Biomolecules: Carbohydrates

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

The word carbohydrate derives historically from the fact that glucose, the first simple carbohydrate to be obtained pure, has the molecular formula $\text{C}_6\text{H}_{12}\text{O}_6$ and was originally thought to be a "hydrate of carbon, $\text{C}_6\text{H}_2\text{O}_4$"
This view was soon abandoned, but the name persisted. Today, the term carbohydrate is used to refer loosely to the broad class of polyhydroxylated aldehydes and ketones commonly called sugars.

\[
\begin{align*}
H & \quad C \quad O \\
H & \quad C \quad OH \\
Ho & \quad C \quad H \\
H & \quad C \quad OH \\
H & \quad C \quad OH \\
CH_2OH
\end{align*}
\]

Glucose (also called dextrose), a pentahydroxyhexanal

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

\[
6 \text{CO}_2 + 6 \text{H}_2\text{O} \xrightarrow{\text{Sunlight}} 6 \text{O}_2 + \text{C}_6\text{H}_{12}\text{O}_6 \quad \text{Cellulose, starch}
\]

Glucose

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

25.1 Classification of Carbohydrates

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

\[
\begin{align*}
1 \text{ Sucrose} & \xrightleftharpoons{H_2O^+} \text{ 1 Glucose + 1 Fructose} \\
\text{Cellulose} & \xrightleftharpoons{H_2O^+} \sim 3000 \text{ Glucose}
\end{align*}
\]

Monosaccharides are further classified as either \textbf{aldoses} or \textbf{keto} \textbf{oses}. The \textit{-ose} suffix designates a carbohydrate, and the \textit{aldo}- and \textit{keto-} prefix identify the nature of the carbonyl group. The number of carbon atoms in the monosaccharide is indicated by using \textit{tri-}, \textit{tetra-}, \textit{penta-}, \textit{hexa-}, and so forth in the name. For example, glucose is an \textit{aldohexose} (a six-carbon aldehydic sugar); fructose is a \textit{ketohexose} (a six-carbon ketonic sugar); and ribose is an \textit{aldopentose} (a five-carbon aldehydic sugar). Most of the commonly occurring sugars are either aldopentoses or aldohexoses.

\begin{align*}
\text{Glucose} & & \text{Fructose} & & \text{Ribose} \\
\text{(an aldohexose)} & & \text{(a ketohexose)} & & \text{(an aldopentose)}
\end{align*}

\begin{itemize}
\item[(a)] \begin{align*}
\text{H} & \text{C} = \text{O} \\
\text{HO} & \text{C} - \text{H} \\
\text{H} & \text{C} - \text{OH} \\
\text{CH}_2\text{OH}
\end{align*}
\begin{align*}
\text{HO} & \text{C} - \text{H} \\
\text{H} & \text{C} - \text{OH} \\
\text{H} & \text{C} - \text{OH} \\
\text{CH}_2\text{OH}
\end{align*}
\begin{align*}
\text{HO} & \text{C} - \text{H} \\
\text{H} & \text{C} - \text{OH} \\
\text{H} & \text{C} - \text{OH} \\
\text{CH}_2\text{OH}
\end{align*}
\begin{align*}
\text{H} & \text{C} - \text{H} \\
\text{H} & \text{C} - \text{OH} \\
\text{H} & \text{C} - \text{OH} \\
\text{CH}_2\text{OH}
\end{align*}
\item[(b)] \begin{align*}
\text{H} & \text{C} - \text{OH} \\
\text{H} & \text{C} - \text{OH} \\
\text{CH}_2\text{OH}
\end{align*}
\item[(c)] \begin{align*}
\text{H} & \text{C} - \text{OH} \\
\text{H} & \text{C} - \text{OH} \\
\text{CH}_2\text{OH}
\end{align*}
\item[(d)] \begin{align*}
\text{H} & \text{C} - \text{OH} \\
\text{H} & \text{C} - \text{OH} \\
\text{CH}_2\text{OH}
\end{align*}
\end{itemize}

\textbf{Problem 25.1} Classify each of the following monosaccharides:

\begin{itemize}
\item[(a)] Threose
\item[(b)] Ribulose
\item[(c)] Tagatose
\item[(d)] 2-Deoxyribose
\end{itemize}
25.2 Configurations of Monosaccharides: Fischer Projections

Since all carbohydrates have chiral carbon atoms, it was recognized long ago that a standard method of representation is needed to describe carbohydrate stereochemistry. The method most commonly used employs Fischer projections for depicting chirality centers on a flat page.

Recall from Section 9.18 that a tetrahedral carbon atom is represented in a Fischer projection by two crossed lines. The horizontal lines represent bonds coming out of the page, and the vertical lines represent bonds going into the page. By convention, the carbonyl carbon is placed at or near the top in Fischer projections. Thus, \((R)\)-glyceraldehyde, the simplest monosaccharide, is drawn as shown in Figure 25.1.

FIGURE 25.1

A Fischer projection of \((R)\)-glyceraldehyde.

Recall also that Fischer projections can be rotated on the page by 180° without changing their meaning, but not by 90° or 270°.

\[
\begin{pmatrix}
180° & \text{CHO} \\
\text{H} & \text{HO} \\
\text{CH}_2\text{OH} & \\
\end{pmatrix}
\text{same as}
\begin{pmatrix}
\text{HO} \\
\text{CH}_2\text{OH} \\
\text{CHO} \\
\end{pmatrix}
\]

\((R)\)-Glyceraldehyde

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

\[
\begin{align*}
\text{Glucose} \\
(\text{carbonyl group at top})
\end{align*}
\]

**Problem 25.2** Which of the following Fischer projections of glyceraldehyde represent the same enantiomer?

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} & \quad \text{CHO} & \quad \text{CHO} \\
\text{HO} & \quad \text{HO} & \quad \text{HO} & \quad \text{HO} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

**Problem 25.3** Convert the following Fischer projections into tetrahedral representations, and assign \( R \) or \( S \) stereochemistry to each:

\[
\begin{align*}
\text{(a) COOH} & \quad \text{(b) CHO} & \quad \text{(c) CH}_3 \\
\text{H}_2\text{N} & \quad \text{H} & \quad \text{H} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_2\text{CH}_3
\end{align*}
\]

### 25.3 \textbf{D,L Sugars}

Glyceraldehyde, the simplest aldose, has only one chirality center and thus has two enantiomeric (mirror-image) forms. Only the dextrorotatory enantiomer occurs naturally, however. That is, a sample of naturally occurring glyceraldehyde placed in a polarimeter rotates plane-polarized light in a clockwise direction, denoted (+).

