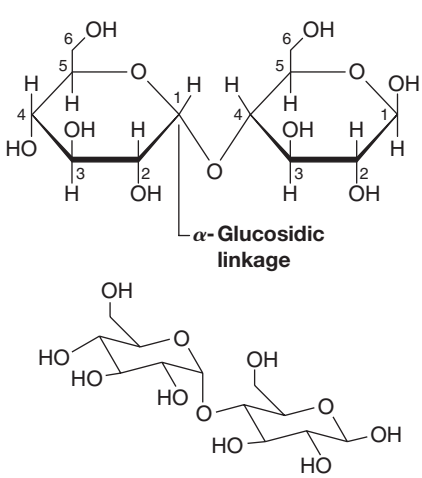


FIGURE 22.9 Two representations of the structure of the β anomer of (+)-maltose, 4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranose.

22.12B Maltose

When starch (Section 22.13A) is hydrolyzed by the enzyme *diastase*, one product is a disaccharide known as *maltose* (Fig. 22.9). The structure of maltose was deduced based on the following evidence:

1. When 1 mol of maltose is subjected to acid-catalyzed hydrolysis, it yields 2 mol of D-(+)-glucose.

2. Unlike sucrose, *maltose is a reducing sugar*; it gives positive tests with Fehling's, Benedict's, and Tollens' solutions. Maltose also reacts with phenylhydrazine to form a monophenylosazone (i.e., it incorporates two molecules of phenylhydrazine).
3. Maltose exists in two anomeric forms: α-(+)-maltose, $[\alpha]_D^{25} = +168$, and β-(+)-maltose, $[\alpha]_D^{25} = +112$. The maltose anomers undergo mutarotation to yield an equilibrium mixture, $[\alpha]_D^{25} = +136$.

Facts 2 and 3 demonstrate that one of the glucose residues of maltose is present in a hemiacetal form; the other, therefore, must be present as a glucoside. The configuration of this glucosidic linkage can be inferred as α, because maltose is hydrolyzed by α-glucosidase enzymes and not by β-glucosidase enzymes.

4. Maltose reacts with bromine water to form a monocarboxylic acid, maltonic acid (Fig. 22.10*a*). This fact, too, is consistent with the presence of only one hemiacetal group.
5. Methylation of maltonic acid followed by hydrolysis gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,5,6-tetra-*O*-methyl-D-gluconic acid. That the first product has a free

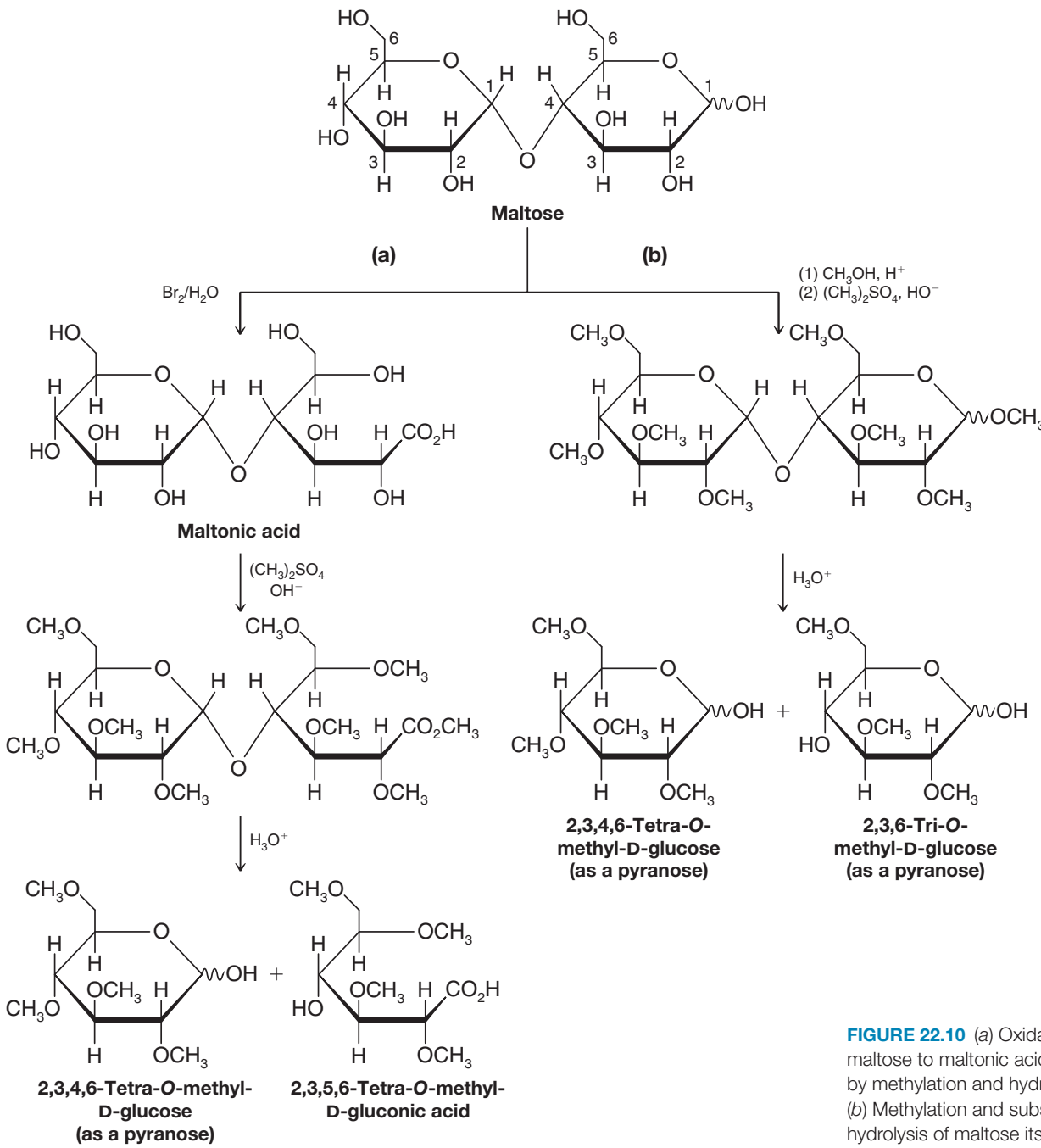


FIGURE 22.10 (*a*) Oxidation of maltose to maltonic acid followed by methylation and hydrolysis. (*b*) Methylation and subsequent hydrolysis of maltose itself.

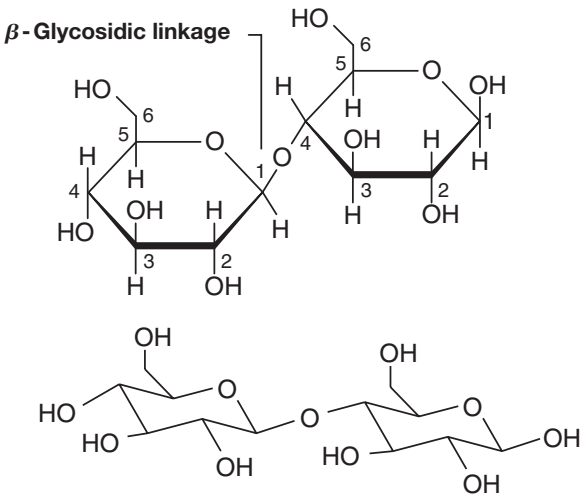


FIGURE 22.11 Two representations of the β anomer of cellobiose, 4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose.

—OH at C5 indicates that the nonreducing glucose portion is present as a pyranoside; that the second product, 2,3,5,6-tetra-*O*-methyl-D-gluconic acid, has a free —OH at C4 indicates that this position was involved in a glycosidic linkage with the nonreducing glucose. Only the size of the reducing glucose ring needs to be determined.

6. Methylation of maltose itself, followed by hydrolysis (Fig. 22.10*b*), gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,6-tri-*O*-methyl-D-glucose. The free —OH at C5 in the latter product indicates that it must have been involved in the oxide ring and that the reducing glucose is present as a *pyranose*.

22.12C Cellobiose

Partial hydrolysis of cellulose (Section 22.13C) gives the disaccharide cellobiose ($C_{12}H_{22}O_{11}$) (Fig. 22.11). Cellobiose resembles maltose in every respect except one: the configuration of its glycosidic linkage.

Cellobiose, like maltose, is a reducing sugar that, on acid-catalyzed hydrolysis, yields two molar equivalents of D-glucose. Cellobiose also undergoes mutarotation and forms a monophenylosazone. Methylation studies show that C1 of one glucose unit is connected in glycosidic linkage with C4 of the other and that both rings are six membered. Unlike maltose, however, cellobiose is hydrolyzed by *β-glucosidase* enzymes and not by α-glucosidase enzymes: This indicates that the glycosidic linkage in cellobiose is β (Fig. 22.11).

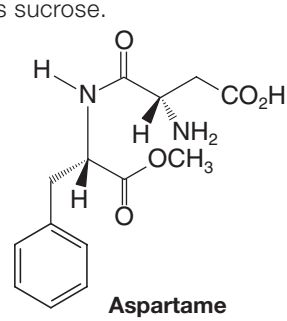
THE CHEMISTRY OF... Artificial Sweeteners (How Sweet It Is)

Sucrose (table sugar) and fructose are the most common natural sweeteners. We all know, however, that they add to our calorie intake and promote tooth decay. For these reasons, many people find artificial sweeteners to be an attractive alternative to the natural and calorie-contributing counterparts.

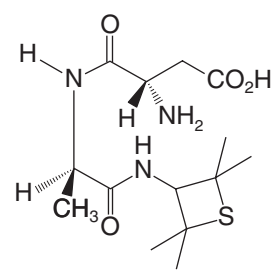
Charles D. WInters/PhotoResearchers, Inc.

Some products that contain the artificial sweetener aspartame.

Perhaps the most successful and widely used artificial sweetener is aspartame, the methyl ester of a dipeptide formed from phenylalanine and aspartic acid. Aspartame is roughly 100 times as sweet as sucrose. It undergoes slow hydrolysis in solution, however, which limits its shelf life in products such as soft drinks. It also cannot be used for baking because it decomposes with heat. Furthermore, people with a genetic condition known as phenylketonuria cannot use aspartame because their metabolism causes a buildup of phenylpyruvic acid derived from aspartame. Accumulation of phenylpyruvic acid is harmful, especially to infants. Alitame, on the other hand, is a compound related to aspartame, but with improved properties. It is more stable than aspartame and roughly 2000 times as sweet as sucrose.

