20

CARBOHYDRATES

Carbohydrates are a major class of naturally occurring organic compounds, which come by their name because they usually have, or approximate, the general formula $C_n(H_2O)_m$, with n equal to or greater than three. Among the well-known carbohydrates are various sugars, starches, and cellulose, all of which are important for the maintenance of life in both plants and animals.

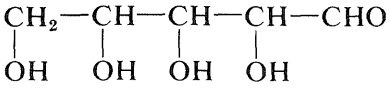
Although the structures of many carbohydrates appear to be quite complex, the chemistry of these substances usually involves only two functional groups—*ketone* or *aldehyde carbonyls* and *alcohol hydroxyl* groups. The carbonyl groups normally do not occur as such, but are combined with hydroxyl groups to form hemiacetal or acetal linkages of the kind discussed in Section 15-4E.

An understanding of stereochemistry is particularly important to understanding the properties of carbohydrates. Configurational and conformational isomerism play an important role. For this reason, you may wish to review Chapter 5 and Sections 12-3 and 19-5.

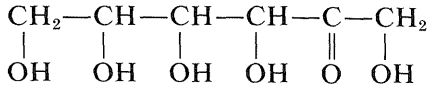
20-1 CLASSIFICATION AND OCCURRENCE OF CARBOHYDRATES

The simple sugars, or **monosaccharides,** are the building blocks of carbohydrate chemistry. They are polyhydroxy aldehydes or ketones with five, six, seven, or eight carbon atoms that are classified appropriately as **pentoses, hexoses, heptoses,** or **octoses,** respectively. They can be designated by more

specific names, such as **aldohexose** or **ketohexose,** to denote the kind of carbonyl compound they represent. For example, an aldopentose is a five-carbon sugar with an aldehyde carbonyl; a ketohexose is a six-carbon sugar with a ketone carbonyl:

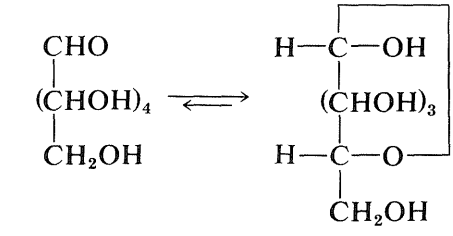


aldopentose



ketohexose

However, it is important to keep in mind that the carbonyl groups of sugars usually are combined with one of the hydroxyl groups in the same molecule to form a cyclic hemiacetal or hemiketal. These structures once were written as follows, and considerable stretch of the imagination is needed to recognize that they actually represent oxacycloalkane ring systems:



an aldohexose (open-chain form)

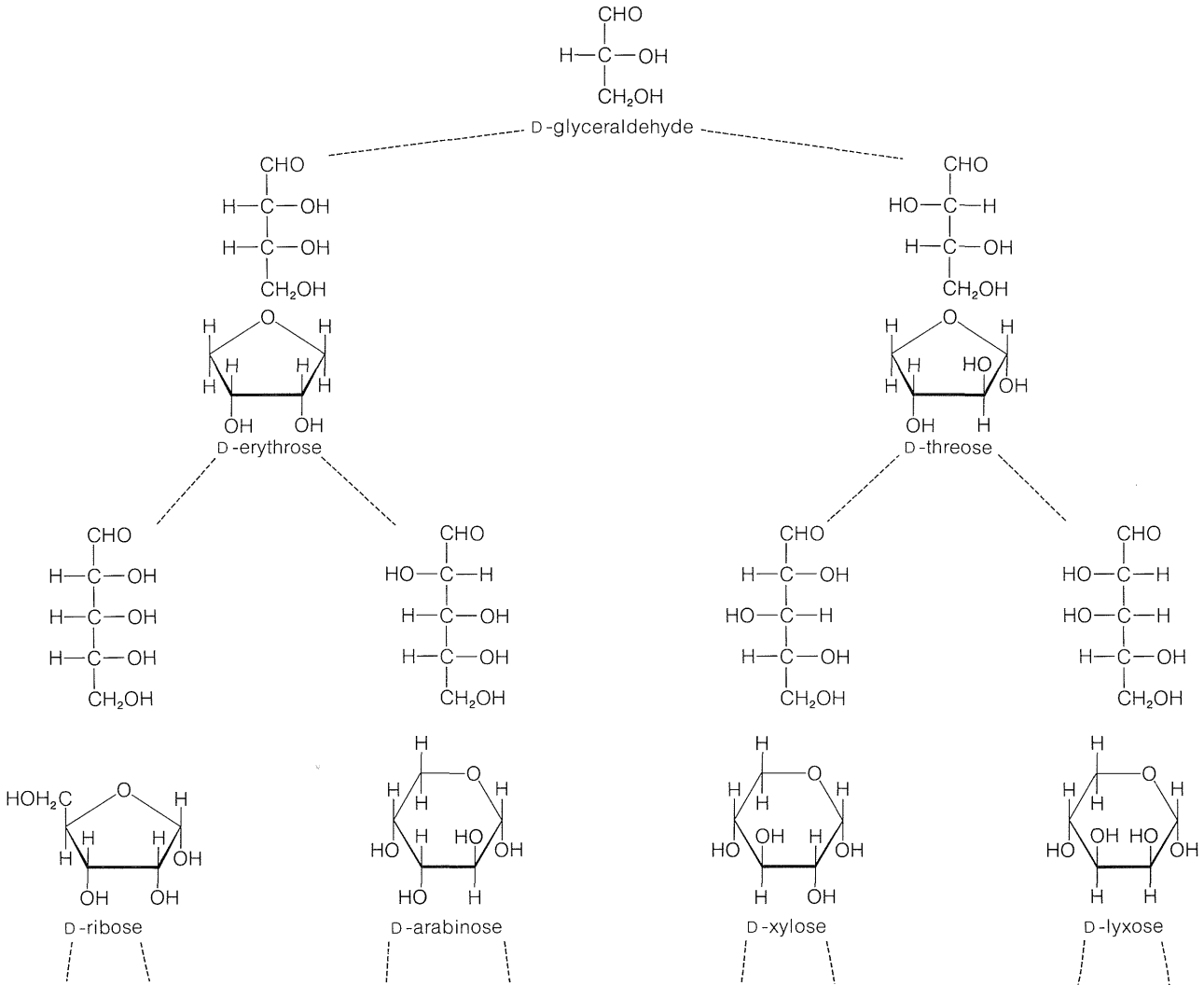
a 1,5-cyclic hemiacetal of an aldohexose

The saccharides have long and awkward names by the IUPAC system, consequently a highly specialized nomenclature system has been developed for carbohydrates. Because this system (and those like it for other natural products) is unlikely to be replaced by more systematic names, you will find it necessary to memorize some names and structures. It will help you to remember the meaning of names such as aldopentose and ketohexose, and to learn the names and details of the structures of glucose, fructose, and ribose. For the rest of the carbohydrates, the nonspecialist needs only to remember the kind of compounds that they are.

The most abundant five-carbon sugars are L-arabinose, D-ribose, 2-deoxy-D-ribose,[1] and D-xylose, which all are **aldopentoses.** Both the open-chain and cyclic structures of the D-aldoses up to C_6 are shown in Figure 20-1.

The common six-carbon sugars (hexoses) are D-glucose, D-fructose, D-galactose, and D-mannose. They all are **aldohexoses,** except D-fructose, which is a **ketohexose.** The structures of the ketoses up to C_6 are shown for reference in Figure 20-2. The occurrence and uses of the more important ketoses and aldoses are summarized in Table 20-1.

[1]*Deoxy* means lacking a hydroxyl group, and 2-deoxyribose is simply ribose without an OH group at the 2-carbon.


triose
tetrose
pentose
D-glyceraldehyde
D-erythrose
D-threose
D-ribose
D-arabinose
D-xylose
D-lyxose

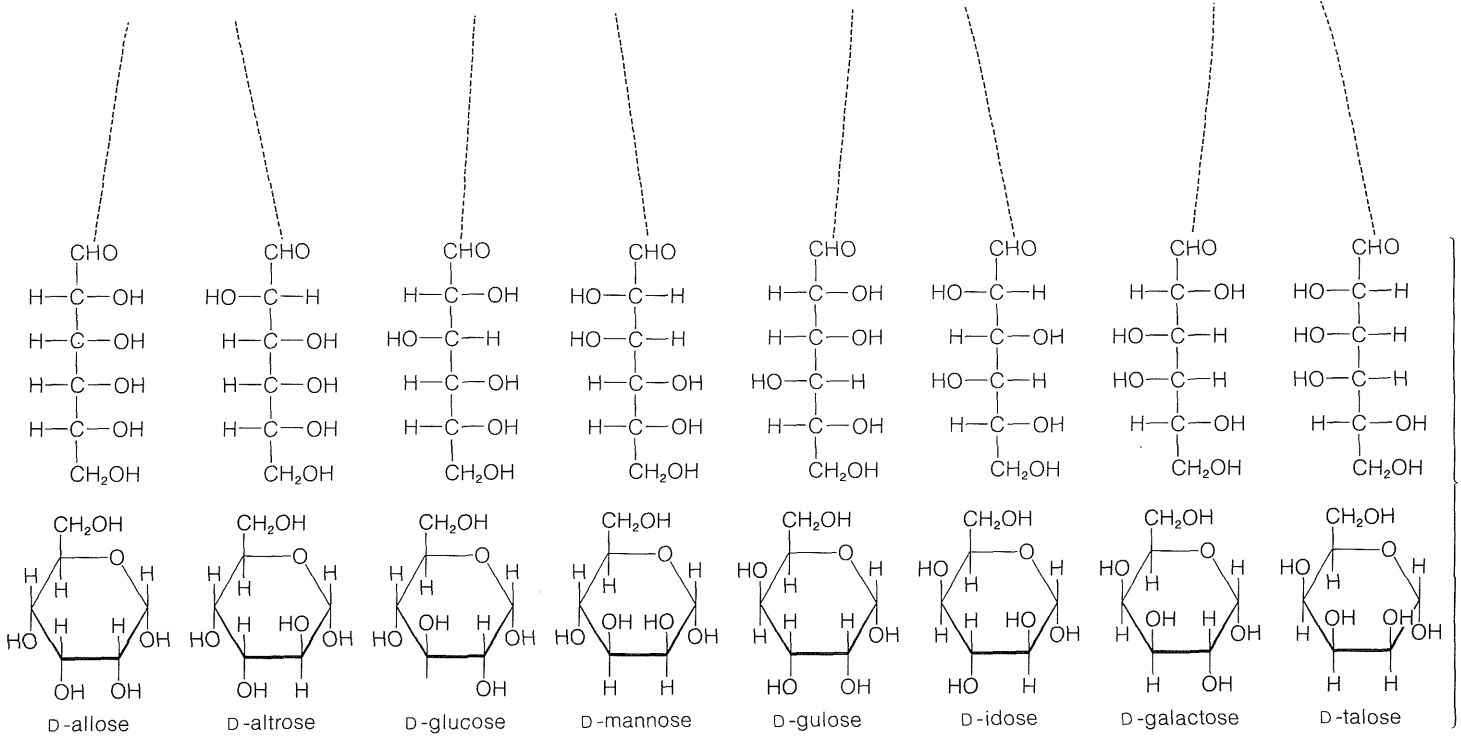


Figure 20-1 Structure and configuration of the D-**aldoses** from C_3 to C_6, showing the configurational relationship to D-glyceraldehyde. Open-chain and cyclic forms are shown. The oxacyclohexane (pyranose) form is more stable than the oxacyclopentane (furanose) form for the free sugar. The oxacyclopentane structure is shown for ribose because this is the form in which it occurs in many important substances, such as the nucleic acids. Only the α anomers are shown (see Section 20-2B).