Since (+)-glyceraldehyde has been shown to have an \( R \) configuration at \( C_2 \), it can be represented in a Fischer projection as shown in Figure 25.1. For historical reasons dating back long before the adoption of the \( R,S \) system, (\( R \))-(-)-glyceraldehyde is also referred to as D-glyceraldehyde (D \( \beta \) dextrorotatory). The other enantiomer, (\( S \))-(-)-glyceraldehyde, is known as L-glyceraldehyde (L for levorotatory).
Because of the way monosaccharides are biosynthesized in nature, glucose, fructose, and almost all other naturally occurring monosaccharides have the same R stereochemical configuration as D-glyceraldehyde at the chirality center farthest from the carbonyl group. In Fischer projections, therefore, most naturally occurring sugars have the hydroxyl group at the lowest chirality center pointing to the right (Figure 25.2). All such compounds are referred to as D sugars.

![Image](image)

**FIGURE 25.2**

Some naturally occurring D sugars. The hydroxyl group at the chirality center farthest from the carbonyl group has the same R configuration as that in (+)-glyceraldehyde. When the molecule is drawn in Fischer projection with the carbonyl group at or near the top, the -OH group at the lowest chirality center points toward the right.

In contrast to D sugars, L sugars have an S configuration at the lowest chirality center, with the -OH group pointing to the left in Fischer projections. Thus, an L sugar is the mirror image (enantiomer) of the corresponding D sugar and has the opposite configuration from the D sugar at all chirality centers. Note that the D and L notations have no relation to the direction in which a given sugar rotates plane-polarized light; a D sugar can be either dextrorotatory or levorotatory. The prefix D indicates only that the -OH group at the lowest chirality center is to the right when the molecule is drawn in a Fischer projection with the carbonyl group at or near the top.

![Image](image)
Note also that the \(D,L\) system of carbohydrate nomenclature describes the configuration at only one chirality center and says nothing about the configuration of other chirality centers that may be present. The advantage of the system, though, is that it allows us to relate one sugar to another rapidly and visually.

**Problem 25.4** Assign \(R\) or \(S\) configuration to each chirality center in the following sugars, and tell whether each is a \(D\) sugar or an \(L\) sugar:

(a)  
\[
\begin{align*}
\text{CHO} & \quad \text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{H} & \quad \text{H} \\
\text{CH}_3\text{OH} & \\
\end{align*}
\]

(b)  
\[
\begin{align*}
\text{CHO} & \quad \text{OH} & \quad \text{H} \\
\text{HO} & \quad \text{H} & \quad \text{OH} \\
\text{CH}_3\text{OH} & \\
\end{align*}
\]

(c)  
\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{C} & \quad \text{O} \\
\text{HO} & \quad \text{H} & \quad \text{OH} \\
\text{H} & \quad \text{OH} & \quad \text{CH}_3\text{OH} \\
\end{align*}
\]

**Problem 25.5** \((+)-\text{Arabinose}\), an aldopentose that is widely distributed in plants, is systematically named \((2R,3S,4S)-2,3,4,5\)-tetrahydroxypentanal. Draw a Fischer projection of \((+)-\text{arabinose}\), and identify it as a \(D\) sugar or an \(L\) sugar.

---

### 25.4 Configurations of the Aldoses

Aldotetroses are four-carbon sugars with two chirality centers. There are \(2^2 = 4\) possible stereoisomeric aldotetroses, or two \(D,L\) pairs of enantiomers, called erythrose and threose.

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

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

Fischer projections of the four-, five-, and six-carbon \(D\) aldoses are shown in Figure 25.3. Starting from \(D\)-glyceraldehyde, we can imagine constructing the two \(D\) aldotetroses by inserting a new chirality center just below the aldehyde carbon. Each of the two \(D\) aldotetroses leads to two \(D\) aldopentoses (four total), and each of the four \(D\) aldopentoses leads to two \(D\) aldohexoses (eight total). Each of the \(D\) aldoses in Figure 25.3 has an \(L\) enantiomer, which is not shown.
FIGURE 25.3

Configurations of d aldoses. The structures are arranged in order from left to right so that the -OH groups on C2 alternate right/left (R/L) in going across a series. Similarly, the -OH groups at C3 alternate two right/two left (2R/2L); the -OH groups at C4 alternate 4R/4L; and the -OH groups at C5 are to the right in all eight (8R). Each d aldose has a corresponding l enantiomer, which is not shown.
Louis F. Fieser of Harvard University suggested the following procedure for remembering the names and structures of the eight D aldohexoses (Figure 25.3):

**STEP 1** Set up eight Fischer projections with the –CHO group on top and the –CH₂OH group at the bottom.

**STEP 2** Indicate stereochemistry at C5 by placing all eight –OH groups to the right (D series).

**STEP 3** Indicate stereochemistry at C4 by alternating four –OH groups to the right and four to the left.

**STEP 4** Indicate stereochemistry at C3 by alternating two –OH groups to the right, two to the left, and so on.

**STEP 5** Indicate stereochemistry at C2 by alternating –OH groups right, left, right, left, and so on.

**STEP 6** Name the eight isomers using the mnemonic “All altruists gladly make gum in gallon tanks.”

The structures of the four D aldopentoses can be generated in a similar way and can be named by the mnemonic suggested by a Cornell undergraduate: “Ribs are extra lean.”

**Practice Problem 25.1** Draw a Fischer projection of L-fructose.

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

**Solution**

![Fischer projection of D-fructose and L-fructose](image)

**Problem 25.6** Only the D sugars are shown in Figure 25.3. Draw Fischer projections for the following L sugars:
(a) L-Xylose  (b) L-Galactose  (c) L-Allose
25.5 Cyclic Structures of Monosaccharides: Hemiacetal Formation

We said in Section 19.11 that aldehydes and ketones undergo a rapid and reversible nucleophilic addition reaction with alcohols to form hemiacetals:

\[ \text{An aldehyde} + \text{R'OH} \xrightleftharpoons{\text{H}^+ \text{ catalyst}} \text{A hemiacetal} \]

If the carbonyl and the hydroxyl groups are in the same molecule, an intramolecular nucleophilic addition can take place, leading to the formation of a cyclic hemiacetal. Five- and six-membered cyclic hemiacetals are particularly stable, and many carbohydrates therefore exist in an equilibrium between open-chain and cyclic forms. Glucose, for example, exists in aqueous solution primarily as the six-membered, or pyranose, form resulting from intramolecular nucleophilic addition of the –OH group at C5 to the C1 carbonyl group. Fructose, on the other hand, exists to the extent of about 80% in the pyranose form and about 20% as the five-membered, or furanose, form resulting from addition of the –OH group at C5 to the C2 carbonyl. The words pyranose for a six-membered ring and furanose for a five-membered ring are derived from the names of the simple cyclic ethers pyran and furan. The cyclic forms of glucose and fructose are shown in Figure 25.4.