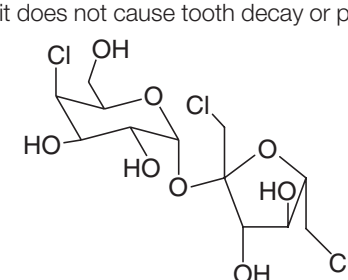


Aspartame



Alitame

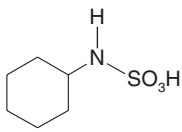
Sucralose is a trichloro derivative of sucrose that is an artificial sweetener. Like aspartame, it is also approved for use by the U.S. Food and Drug Administration (FDA). Sucralose is 600 times sweeter than sucrose and has many properties desirable in an artificial sweetener. Sucralose looks and tastes like sugar, is stable at the temperatures used for cooking and baking, and it does not cause tooth decay or provide calories.



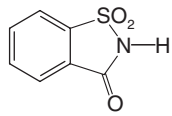
Sucralose

Cyclamate and saccharin, used as their sodium or calcium salts, were popular sweeteners at one time. A common formulation involved a 10:1 mixture of cyclamate and saccharin that proved sweeter than either compound individually. Tests showed, however, that this mixture produced tumors in

animals, and the FDA subsequently banned it. Certain exclusions to the regulations nevertheless allow continued use of saccharin in some products.

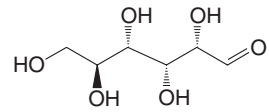


Cyclamate



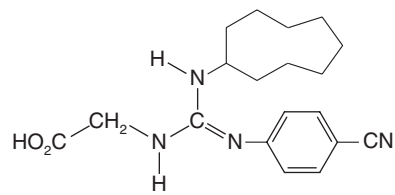
Saccharin

Many other compounds have potential as artificial sweeteners. For example, L sugars are also sweet, and they presumably would provide either zero or very few calories because our enzymes have evolved to selectively metabolize their enantiomers instead, the D sugars. Although sources of L sugars are rare in nature, all eight L-hexoses have been synthesized by S. Masamune and K. B. Sharpless using the Sharpless asymmetric epoxidation (Sections 11.13 and 22.11) and other enantioselective synthetic methods.



L-Glucose

Much of the research on sweeteners involves probing the structure of sweetness receptor sites. One model proposed for a sweetness receptor incorporates eight binding interactions that involve hydrogen bonding as well as van der Waals forces. Sucronic acid is a synthetic compound designed on the basis of this model. Sucronic acid is reported to be 200,000 times as sweet as sucrose.



Sucronic acid

22.12D Lactose

Lactose (Fig. 22.12) is a disaccharide present in the milk of humans, cows, and almost all other mammals. Lactose is a reducing sugar that hydrolyzes to yield D-glucose and D-galactose; the glycosidic linkage is β.

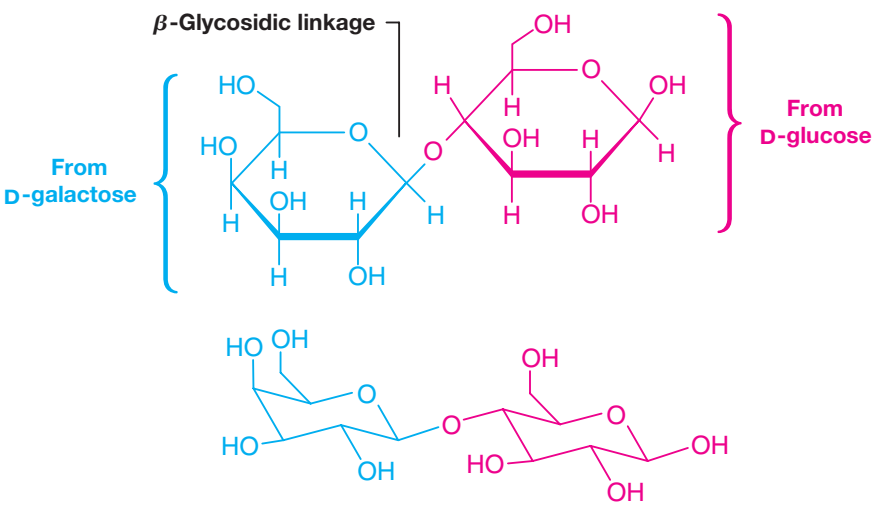


FIGURE 22.12 Two representations of the β anomer of lactose, 4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranose.

22.13 POLYSACCHARIDES

- **Polysaccharides**, also known as **glycans**, consist of monosaccharides joined together by glycosidic linkages.

Polysaccharides that are polymers of a single monosaccharide are called **homopolysaccharides**; those made up of more than one type of monosaccharide are called **heteropolysaccharides**. Homopolysaccharides are also classified on the basis of their monosaccharide units. A homopolysaccharide consisting of glucose monomeric units is called a **glucan**; one consisting of galactose units is a **galactan**, and so on.

Three important polysaccharides, all of which are glucans, are starch, glycogen, and cellulose.

- Starch is the principal food reserve of plants, glycogen functions as a carbohydrate reserve for animals, and cellulose serves as structural material in plants.

As we examine the structures of these three polysaccharides, we shall be able to see how each is especially suited for its function.

22.13A Starch

Starch occurs as microscopic granules in the roots, tubers, and seeds of plants. Corn, potatoes, wheat, and rice are important commercial sources of starch. Heating starch with water causes the granules to swell and produce a colloidal suspension from which two major components can be isolated. One fraction is called *amylose* and the other *amylopectin*. Most starches yield 10–20% amylose and 80–90% amylopectin.

- Amylose typically consists of more than 1000 D-glucopyranoside units *connected in α linkages* between C1 of one unit and C4 of the next (Fig. 22.13).

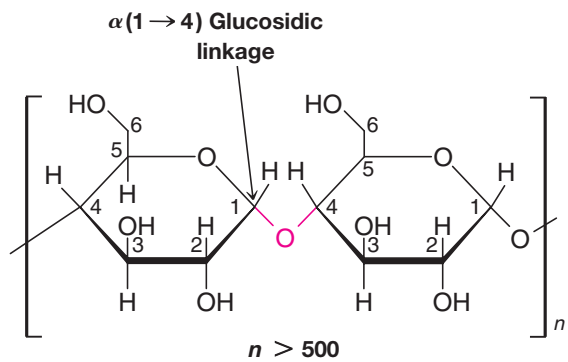


FIGURE 22.13 Partial structure of amylose, an unbranched polymer of D-glucose connected in α(1 → 4) glycosidic linkages.

Thus, in the ring size of its glucose units and in the configuration of the glycosidic linkages between them, amylose resembles maltose.

Chains of D-glucose units with α-glycosidic linkages such as those of amylose tend to assume a helical arrangement (Fig. 22.14). This arrangement results in a compact shape for the amylose molecule even though its molecular weight is quite large (150,000–600,000).

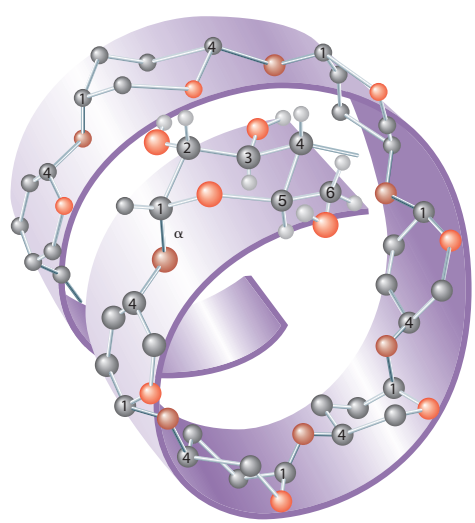


FIGURE 22.14 Amylose. The α(1 → 4) linkages cause it to assume the shape of a left-handed helix.
(Illustration, Irving Geis. Image from the Irving Geis Collection, HHMI. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.)

- Amylopectin has a structure similar to that of amylose [i.e., α(1 → 4) links], except that in amylopectin the chains are branched. Branching takes place between C6 of one glucose unit and C1 of another and occurs at intervals of 20–25 glucose units (Fig. 22.15).

Physical measurements indicate that amylopectin has a molecular weight of 1–6 million; thus amylopectin consists of hundreds of interconnecting chains of 20–25 glucose units each.

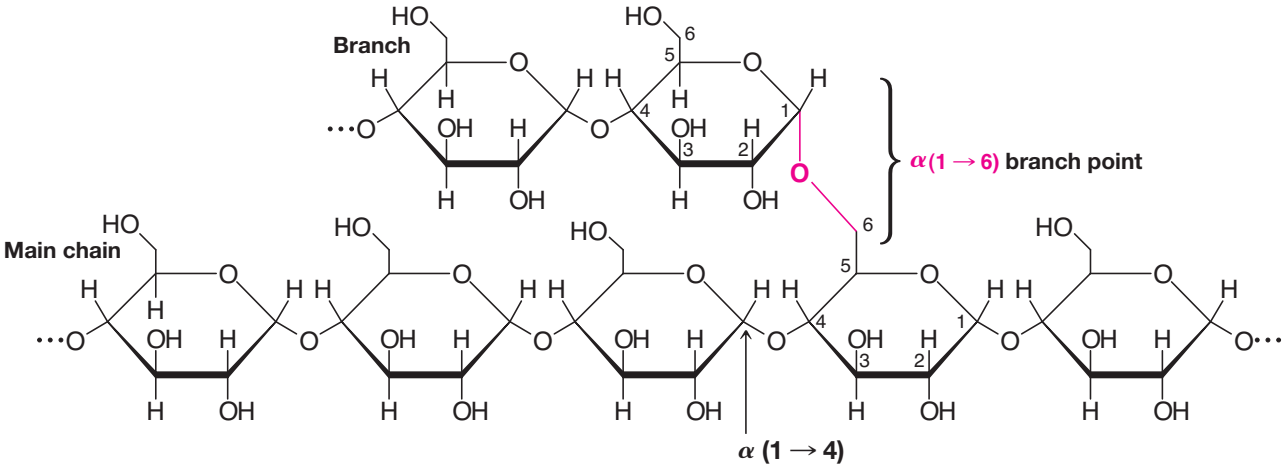


FIGURE 22.15 Partial structure of amylopectin.

22.13B Glycogen

- Glycogen has a structure very much like that of amylopectin; however, in glycogen the chains are much more highly branched.

Methylation and hydrolysis of glycogen indicate that there is one end group for every 10–12 glucose units; branches may occur as often as every 6 units. Glycogen has a very high molecular weight. Studies of glycogens isolated under conditions that minimize the likelihood of hydrolysis indicate molecular weights as high as 100 million.