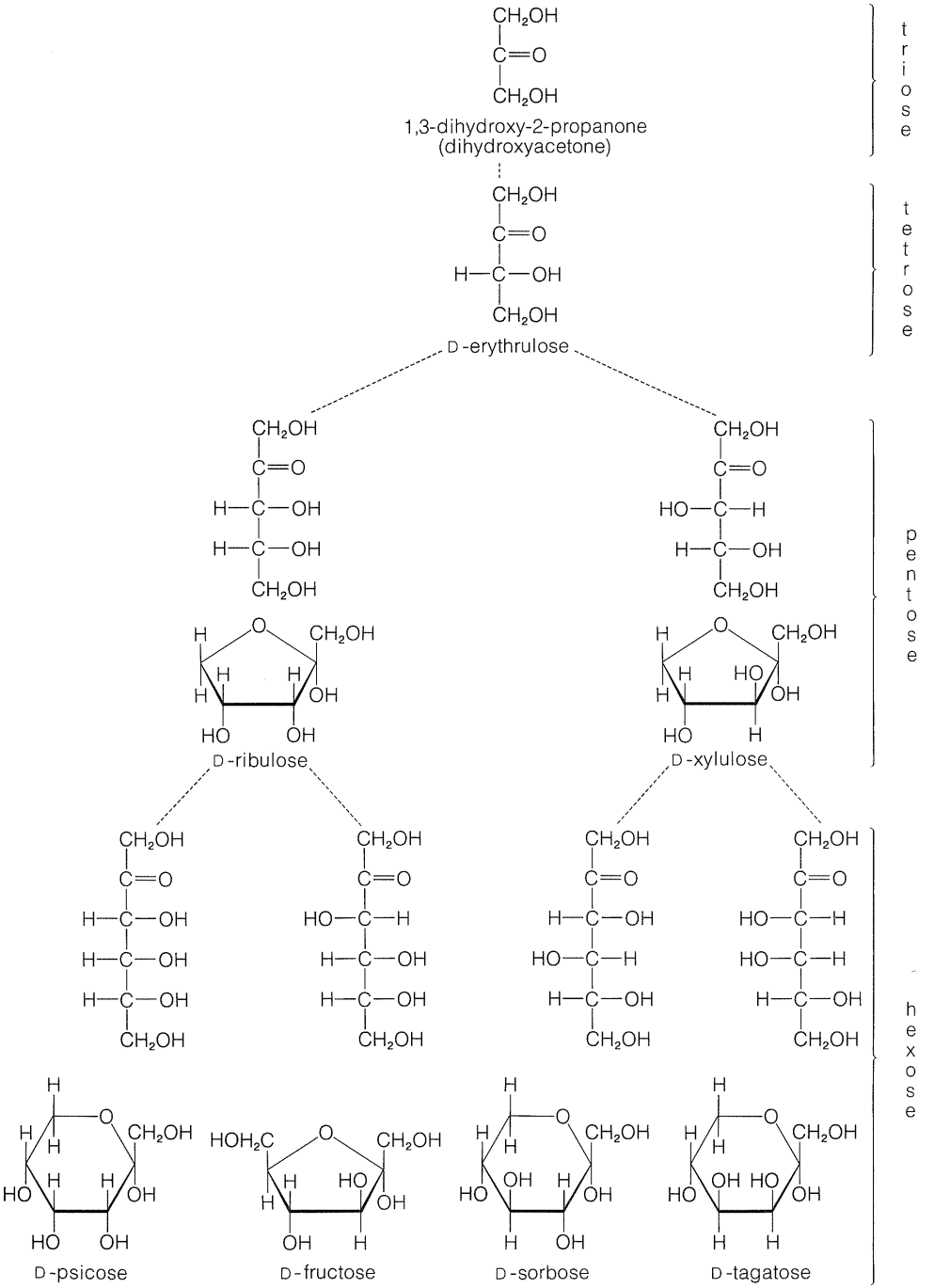


Figure 20-2 Structure and configuration of the D-**ketoses** from C_3 to C_6. As with the aldoses (Figure 20-1), the cyclic form is predominantly an oxacyclohexane (pyranose) ring in the free sugar, but the oxacyclopentane (furanose) form is shown for fructose because it occurs widely in this form as the disaccharide, sucrose. Only the α anomers are shown (see Section 20-2B).

Table 20-1
Occurrence, Physical Properties, and Uses of Some Natural Sugars

Sugar	Mp, °C	$[\alpha]_D^{20-25}$ in H_2O[a]	Occurrence and use
Monosaccharides			
Trioses, $C_3H_6O_3$			
D-glyceraldehyde	syrup	+8.7	Intermediate in carbohydrate biosynthesis and metabolism.
1,3-dihydroxy-2-propanone	81	—	As above.
Tetroses, $C_4H_8O_4$			
D-erythrose	syrup	−14.5	As above.
Pentoses, $C_5H_{10}O_5$			
L-arabinose	160	+105	Free in heartwood of coniferous trees; widely distributed in combined form as glycosides and polysaccharides.
D-ribose	87	−23.7	Carbohydrate component of nucleic acids and coenzymes.
D-xylose	145	+18.8	Called *wood sugar* because it is widely distributed in combined form in polysaccharides, such as in agricultural *wastes* as corn cobs, straw, cottonseed hulls.
Hexoses, $C_6H_{12}O_6$			
D-glucose	146	+52.7	Free in blood, other body fluids, and in plants; abundant combined as polysaccharides.
D-fructose	102	−92.4	Free in fruit juices and honey; combined as in sucrose and plant polysaccharides.
D mannose	132	+14.6	Component of polysaccharides.
D-galactose	167	+80.2	Called *brain sugar* because it is a component of glycoproteins in brain and nerve tissue; also found in oligo- and polysaccharides of plants.
Heptoses, $C_7H_{14}O_7$			
sedoheptulose	syrup	+8.2	Detected in succulent plants; an intermediate in carbohydrate biosynthesis and metabolism.
Oligosaccharides			
Disaccharides			
sucrose	160–186	+66.5	Beet sugar and cane sugar. (D-glucose + D-fructose)
lactose	202	+52.6	Milk sugar of mammals. (D-galactose + D-glucose)
maltose	103	+130	Hydrolytic product of starch. (D-glucose + D-glucose)
Trisaccharides			
raffinose	78	+105	(D-glucose + D-fructose + D-galactose)

(Table continued on following page.)

Table 20-1 (continued)
Occurrence, Physical Properties, and Uses of Some Natural Sugars

Sugar	Mp, °C	$[\alpha]_D^{\omega-25}$ in H_2O[a]	Occurrence and use
Polysaccharides			
cellulose (poly-D-glucose)			Occurs in all plants as a constituent of cell walls; as structural component of woody and fibrous plants.
starch (poly-D-glucose)			As food reserves in animals (glycogen), and in plants.
chitin (polyethanamido sugar)			Found in marine animals, insects, fungi, and green algae.
hemicelluloses			
plant gums			

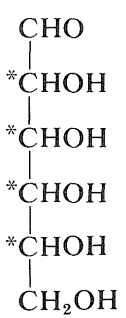
[a]Rotation at equilibrium concentration of anomers and of pyranose and furanose forms (Sections 20-2B and 20-2C).

20-2 THE STRUCTURE AND PROPERTIES OF D-GLUCOSE

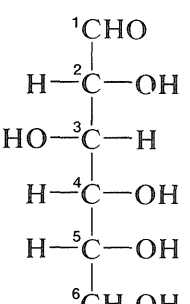
20-2A Configuration

Glucose is by far the most abundant monosaccharide; it occurs free in fruits, plants, honey, in the blood of animals, and combined in many glycosides, disaccharides, and polysaccharides. The structure and properties of glucose will be considered in greater detail than those of the other monosaccharides, not only because of its importance, but because much of what can be said about glucose also can be said about the other monosaccharides.

Glucose is an aldohexose, which means that it is a six-carbon sugar with a terminal aldehyde group, shown by **1**:

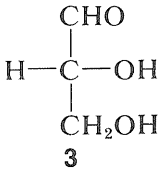


1



2

The carbons labeled with an asterisk in **1** are chiral; thus there are 2^4, or sixteen, possible configurational isomers. All are known—some occur naturally and the others have been synthesized (see Table 20-1). The problem of identifying glucose as a particular one of the sixteen possibilities was solved by Emil Fischer during the latter part of the nineteenth century, for which he was awarded the Nobel Prize in chemistry in 1902. The configurations he deduced for each of the chiral carbons, C2–C5, are shown in the projection formula **2**.[2] Although Fischer was aware that natural glucose could be the enantiomer of Structure **2**, his original guess at the *absolute* configuration proved to be correct and the configuration at C5 is the same as the configuration of the simplest "sugar," D-(+)-glyceraldehyde, **3**, (see Section 19-5). Therefore natural glucose is specifically D-glucose:



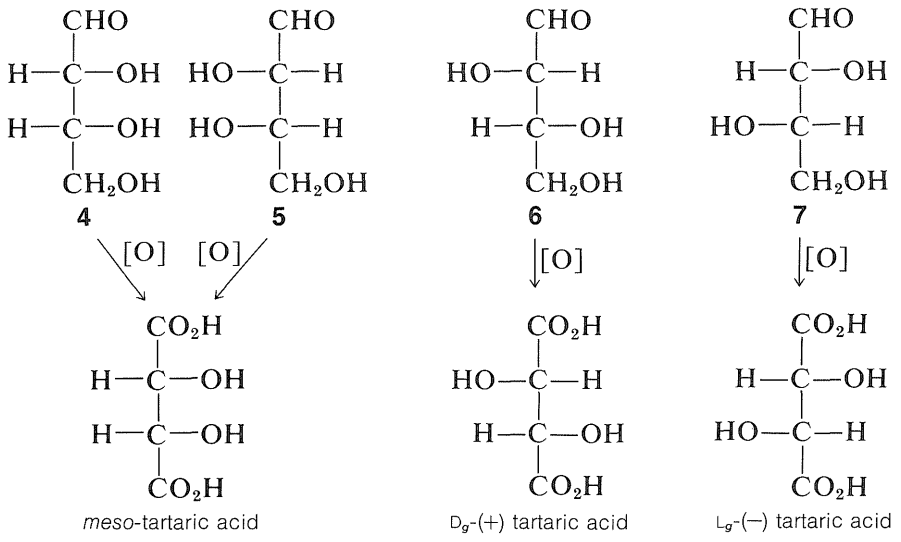
3

The complete logic of Fischer's procedures for determination of the configuration of glucose is too involved to be explained here in detail; instead, much of it is incorporated into Exercise 20-1. This exercise will give you the sense of one of the finest achievements of organic chemistry, made long before the development of the spectroscopic techniques described in Chapter 9. What you will be unable to fully appreciate is the great difficulties of working with carbohydrates—that is, their considerable solubility in water, instability to strong oxidizing agents and acidic or basic reagents, reluctance to crystallize, and their tendency to decompose rather than give sharp melting points. Fortunately for Fischer, many different pentoses and hexoses already were available from the efforts of earlier investigators, and the principles of optical isomerism were well understood as the result of the work of van't Hoff.

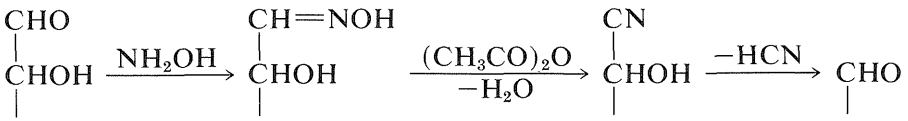
Two of the key ideas used by Fischer can be illustrated best with aldotetroses because they have only two chiral carbons and far fewer possible structures to consider. Writing the four possibilities as the aldehyde rather than hemiacetal structures, we have **4**–**7**. Of these, **4** and **5** constitute a pair of enantiomers, as do **6** and **7**. These pairs can be identified by careful oxidation of the terminal groups to give the corresponding tartaric (2,3-dihydroxy-

[2]We will rely heavily on projection formulas in this chapter as a way of representing the configurations of carbohydrates. If you are unsure of their meaning, we suggest that you review Sections 5-3C and 5-4. It is especially important to be able to translate projection formulas into models and sawhorse drawings, as shown in Figures 5-12 and 5-13.