Like cyclohexane rings (Section 4.9), pyranose rings have a chair-like geometry with axial and equatorial substituents. By convention, the rings are usually drawn by placing the hemiacetal oxygen atom at the right rear, as shown in Figure 25.4. Note that an –OH group on the right in a Fischer projection is on the bottom face of the pyranose ring, and an –OH group on the left in a Fischer projection is on the top face of the ring. For D sugars,
the terminal \(-\text{CH}_2\text{OH}\) group is on the top of the ring, whereas for \(l\) sugars, the \(-\text{CH}_2\text{OH}\) group is on the bottom.

**Practice Problem 25.2** 
\(d\)-Mannose differs from \(d\)-glucose in its stereochemistry at C2. Draw \(d\)-mannose in its chair-like pyranose form.

**Strategy** First draw a Fischer projection of \(d\)-mannose. Then lay it on its side, and curl it around so that the \(-\text{CHO}\) group (C1) is on the right front and the \(-\text{CH}_2\text{OH}\) group (C6) is toward the left rear. Now, connect the \(-\text{OH}\) at C5 to the C1 carbonyl group to form the pyranose ring. In drawing the chair form, raise the leftmost carbon (C4) up and drop the rightmost carbon (C1) down.
25.6 Monosaccharide Anomers: Mutarotation

Solution

\[ \begin{align*}
\text{H}_2\text{C} &= \text{O} \\
\text{HO} &- \\
\text{HO} &- \\
\text{HO} &- \\
\text{HO} &- \\
\text{CH}_2\text{OH} &
\end{align*} \]

\( \alpha \)-Mannose

\[ \begin{align*}
\text{CH}_2\text{OH} &- \\
\text{CH}_2\text{OH} &- \\
\text{HO} &- \\
\text{HO} &- \\
\text{HO} &- \\
\text{HO} &- \\
\text{H} &
\end{align*} \]

Pyranose form

Problem 25.9 \( \alpha \)-Allose differs from \( \alpha \)-glucose in its stereochemistry at C3. Draw \( \alpha \)-allose in its pyranose form.

Problem 25.10 Draw \( \beta \)-ribose in its furanose form.

25.6 Monosaccharide Anomers: Mutarotation

When an open-chain monosaccharide cyclizes to a pyranose or furanose form, a new chirality center is generated at the former carbonyl carbon. The two diastereomers produced are called anomers, and the hemiacetal carbon atom is referred to as the anomeric center. For example, glucose cyclizes reversibly in aqueous solution to a 36:64 mixture of two anomers. The minor anomer, which has the \(-\text{OH}\) group at C1 trans to the \(-\text{CH}_2\text{OH}\) substituent at C5, is called the \( \alpha \) anomer; its full name is \( \alpha \)-\( \text{D} \)-glucopyranose. The major anomer, which has the \(-\text{OH}\) group at C1 cis to the \(-\text{CH}_2\text{OH}\) substituent at C5, is called the \( \beta \) anomer; its full name is \( \beta \)-\( \text{D} \)-glucopyranose (Figure 25.5, p. 1042). Note that in \( \beta \)-\( \text{D} \)-glucopyranose, all the substituents on the ring are equatorial. Thus, \( \beta \)-\( \text{D} \)-glucopyranose is the least sterically crowded and most stable of the eight \( \text{D} \) aldohexoses.

Both anomers of \( \text{D} \)-glucopyranose can be crystallized and purified. Pure \( \alpha \)-\( \text{D} \)-glucopyranose has a melting point of 146°C and a specific rotation, \([\alpha]_D\), of +112.2°; pure \( \beta \)-\( \text{D} \)-glucopyranose has a melting point of 148-155°C and a specific rotation of +18.7°. When a sample of either pure anomer is dissolved in water, however, its optical rotation slowly changes and ultimately reaches a constant value of +52.6°. The specific rotation of the \( \alpha \)-anomer solution decreases from +112.2° to +52.6°, and the specific rotation of the \( \beta \)-anomer solution increases from +18.7° to +52.6°. Called mutarotation, this change in optical rotation is due to the slow conversion of the pure anomers into a 36:64 equilibrium mixture.
Alpha and beta anomers of glucose.

\[ \text{\textalpha{-}\text{D-Glucopyranose (36\%)} } \]
\[ \text{\textalpha{} anomer: OH and CH}_2\text{OH are trans} \]

\[ \text{\textbeta{-}\text{D-Glucopyranose (64\%)} } \]
\[ \text{\textbeta{} anomer: OH and CH}_2\text{OH are cis} \]

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

\[ \text{\textalpha{-}\text{D-Glucopyranose (36\%)} } \]
\[ [\alpha]_D = +112.2^\circ \]

\[ \text{\textbeta{-}\text{D-Glucopyranose (64\%)} } \]
\[ [\alpha]_D = +18.7^\circ \]

**Practice Problem 25.3** Draw \( \text{\textbeta{-}\text{L-Glucopyranose}} \) in its more stable chair conformation.

**Strategy** It's probably easiest to begin by drawing the chair conformation of \( \text{\textbeta{-}\text{D-Glucopyranose}} \). Then draw its mirror image by changing the stereochemistry at every position on the ring, and carry out a ring-flip to give the more stable chair conformation. Note that the \(-\text{CH}_2\text{OH}\) group is on the bottom face of the ring in the \( \text{L} \) enantiomer.
25.7 Reactions of Monosaccharides

Since monosaccharides contain only two kinds of functional groups, carbonyls and hydroxyls, most of the chemistry of monosaccharides is the now familiar chemistry of these two groups.

Ester and Ether Formation

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

Esterification is normally carried out by treating the carbohydrate with an acid chloride or acid anhydride in the presence of a base (Sections 21.4 and 21.5). All the hydroxyl groups react, including the anomeric one. For example, β-D-glucopyranose is converted into its pentaacetate by treatment with acetic anhydride in pyridine solution.
Carbohydrates are converted into ethers by treatment with an alkyl halide in the presence of base—the Williamson ether synthesis (Section 18.3). Standard Williamson conditions using a strong base tend to degrade sensitive sugar molecules, but silver oxide works well and gives high yields of ethers. For example, α-d-glucopyranose is converted into its pentamethyl ether in 85% yield on reaction with iodomethane and Ag₂O.

\[
\text{α-d-Glucopyranose} \xrightarrow{\text{Ag}_2\text{O}, \text{CH}_3\text{I}} \text{α-d-Glucopyranose pentamethyl ether (85\%)}
\]