The size and structure of glycogen beautifully suit its function as a reserve carbohydrate for animals. First, its size makes it too large to diffuse across cell membranes; thus, glycogen remains inside the cell, where it is needed as an energy source. Second, because glycogen incorporates tens of thousands of glucose units in a single molecule, it solves an important osmotic problem for the cell. Were so many glucose units present in the cell as individual molecules, the osmotic pressure within the cell would be enormous—so large that the cell membrane would almost certainly break.* Finally, the localization of glucose units within a large, highly branched structure simplifies one of the cell's logistical problems: that of having a ready source of glucose when cellular glucose concentrations are low and of being able to store glucose rapidly when cellular glucose concentrations are high. There are enzymes within the cell that catalyze the reactions by which glucose units are detached from (or attached to) glycogen. These enzymes operate at end groups by hydrolyzing (or forming) $\alpha(1 \rightarrow 4)$ glycosidic linkages. Because glycogen is so highly branched, a very large number of end groups is available at which these enzymes can operate. At the same time the overall concentration of glycogen (in moles per liter) is quite low because of its enormous molecular weight.

Amylopectin presumably serves a similar function in plants. The fact that amylopectin is less highly branched than glycogen is, however, not a serious disadvantage. Plants have a much lower metabolic rate than animals—and plants, of course, do not require sudden bursts of energy.

Animals store energy as fats (triacylglycerols) as well as glycogen. Fats, because they are more highly reduced, are capable of furnishing much more energy. The metabolism of a typical fatty acid, for example, liberates more than twice as much energy per carbon as glucose or glycogen. Why, then, we might ask, have two different energy repositories evolved? Glucose (from glycogen) is readily available and is highly water soluble.** Glucose, as a result, diffuses rapidly through the aqueous medium of the cell and serves as an ideal source of "ready energy." Long-chain fatty acids, by contrast, are almost insoluble in water, and their concentration inside the cell could never be very high. They would be

*The phenomenon of osmotic pressure occurs whenever two solutions of different concentrations are separated by a membrane that allows penetration (by osmosis) of the solvent but not of the solute. The osmotic pressure (π) on one side of the membrane is related to the number of moles of solute particles (n), the volume of the solution (V), and the gas constant times the absolute temperature (RT): $\pi V = nRT$.

**Glucose is actually liberated as glucose-6-phosphate (G6P), which is also water soluble.

a poor source of energy if the cell were in an energy pinch. On the other hand, fatty acids (as triacylglycerols), because of their caloric richness, are an excellent energy repository for long-term energy storage.

22.13C Cellulose

When we examine the structure of cellulose, we find another example of a polysaccharide in which nature has arranged monomeric glucose units in a manner that suits its function.

- Cellulose contains D-glucopyranoside units linked in (1 → 4) fashion in very long unbranched chains. Unlike starch and glycogen, however, the linkages in cellulose are *β-glycosidic linkages* (Fig. 22.16).

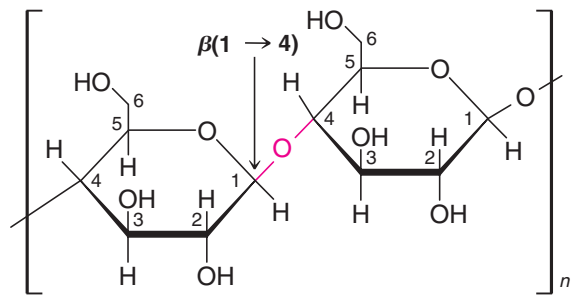


FIGURE 22.16 A portion of a cellulose chain. The glycosidic linkages are β(1 → 4).

The β-glycosidic linkages of cellulose make cellulose chains essentially linear; they do not tend to coil into helical structures as do glucose polymers when linked in an α(1 → 4) manner.

The linear arrangement of β-linked glucose units in cellulose presents a uniform distribution of —OH groups on the outside of each chain. When two or more cellulose chains make contact, the hydroxyl groups are ideally situated to "zip" the chains together by forming hydrogen bonds (Fig. 22.17). Zipping many cellulose chains together in this way gives a highly insoluble, rigid, and fibrous polymer that is ideal as cell-wall material for plants.

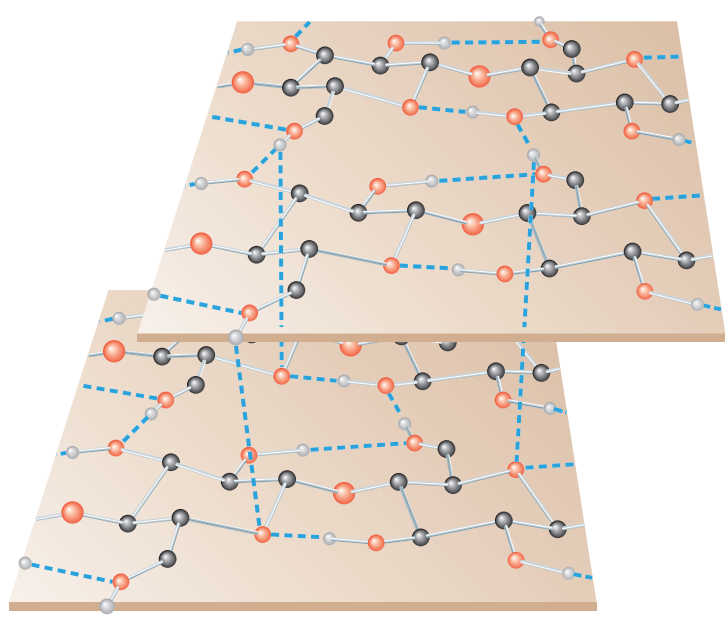


FIGURE 22.17 A proposed structure for cellulose. A fiber of cellulose may consist of about 40 parallel strands of glucose molecules linked in a β(1 → 4) fashion. Each glucose unit in a chain is turned over with respect to the preceding glucose unit and is held in this position by hydrogen bonds (dashed lines) between the chains. The glucan chains line up laterally to form sheets, and these sheets stack vertically so that they are staggered by one-half of a glucose unit. (Hydrogen atoms that do not participate in hydrogen bonding have been omitted for clarity.)

This special property of cellulose chains, we should emphasize, is not just a result of β(1 → 4) glycosidic linkages; it is also a consequence of the precise stereochemistry of D-glucose at each chirality center. Were D-galactose or D-allose units linked in a similar fashion, they almost certainly would not give rise to a polymer with properties like

cellulose. Thus, we get another glimpse of why D-glucose occupies such a special position in the chemistry of plants and animals. Not only is it the most stable aldohexose (because it can exist in a chair conformation that allows all of its bulky groups to occupy equatorial positions), but its special stereochemistry also allows it to form helical structures when α linked as in starches, and rigid linear structures when β linked as in cellulose.

There is another interesting and important fact about cellulose: the digestive enzymes of humans cannot attack its $\beta(1 \rightarrow 4)$ linkages. Hence, cellulose cannot serve as a food source for humans, as can starch. Cows and termites, however, can use cellulose (of grass and wood) as a food source because symbiotic bacteria in their digestive systems furnish β-glucosidase enzymes.

Perhaps we should ask ourselves one other question: Why has D-(+)-glucose been selected for its special role rather than L-(−)-glucose, its mirror image? Here an answer cannot be given with any certainty. The selection of D-(+)-glucose may simply have been a random event early in the course of the evolution of enzyme catalysts. Once this selection was made, however, the chirality of the active sites of the enzymes involved would retain a bias toward D-(+)-glucose and against L-(−)-glucose (because of the improper fit of the latter). Once introduced, this bias would be perpetuated and extended to other catalysts.

Finally, when we speak about evolutionary selection of a particular molecule for a given function, we do not mean to imply that evolution operates on a molecular level. Evolution, of course, takes place at the level of organism populations, and molecules are selected only in the sense that their use gives the organism an increased likelihood of surviving and procreating.

22.13D Cellulose Derivatives

A number of derivatives of cellulose are used commercially. Most of these are compounds in which two or three of the free hydroxyl groups of each glucose unit have been converted to an ester or an ether. This conversion substantially alters the physical properties of the material, making it more soluble in organic solvents and allowing it to be made into fibers and films. Treating cellulose with acetic anhydride produces the triacetate known as "Arnel" or "acetate," used widely in the textile industry. Cellulose trinitrate, also called "gun cotton" or nitrocellulose, is used in explosives.

Rayon is made by treating cellulose (from cotton or wood pulp) with carbon disulfide in a basic solution. This reaction converts cellulose to a soluble xanthate:

$$\text{Cellulose—OH} + CS_2 \xrightarrow{\text{NaOH}} \text{cellulose—O—C(=S)—S}^- \text{Na}^+$$

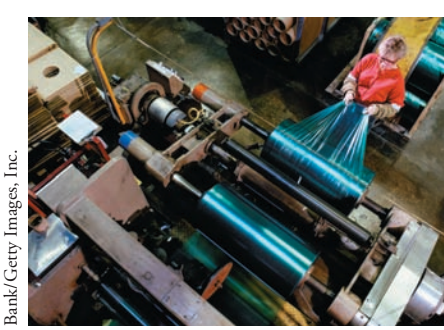
Cellulose xanthate

The solution of cellulose xanthate is then passed through a small orifice or slit into an acidic solution. This operation regenerates the —OH groups of cellulose, causing it to precipitate as a fiber or a sheet:

$$\text{Cellulose—O—C(=S)—S}^- \text{Na}^+ \xrightarrow{H_3O^+} \text{cellulose—OH}$$

Rayon or cellophane

The fibers are *rayon*; the sheets, after softening with glycerol, are *cellophane*.



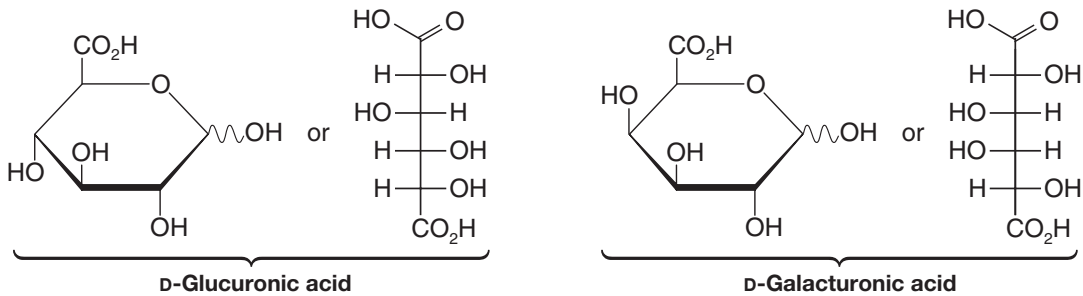
Harry Sieplinga/HMS Images/The Image Bank/Getty Images, Inc.

Cellophane on rollers at a manufacturing plant.