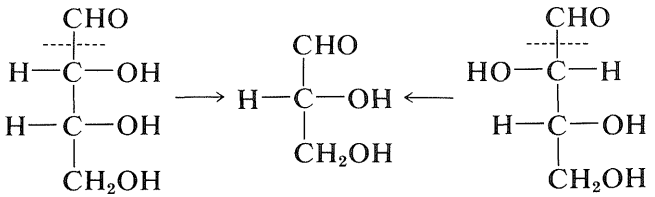
butanedioic) acids. Oxidation of both **4** and **5** gives *meso*-tartaric acid, whereas oxidation of **6** and **7** gives, respectively, (+) and (−) tartaric acids:



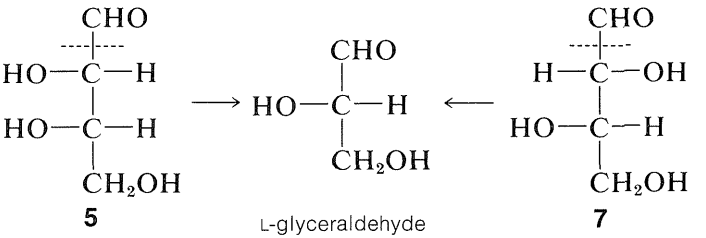
It should be clear from this that the configurations of **6** and **7** are established by being related to the respective *chiral* tartaric acids. However, we have no way of telling which of the tetroses represented by **4** and **5** is D and which is L, because, on oxidation, they give the same achiral tartaric acid. What we need to do is relate one or the other of the chiral carbons of these tetroses to the corresponding carbon of either **6** or **7**. One way that this can be done is by the **Wohl degradation,** whereby the chain length is reduced by one carbon by removing the aldehyde carbon:



As applied to **4**, **5**, **6**, and **7**, the Wohl degradation forms enantiomers of glyceraldehyde:

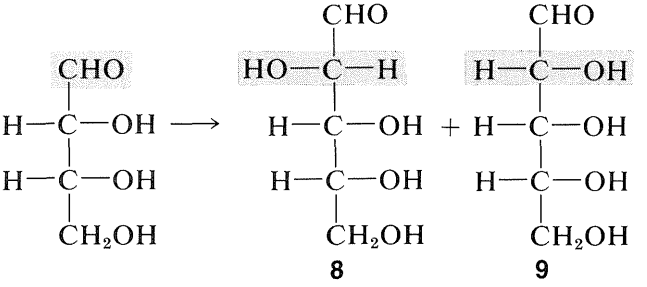


4 D-glyceraldehyde **6**



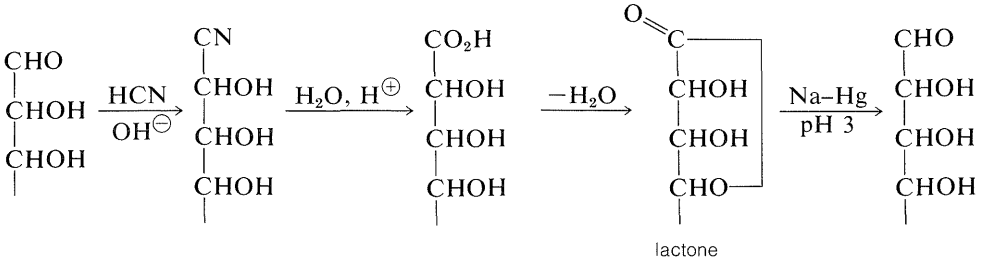
Here we see that **4** and **6** give the same enantiomer, D-glyceraldehyde, and therefore have the same configuration of their highest-numbered asymmetric carbon. In contrast, **5** and **7** give L-glyceraldehyde and thus must be similarly related. By this kind of procedure, the configurations of **4** to **7** can be established unequivocally, although, as you might imagine, it is far easier to do on paper than in the laboratory.

Knowing the configurations of the tetroses aids in establishing the configurations of the pentoses. Thus **4**, by **Kiliani–Fischer cyanohydrin synthesis,**[3] can be converted to a mixture of two aldopentoses, **8** and **9**, by *adding* a carbon at the aldehyde end of the molecule. The configurations of the two carbons at the lower end of the starting material remain unchanged, but two diastereomeric aldopentoses are formed in the syntheses because a new chiral center is created:

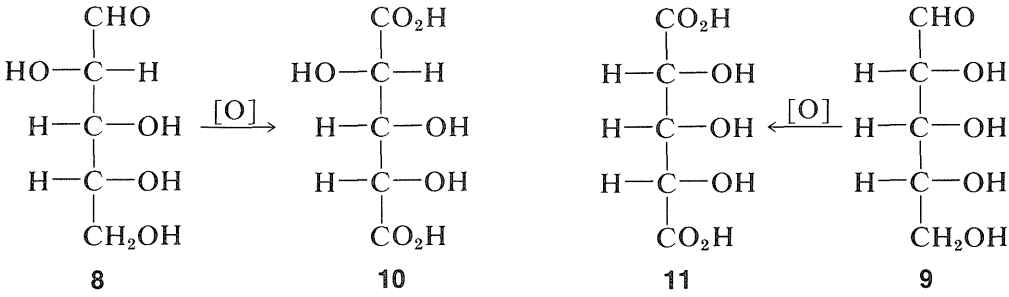


Products **8** and **9** present a new configurational problem, but a less difficult one than before, because the configurations of two of the three chiral

[3]The steps of the Kiliani–Fischer synthesis are:



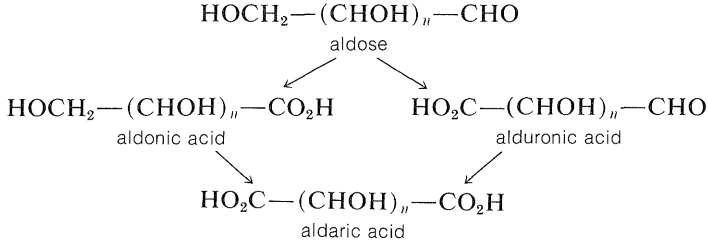
centers already are known. Controlled oxidation of **8** and **9** will give *different* diastereomeric 2,3,4-trihydroxypentanedioic acids, **10** and **11**, respectively:



8 **10** **11** **9**

Of these, **11** is *achiral* (*meso*), whereas **10** is *chiral*. Therefore, by simply determining which oxidation product is optically active, and hence chiral, we can assign the configurations of **8** and **9**. Direct comparison of these synthetic aldopentoses with the naturally occurring compounds then could be used as proof of the structure of natural aldopentoses. By this reasoning **8** turns out to be D-arabinose and **9** is D-ribose.

Some of the key reactions in carbohydrate chemistry involve oxidation of aldoses to carboxylic acids. You will encounter some of these if you work Exercise 20-1. There is a simple nomenclature system for these acids. In abbreviated notation, the products of oxidation at C1, C6, or both are called:



The carboxylic acids derived from glucose are therefore gluconic acid, glucuronic acid, and glucaric acid.

Exercise 20-1 The logic necessary to solve this problem essentially is that used by Fischer in his classic work which established the configurations of glucose, arabinose, and mannose.

a. The projection formulas for all the theoretically possible D-aldopentoses, $HOCH_2(CHOH)_3CHO$, are shown in Figure 20-1. One of the D-aldopentoses is the naturally occurring D-arabinose, which is enantiomeric with the more abundant L-arabinose. Oxidation of D-arabinose with nitric acid gives an optically active 2,3,4-trihydroxypentanedioic acid. Which of the D-aldopentoses could be D-arabinose?

b. D-Arabinose is converted by the Kiliani–Fischer synthesis[3] to D-glucose and D-mannose. What do these transformations tell about the relationship between the configurations of mannose and glucose?

c. Oxidation of D-glucose and D-mannose gives the 2,3,4,5-tetrahydroxyhexanedioic acids, glucaric and mannaric acids, respectively. Both are optically active. What are the configurations of the D- and L-arabinoses?

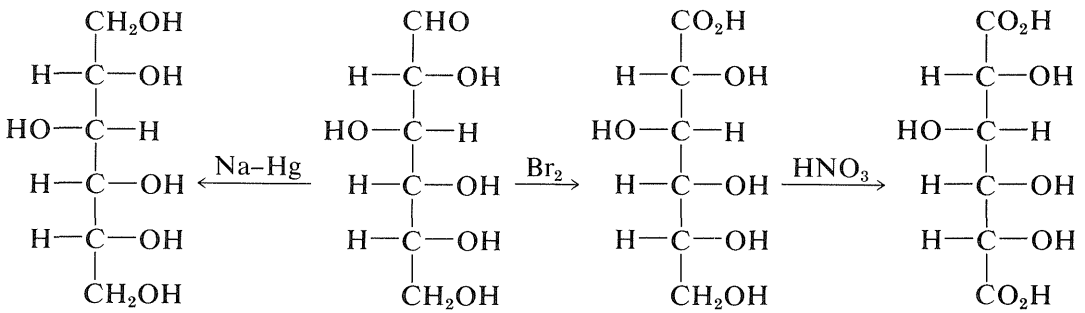
d. D-Glucaric acid can form *two different* γ-monolactones, whereas D-mannaric acid can form only *one* γ-monolactone. What are the configurations of D-glucose and D-mannose?

Exercise 20-2 a. Deduce possible configurations of natural galactose from the following observations. Give your reasoning. (1) D-Galactose gives a pentose by one Wohl degradation. On nitric acid oxidation this pentose gives an optically active 2,3,4-trihydroxypentanedioic acid. (2) The pentose by a second Wohl degradation followed by nitric acid oxidation gives D-tartaric acid.

b. Write reasonable mechanisms for the reactions involved in the Wohl degradation.

20-2B Hemiacetal Formation. Anomers of Glucose

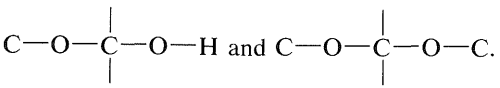
Although glucose has some of the properties expected of an aldehyde, it lacks others. For example, it forms certain carbonyl derivatives (e.g., oxime and cyanohydrin), and can be reduced to the hexahydroxyhexane (sorbitol), and oxidized with bromine to gluconic acid (a monocarboxylic acid). (With nitric acid, oxidation proceeds further to give the dicarboxylic acid, D-glucaric acid.)



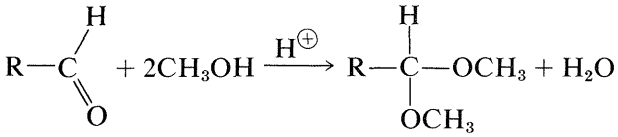
sorbitol D-glucose D-gluconic acid D-glucaric acid

Glucose also will reduce Fehling's solution [Cu(II) ⟶ Cu(I)] and Tollen's reagent [Ag(I) ⟶ Ag(0)] and, for this reason, is classified as a **reducing sugar.**[4]

[4]In general, reducing sugars are hemiacetals or hemiketals and the nonreducing sugars are acetals or ketals. The difference is between the presence of the structural elements



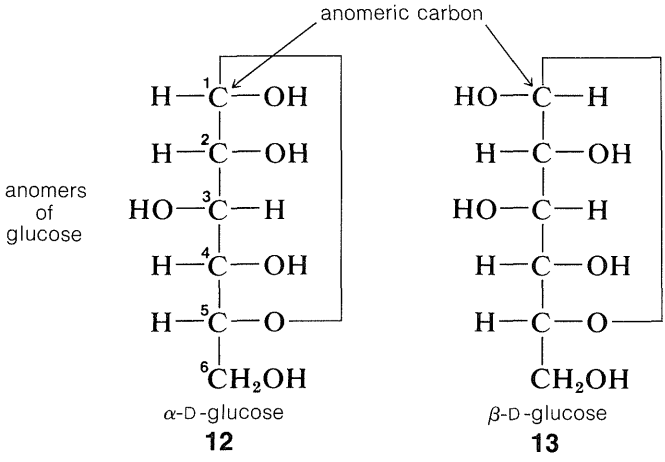
However, it fails to give a hydrogen sulfite addition compound and, although it will react with amines (RNH_2), the products are not the expected Schiff's bases of the type $\rangle C{=}NR$. Furthermore, glucose forms two *different* monomethyl derivatives (called methyl α-D-glucoside and methyl β-D-glucoside) under conditions that normally convert an aldehyde to a dimethyl acetal:



$$C_6H_{12}O_6 + CH_3OH \xrightarrow{H^\oplus} (C_6H_{11}O_5)OCH_3 + H_2O$$

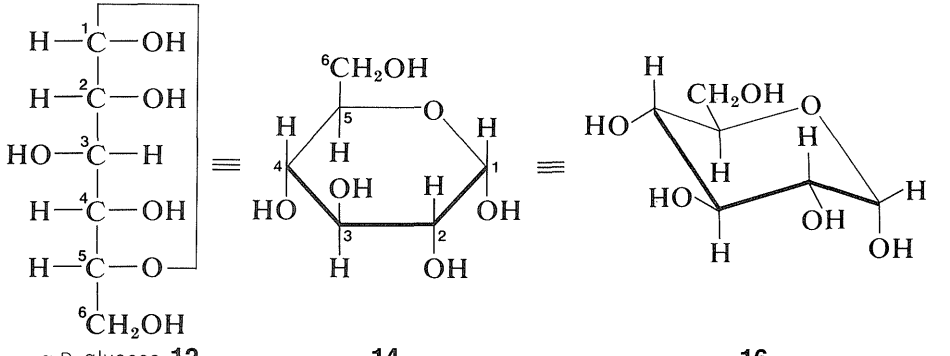
methyl α- and β-D-glucoside

All of these reactions can be explained on the basis that the carbonyl group is not free in glucose but is combined with one of the hydroxyl groups, which turns out to be the one at C5, to form a hemiacetal, **12** or **13**. Why are two hemiacetals possible? Because a new asymmetric center is created at C1 by hemiacetal formation, and this leads to diastereomeric forms of D-glucose called α-D-glucose and β-D-glucose. In general, carbohydrate stereoisomers that differ only in configuration at the hemiacetal carbon are called **anomers**:

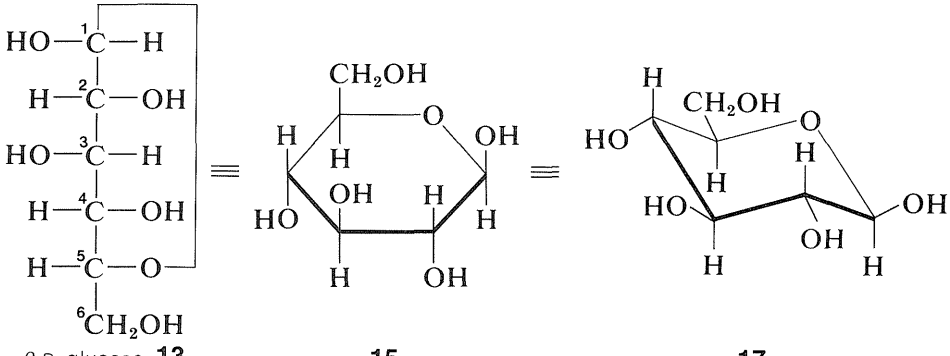


Although formulas **12** and **13** show the *configurations* at each of the chiral centers, they do not provide the crucial information for understanding the properties of glucose with respect to the *arrangement of the atoms in space.* Conversion of a projection formula such as **12** or **13** to a three-dimensional representation is not at all a trivial task. We have indicated the procedure for doing it before (Sections 5-3C and 5-5) and, if you wish practice, there are

examples in Exercise 20-3. The result of these procedures applied to **12** and **13** are the so-called Haworth projection formulas, **14** and **15**, and the sawhorse conformations, **16** and **17**:

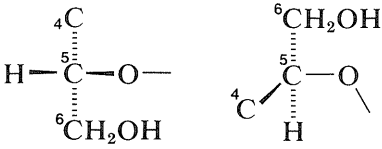


α-D-glucose, **12** **14** **16**



β-D-glucose, **13** **15** **17**

You should be able to satisfy yourself that the configuration at C5 is the same in both Fischer and Haworth representations. This amounts to asking if **18** and **19** represent the same configurations:



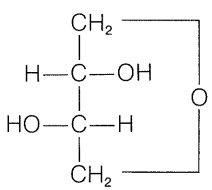
18 **19**

They do, but if you have trouble visualizing this, it will be very helpful to use a ball-and-stick model to see that **18** and **19** are different representations of the same configuration. If you do not have models, remember that if transposition of any three groups converts one projection into the other, the formulas are identical. Thus **18** and **19** have the same configuration because **18** becomes **19** by transposition of C4 with CH_2OH, then C4 with H.

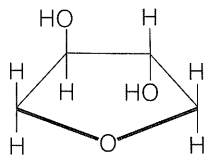
X-ray studies of crystalline α- and β-D-glucose show that these molecules have their atoms arranged in space as correspond to **16** and **17**. This is what we would expect from our studies of cyclohexane conformations (Sections 12-3A to 12-3D), because for the β form, *all* of the substituents on the oxacyclohexane ring are in equatorial positions, and for the α form, all except the hydroxyl at the **anomeric** carbon (C1) are equatorial.

Exercise 20-3 Determine for each of the following sets of structures whether they correspond to the *same* stereoisomer. The left structure in each example is a Fischer projection formula. Models will be helpful!

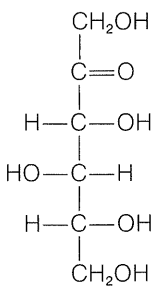
a.



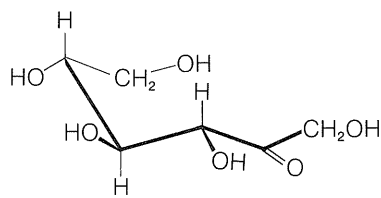
and



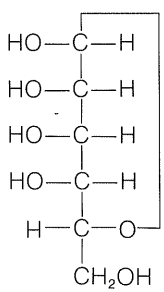
b.



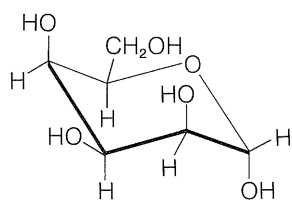
and



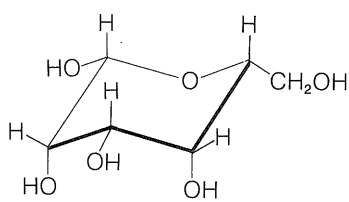
c.



and

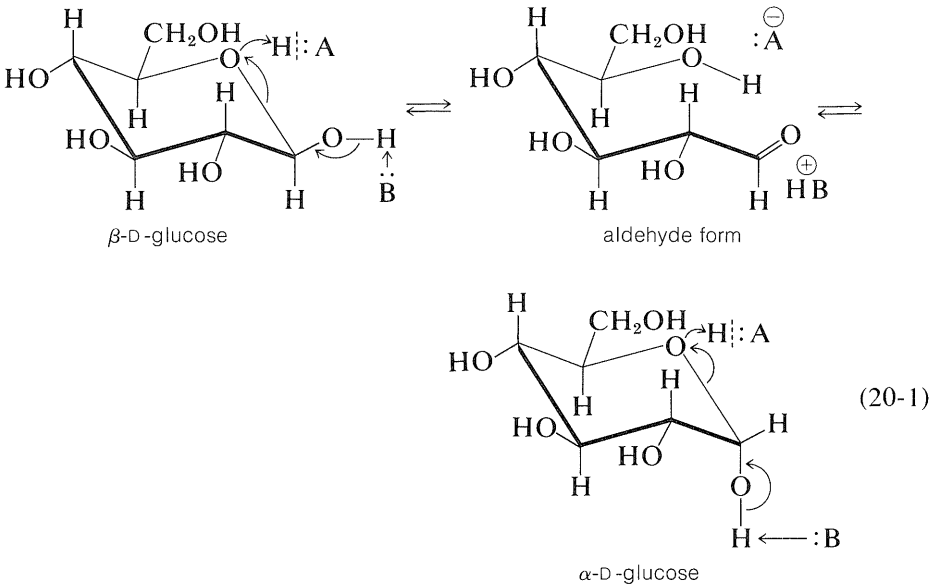


and



20-2C Mutarotation of the Anomeric Forms of Glucose

Although the crystalline forms of α- and β-D-glucose are quite stable, in solution each form slowly changes into an equilibrium mixture of both. The process can be observed as a decrease in the optical rotation of the α anomer (+112°) or an increase for the β anomer (+18.7°) to the equilibrium value of 52.5°. The phenomenon is known as **mutarotation** and commonly is observed for reducing sugars. Both acids and bases catalyze mutarotation; the mechanism, Equation 20-1, is virtually the same as described for acid- and base-catalyzed hemiacetal and hemiketal equilibria of aldehydes and ketones (see Section 15-4E):



(20-1)

At equilibrium, about 64% of the β anomer and 36% of the α anomer are present. The amount of the free aldehyde form at equilibrium is very small (about 0.024 mole percent in neutral solution). Preponderance of the β anomer is attributed to the fact that glucose exists in solution in the chair conformation with the large —CH_2OH group equatorial. In this conformation, the hydroxyl substituent at C1 is equatorial in the β anomer and axial in the α anomer; hence the β anomer is slightly more stable. When glucose is in the aldehyde form, the hydroxyl at C4 also could add to the aldehyde carbonyl to produce a hemiacetal with a five-membered ring. This does not occur to a significant degree with glucose because the hemiacetal with the six-membered ring and many equatorial groups is more stable. With other sugars, mixtures of five- and six-membered hemiacetal or ketal rings and their respective anomers are produced in water solution.

Carbon-13 nmr spectra (Section 9-10L) provide an especially powerful tool for studying the anomeric forms of sugars. For example, with glucose the

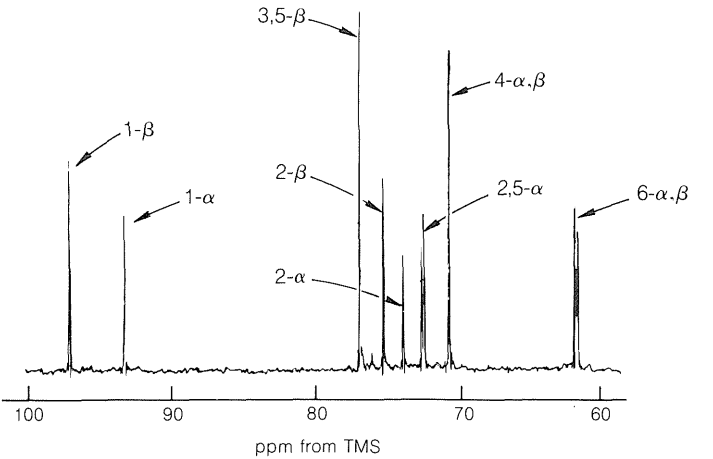


Figure 20-3 Proton-decoupled ^{13}C nmr spectrum at 15.1 MHz of glucose in water solution, showing the peaks of both the α and β anomers. (As in Figure 9-50 the relative peak heights do not correspond to relative amounts of α and β forms present.)

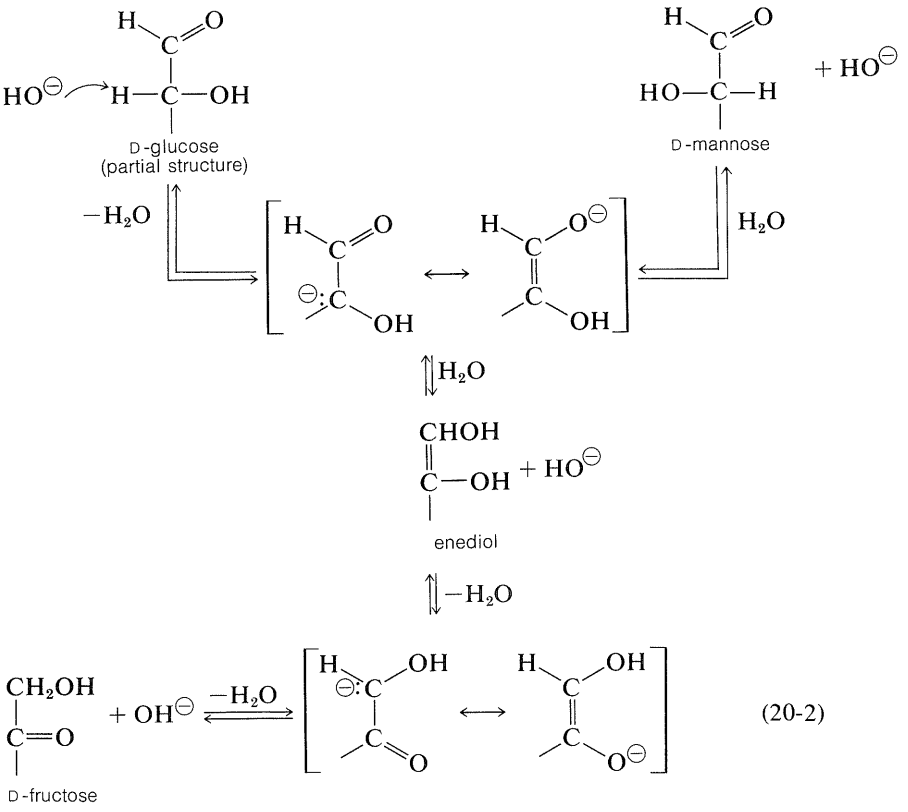
resonances of C1, C3, and C5 of the α anomer are seen in Figure 20-3 to be shifted substantially upfield relative to those of the β anomer because of the axial substituent effect (Section 12-3D).

Exercise 20-4 Draw the chair conformation of β-D-glucose with all of the substituent groups *axial*. Explain how hydrogen bonding may complicate the usual considerations of steric hindrance in assessing the stability of this conformation relative to the form with all substituent groups equatorial.