**Problem 25.14** Draw the products you would obtain by reaction of β-d-ribofuranose with:
(a) CH₃I, Ag₂O   (b) (CH₃CO)₂O, pyridine

\[
\text{β-d-Ribofuranose}
\]

**Glycoside Formation**

We saw in Section 19.11 that treatment of a hemiacetal with an alcohol and an acid catalyst yields an acetal:

\[
\text{C}_\text{OR} + \text{ROH} \xrightarrow{\text{HCl}} \text{C}_\text{OR} + \text{H}_2\text{O}
\]

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

\[
\text{β-d-Glucopyranose (a cyclic hemiacetal)} \xrightarrow{(\text{CH}_3\text{OH, HCl})} \text{Methyl α-d-glucopyranoside (66\%)} + \text{Methyl β-d-glucopyranoside (33\%)}
\]

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

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

![Trisaccharide diagram]

The laboratory synthesis of glycosides is often difficult, but one method that is particularly suitable for preparing glucose β-glycosides involves treatment of glucose pentaacetate with HBr, followed by addition of the appropriate alcohol in the presence of silver oxide. Called the Koenigs-Knorr reaction, the sequence involves formation of a pyranosyl bromide, followed by nucleophilic substitution. For example, methylarbutin, a glycoside found in pears, has been prepared by reaction of tetraacetyl-α-D-glucopyranosyl bromide with p-methoxyphenol:

![Chemical reaction diagram]

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

The results can be understood by assuming that tetraacetyl-d-glucopyranosyl bromide (either α or β anomer) undergoes a spontaneous loss of Br⁻, followed by internal reaction with the ester group at C2 to form an oxonium ion. Since the acetate at C2 is on the bottom of the glucose ring, the new carbon-oxygen bond also forms from the bottom. An S₈⁻₂ displacement of the oxonium ion by back-side attack at C1 then occurs with the usual inversion of configuration, yielding a β-glycoside and regenerating the acetate at C2 (Figure 25.6).

The participation shown by the nearby acetate in the Koenigs-Knorr reaction is referred to as a neighboring-group effect and is a common occurrence in organic chemistry. Neighboring-group effects are usually noticeable only because they affect the rate or stereochemistry of a reaction; the nearby group itself does not undergo any evident change during the reaction.

**Reduction of Monosaccharides**

Treatment of a monosaccharide with NaBH₄ reduces it to a polyalcohol called an alditol. The reduction occurs by interception of the open-chain form present in the aldehyde/ketone-hemiacetal equilibrium. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced; then more is produced by opening of the pyranose form and that additional amount is reduced; and so on, until the entire sample has undergone reaction.
D-Glucitol, the alditol produced by reduction of D-glucose, is itself a naturally occurring substance present in many fruits and berries. It is used under its alternative name D-sorbitol as an artificial sweetener and sugar substitute in foods.

Problem 25.15 How can you account for the fact that reduction of D-galactose with NaBH₄ yields an alditol that is optically inactive?

Problem 25.16 Reduction of L-gulose with NaBH₄ leads to the same alditol (D-glucitol) as reduction of D-glucose. Explain.

Oxidation of Monosaccharides

Like other aldehydes, aldoses are easily oxidized to yield the corresponding monocarboxylic acids, called aldonic acids. Aldoses react with Tollens' reagent (Ag⁺ in aqueous NH₃), Fehling's reagent (Cu²⁺ in aqueous sodium tartrate), or Benedict's reagent (Cu²⁺ in aqueous sodium citrate) to yield the oxidized sugar and a reduced metallic species. All three reactions serve as simple chemical tests for reducing sugars—reducing because the sugar reduces the oxidizing reagent.

If Tollens' reagent is used, metallic silver is produced as a shiny mirror on the walls of the reaction flask or test tube. If Fehling's or Benedict's reagent is used, a reddish precipitate of Cu₂O signals a positive result. Some diabetes self-test kits sold for home use still employ the Benedict test, although more modern methods have largely replaced the chemical test. As little as 0.1% glucose in urine gives a positive test.

All aldoses are reducing sugars because they contain an aldehyde carbonyl group, but some ketoses are reducing sugars as well. Fructose reduces Tollens' reagent, for example, even though it contains no aldehyde group. Reduction occurs because fructose is readily isomerized to an aldose in basic solution by a series of keto–enol tautomeric shifts (Figure 25.7). Glycosides, however, are nonreducing. They don't react with Tollens' reagent because the acetal group is not hydrolyzed to an aldehyde under basic conditions.
**FIGURE 25.7**

Fructose is a reducing sugar because it undergoes two base-catalyzed keto-enol tautomerizations that result in conversion to an aldohexose. (The wavy bonds indicate unknown stereochemistry.)

Although the Tollens and Fehling reactions serve as useful tests for reducing sugars, they don't give good yields of aldonic acid products because the alkaline conditions cause decomposition of the carbohydrate. For preparative purposes, a buffered solution of aqueous Br₂ is a better oxidant. The reaction is specific for aldoses; ketoses are not oxidized by aqueous Br₂.

If a more powerful oxidizing agent such as warm dilute HNO₃ is used, aldoses are oxidized to dicarboxylic acids, called aldonic acids. Both the −CHO group at C1 and the terminal −CH₂OH group are oxidized in this reaction.
Problem 25.17  D-Glucose yields an optically active aldaric acid on treatment with HNO₃, but D-allose yields an optically inactive aldaric acid. Explain.

Problem 25.18  Which of the other six D aldohexoses yield optically active aldaric acids on oxidation, and which yield meso aldaric acids? (See Problem 25.17.)

---

**Chain Lengthening: The Kiliani–Fischer Synthesis**

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

Discovery of the chain-lengthening sequence was initiated by the observation of Heinrich Kiliani in 1886 that aldoses react with HCN to form cyanohydrins (Section 19.7). Emil Fischer immediately realized the importance of Kiliani’s discovery and devised a method for converting the cyanohydrin nitrile group into an aldehyde.

\[
\begin{align*}
\text{H} & \text{C} = \text{O} \quad \text{H} \equiv \text{C} \equiv \text{OH} \\
\text{H} \equiv \text{OH} & \quad \text{H} \equiv \text{C} \equiv \text{OH}
\end{align*}
\]

An aldose  A cyanohydrin  A chain-lengthened aldose

Fischer’s original method for conversion of the nitrile into an aldehyde involved hydrolysis to a carboxylic acid, ring closure to a cyclic ester (lactone), and subsequent reduction. A modern improvement is to reduce the nitrile over a palladium catalyst, yielding an imine intermediate that is hydrolyzed. Note that the cyanohydrin is formed as a mixture of stereoisomers at the new chirality center. Thus, two new aldoses, differing only in their stereochemistry at C2, result from Kiliani–Fischer synthesis. Chain extension of D-arabinose, for example, yields a mixture of D-glucose and D-mannose (Figure 25.8, p. 1050).