22.14 OTHER BIOLOGICALLY IMPORTANT SUGARS

Monosaccharide derivatives in which the —CH_2OH group at C6 has been specifically oxidized to a carboxyl group are called **uronic acids**. Their names are based on the monosaccharide from which they are derived. For example, specific oxidation of C6 of

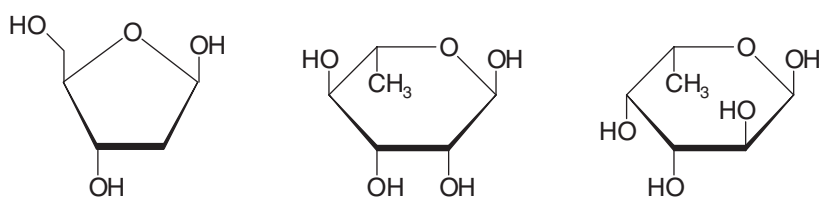
glucose to a carboxyl group converts *glucose* to **glucuronic acid**. In the same way, specific oxidation of C6 of *galactose* would yield **galacturonic acid**:



PRACTICE PROBLEM 22.19 Direct oxidation of an aldose affects the aldehyde group first, converting it to a carboxylic acid (Section 22.6B), and most oxidizing agents that will attack 1° alcohol groups will also attack 2° alcohol groups. Clearly, then, a laboratory synthesis of a uronic acid from an aldose requires protecting these groups from oxidation. Keeping this in mind, suggest a method for carrying out a specific oxidation that would convert D-galactose to D-galacturonic acid. (*Hint*: See Section 22.5E.)

- Monosaccharides in which an —OH group has been replaced by —H are known as **deoxy sugars**.

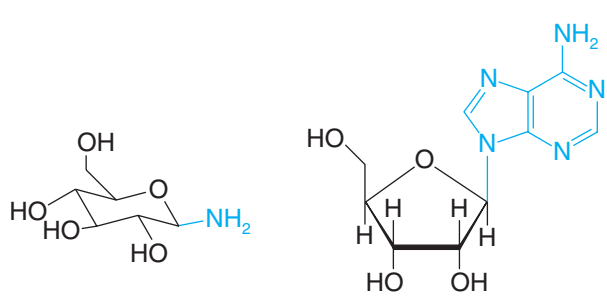
The most important deoxy sugar, because it occurs in DNA, is **deoxyribose**. Other deoxy sugars that occur widely in polysaccharides are L-rhamnose and L-fucose:



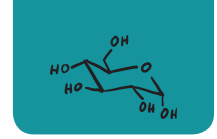
22.15 SUGARS THAT CONTAIN NITROGEN

22.15A Glycosylamines

A sugar in which an amino group replaces the anomeric —OH is called a glycosylamine. Examples are β-D-glucopyranosylamine and adenosine:



Adenosine is an example of a glycosylamine that is also called a nucleoside.



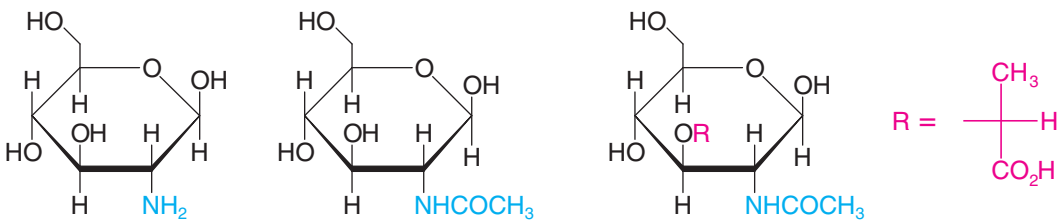
- **Nucleosides** are glycosylamines in which the amino component is a pyrimidine or a purine (Section 20.1B) and in which the sugar component is either D-ribose or 2-deoxy-D-ribose (i.e., D-ribose minus the oxygen at the 2 position).

Nucleosides are the important components of RNA (ribonucleic acid) and DNA (deoxyribonucleic acid). We shall describe their properties in detail in Section 25.2.

22.15B Amino Sugars

- A sugar in which an amino group replaces a nonanomeric —OH group is called an **amino sugar**.

D-Glucosamine is an example of an amino sugar. In many instances the amino group is acetylated as in *N*-**acetyl-D-glucosamine**. *N*-**Acetylmuramic acid** is an important component of bacterial cell walls (Section 24.10).



D-Glucosamine can be obtained by hydrolysis of **chitin**, a polysaccharide found in the shells of lobsters and crabs and in the external skeletons of insects and spiders. The amino group of D-glucosamine as it occurs in chitin, however, is acetylated; thus, the repeating unit is actually *N*-acetylglucosamine (Fig. 22.18). The glycosidic linkages in chitin are $\beta(1 \rightarrow 4)$. X-Ray analysis indicates that the structure of chitin is similar to that of cellulose.

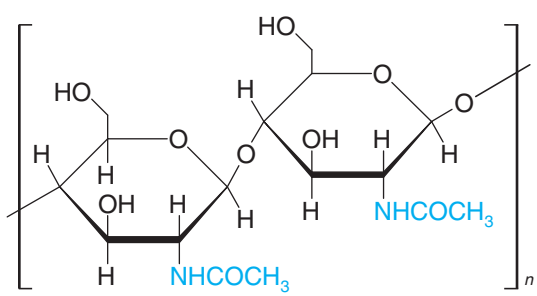


FIGURE 22.18 A partial structure of chitin. The repeating units are *N*-acetylglucosamines linked $\beta(1 \rightarrow 4)$.

D-Glucosamine can also be isolated from **heparin**, a sulfated polysaccharide that consists predominately of alternating units of D-glucuronate-2-sulfate and *N*-sulfo-D-glucosamine-6-sulfate (Fig. 22.19). Heparin occurs in intracellular granules of mast cells that line arterial walls, where, when released through injury, it inhibits the clotting of blood. Its purpose seems to be to prevent runaway clot formation. Heparin is widely used in medicine to prevent blood clotting in postsurgical patients.

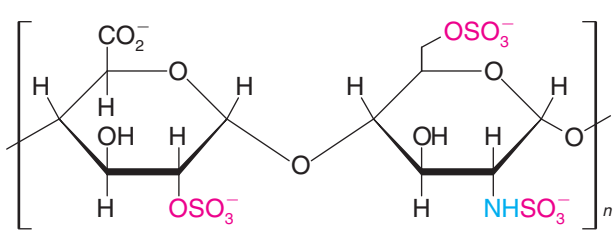
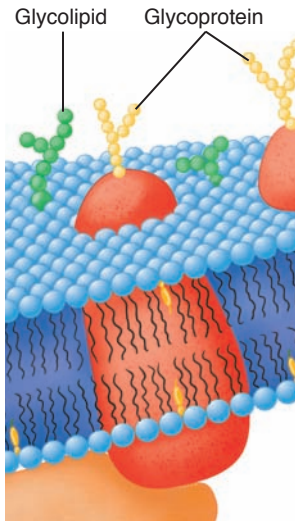


FIGURE 22.19 A partial structure of heparin, a polysaccharide that prevents blood clotting.

22.16 GLYCOLIPIDS AND GLYCOPROTEINS OF THE CELL SURFACE: CELL RECOGNITION AND THE IMMUNE SYSTEM



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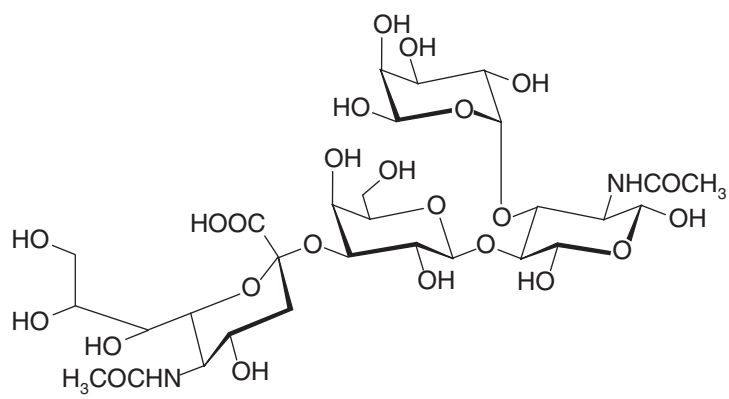
Before 1960, it was thought that the biology of carbohydrates was rather uninteresting—that, in addition to being a kind of inert filler in cells, carbohydrates served only as an energy source and, in plants, as structural materials. Research has shown, however, that carbohydrates joined through glycosidic linkages to lipids (Chapter 23) and to proteins (Chapter 24), called **glycolipids** and **glycoproteins**, respectively, have functions that span the entire spectrum of activities in the cell. Indeed, most proteins are glycoproteins, of which the carbohydrate content can vary from less than 1% to greater than 90%.

Glycolipids and glycoproteins on the cell surface (Section 23.6A) are now known to be the agents by which cells interact with other cells and with invading bacteria and viruses. The immune system's role in healing and in autoimmune diseases such as rheumatoid arthritis involves cell recognition through cell surface carbohydrates. Important carbohydrates in this role are sialyl Lewis^x acids (see "The Chemistry of . . . Patroling Leukocytes and Sialyl Lewis^x Acids" below). Tumor cells also have specific carbohydrate markers on their surface as well, a fact that may make it possible to develop vaccines against cancer. (See "The Chemistry of . . . Vaccines Against Cancer" in *WileyPLUS*.)



A sialyl Lewis^x acid

The human blood groups offer another example of how carbohydrates, in the form of glycolipids and glycoproteins, act as biochemical markers. The A, B, and O blood types are determined, respectively, by the A, B, and H determinants on the blood cell surface. (The odd naming of the type O determinant came about for complicated historical reasons.) Type AB blood cells have both A and B determinants. These determinants are the carbohydrate portions of the A, B, and H **antigens**.

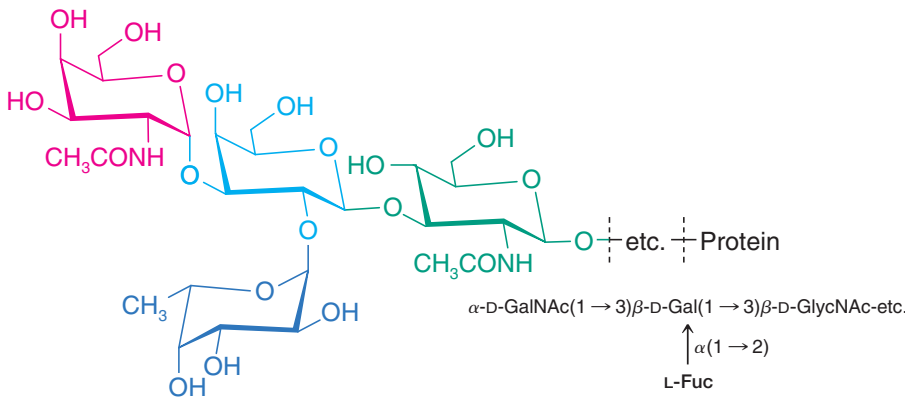
Antigens are characteristic chemical substances that cause the production of **antibodies** when injected into an animal. Each antibody can bind at least two of its corresponding antigen molecules, causing them to become linked. Linking of red blood cells causes them to agglutinate (clump together). In a transfusion this agglutination can lead to a fatal blockage of the blood vessels.