20-2D Aldose $\rightleftharpoons$ Ketose Rearrangements

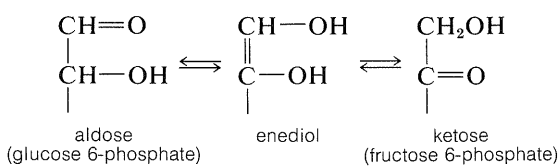
In the presence of dilute base, D-glucose rearranges to a mixture containing the anomers of D-glucose (~64%), D-fructose (~31%), and D-mannose (3%). This interconversion undoubtedly involves enolization of the hexoses by way

of a common enediol intermediate according to Equation 20-2:



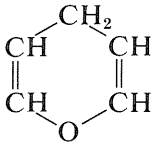
(20-2)

The rearrangement is of interest because the corresponding enzymatic interconversion of aldoses and ketoses is an important part of the biosynthetic, photosynthetic, and metabolic pathways, as we shall see in Section 20-9. Although the biochemical rearrangement also may proceed by way of enediol intermediates, it is highly stereospecific and yields only *one* of two possible stereoisomeric aldoses. For example, glucose, but not mannose, can be enzymatically interconverted with fructose as the 6-phosphate ester derivative:

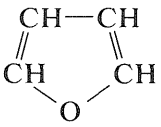


20-3 CONVENTIONS FOR INDICATING RING SIZE AND ANOMER CONFIGURATIONS OF MONOSACCHARIDES

The oxide ring is six-membered in some sugars and five-membered in others, and it is helpful to use names that indicate the ring size. The five- and six-membered oxide rings bear a formal relationship to oxa-2,5-cyclohexadiene and oxa-2,4-cyclopentadiene that commonly are known as pyran and furan, respectively:



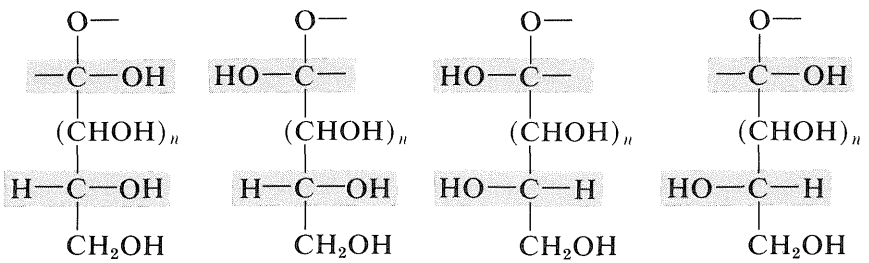
pyran



furan

For this reason, the names **furanose** and **pyranose** have been coined to denote five- and six-membered rings in cyclic sugars. The two forms of glucose are appropriately identified by the names α-D-glucopyranose and β-D-glucopyranose. Likewise, L-arabinose, D-xylose, D-galactose, and D-mannose occur naturally as pyranoses, but D-ribose (in combined form) and D-fructose occur as furanoses (see Figures 20-1 and 20-2).

There is an important question as to which one of the two anomeric forms of a sugar should be designated as α and which one as β. The convention is simple; the α anomer is the one that has the *same* configuration of the OH at the anomeric carbon as the carbon which determines the configuration of the sugar itself:



D sugar α anomer | D sugar β anomer | L sugar α anomer | L sugar β anomer

Exercise 20-5 Make a sawhorse drawing of what you believe to be the favored conformations of α- and β-D-ribopyranose and of α- and β-D-idopyranose.

20-4 DERIVATIVES OF GLUCOSE

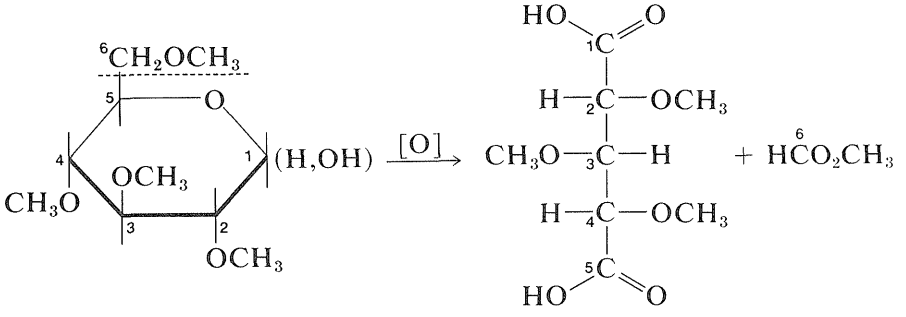
20-4A Determination of the Oxide Ring Size

Although we now have powerful spectroscopic methods available to determine the sizes of the oxide rings formed by the simple monosaccharides, the way in which this was done chemically for glucose highlights the difference in reactivity between ether and alcohol functions.

The acid-catalyzed methylation of glucose with methanol to give two distinct glucosides, methyl α-D-glucoside and methyl β-D-glucoside, corresponds to displacement of the hemiacetal hydroxyl by methoxyl to form an acetal (see left side of Figure 20-4).

The remaining four hydroxyl groups can be methylated in basic solution by dimethyl sulfate or by methyl iodide and silver oxide in *N,N*-dimethylmethanamide, $HCON(CH_3)_2$, solution. Hydrolysis of either of these pentamethyl glucose derivatives with aqueous acid affects only the acetal linkage and leads to a tetramethylated glucose, **20**, as shown in Figure 20-4.

The pyranose ring structure of D-glucose originally was established by Hirst, in 1926, by converting D-glucose to a tetra-*O*-methyl-D-glucose and showing that this substance actually was 2,3,4,6-tetra-*O*-methyl-D-glucose, **20**. The key feature of **20** is the fact that all but the two carbons involved in hemiacetal formation are protected from oxidation by being substituted with *O*-methyl groups in place of hydroxy groups. The largest fragment isolated from oxidation of Hirst's tetra-*O*-methyl-D-glucose was a trimethoxypentanedioic acid, **21**, and because the two carboxyl carbons must have been the ones originally involved in ring formation, the oxide ring must be between C1 and C5:



20 **21**

Reagents that specifically oxidize vicinal glycols [e.g., $NaIO_4$, $Pb(O_2CCH_3)_4$, and $NaBiO_3$; Section 16-9A] are quite helpful in determining the cyclic structures of sugars. With periodate, the numbers of moles of oxidant consumed and the moles of methanoic acid and methanal produced are

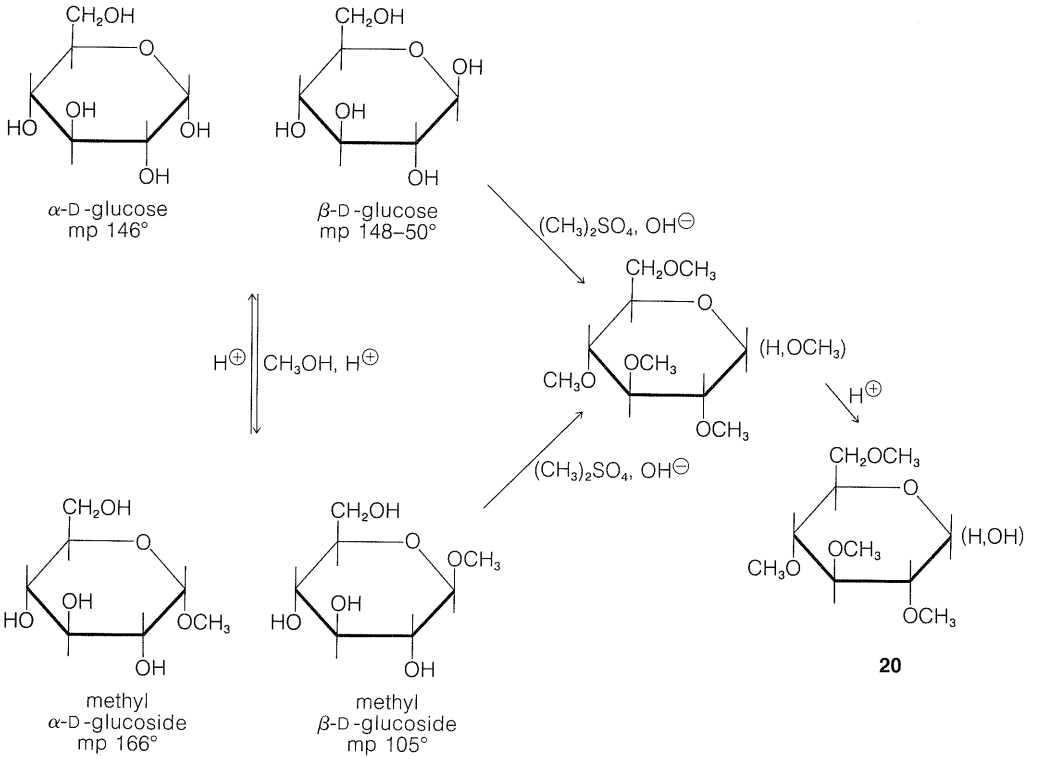
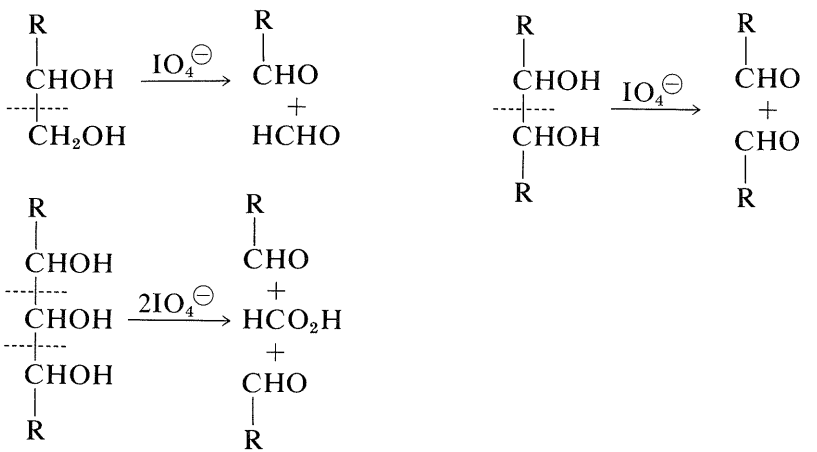


Figure 20-4 Haworth projection formulas showing the formation and reactions of *O*-methyl derivatives of glucose. The notation (H,OH) in **20** means that the anomeric configuration is unspecified.

different for each type of ring structure. The cleavage reactions that normally are observed follow:

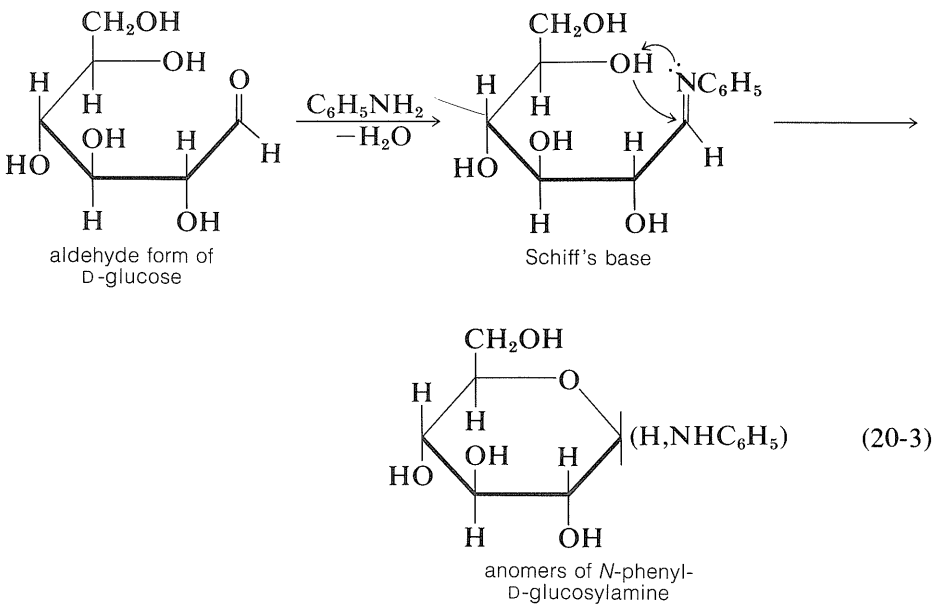


Exercise 20-6 From the following information deduce the ring structures of the sugars. Give your reasoning.