---

Problem 25.19  What product(s) would you expect from Kiliani–Fischer reaction of D-ribose?

Problem 25.20  What aldopentose would give a mixture of L-gulose and L-idose on Kiliani–Fischer chain extension?
Chain Shortening: The Wohl Degradation

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

Conversion of the aldehyde into a nitrile is accomplished by treatment of an aldose with hydroxylamine to give an oxime (Section 19.9), followed by dehydration of the oxime with acetic anhydride. The Wohl degradation does not give particularly high yields of chain-shortened aldoses, but the reaction is general for all aldopentoses and aldohexoses. For example, D-galactose is converted by Wohl degradation into D-lyxose:
Problem 25.21 What two \( d \) aldopentoses yield \( d \)-threose on Wohl degradation?

### 25.8 Stereochemistry of Glucose: The Fischer Proof

In the late 1800s, the stereochemical theories of van't Hoff and Le Bel on the tetrahedral geometry of carbon were barely a decade old, modern methods of product purification were unknown, and modern spectroscopic techniques of structure determination were undreamed of. Despite these obstacles, Emil Fischer published in 1891 what remains today perhaps the finest use of chemical logic ever recorded—a structure proof of the stereochemistry of naturally occurring \((+)-\text{glucose}\). Let’s follow Fischer’s logic and see how he arrived at his conclusions.

1. **\((+)-\text{Glucose is an aldohexose.}\)** \((+)-\text{Glucose has four chirality centers and can therefore be any one of } 2^4 = 16 \text{ possible stereoisomers. Since no method was available at the time for determining the absolute three-dimensional stereochemistry of a molecule, Fischer decided to simplify matters by considering only the eight enantiomers having the C5 hydroxyl group on the right in Fischer projections—what we now call \( d \) sugars. Fischer knew that this arbitrary choice of \( d \)-series stereochemistry had only a 50:50 chance of being right, but it was finally shown in 1953 by X-ray spectroscopy that the choice was indeed correct.**

   The four \( d \) aldopentoses and the eight \( d \) aldohexoses derived from them by Kiliani–Fischer synthesis are shown in Figure 25.9 (p. 1052). One of the eight aldohexoses is glucose, but which one?

2. **Arabinose, an aldopentose, is converted by Kiliani–Fischer chain extension into a mixture of glucose and mannose.** This means that glucose and mannose have the same stereochemistry at C3, C4, and C5, and differ only at C2. Glucose and mannose are therefore represented by one of the pairs of structures 1 and 2, 3 and 4, 5 and 6, or 7 and 8 in Figure 25.9.
3. **Arabinose is oxidized by warm HNO₃ to an optically active aldaric acid.** Of the four aldopentoses (A, B, C, and D in Figure 25.9), A and C give optically inactive meso aldaric acids when oxidized, whereas B and D give optically active products. Thus, arabinose must be either B or D, and mannose and glucose must be either 3 and 4 or 7 and 8 (Figure 25.10).

4. **Both glucose and mannose are oxidized by warm HNO₃ to optically active aldaric acids.** Of the possibilities left at this point, the pair represented by structures 3 and 4 would both be oxidized to optically active aldaric acids, but the pair represented by 7 and 8 would not both give optically active products. Compound 7 would give an optically inactive, meso aldaric acid (Figure 25.11). Thus, glucose and mannose must be 3 and 4, though we can't yet tell which is which.

5. **One of the other 15 aldohexose stereoisomers gives the same aldaric acid as that derived from glucose on oxidation.** How can two aldohexoses give the same aldaric acid? Since aldaric acids have –COOH groups at both ends of the carbon chain, there is no way to tell which was originally the –CHO end and which was the –CH₂OH end. Thus, a given aldaric acid has two different precursors. The aldaric acid from compound 3, for example, might also come from oxidation of a
FIGURE 25.10
Oxidation of aldopenoses to aldaric acids. Only structures B and D lead to optically active products.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHO</td>
<td>CHO</td>
<td>CHO</td>
<td>CHO</td>
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<td>HO—H</td>
<td>H—OH</td>
<td>HO—H</td>
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<td>H—OH</td>
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<td>H—OH</td>
<td>H—OH</td>
</tr>
<tr>
<td>CH₂OH</td>
<td>CH₂OH</td>
<td>CH₂OH</td>
<td>CH₂OH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meso (plane of symmetry)</th>
<th>Optically active</th>
<th>Meso (plane of symmetry)</th>
<th>Optically active</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOH</td>
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<td>H—OH</td>
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<td>HO—H</td>
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<tr>
<td>COOH</td>
<td>COOH</td>
<td>COOH</td>
<td>COOH</td>
</tr>
</tbody>
</table>

FIGURE 25.11
Oxidation of aldohexoses to aldaric acids. Only the pair of structures 3 and 4 both give optically active products.

<table>
<thead>
<tr>
<th>3</th>
<th>4</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
<tr>
<td>CHO</td>
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<td>HO—H</td>
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<td>H—OH</td>
<td>H—OH</td>
<td>H—OH</td>
<td>H—OH</td>
</tr>
<tr>
<td>CH₂OH</td>
<td>CH₂OH</td>
<td>CH₂OH</td>
<td>CH₂OH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Optically active</th>
<th>Optically active</th>
<th>Meso (plane of symmetry)</th>
<th>Optically active</th>
</tr>
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<tr>
<td>COOH</td>
<td>H—OH</td>
<td>COOH</td>
<td>H—OH</td>
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<tr>
<td>H—OH</td>
<td>HO—H</td>
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<tr>
<td>COOH</td>
<td>COOH</td>
<td>COOH</td>
<td>COOH</td>
</tr>
</tbody>
</table>
second aldohexose, and the aldric acid from compound 4 might come from oxidation of a second aldohexose (Figure 25.12).

If we look carefully at the aldric acids derived from compounds 3 and 4, we find that the aldric acid derived from 3 could also come from oxidation of another aldohexose (D-gulose), but that the aldric acid derived from 4 could not. The “other” aldohexose that could produce the same aldric acid as that from compound 4 is in fact identical to 4. Thus, glucose must have structure 3 and mannose must have structure 4 (Figure 25.12).

Further reasoning allowed Fischer to determine the stereochemistry of 12 of the 16 aldohexoses. For this remarkable achievement, he was awarded the 1902 Nobel Prize in chemistry.

**Problem 25.22** The structures of the four aldopentoses, A, B, C, and D, are shown in Figure 25.9. In light of point 2 presented by Fischer, what is the structure of arabinose? In light of point 3, what is the structure of lyxose, another aldopentose that yields an optically active aldric acid?
25.9 Disaccharides

We saw in Section 25.7 that reaction of a monosaccharide with an alcohol yields a glycoside in which the anomic –OH group is replaced by an –OR substituent. If the alcohol is itself a sugar, the glycosidic product is a disaccharide.