Individuals with type A antigens on their blood cells carry anti-B antibodies in their serum; those with type B antigens on their blood cells carry anti-A antibodies in their serum. Individuals with type AB cells have both A and B antigens but have neither anti-A nor anti-B antibodies. Type O individuals have neither A nor B antigens on their blood cells but have both anti-A and anti-B antibodies.

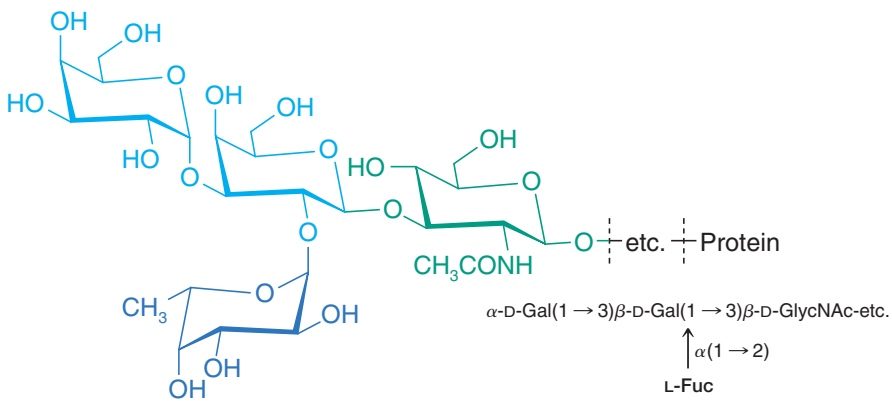
The A, B, and H antigens differ only in the monosaccharide units at their nonreducing ends. The type H antigen (Fig. 22.20) is the precursor oligosaccharide of the type A and B antigens. Individuals with blood type A have an enzyme that specifically adds an *N*-acetylgalactosamine unit to the 3-OH group of the terminal galactose unit of the H antigen. Individuals with blood type B have an enzyme that specifically adds galactose instead. In individuals with type O blood, the enzyme is inactive.

Helpful Hint

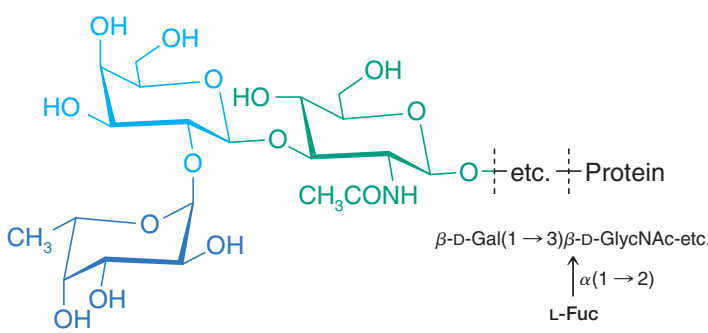
See "The Chemistry of . . . Oligosaccharide Synthesis on a Solid Support–the Glycal Assembly Approach" in *WileyPLUS* regarding the synthesis of promising carbohydrate anticancer vaccines.



Type A determinant



Type B determinant



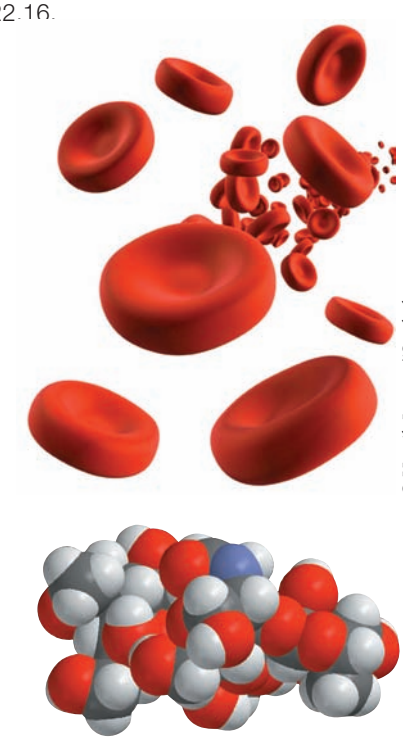
Type H determinant

FIGURE 22.20 The terminal monosaccharides of the antigenic determinants for types A, B, and O blood. The type H determinant is present in individuals with blood type O and is the precursor of the type A and B determinants. These oligosaccharide antigens are attached to carrier lipid or protein molecules that are anchored in the red blood cell membrane (see Fig. 23.9 for a depiction of a cell membrane). Ac = acetyl, Gal = D-galactose, GalNAc = *N*-acetylgalactosamine, GlycNAc = *N*-acetylglucosamine, Fuc = fucose.

Antigen–antibody interactions like those that determine blood types are the basis of the immune system. These interactions often involve the chemical recognition of a glycolipid or glycoprotein in the antigen by a glycolipid or glycoprotein of the antibody. In "The Chemistry of…Antibody-Catalyzed Aldol Condensations" (in *WileyPLUS,* Chapter 19), however, we saw a different and emerging dimension of chemistry involving antibodies. We shall explore this topic further in the Chapter 24 opening vignette on designer catalysts and in "The Chemistry of…Some Catalytic Antibodies" (Section 24.12).

THE CHEMISTRY OF... Patroling Leukocytes and Sialyl Lewis^x Acids

White blood cells continually patrol the circulatory system and interstitial spaces, ready for mobilization at a site of trauma. The frontline scouts for leukocytes are carbohydrate groups on their surface called sialyl Lewis^x acids. When injury occurs, cells at the site of trauma display proteins, called selectins, that signal the site of injury and bind sialyl Lewis^x acids. Binding between selectins and the sialyl Lewis^x acids on the leukocytes causes adhesion of leukocytes at the affected area. Recruitment of leukocytes in this way is an important step in the inflammatory cascade. It is a necessary part of the healing process as well as part of our natural defense against infection. A molecular model of a sialyl Lewis^x acid is shown below, and its structural formula is given in Section 22.16.



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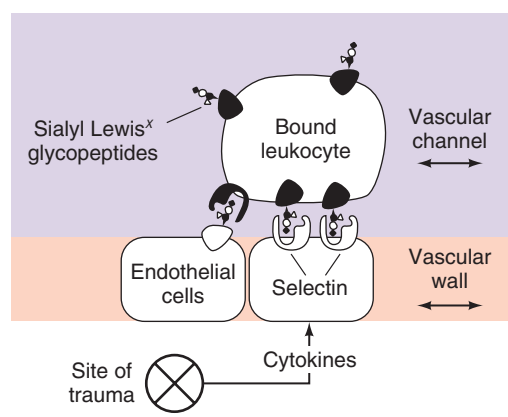
Sialyl Lewis^x, a carbohydrate that is important in the recognition and healing of traumatized tissue.

There are some maladies, however, that result from the over-enthusiastic recruitment of leukocytes. Rheumatoid arthritis, strokes, and injuries related to perfusion during surgery and organ transplantation are a few examples. In these conditions, the body perceives that certain cells are under duress, and it reacts accordingly to initiate the inflammatory cascade. Unfortunately, under these circumstances the inflammatory cascade actually causes greater harm than good.

A strategy for combating undesirable initiation of the inflammatory cascade is to disrupt the adhesion of leukocytes. This can be done by blocking the selectin binding sites for sialyl Lewis^x acids. Chemists have advanced this approach by synthesizing both natural and mimetic sialyl Lewis^x acids for studies on the binding process. These compounds have helped identify key functional groups in sialyl Lewis^x acids that are required for recognition and binding. Chemists have even designed and synthesized novel compounds that have tighter binding affinities than the natural sialyl Lewis^x acids. Among them are polymers with repeating occurrences of the structural motifs essential for binding. These polymeric species presumably occupy multiple sialyl Lewis^x acid binding sites at once, thereby binding more tightly than monomeric sialyl Lewis^x acid analogs.

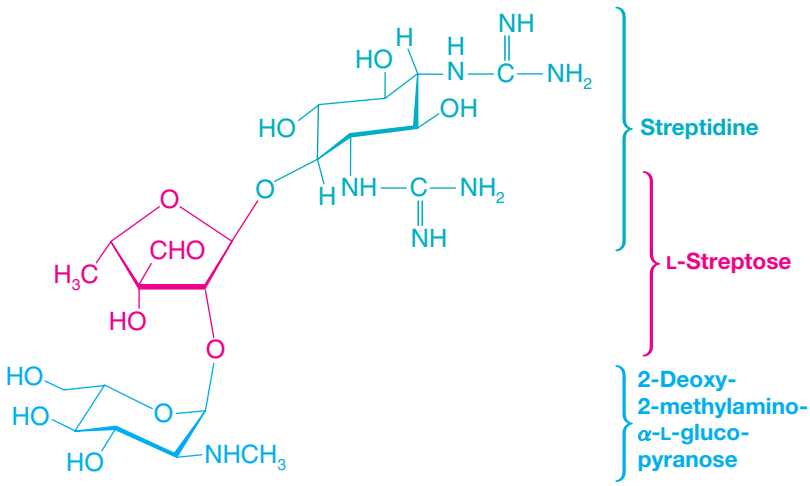
Efforts like these to prepare finely tuned molecular agents are typical of research in drug discovery and design. In the case of sialyl Lewis^x acid analogs, chemists hope to create new therapies for chronic inflammatory diseases by making ever-improved agents for blocking undesired leukocyte adhesion.



Patrolling leukocytes bind at the site of trauma by interactions between sialyl Lewis^x glycoproteins on their surface and selectin proteins on the injured cell. (Reprinted with permission from Simanek, E. E.; McGarvey, G. J.; Jablonowski, J. A.; Wong, C. A., *Chemical Reviews*, *98*, p. 835, Figure 1, 1998. Copyright 1998 American Chemical Society.)

22.17 CARBOHYDRATE ANTIBIOTICS

One of the important discoveries in carbohydrate chemistry was the isolation (in 1944) of the carbohydrate antibiotic called *streptomycin*. Streptomycin disrupts bacterial protein synthesis. Its structure is made up of the following three subunits:



All three components are unusual: the amino sugar is based on L-glucose; streptose is a branched-chain monosaccharide; and streptidine is not a sugar at all, but a cyclohexane derivative called an amino cyclitol.