Sugar (as methyl glycoside)	Moles of $IO_4^{\ominus}$ consumed	Moles of HCO_2H formed	Moles of H_2CO formed
methyl α-D-mannoside	2	1	0
methyl α-D-riboside	1	0	0
a methyl glycoside of an aldohexose	3	2	0
a methyl glycoside of an aldohexose	2	0	1

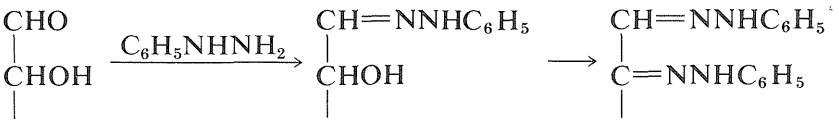
20-4B Reactions with Amines and Hydrazines; Osazone Formation

As we stated previously, glucose forms some, but not all, of the common carbonyl derivatives. The amount of free aldehyde present in solution is so small that it is not surprising that no hydrogen sulfite derivative forms. With amines, the product is not a Schiff's base but a glucosylamine of cyclic structure analogous to the hemiacetal structure of glucose, Equation 20-3. The Schiff's base is likely to be an intermediate that rapidly cyclizes to the glucosylamine:



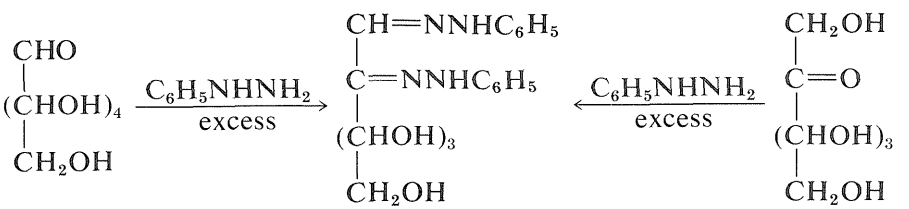
(20-3)

The reaction of glucose with an excess of phenylhydrazine (phenyldiazane) is particularly noteworthy because *two* phenylhydrazine molecules are incorporated into one of glucose. Subsequent to the expected phenylhydrazone formation, and in a manner that is not entirely clear, the —CHOH— group adjacent to the original aldehyde function is oxidized to a carbonyl group, which then consumes more phenylhydrazine to form a crystalline derivative called an **osazone,** or specifically **glucose phenylosazone:**



glucose — phenylhydrazone of glucose — glucose phenylosazone

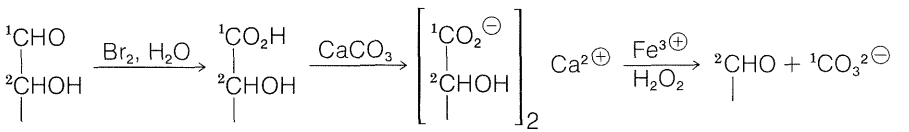
The sugar osazones usually are crystalline and are useful for characterization and identification of sugars. Fischer employed them in his work that established the configuration of the sugars. The kind of information that can be obtained is illustrated by the following example:



glucose and mannose — phenylosazone from glucose, mannose and fructose — fructose

Because the *same* phenylosazone arises from glucose, mannose, and fructose, the configurations of C3, C4, and C5 must be the *same* for all three sugars.

Exercise 20-7 D-Arabinose and D-ribose give the *same* phenylosazone. D-Ribose is reduced to the optically inactive 1,2,3,4,5-pentanepentol, ribitol. D-Arabinose can be degraded by the Ruff method, which involves the following reactions:

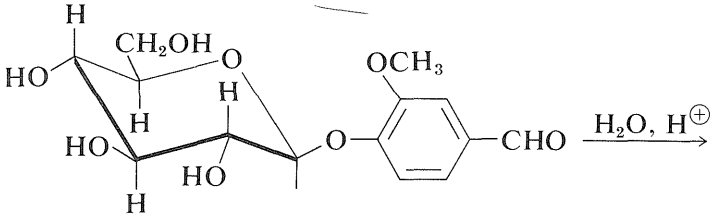


The tetrose, D-erythrose, so obtained can be oxidized with nitric acid to *meso*-tartaric acid. Show how this information can be organized to establish the configurations of D-arabinose, D-ribose, ribitol, and D-erythrose.

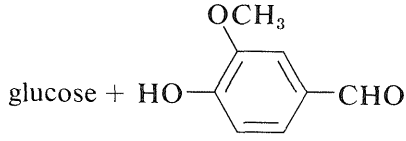
20-5 GLYCOSIDES

Although abundant quantities of glucose and fructose are found in the free state, they and less common sugars occur widely in plants and animals combined with various hydroxy compounds. The bonding is through oxygen to the carbonyl carbon, as in the α- and β-methylglucosides discussed in Section 20-4A, to give acetal or ketal structures. These substances are sometimes simply called **glycosides,** but it is desirable to specify that the bonding is through oxygen by using the name *O*-glycoside. Hydrolysis of an *O*-glycoside gives the sugar and the hydroxy compound, called the **aglycone** component of the glycoside.

A specific example is glucovanillin, which can be isolated from the green fruit pods of vanilla, a climbing orchid cultivated in several tropical countries. Hydrolysis gives glucose and the aglycone, vanillin, which is the principal ingredient of vanilla flavoring. As the vanilla pods mature, a natural hydrolysis reaction proceeds to the extent that the pods may be covered with small crystals of vanillin.



glucovanillin
(β isomer)



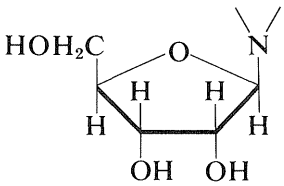
vanillin

The configurations of glycosides are designated by the same convention used for the sugar anomers. Thus if a glycoside of a D sugar has the D configuration at the anomeric carbon, it is designated as the α-D-glycoside, and if it has the L configuration it is called the β-D-glycoside (see Section 20-3). If the sugar involved in glycoside formation is glucose, the derivative is a **glucoside;** if fructose, a **fructoside;** if galactose, a **galactoside,** and so on. When the hydroxy compound, or aglycone, is another sugar, then the glycoside is a **disaccharide,** and if the sugar is already a disaccharide, the glycoside is a **trisaccharide,** and so on.

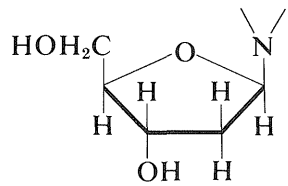
Among the natural products that occur as glycosides (most commonly as β-D-glucosides) are many plant pigments (the anthocyanins), the flavorings

vanillin and amygdalin, and many steroids (such as the cardiac glycosides and and saponins). The structures of some of these substances will be discussed in later chapters.

Not all glycosides are *O*-glycosides. A group of *N*-glycosides of special biological importance are derived from heterocyclic nitrogen bases and D-ribose and 2-deoxy-D-ribose. They commonly are known as *nucleosides,* or more specifically, as **ribonucleosides** and **deoxyribonucleosides;** the *N*-glycoside linkage is always β:

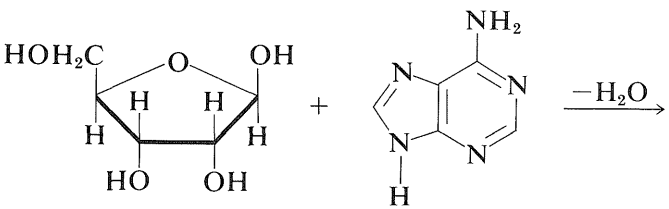


ribonucleoside
(partial structure)

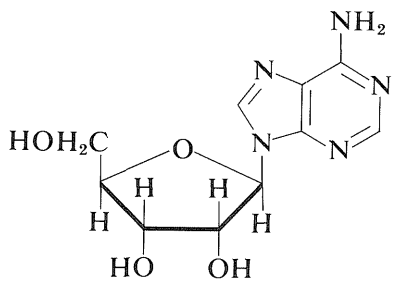


deoxyribonucleoside
(partial structure)

The *N*-glycoside of D-ribose and the nitrogen heterocycle, adenine, is **adenosine:**



β-D-ribose adenine



adenosine
(a nucleoside)

A **nucleotide** is a phosphate ester of a nucleoside. The hydroxyl group at the C5 position of the pentose is the most common site of esterification. The nucleotides of adenosine are ATP, ADP, and AMP (Section 15-5F).

A **dinucleotide** is a combination of two nucleosides through a common phosphate ester link. Familiar examples are $NAD^{\oplus}$, NADH, FAD, and

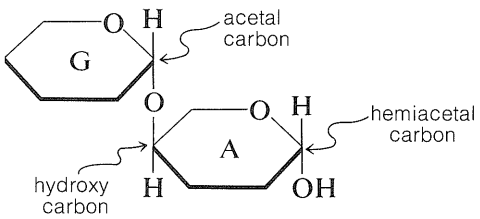
$FADH_2$ (Section 15-6C). Polynucleotides are polymers of nucleosides linked through phosphate ester bonds. Polynucleotides also are called nucleic acids (RNA and DNA) and are the genetic material of cells, as will be discussed in Chapter 25.

Exercise 20-8 Work out a mechanism for the acid-induced hydrolysis of *N*-glycosides. Pay special attention as to where a proton can be added to be most effective in assisting the reaction. Would you expect that adenosine would hydrolyze more, or less, readily than *N*-methyl-α-ribosylamine? Give your reasoning.

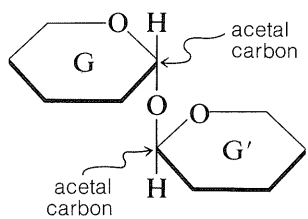
20-6 DISACCHARIDES

20-6A General Types and Properties

Combinations of two or more of the simple sugars through glycoside linkages give substances known as **polysaccharides.** They also are called **oligosaccharides** if made from two to ten sugar units. The simplest oligosaccharides are disaccharides made of two molecules of simple sugars that can be the same or different. There are two ways in which the simple sugars can be joined with *O*-glycoside links, and it probably is easiest to visualize these as shown in the "stripped-down" formulas, **22** and **23**:



22

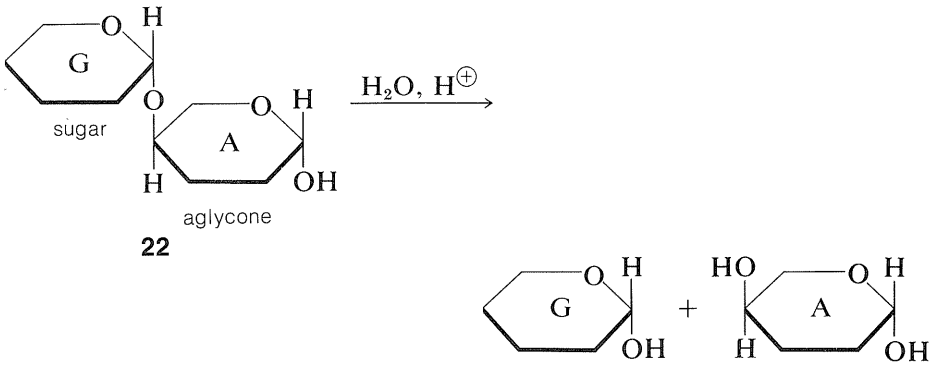


23

You should look at **22** and **23** carefully to be sure that you recognize the difference between them.[5] In **22**, sugar A is acting as a simple hydroxy compound, the aglycone of the sugar G to which it is linked by an *O*-glycoside

[5]For now, we will ignore the possibility of different anomers of the disaccharide or their component sugars.

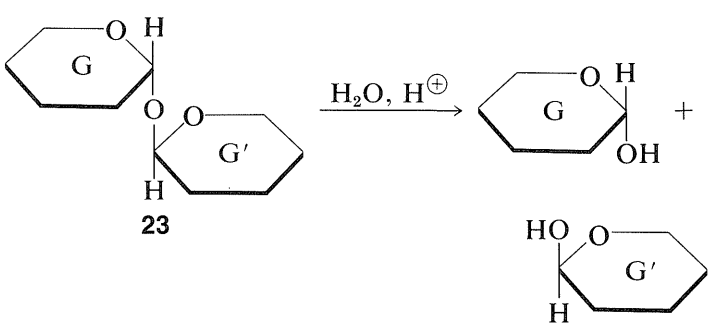
linkage.[6] Hydrolysis of **22** at the glycoside link then will proceed as follows:



22

Disaccharides such as **22** are like glucose in being reducing sugars (Section 20-2B), because Component A has the hemiacetal grouping that is opened easily to the aldehyde form in the mildly alkaline conditions used for the Tollen's and Fehling's solution oxidations. Because there is a free hemiacetal group, reducing sugars also form osazones and they mutarotate (Sections 20-4B and 20-2C).