**Celllobiose and Maltose**

Disaccharides contain a glycosidic acetal bond between the anomic carbon (the carbonyl carbon) of one sugar and an –OH group at any position on the other sugar. A glycosidic bond between C1 of the first sugar and the –OH at C4 of the second sugar is particularly common. Such a bond is called a 1,4’ link (read as “one, four-prime”). The prime superscript indicates that the 4’ position is on a different sugar than the 1 position.

A glycosidic bond to the anomic carbon can be either α or β. Maltose, the disaccharide obtained by enzyme-catalyzed hydrolysis of starch, consists of two D-glucopyranose units joined by a 1,4’-α-glycoside bond. Celllobiose, the disaccharide obtained by partial hydrolysis of cellulose, consists of two D-glucopyranose units joined by a 1,4’-β-glycoside bond.
Maltose and cellobiose are both reducing sugars because the anomic carbons on the right-hand glucopyranose units have hemiacetal groups. Both are therefore in equilibrium with aldehyde forms, which can reduce Tollens' or Fehling's reagent. For a similar reason, both maltose and cellobiose exhibit mutarotation of α and β anomers of the glucopyranose unit on the right (Figure 25.13).

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

**Problem 25.24** Show the product you would obtain from the reaction of cellobiose with the following reagents:
(a) NaBH₄    
(b) Br₂, H₂O 
(c) CH₃COCl, pyridine
Lactose

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

Sucrose

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

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

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

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

**Cellulose**

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

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

**Starch and Glycogen**

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

![Amylose, a 1,4'-O-(α-D-glucopyranoside) polymer](image)

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

![Amylopectin](image)

Starch is digested in the mouth and stomach by *glycosidase* enzymes, which catalyze the hydrolysis of glycoside bonds and release individual molecules of glucose. Like most enzymes, glycosidases are highly selective in their action. They hydrolyze only the α-glycoside links in starch and leave the β-glycoside links in cellulose untouched. Thus, humans can eat potatoes and grains but not grass and leaves.
Glycogen is a polysaccharide that serves the same energy storage function in animals that starch serves in plants. Dietary carbohydrates not needed for immediate energy are converted by the body to glycogen for long-term storage. Like the amylpectin found in starch, glycogen contains a complex branching structure with both 1,4' and 1,6' links (Figure 25.14). Glycogen molecules are larger than those of amylpectin—up to 100,000 glucose units—and contain even more branches.

**Figure 25.14**

A representation of the structure of glycogen. The hexagons represent glucose units linked by 1,4' and 1,6' acetal bonds.

**Polysaccharide Synthesis**

With numerous -OH groups of similar reactivity, polysaccharides are so structurally complex that their laboratory synthesis has been a particularly difficult problem. Several methods are now under development, however, that appear poised to revolutionize the field. Among the most promising of these new approaches is the *glycal assembly method*.

Easily prepared from the appropriate monosaccharide, a *glycal* is an unsaturated sugar with a C1-C2 double bond. To ready it for use in polysaccharide synthesis, the glycal is first protected at its primary -OH group by formation of a silyl ether (Section 17.9) and at its two adjacent secondary -OH groups by formation of a cyclic carbonate. Then, the protected glycal is epoxidized.

![A glycal](image1)
![A protected glycal](image2)
![An epoxide](image3)

Treatment of the glycal epoxide in the presence of ZnCl₂ with a second glycal having a free -OH group causes acid-catalyzed opening of the epoxide ring by back-side attack (Section 18.8) and yields a disaccharide. The disaccharide is itself a glycal, so it can be epoxidized and coupled again to yield a trisaccharide, and so on. Using the appropriate sugars at each step a great variety of polysaccharides can, in principle, be prepared.
25.11 Other Important Carbohydrates

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

**Deoxy sugars** have an oxygen atom "missing." That is, an –OH group is replaced by an –H. The most common deoxy sugar is 2-deoxyribose, a sugar found in DNA (deoxyribonucleic acid). Note that 2-deoxyribose adopts a furanose (five-membered) form.

![Deoxyribose and 2-Deoxyribose](image)

**Amino sugars**, such as D-glucosamine, have an –OH group replaced by an –NH₂. The N-acetyl amide derived from D-glucosamine is the monosaccharide unit from which *chitin*, the hard crust that protects insects and shellfish, is built. Still other amino sugars are found in antibiotics such as streptomycin and gentamicin.
25.12 Cell-Surface Carbohydrates and Carbohydrate Vaccines

It was once thought that the only biological roles of carbohydrates were as structural materials and energy sources. Although carbohydrates do indeed serve these two purposes, they also have many other important biochemical functions. For example, polysaccharides are centrally involved in cell recognition, the critical process by which one type of cell distinguishes another. Small polysaccharide chains, covalently bound by glycosidic links to hydroxyl groups on proteins (glycoproteins), act as biochemical markers on cell surfaces, as illustrated by the human blood-group antigens.

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

<table>
<thead>
<tr>
<th>TABLE 25.1 Human Blood-Group Compatibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor blood type</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>AB</td>
</tr>
<tr>
<td>O</td>
</tr>
</tbody>
</table>

* o = Compatible; x = Incompatible.

The agglutination of incompatible red blood cells, which indicates that the body's immune system has recognized the presence of foreign cells in the body and has formed antibodies against them, results from the presence of polysaccharide markers on the surface of the cells. Types A, B, and O red blood cells each have characteristic markers, called antigenic determinants; type AB cells have both type A and type B markers. The structures of all three blood-group determinants are shown in Figure 25.15.