Other members of this family are antibiotics called kanamycins, neomycins, and gentamicins (not shown). All are based on an amino cyclitol linked to one or more amino sugars. The glycosidic linkage is nearly always α. These antibiotics are especially useful against bacteria that are resistant to penicillins.

22.18 SUMMARY OF REACTIONS OF CARBOHYDRATES

The reactions of carbohydrates, with few exceptions, are the reactions of functional groups that we have studied in earlier chapters, especially those of aldehydes, ketones, and alcohols. The most central reactions of carbohydrates are those of hemiacetal and acetal formation and hydrolysis. Hemiacetal groups form the pyranose and furanose rings in carbohydrates, and acetal groups form glycoside derivatives and join monosaccharides together to form di-, tri-, oligo-, and polysaccharides.

Other reactions of carbohydrates include those of alcohols, carboxylic acids, and their derivatives. Alkylation of carbohydrate hydroxyl groups leads to ethers. Acylation of their hydroxyl groups produces esters. Alkylation and acylation reactions are sometimes used to protect carbohydrate hydroxyl groups from reaction while a transformation occurs elsewhere. Hydrolysis reactions are involved in converting ester and lactone derivatives of carbohydrates back to their polyhydroxy form. Enolization of aldehydes and ketones leads to epimerization and interconversion of aldoses and ketoses. Addition reactions of aldehydes and ketones are useful, too, such as the addition of ammonia derivatives in osazone formation, and of cyanide in the Kiliani–Fischer synthesis. Hydrolysis of nitriles from the Kiliani–Fischer synthesis leads to carboxylic acids.

Oxidation and reduction reactions have their place in carbohydrate chemistry as well. Reduction reactions of aldehydes and ketones, such as borohydride reduction and catalytic hydrogenation, are used to convert aldoses and ketoses to alditols. Oxidation by Tollens' and Benedict's reagents is a test for the hemiacetal linkage in a sugar. Bromine water oxidizes the aldehyde group of an aldose to an aldonic acid. Nitric acid oxidizes both the aldehyde group and terminal hydroxymethyl group of an aldose to an aldaric acid (a dicarboxylic acid). And last, periodate cleavage of carbohydrates yields oxidized fragments that can be useful for structure elucidation.

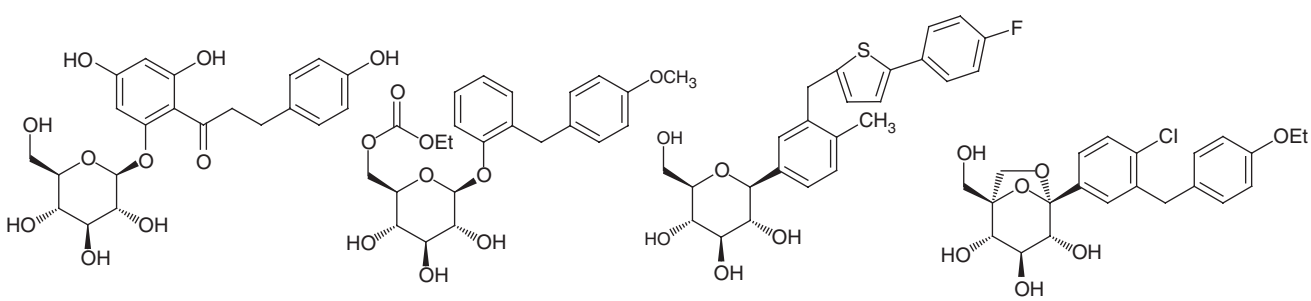
WHY Do These Topics Matter?]

TREATING DIABETES WITH CARBOHYDRATE ANALOGS

Chances are fairly high that you know someone with diabetes, given that it is estimated that at least 26 million people in the United States currently suffer from the condition, while over 50 million more are close to developing the disease. Diabetes is a metabolic disorder that is characterized by an individual having far too much of the carbohydrate glucose in his or her bloodstream—a problem that, if left untreated, can lead to a number of chronic problems such as kidney failure and cardiovascular disease.

Diabetes results because a critical protein known as insulin (see Section 24.6B), whose role is to regulate the overall amount of glucose in our systems by signaling cells to remove it from the bloodstream and store it as glycogen, either is no longer produced in sufficient amounts (affording what is known as Type 1, or juvenile, diabetes) or is no longer used effectively by cells to control glucose levels (affording what is known as Type 2, or adult-onset, diabetes). Either form results in a chronic need for treatment to control blood sugar at as normal a level as possible. For Type 1 patients, that goal often can be achieved simply with insulin treatments. However, for Type 2 patients, alternatives are often needed. Fortunately, there are several treatments available for these individuals, but most of these come with some undesired side effects, including too much glucose removal (leading to hypoglycemia) and/or unwanted weight gain.

Pharmaceutical companies throughout the world are currently working on therapies to counterbalance these side effects with Type 2 patients, and in several recent efforts, it has been a D-glucose-containing natural product that has been critical. That compound is phlorizin. This natural product is an inhibitor of several different types of sodium-dependent glucose transport systems (SDGT) found in cells. Some of these transporters, known as SDGT-1, are found throughout the body and play a role in controlling glucose uptake from our diets. If they are inhibited, then glucose from food will not enter the bloodstream. A second group, known as SDGT-2, is responsible for the reuptake of glucose filtered by our kidneys into our bloodstreams. If this group of transporters is inhibited, then that filtered glucose will be excreted instead in urine. Of the two, it is the second that many scientists believe would have a stronger impact on the disease if inhibited, with the hope that these compounds would not cause unwanted weight gain or hypoglycemia since they act by a different mechanism than other available therapies.



Phlorizin **Sergliflozin** **Canagliflozin** **Pfizer compound**

Pleasingly, altering the structure of this natural product has led to new molecules such as sergliflozin that can selectively inhibit SDGT-2 in cellular assays. When dosed in humans, however, this and related molecules had to be abandoned in clinical trials because they were too easily degraded by glycosidases, enzymes that can cleave the glycosidic bond (Section 22.4) between the sugar portion and the aromatic domain of these pharmaceuticals into inactive molecules. However, if the carbohydrate backbone is changed to a glycosidic linkage based on carbon, not oxygen, then glycosidases cannot cleave the bond at that same position. As a result, new and longer-lived compounds have resulted such as canagliflozin and the unnamed molecule from Pfizer, both of which have been explored in advanced clinical trials and may provide new and highly needed therapies to treat the disease. If so, then it would be a carbohydrate-containing molecule that would be involved in controlling the levels of another key carbohydrate in our bodies.

To learn more about these topics, see:

1. V. Mascitti et al. "Discovery of a Clinical Candidate from the Structurally Unique Dioxa-bicyclo[3.2.1]octane Class of Sodium-Dependent Glucose Cotransporter 2 Inhibitors." *J. Med. Chem*. **2011**, *54*, 2952–2960.

2. E. C. Chao. "Canigliflozin." *Drugs of the Future* **2011**, *36*, 351–357.

SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are highlighted in bold, blue text within the chapter and defined in the Glossary (at the back of the book) and have hyperlinked definitions in the accompanying *WileyPLUS* course (www.wileyplus.com), and a summary of reactions involving monosaccharides.

PROBLEMS

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

CARBOHYDRATE STRUCTURE AND REACTIONS

22.20 Give appropriate structural formulas to illustrate each of the following:

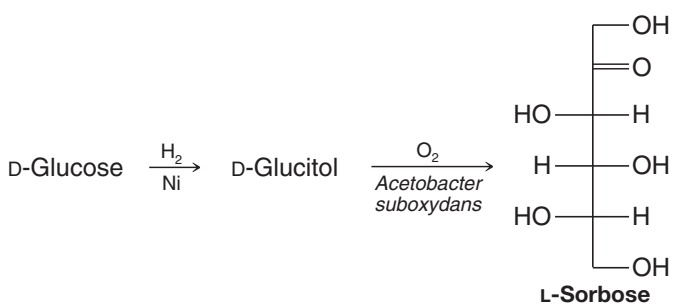
(a) An aldopentose
(b) A ketohexose
(c) An L-monosaccharide
(d) A glycoside
(e) An aldonic acid
(f) An aldaric acid
(g) An aldonolactone
(h) A pyranose
(i) A furanose
(j) A reducing sugar
(k) A pyranoside
(l) A furanoside
(m) Epimers
(n) Anomers
(o) A phenylosazone
(p) A disaccharide
(q) A polysaccharide
(r) A nonreducing sugar

22.21 Draw conformational formulas for each of the following: **(a)** α-D-allopyranose, **(b)** methyl β-D-allopyranoside, and **(c)** methyl 2,3,4,6-tetra-*O*-methyl-β-D-allopyranoside.

22.22 Draw structures for furanose and pyranose forms of D-ribose. Show how you could use periodate oxidation to distinguish between a methyl ribofuranoside and a methyl ribopyranoside.

22.23 One reference book lists D-mannose as being dextrorotatory; another lists it as being levorotatory. Both references are correct. Explain.

22.24 The starting material for a commercial synthesis of vitamin C is L-sorbose (see the following reaction); it can be synthesized from D-glucose through the following reaction sequence:



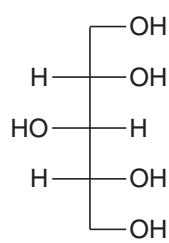
The second step of this sequence illustrates the use of a bacterial oxidation; the microorganism *A. suboxydans* accomplishes this step in 90% yield. The overall result of the synthesis is the transformation of a D-aldohexose (D-glucose) into an L-ketohexose (L-sorbose). What does this mean about the specificity of the bacterial oxidation?

22.25 What two aldoses would yield the same phenylosazone as L-sorbose (Problem 22.24)?

22.26 In addition to fructose (Practice Problem 22.12) and sorbose (Problem 22.24), there are two other 2-ketohexoses, *psicose* and *tagatose*. D-Psicose yields the same phenylosazone as D-allose (or D-altrose); D-tagatose yields the same osazone as D-galactose (or D-talose). What are the structures of D-psicose and D-tagatose?

22.27 **A**, **B**, and **C** are three aldohexoses. Compounds **A** and **B** yield the same optically active alditol when they are reduced with hydrogen and a catalyst; **A** and **B** yield different phenylosazones when treated with phenylhydrazine; **B** and **C** give the same phenylosazone but different alditols. Assuming that all are D sugars, give names and structures for **A**, **B**, and **C**.

22.28 Xylitol is a sweetener that is used in sugarless chewing gum. Starting with an appropriate monosaccharide, outline a possible synthesis of xylitol.