Disaccharides of type **23** are different in that each sugar, G and G′, is acting as both a glycoside sugar *and* as an aglycone. The linkage between them is that of a double-barreled acetal, —O—C—O—C—O—, and there is no hemiacetal grouping in the molecule. Therefore these are *nonreducing* sugars as far as the standard tests go. However, hydrolysis of the *O*-glycoside linkages of **23** does generate reducing sugars with hemiacetal carbons:

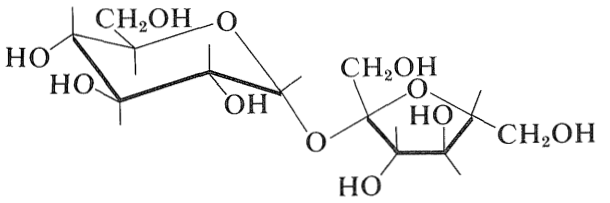


23

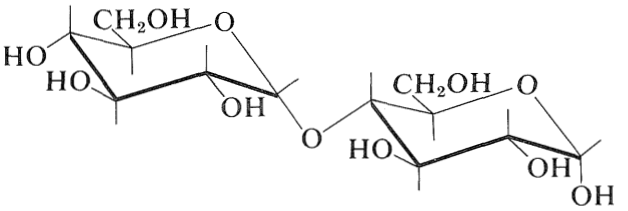
[6]The manner in which sugars are linked together to form oligosaccharides was elucidated by W. N. Haworth, who received the Nobel Prize in chemistry in 1937 for this and other contributions to research on the structures and reactions of carbohydrates.

In general, we find that the nonreducing disaccharides give none of the carbonyl reactions observed for glucose, such as mutarotation and osazone formation, except when the conditions are sufficiently acidic to hydrolyze the acetal linkage.

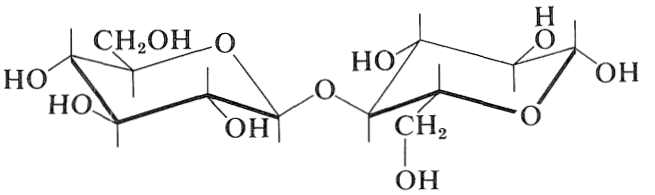
Among the more important disaccharides are sucrose, **24**, maltose, **25**, cellobiose, **26**, and lactose, **27**:



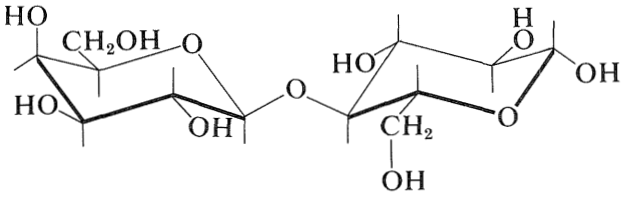
sucrose, **24**



maltose, **25**



cellobiose, **26**



lactose, **27**

Sucrose and lactose occur widely as the free sugars, lactose in the milk of mammals, and sucrose in fruit and plants (especially in sugar cane and sugar beet). Maltose is the product of enzymatic hydrolysis of starch, and cellobiose is a product of hydrolysis of cellulose.

To fully establish the structure of a disaccharide, we must determine (1) the identity of the component monosaccharides; (2) the type of ring junction, furanose or pyranose, in each monosaccharide, as it exists in the disaccharide; (3) the positions that link one monosaccharide with the other; and (4) the anomeric configuration (α or β) of this linkage.

Hydrolysis of disaccharides with enzymes is very helpful in establishing anomeric configurations, because enzymes are highly specific catalysts for hydrolysis of the different types of glycoside linkages. For instance, α-D-glucosidase (maltase) catalyzes hydrolysis of α-D-glycosides more rapidly than of β-D-glycosides. The enzyme emulsin (found in bitter almonds) in contrast shows a strong preference for β-D-glycosides over α-D-glycosides. Yeast invertase catalyzes hydrolysis of β-D-fructosides.

Exercise 20-9 a. Which of the disaccharides, **24** through **27**, would you expect to be reducing sugars?

b. Determine the configuration of each of the *anomeric* carbons in **24** through **27** as either α or β.

c. Determine which monosaccharides (neglect the anomeric forms) will be produced on hydrolysis of **24** through **27**. Be sure you specify the configurations as D or L.

20-6B Structure of Sucrose

We know that sucrose consists of the two monosaccharides, glucose and fructose, because hydrolysis with acids or enzymes gives equal amounts of each hexose. Further, sucrose is not a reducing sugar, it forms no phenylosazone derivative, and it does not mutarotate. Therefore the anomeric carbons of both glucose and fructose must be linked through an *oxygen bridge* in sucrose. Thus sucrose is a **glycosyl fructoside** or, equally, a **fructosyl glucoside.**

Because sucrose is hydrolyzed by enzymes that specifically assist hydrolysis of both α glycosides (such as yeast α-glucosidase) and β-fructosides (such as invertase), it is inferred that the glucose residue is present as an α *glucoside* and the fructose residue as a β *fructoside*. If so, the remaining uncertainty in the structure of sucrose is the size of the rings in the glucose and fructose residues.

The size of the sugar rings in sucrose has been determined by the reactions shown in Figure 20-5. Methylation of sucrose with dimethyl sulfate in basic solution followed by hydrolysis of the octamethyl derivative gives 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (Section 20-4) and a tetra-*O*-methyl-D-fructose. This establishes the glucose residue in sucrose as a *glucopyranose*. The fructose residue must be a *fructofuranose* because periodate oxidation of sucrose consumes three moles of periodate, whereby one mole of methanoic acid and one mole of a tetraaldehyde are formed. On bromine oxidation

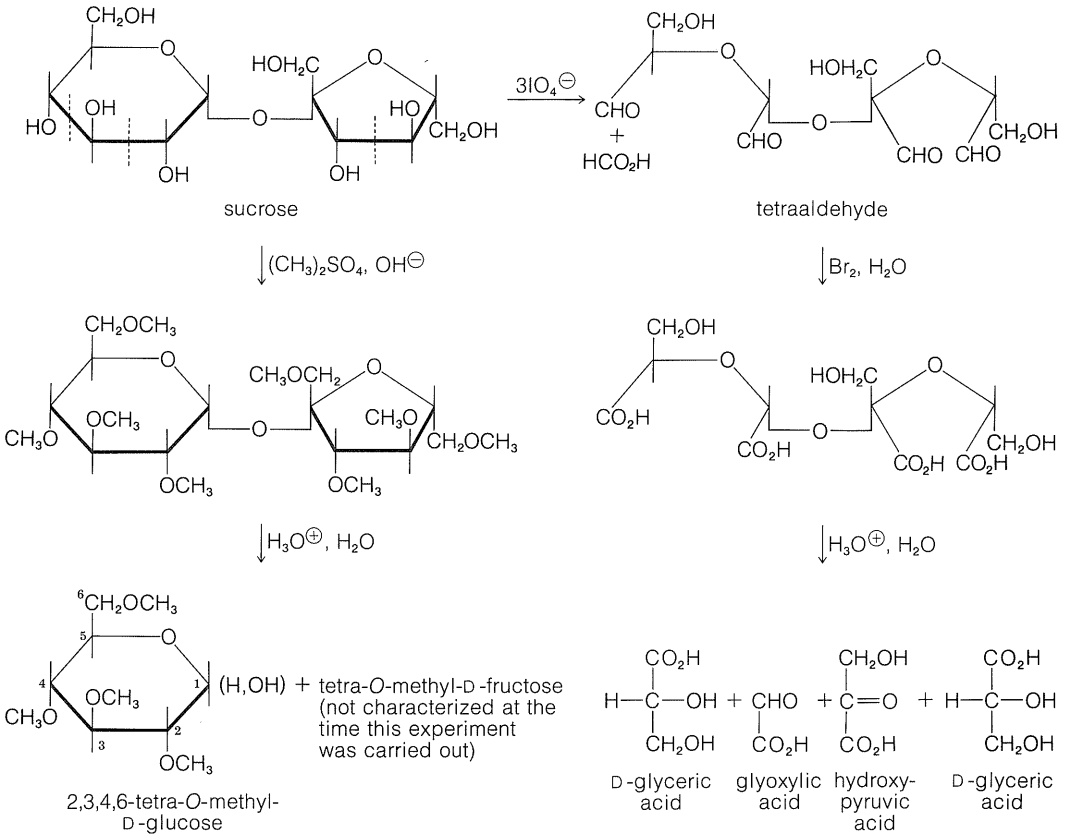


Figure 20-5 Summary of reactions used to establish the ring structure of sucrose

followed by acid hydrolysis, the tetraaldehyde gives 3-hydroxy-2-oxopropanoic acid (hydroxypyruvic acid, $HOCH_2COCO_2H$), oxoethanoic acid (glyoxylic acid, $OCHCO_2H$), and D-glyceric acid ($HOCH_2CHOHCO_2H$). Sucrose therefore has structure **24**, and this structure was confirmed by synthesis (R. Lemieux in 1953).

Exercise 20-10 Draw Haworth and conformational structures for each of the following disaccharides:

a. 6-*O*-β-D-glucopyranosyl-β-D-glucopyranose
b. 4-*O*-β-D-galactopyranosyl-α-D-glucopyranose
c. 4-*O*-β-D-xylopyranosyl-β-L-arabinopyranose
d. 6-*O*-α-D-galactopyranosyl-β-D-fructofuranose

Exercise 20-11 Show how the structure of maltose can be deduced from the following:
(1) The sugar is hydrolyzed by yeast α-D-glucosidase to D-glucose.

(2) Maltose mutarotates and forms a phenylosazone.

(3) Methylation with dimethyl sulfate in basic solution followed by acid hydrolysis gives 2,3,4,6-tetra-*O*-methyl-D-glucopyranose and 2,3,6-tri-*O*-methyl-D-glucose.

(4) Bromine oxidation of maltose followed by methylation and hydrolysis gives 2,3,4,6-tetra-*O*-methyl-D-glucopyranose and a tetramethyl-D-gluconic acid, which readily forms a γ-lactone.

Exercise 20-12 Cellobiose differs from maltose only in its behavior to enzymatic hydrolysis. It is hydrolyzed by yeast β-D-glucosidase. What is its structure?

Exercise 20-13 Show how the structure of lactose may be deduced from the following:
(1) The sugar is hydrolyzed by β-D-galactosidase to a mixture of equal parts of D-glucose and D-galactose.

(2) Lactose mutarotates and forms a phenylosazone.

(3) Bromine oxidation of lactose followed by hydrolysis gives D-gluconic acid and D-galactose.

(4) Methylation and hydrolysis of lactose gives a tetra-*O*-methyl-D-galactose and 2,3,6-tri-*O*-methyl-D-glucose. The same galactose derivative can be obtained from the methylation and hydrolysis of D-galactopyranose.

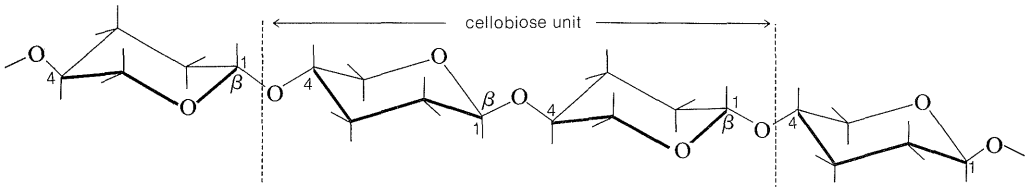
(5) Bromine oxidation of lactose followed by methylation and hydrolysis yields tetra-*O*-methyl-1,4-gluconolactone and the same galactose derivative as in (4).

20-7 POLYSACCHARIDES

20-7A Cellulose

The fibrous tissue in the cell walls of plants contains the polysaccharide **cellulose,** which consists of long chains of glucose units, each of which is connected by a β-glucoside link to the C4 hydroxyl of another glucose as in the

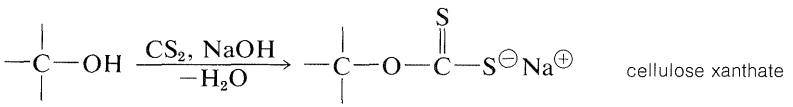
disaccharide **cellobiose** (i.e., β-1,4):



cellulose structure
(the hydroxyls on the rings are omitted for clarity)

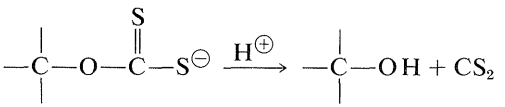
Indeed, enzymatic hydrolysis of cellulose leads to cellobiose. The molecular weight of cellulose varies with the source but is usually high. Cotton cellulose appears to have about 3000 glucose units per molecule.