Note that some unusual carbohydrates are involved. All three blood-group antigenic determinants contain N-acetylamino sugars as well as the unusual monosaccharide L-fucose.
Elucidation of the role of carbohydrates in cell recognition is a vigorous area of current research that offers hope of breakthroughs in the understanding of a wide range of diseases from bacterial infections to cancer. Particularly exciting is the possibility of developing useful anticancer vaccines to help mobilize the body’s immune system against tumor cells. Recent advances along these lines have included a laboratory synthesis of the so-called *globo H antigen*, found on the surface of human breast, prostate, colon, and pancreatic cancer cells. Mice treated with the synthetic globo H hexasaccharide linked to a carrier protein developed large amounts of antibodies, which then recognized tumor cells.
Sweetness

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

**TABLE 25.2 Sweetness of Some Sugars and Sugar Substitutes**

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Sweetness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Disaccharide</td>
<td>0.16</td>
</tr>
<tr>
<td>Glucose</td>
<td>Monosaccharide</td>
<td>0.75</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Disaccharide</td>
<td>1.00</td>
</tr>
<tr>
<td>Fructose</td>
<td>Monosaccharide</td>
<td>1.75</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Synthetic</td>
<td>180</td>
</tr>
<tr>
<td>Acesulfame-K</td>
<td>Synthetic</td>
<td>200</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Synthetic</td>
<td>350</td>
</tr>
</tbody>
</table>

The desire of many people to cut their caloric intake has led to the development of synthetic sweeteners such as saccharin, aspartame, and acesulfame. All are far sweeter than natural sugars, so the choice of one or another depends on personal taste, government regulations, and (for baked goods) heat stability. Saccharin, the oldest synthetic sweetener, has been used for over a century, although it has a somewhat metallic aftertaste. Doubts about its safety and potential carcinogenicity were raised in the early 1970s, but it has now been cleared of suspicion. Acesulfame potassium, the most recently approved sweetener, is proving to be extremely popular in soft drinks because it has little aftertaste. None of the three synthetic sweeteners listed in Table 25.2 has any structural resemblance to a carbohydrate.

The real thing comes from cane fields like this one.
Carbohydrates are polyhydroxy aldehydes and ketones. They are classified according to the number of carbon atoms and the kind of carbonyl group they contain. Glucose, for example, is an aldohexose, a six-carbon aldehydic sugar. Monosaccharides are further classified as either D or L sugars, depending on the stereochemistry of the chirality center farthest from the carbonyl group.

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

Much of the chemistry of monosaccharides is the familiar chemistry of alcohols and aldehydes/ketones. Thus, the hydroxyl groups of carbohydrates form esters and ethers. The carbonyl group of a monosaccharide can be reduced with NaBH₄ to form an alditol, oxidized with aqeous Br₂ to form an aldonic acid, oxidized with HNO₃ to form an aldarial acid, or treated with an alcohol in the presence of acid to form a glycoside. Monosaccharides can also be chain-lengthened by the multistep Kiliani–Fischer synthesis and can be chain-shortened by the Wohl degradation.

Disaccharides are complex carbohydrates in which two simple sugars are linked by a glycoside bond between the anomeric carbon of one unit and a hydroxyl of the second unit. The two sugars can be the same, as in maltose and cellobiose, or different, as in lactose and sucrose. The glycosidic bond can be either α (maltose) or β (cellobiose, lactose) and can involve any hydroxyl of the second sugar. A 1,4′ link is most common (cellobiose, maltose), but others such as 1,2′ (sucrose) are also known.
Summary of Reactions

An ether

\[
\begin{align*}
\text{CH}_3O - & \text{CH} - \\
(\text{CHOCH}_2)_{n-1} & \text{O} \quad \text{(CHOAc)}_{n-1} \quad \text{O} \\
\text{CH} & \\
\text{CH}_2OCH_3 \\
\text{Ac}_2O, & \text{pyridine} \\
\text{Ag}_2O & \\
\end{align*}
\]

An ester

\[
\begin{align*}
\text{RO} - & \text{CH} - \\
(\text{CHOH})_{n-1} & \text{O} \quad \text{(CHOH)}_n \quad \text{O} \\
\text{CH} & \\
\text{CH}_2OH & \\
\text{CH}_2OH \\
\text{HCl} & \\
\text{NaBH}_4 & \\
\end{align*}
\]

A glycoside

\[
\begin{align*}
\text{CH}_2OH & \\
(\text{CHOH})_n & \\
\text{CH}_2OH & \\
\text{Br}_2 & \\
\text{H}_2O & \\
\text{HCN} & \\
\text{H}_2, \text{Pd, BaSO}_4 & \\
\text{HNO}_3 & \\
\end{align*}
\]

An alditol

\[
\begin{align*}
\text{CHO} & \\
(\text{CHOH})_{n-1} & \\
\text{CH}_2OH & \\
\text{CHO} & \\
\text{CHOH} & \\
(\text{CHOH})_n & \\
\text{CH}_2OH & \\
\text{COOH} & \\
(\text{CHOH})_n & \\
\text{COOH} & \\
\end{align*}
\]

An aldonic acid

\[
\begin{align*}
\text{CHO} & \\
(\text{CHOH})_{n-1} & \\
\text{CH}_2OH & \\
\text{CHO} & \\
\text{CHOH} & \\
(\text{CHOH})_n & \\
\text{CH}_2OH & \\
\text{COOH} & \\
(\text{CHOH})_n & \\
\text{COOH} & \\
\end{align*}
\]

An aldonic acid

Visualizing Chemistry

(Problems 25.1–25.24 appear within the chapter.)

25.25 Identify the following aldoses, and tell whether each is a D or L sugar.

(a)

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

(a) ![Fischer projection](image-a)

(b) ![Fischer projection](image-b)

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

![Stereo View](image-c)

25.28 The following model is that of an aldohexose:

![Stereo View](image-d)

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

Additional Problems

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

(a) \( \text{CH}_2\text{OH} \)

(b) \( \text{CH}_2\text{OH} \)

(c) \( \text{CHO} \)

\[
\begin{align*}
\text{C}=\text{O} & \quad \text{H}\quad \text{OH} & \quad \text{H}\quad \text{OH} \\
\text{CH}_2\text{OH} & \quad \text{H}\quad \text{OH} & \quad \text{HO}\quad \text{H} \\
\text{H}\quad \text{OH} & \quad \text{C}=\text{O} & \quad \text{H}\quad \text{OH} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{HO}\quad \text{H} \\
\end{align*}
\]
25.30 Write open-chain structures for the following:
(a) A ketotetrose
(b) A ketopentose
(c) A deoxyaldohexose
(d) A five-carbon amino sugar
(e) An α anomer
(f) A β-1,4-linked disaccharide

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

Ascorbic acid

25.32 Draw the three-dimensional furanose form of ascorbic acid (Problem 25.31) and assign R or S stereochemistry to each chirality center.

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

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

Allose

25.35 What is the complete name of the following sugar?

25.36 Write the following sugars in their open-chain forms:
(a)
(b)
(c)
25.37 Draw D-ribulose in its five-membered cyclic β-hemiacetal form.

\[
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{=O} \\
\text{H} \quad \text{OH} \\
\text{H} \quad \text{OH} \\
\text{CH}_2\text{OH}
\end{array}
\]

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

25.39 Draw structures for the products you would expect to obtain from reaction of β-D-talopyranose with each of the following reagents:
(a) NaBH₄ in H₂O  
(b) Warm dilute HNO₃  
(c) Br₂, H₂O  
(d) CH₃CH₂OH, HCl  
(e) CH₃I, Ag₂O  
(f) (CH₃CO)₂O, pyridine

25.40 Many other sugars besides glucose exhibit mutarotation. For example, α-D-galactopyranose has \([\alpha]_D = +150.7^\circ\), and β-D-galactopyranose has \([\alpha]_D = +52.8^\circ\). If either anomer is dissolved in water and allowed to reach equilibrium, the specific rotation of the solution is +80.2°. What are the percentages of each anomer at equilibrium? Draw the pyranose forms of both anomers.