Xylitol

22.29 Although monosaccharides undergo complex isomerizations in base (see Section 22.5A), aldonic acids are epimerized specifically at C2 when they are heated with pyridine. Show how you could make use of this reaction in a synthesis of D-mannose from D-glucose.

22.30 The most stable conformation of most aldopyranoses is one in which the largest group, the $-CH_2OH$ group, is equatorial. However, D-idopyranose exists primarily in a conformation with an axial $-CH_2OH$ group. Write formulas for the two chair conformations of α-D-idopyranose (one with the $-CH_2OH$ group axial and one with the $-CH_2OH$ group equatorial) and provide an explanation.

STRUCTURE ELUCIDATION

22.31 **(a)** Heating D-altrose with dilute acid produces a nonreducing *anhydro sugar* ($C_6H_{10}O_5$). Methylation of the anhydro sugar followed by acid hydrolysis yields 2,3,4-tri-*O*-methyl-D-altrose. The formation of the anhydro sugar takes place through a chair conformation of β-D-altropyranose in which the $-CH_2OH$ group is axial. What is the structure of the anhydro sugar, and how is it formed? **(b)** D-Glucose also forms an anhydro sugar but the conditions required are much more drastic than for the corresponding reaction of D-altrose. Explain.

22.32 Show how the following experimental evidence can be used to deduce the structure of lactose (Section 22.12D):

1. Acid hydrolysis of lactose ($C_{12}H_{22}O_{11}$) gives equimolar quantities of D-glucose and D-galactose. Lactose undergoes a similar hydrolysis in the presence of a *β-galactosidase*.

2. Lactose is a reducing sugar and forms a phenylosazone; it also undergoes mutarotation.

3. Oxidation of lactose with bromine water followed by hydrolysis with dilute acid gives D-galactose and D-gluconic acid.

4. Bromine water oxidation of lactose followed by methylation and hydrolysis gives 2,3,6-tri-*O*-methylgluconolactone and 2,3,4,6-tetra-*O*-methyl-D-galactose.

5. Methylation and hydrolysis of lactose give 2,3,6-tri-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-galactose.

22.33 Deduce the structure of the disaccharide *melibiose* from the following data:

1. Melibiose is a reducing sugar that undergoes mutarotation and forms a phenylosazone.

2. Hydrolysis of melibiose with acid or with an *α-galactosidase* gives D-galactose and D-glucose.

3. Bromine water oxidation of melibiose gives *melibionic acid*. Hydrolysis of melibionic acid gives D-galactose and D-gluconic acid. Methylation of melibionic acid followed by hydrolysis gives 2,3,4,6-tetra-*O*-methyl-D-galactose and 2,3,4,5-tetra-*O*-methyl-D-gluconic acid.

4. Methylation and hydrolysis of melibiose give 2,3,4,6-tetra-*O*-methyl-D-galactose and 2,3,4-tri-*O*-methyl-D-glucose.

22.34 Trehalose is a disaccharide that can be obtained from yeasts, fungi, sea urchins, algae, and insects. Deduce the structure of trehalose from the following information:

1. Acid hydrolysis of trehalose yields only D-glucose.

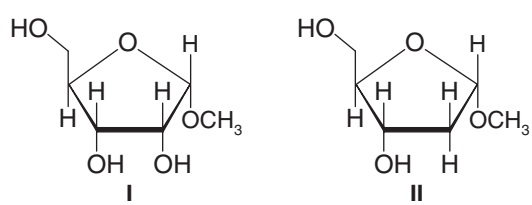
2. Trehalose is hydrolyzed by α-glucosidase but not by β-glucosidase enzymes.

3. Trehalose is a nonreducing sugar; it does not mutarotate, form a phenylosazone, or react with bromine water.

4. Methylation of trehalose followed by hydrolysis yields two molar equivalents of 2,3,4,6-tetra-*O*-methyl-D-glucose.

22.35 Outline chemical tests that will distinguish between members of each of the following pairs:

(a) D-Glucose and D-glucitol
(b) D-Glucitol and D-glucaric acid
(c) D-Glucose and D-fructose
(d) D-Glucose and D-galactose
(e) Sucrose and maltose
(f) Maltose and maltonic acid
(g) Methyl β-D-glucopyranoside and 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranose
(h) Methyl α-D-ribofuranoside (**I**) and methyl 2-deoxy-α-D-ribofuranoside (**II**):



I II

22.36 A group of oligosaccharides called *Schardinger dextrins* can be isolated from *Bacillus macerans* when the bacillus is grown on a medium rich in amylose. These oligosaccharides are all *nonreducing*. A typical Schardinger dextrin undergoes hydrolysis when treated with an acid or an α-glucosidase to yield six, seven, or eight molecules of D-glucose. Complete methylation of a Schardinger dextrin followed by acid hydrolysis yields only 2,3,6-tri-*O*-methyl-D-glucose. Propose a general structure for a Schardinger dextrin.

22.37 *Isomaltose* is a disaccharide that can be obtained by enzymatic hydrolysis of amylopectin. Deduce the structure of isomaltose from the following data:

1. Hydrolysis of 1 mol of isomaltose by acid or by an α-glucosidase gives 2 mol of D-glucose.

2. Isomaltose is a reducing sugar.

3. Isomaltose is oxidized by bromine water to isomaltonic acid. Methylation of isomaltonic acid and subsequent hydrolysis yields 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,4,5-tetra-*O*-methyl-D-gluconic acid.

4. Methylation of isomaltose itself followed by hydrolysis gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-D-glucose.

22.38 *Stachyose* occurs in the roots of several species of plants. Deduce the structure of stachyose from the following data:

1. Acidic hydrolysis of 1 mol of stachyose yields 2 mol of D-galactose, 1 mol of D-glucose, and 1 mol of D-fructose.

2. Stachyose is a nonreducing sugar.

3. Treating stachyose with an α-galactosidase produces a mixture containing D-galactose, sucrose, and a nonreducing trisaccharide called *raffinose*.

4. Acidic hydrolysis of raffinose gives D-glucose, D-fructose, and D-galactose. Treating raffinose with an α-galactosidase yields D-galactose and sucrose. Treating raffinose with invertase (an enzyme that hydrolyzes sucrose) yields fructose and *melibiose* (see Problem 22.33).

5. Methylation of stachyose followed by hydrolysis yields 2,3,4,6-tetra-*O*-methyl-D-galactose, 2,3,4-tri-*O*-methyl-D-galactose, 2,3,4-tri-*O*-methyl-D-glucose, and 1,3,4,6-tetra-*O*-methyl-D-fructose.

SPECTROSCOPY

22.39 *Arbutin*, a compound that can be isolated from the leaves of barberry, cranberry, and pear trees, has the molecular formula $C_{12}H_{16}O_7$. When arbutin is treated with aqueous acid or with a β-glucosidase, the reaction produces D-glucose and a compound **X** with the molecular formula $C_6H_6O_2$. The ^{1}H NMR spectrum of compound **X** consists of two singlets, one at δ 6.8 (4H) and one at δ 7.9 (2H). Methylation of arbutin followed by acidic hydrolysis yields 2,3,4,6-tetra-*O*-methyl-D-glucose and a compound **Y** ($C_7H_8O_2$). Compound **Y** is soluble in dilute aqueous NaOH but is insoluble in aqueous $NaHCO_3$. The ^{1}H NMR spectrum of **Y** shows a singlet at δ 3.9 (3H), a singlet at δ 4.8 (1H), and a multiplet (that resembles a singlet) at δ 6.8 (4H). Treating compound **Y** with aqueous NaOH and $(CH_3)_2SO_4$ produces compound **Z** ($C_8H_{10}O_2$). The ^{1}H NMR spectrum of **Z** consists of two singlets, one at δ 3.75 (6H) and one at δ 6.8 (4H). Propose structures for arbutin and for compounds **X**, **Y**, and **Z**.

22.40 When subjected to a Ruff degradation, a D-aldopentose, **A**, is converted to an aldotetrose, **B**. When reduced with sodium borohydride, the aldotetrose **B** forms an optically active alditol. The ^{13}C NMR spectrum of this alditol displays only two signals. The alditol obtained by direct reduction of **A** with sodium borohydride is not optically active. When **A** is used as the starting material for a Kiliani–Fischer synthesis, two diastereomeric aldohexoses, **C** and **D**, are produced. On treatment with sodium borohydride, **C** leads to an alditol **E**, and **D** leads to **F**. The ^{13}C NMR spectrum of **E** consists of three signals; that of **F** consists of six. Propose structures for **A**–**F**.

22.41 Figure 22.21 shows the ^{13}C NMR spectrum for the product of the reaction of D-(+)-mannose with acetone containing a trace of acid. This compound is a mannofuranose with some hydroxyl groups protected as acetone acetals (as acetonides). Use the ^{13}C NMR spectrum to determine how many acetonide groups are present in the compound.

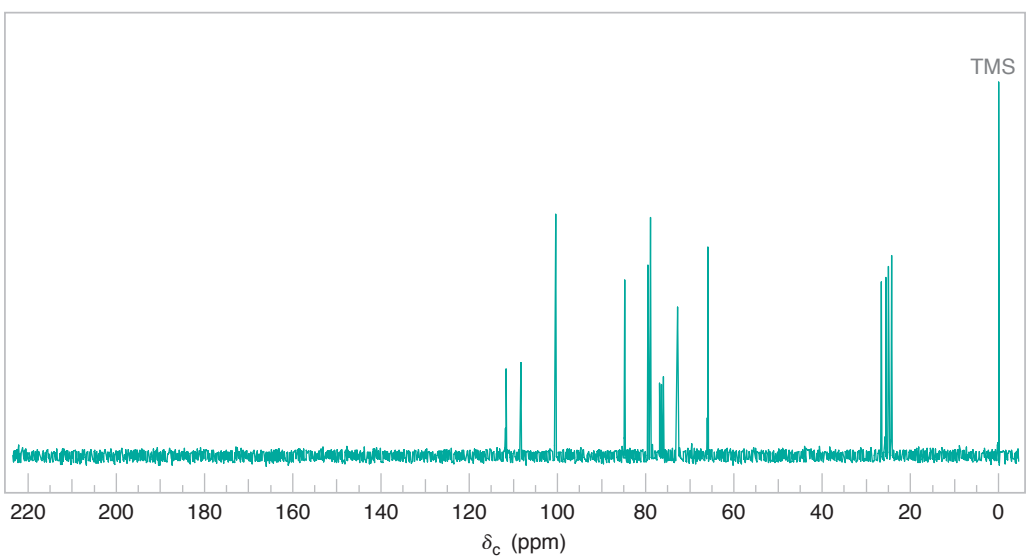
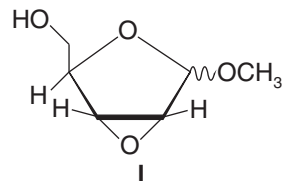


FIGURE 22.21 The broadband proton-decoupled ^{13}C NMR spectrum for the reaction product in Problem 22.41.