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

25.42 One of the D-2-ketohexoses is called sorbose. On treatment with NaBH₄, sorbose yields a mixture of gulitol and iditol. What is the structure of sorbose? (See Problem 25.41.)

25.43 Another D-2-ketohexose, psicose, yields a mixture of allitol and altritol when reduced with NaBH₄. What is the structure of psicose? (See Problem 25.41.)

25.44 Fischer prepared the L-gulose needed for his structure proof of glucose in the following way: D-Glucose was oxidized to D-glucaric acid, which can form two six-membered-ring lactones. These were separated and reduced with sodium amalgam to give D-glucose and L-gulose. What are the structures of the two lactones, and which one is reduced to L-gulose?

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

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

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

25.48 Draw the structure of L-galactose, and then answer the following questions:
(a) Which other aldohexose gives the same aldaric acid as L-galactose on oxidation with warm HNO₃?
(b) Is this other aldohexose a D sugar or an L sugar?
(c) Draw this other aldohexose in its most stable pyranose conformation.

25.49 Gentiobiose, a rare disaccharide found in saffron and gentian, is a reducing sugar and forms only D-glucose on hydrolysis with aqueous acid. Reaction of gentiobiose with iodomethane and Ag₂O yields an octamethyl derivative, which can be hydrolyzed with aqueous acid to give 1 equivalent of 2,3,4,6-tetra-O-methyl-D-glucopyranose and 1 equivalent of 2,3,4-tri-O-methyl-D-glucopyranose. If gentiobiose contains a β-glycoside link, what is its structure?
25.50 Amygdalin, or laetrile, is a glycoside isolated in 1830 from almond and apricot seeds. It is known as a cyanogenic glycoside because acidic hydrolysis liberates HCN, also with benzaldehyde and 2 equivalents of \( \beta \)-glucose. Structural studies have shown amygdalin to be a \( \beta \)-glycoside of benzaldehyde cyanohydrin with gentiobiose (Problem 25.49). Draw the structure of amygdalin.

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

25.52 Trehalose (Problem 25.51) is cleaved by enzymes that hydrolyze \( \alpha \)-glycosides but not by enzymes that hydrolyze \( \beta \)-glycosides. What is the structure and systematic name of trehalose?

25.53 Isotrehalose and neotrehalose are chemically similar to trehalose (Problems 25.51 and 25.52) except that neotrehalose is hydrolyzed only by \( \beta \)-glycosidase enzymes, whereas isotrehalose is hydrolyzed by both \( \alpha \)- and \( \beta \)-glycosidase enzymes. What are the structures of isotrehalose and neotrehalose?

25.54 \( \beta \)-Glucose reacts with acetone in the presence of acid to yield the nonreducing 1,2,5,6-diisopropylidene-\( \beta \)-glucofuranose. Propose a mechanism.

![Chemical reaction diagram]

1,2:5,6-Diisopropylidene-\( \beta \)-glucofuranose

25.55 \( \alpha \)-Mannose reacts with acetone to give a diisopropylidene derivative (see Problem 25.54) that is still reducing toward Tollens' reagent. Propose a likely structure for this derivative.

25.56 Propose a mechanism to account for the fact that \( \beta \)-gluconic acid and \( \alpha \)-mannonic acid are interconverted when either is heated in pyridine solvent.

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

25.58 Compound A is a \( \beta \) aldopentose that can be oxidized to an optically inactive aldaric acid B. On Kiliani–Fischer chain extension, A is converted into C and D; C can be oxidized to an optically active aldaric acid E, but D is oxidized to an optically inactive aldaric acid F. What are the structures of A–F?
25.59 Simple sugars undergo reaction with phenylhydrazine, PhNHNH₂, to yield crystalline derivatives called osazones. The reaction is a bit complex, however, as shown by the fact that glucose and fructose yield the same osazone.

\[
\begin{align*}
\text{CHO} & \quad \text{H} \quad \text{N} \quad \text{NPh} \\
\text{HO} & \quad \text{H} \quad \text{= N} \quad \text{NPh} \\
\text{H} & \quad \text{OH} \\
\text{H} & \quad \text{OH} \\
\text{CH}_2\text{OH} & \\
\text{d-Glucose} & + \text{NH}_3 + \text{PhNH}_2 + 2 \text{H}_2\text{O} \\
\text{CHO} & \quad \text{H} \quad \text{N} \quad \text{NPh} \\
\text{HO} & \quad \text{H} \quad \text{= O} \\
\text{H} & \quad \text{OH} \\
\text{H} & \quad \text{OH} \\
\text{CH}_2\text{OH} & \\
\text{d-Fructose} & \\
\end{align*}
\]

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

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

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

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

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

\[
\begin{align*}
\text{CHO} & \quad \text{H} \quad \text{H} \\
\text{HO} & \quad \text{H} \quad \text{OH} \\
\text{H} & \quad \text{OH} \\
\text{HO} & \quad \text{H} \\
\text{H} & \quad \text{OH} \\
\text{OCH}_2 & \\
\text{d-Idose} & \quad \text{1,6-Anhydro-d-idopyranose} \\
\end{align*}
\]

(a) Draw d-idose in its pyranose form, showing the more stable chair conformation of the ring.

(b) Which is more stable, \(\alpha\)-d-idopyranose or \(\beta\)-d-idopyranose? Explain.

(c) Draw 1,6-anhydro-d-idopyranose in its most stable conformation.

(d) When heated to 100°C under the same conditions as those used for d-idose, d-glucose does not lose water and does not exist in a 1,6-anhydro form. Explain.
A Look Ahead

25.61 Acetyl coenzyme A (acetyl CoA) is the key intermediate in food metabolism. What sugar is present in acetyl CoA? (See Section 29.5.)

![Acetyl coenzyme A structure](image)

Molecular Modeling

25.62 Use SpartanView to examine an electrostatic potential map of ascorbic acid. Identify the most acidic hydrogen, and then examine the geometry and electrostatic potential map of ascorbate anion. Draw resonance structures for this ion.

![Ascorbic acid structure](image)

25.63 Use SpartanView to compare the energies of the six-membered-ring (pyranose) and seven-membered-ring cyclization products of glucose. Which of the two products is favored thermodynamically?

![Glucose structures](image)