22.42 D-(+)-Mannose can be reduced with sodium borohydride to form D-mannitol. When D-mannitol is dissolved in acetone containing a trace amount of acid and the product of this reaction subsequently oxidized with $NaIO_4$, a compound whose ^{13}C NMR spectrum consists of six signals is produced. One of these signals is near δ 200. What is the structure of this compound?

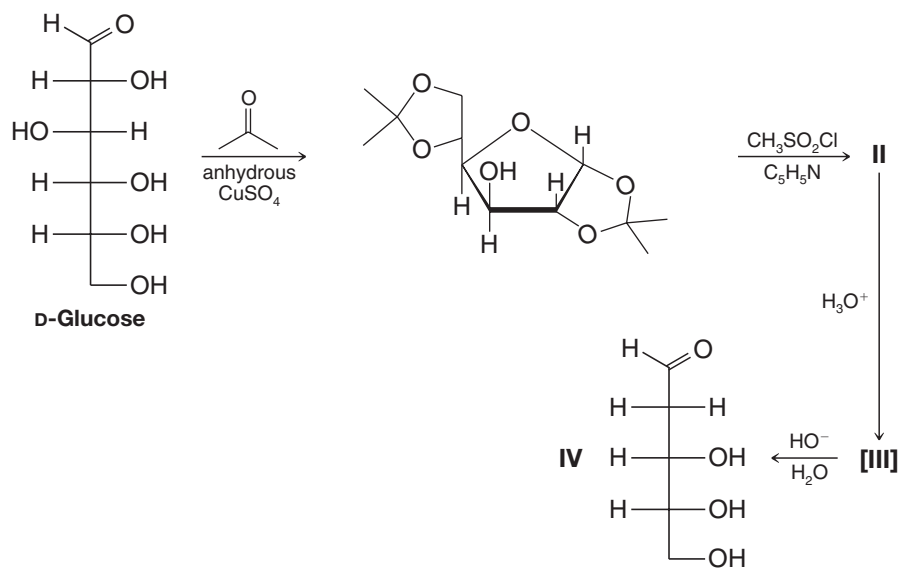
CHALLENGE PROBLEMS

22.43 Of the two anomers of methyl 2,3-anhydro-D-ribofuranoside, **I**, the β form has a strikingly lower boiling point. Suggest an explanation using their structural formulas.



I

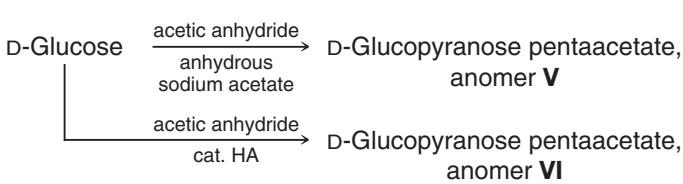
22.44 The following reaction sequence represents an elegant method of synthesis of 2-deoxy-D-ribose, **IV**, published by D. C. C. Smith in 1955:



(a) What are the structures of **II** and **III**?

(b) Propose a mechanism for the conversion of **III** to **IV**.

22.45



The ^{1}H NMR data for the two anomers included very comparable peaks in the δ 2.0–5.6 region but differed in that, as their highest δ peaks, anomer **V** had a doublet at δ 5.8 (1H, $J = 12$ Hz) while anomer **VI** had a doublet at δ 6.3 (1H, $J = 4$ Hz).

(a) Which proton in these anomers would be expected to have these highest δ values?

(b) Why do the signals for these protons appear as doublets?

(c) The relationship between the magnitude of the observed coupling constant and the dihedral angle (when measured using a Newman projection) between C—H bonds on the adjacent carbons of a C—C bond is given by the Karplus equation. It indicates that an axial–axial relationship results in a coupling constant of about 9 Hz (observed range is 8–14 Hz) and an equatorial–axial relationship results in a coupling constant of about 2 Hz (observed range is 1–7 Hz). Which of **V** and **VI** is the α anomer and which is the β anomer?

(d) Draw the most stable conformer for each of **V** and **VI**.

LEARNING GROUP PROBLEMS

1. **(a)** The members of one class of low-calorie sweeteners are called polyols. The chemical synthesis of one such polyol sweetener involves reduction of a certain disaccharide to a mixture of diastereomeric glycosides. The alcohol (actually polyol) portion of the diastereomeric glycosides derives from one of the sugar moieties in the original disaccharide. Exhaustive methylation of the sweetener (e.g., with dimethyl sulfate in the presence of hydroxide) followed by hydrolysis would be expected to produce 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose, 1,2,3,4,5-penta-*O*-methyl-D-sorbitol, and 1,2,3,4,5-penta-*O*-methyl-D-mannitol, in the ratio of 2:1:1. On the basis of this information, deduce the structure of the two disaccharide glycosides that make up the diastereomeric mixture in this polyol sweetener.

(b) Knowing that the mixture of two disaccharide glycosides in this sweetener results from reduction of a single disaccharide starting material (e.g., reduction by sodium borohydride), what would be the structure of the disaccharide *reactant* for the reduction step? Explain how reduction of this compound would produce the two glycosides.

(c) Write the lowest energy chair conformational structure for 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose.

2. Shikimic acid is a key biosynthetic intermediate in plants and microorganisms. In nature, shikimic acid is converted to chorismate, which is then converted to prephenate, ultimately leading to aromatic amino acids and other essential plant and microbial metabolites (see the Chapter 21 Learning Group problem). In the course of research on biosynthetic pathways involving shikimic acid, H. Floss (University of Washington) required shikimic acid labeled with ^{13}C to trace the destiny of the labeled carbon atoms in later biochemical transformations. To synthesize the labeled shikimic acid, Floss adapted a synthesis of optically active shikimic acid from D-mannose reported earlier by G. W. J. Fleet (Oxford University). This synthesis is a prime example of how natural sugars can be excellent chiral starting materials for the chemical synthesis of optically active target molecules. It is also an excellent example of classic reactions in carbohydrate chemistry. The Fleet–Floss synthesis of D-(−)-[1,7-^{13}C]-shikimic acid **(1)** from D-mannose is shown in Scheme 1.

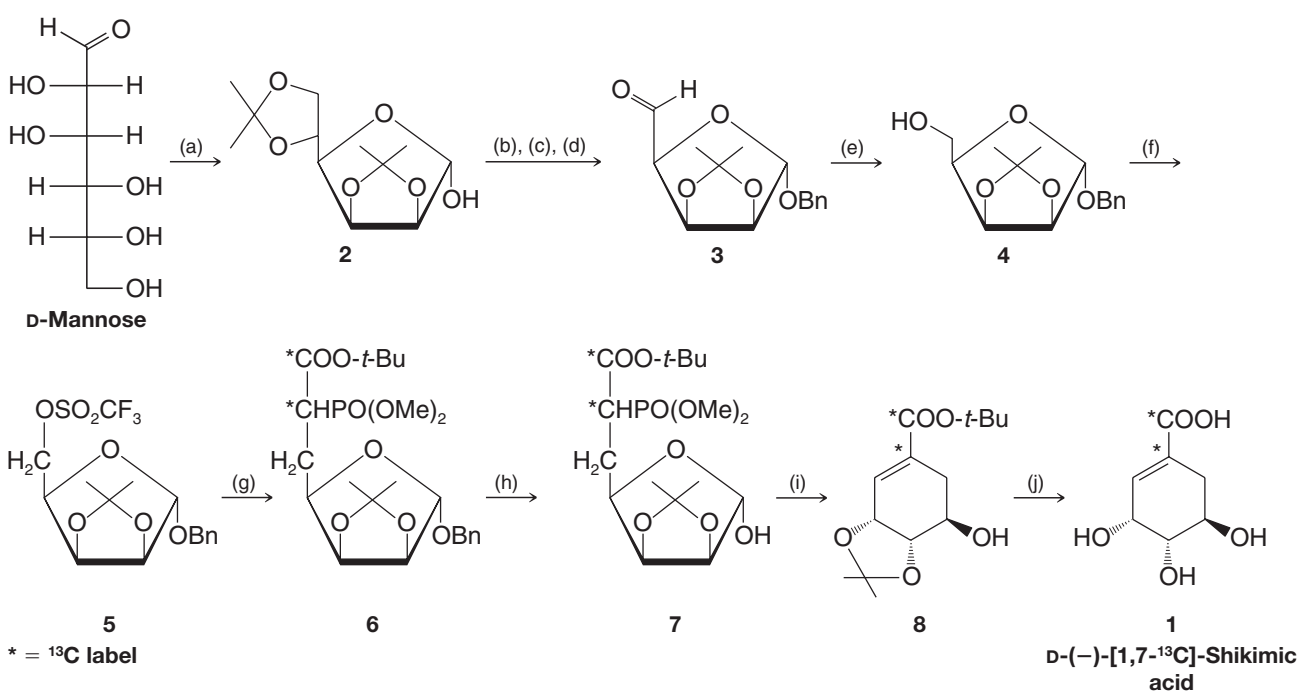
(a) Comment on the several transformations that occur between D-mannose and **2**. What new functional groups are formed?

(b) What is accomplished in the steps from **2** to **3**, **3** to **4**, and **4** to **5**?

(c) Deduce the structure of compound **9** (a reagent used to convert **5** to **6**), knowing that it was a carbanion that displaced the trifluoromethanesulfonate (triflate) group of **5**. Note that it was compound **9** that brought with it the required ^{13}C atoms for the final product.

(d) Explain the transformation from **7** to **8**. Write out the structure of the compound in equilibrium with **7** that would be required for the process from **7** to **8** to occur. What is the name given to the reaction from this intermediate to **8**?

(e) Label the carbon atoms of D-mannose and **1** by number or letter so as to show which atoms in **1** came from which atoms of D-mannose.



SCHEME 1 The synthesis of D-(−)-[1,7-^{13}C]-shikimic acid (1) by H. G. Floss, based on the route of Fleet et al. Conditions: (a) acetone, HA; (b) BnCl, NaH; (c) HCl, aq. MeOH; (d) $NaIO_4$; (e) $NaBH_4$; (f) $(CF_3SO_2)_2O$, pyridine; (g) **9**, NaH; (h) $HCOO^-NH_4^+$, Pd/C; (i) NaH; (j) 60% aq. CF_3COOH.

SUMMARY AND REVIEW TOOLS

A Summary of Reactions Involving Monosaccharides