The natural fibers obtained from cotton, wood, flax, hemp, and jute all are cellulose fibers and serve as raw materials for the textile and paper industries. In addition to its use as a natural fiber and in those industries that depend on wood as a construction material, cellulose is used to make cellulose acetate (for making rayon acetate yarn, photographic film, and cellulose acetate butyrate plastics), nitric acid esters (gun cotton and celluloid[7]), and cellulose xanthate (for making viscose rayon fibers). The process by which viscose rayon is manufactured involves converting wood pulp or cotton linters into cellulose xanthate by reaction with carbon disulfide and sodium hydroxide:



cellulose xanthate

The length of the chains of the cellulose decreases about 300 monomer units in this process. At this point, the cellulose is regenerated in the form of fine filaments by forcing the xanthate solution through a spinneret into an acid bath:



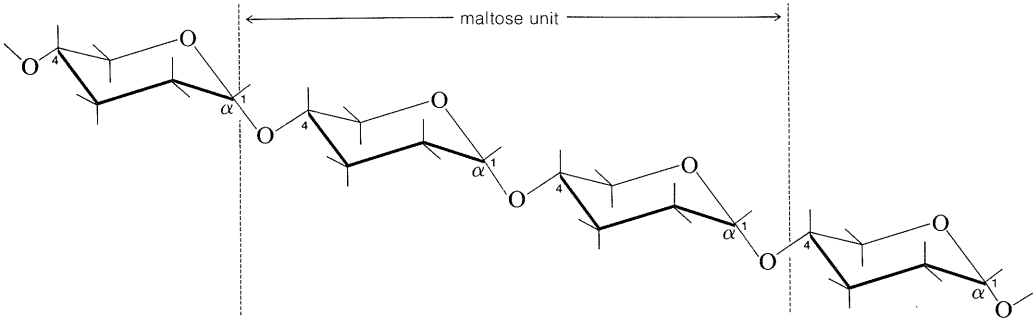
[7]Celluloid, one of the first plastics, is partially nitrated cellulose (known as pyroxylin) plasticized with camphor.

A few animals (especially ruminants and termites) are able to metabolize cellulose, but even these animals depend on appropriate microorganisms in their intestinal tracts to hydrolyze the β-1,4 links; other animals, including man, cannot utilize cellulose as food because they lack the necessary hydrolytic enzymes. However, such enzymes are distributed widely in nature. In fact, deterioration of cellulose materials—textiles, paper, and wood—by enzymatic degradation (such as by dry rot) is an economic problem that is not yet adequately solved. Efforts to turn this to advantage through enzymatic hydrolysis of cellulose to glucose for practical food production have not been very successful (see Section 25-12).

20-7B Starch and Related Compounds

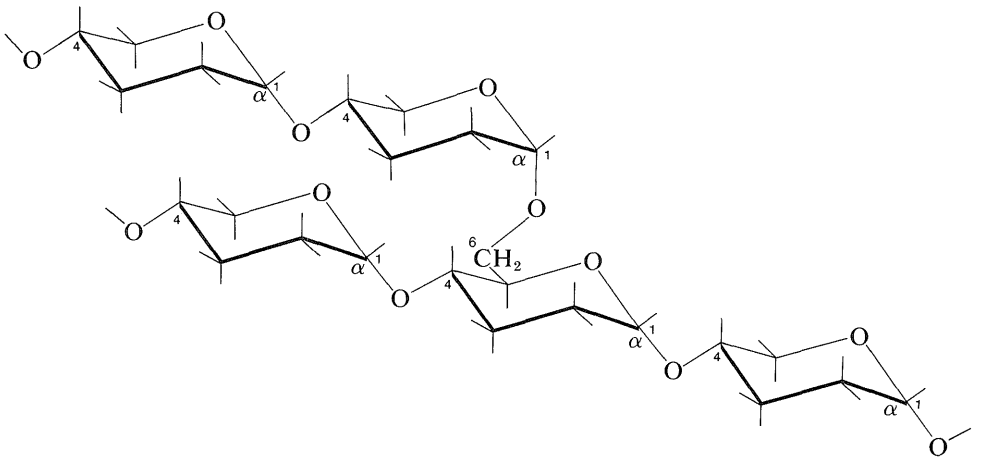
A second very widely distributed polysaccharide is **starch,** which is stored in the seeds, roots, and fibers of plants as a food reserve—a potential source of glucose. The chemical composition of starch varies with the source, but in any one starch there are two structurally different polysaccharides. Both consist entirely of glucose units, but one is a linear structure (**amylose**) and the other is a branched structure (**amylopectin**).

The amylose form of starch consists of repeating 1,4-glucopyranose links as in cellulose, but unlike cellulose the linkage is α rather than β (i.e., α-1,4):



Hydrolysis by the enzyme diastase leads to maltose.

In amylopectin, amylose chains are joined by α-1,6 linkages:



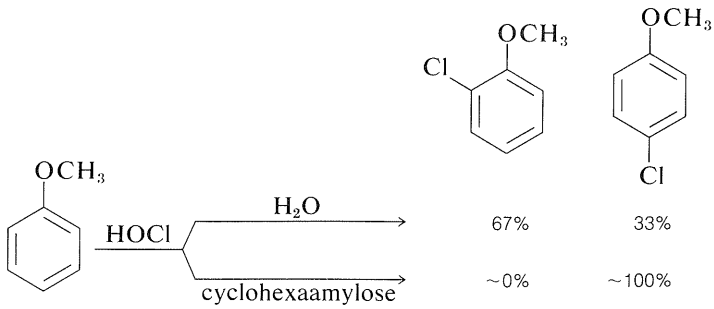
amylopectin

Animals also store glucose in the form of starchlike substances called **glycogens.** These substances resemble amylopectin more than amylose, in that they are branched chains of glucose units with α-1,4- and α-1,6-glucoside links.

Starch is used in paper manufacture and in the textile and food industries. Fermentation of grain starches is an important source of ethanol. Hydrolysis of starch catalyzed by hydrochloric acid results in a syrupy mixture of glucose, maltose, and higher-molecular-weight saccharides. This mixture is called **dextrin** and is marketed as corn syrup. The hydrolysis does not proceed all the way to glucose because the α-1,6 glucosidic link at the branch point is not easily hydrolyzed. Enzymes also catalyze hydrolysis of starch, but the enzyme α *amylase* is specific for α-1,4 links and, like acid-catalyzed hydrolysis, gives a mixture of glucose, maltose, and polysaccharides (dextrin). The enzyme α-1,6-*glucosidase* can hydrolyze the α-1,6 links at the branch points and, when used in conjunction with α amylase, completes the hydrolysis of starch to glucose.

A very interesting group of polysaccharides isolated from cornstarch hydrolysates are known as **cyclodextrins.** One of these compounds, **cyclohexaamylose,** is a large doughnut-shaped molecule with a central cavity that literally can engulf a small, relatively nonpolar organic molecule and hold it in water solution, similar to a micelle (Section 18-2F). As with micelles, unusual reactivity is exhibited by the bound molecules. An example is the change in the ortho-para

ratio in electrophilic substitution of methoxybenzene by hypochlorous acid, HOCl, in the presence and absence of cyclohexaamylose:

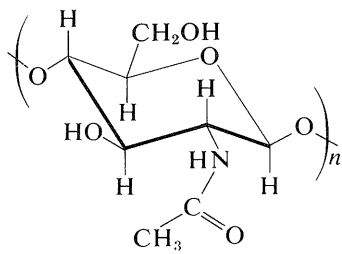


Apparently the cyclohexaamylose wraps around the methoxybenzene in such a way as to protect the ortho carbons from attack by HOCl but to leave the para carbon exposed. It is this kind of specificity that we need to generate in reactions before we can claim to have synthetic reactions under control.

Exercise 20-14 Explain how the β-D-glucoside units of cellulose produce a polymer with a stronger, more compact physical structure than the α-D-glucose units of starch. Models will be helpful.

20-7C Other Important Polysaccharides

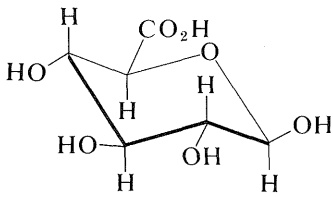
Many polysaccharides besides starch and cellulose are important components of animal tissues, or play a vital role in biochemical processes. One example is **chitin,** a celluloselike material that is the structural component of the hard shells of insects and crustaceans. The difference between chitin and cellulose is that instead of being a polymer of glucose, chitin is a polymer of 2-deoxy-2-*N*-ethanamidoglucose (*N*-acetyl-β-D-glucosamine):



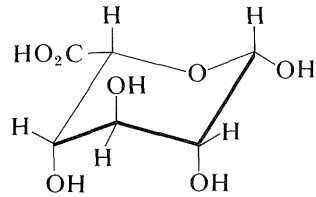
chitin

Heparin is a very important and complex polysaccharide derivative that occurs in intestinal walls and has a major use as a blood anticoagulant, especially in connection with artificial kidney therapy. Heparin also has shown great

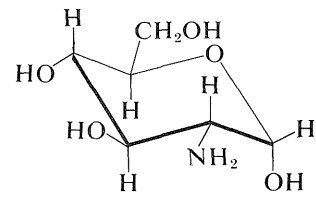
promise in the treatment of patients with extensive burns, by promoting blood circulation to burn-damaged tissue. The structure of heparin can not be defined precisely because its composition depends on the source of supply. The major components of the polysaccharide chain are D-glucuronic acid, L-iduronic acid, and the same 2-deoxy-2-aminoglucose (D-glucosamine) that is a constituent of chitin (although in heparin it occurs as the α anomer):



D-glucuronic acid
(β anomer)



L-iduronic acid
(α anomer)

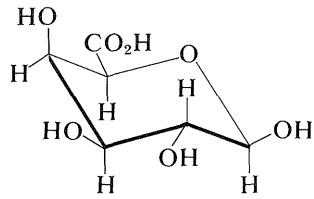


2-deoxy-2-amino-D-glucose
(α anomer)

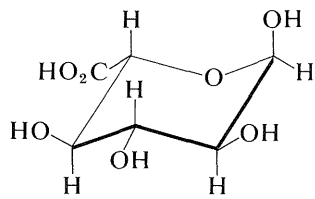
The general construction of heparin involves the linkage of the anomeric carbons of one of the components with the 4-hydroxyl of another. A key feature of the heparin structure is the presence of sulfate groups that occur as hydrogen sulfate esters (Section 15-5B) and as sulfamido groups, $-NHSO_3H$, on the 2-deoxy-2-amino-D-glucose units in the chain. Hydrogen sulfate groups also are located on the 2-hydroxyls of the L-iduronic acid units of the chain. In addition there are *N*-ethanoyl groups attached to some of the 2-deoxy-2-amino-D-glucose nitrogens that are not connected to $-SO_3H$.

Heparin is clearly an extraordinarily complex substance with many highly polar groups, and its mode of action as an anticoagulant is not clear. At present, because of increases in the use of artificial kidney machines, heparin is in rather short supply.

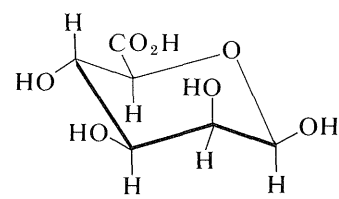
Among the plant polysaccharides are the **pectins,** which are used as jelling agents in the making of preserves and jellies from fruit. Also important are the **alginates** from seaweeds and **gums** from trees, which are used as stabilizers and emulsifiers in the food, pharmaceutical, cosmetic, and textile industries. The pectins principally are polysaccharides of the methyl ester of D-galacturonic acid, whereas the alginates are polysaccharides made up of varying proportions of D-mannuronic acid and L-guluronic acid. The plant gums are similar materials.



β-D-galacturonic acid



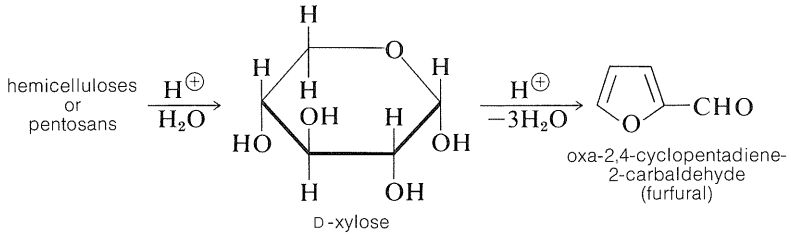
α-L-guluronic acid



β-D-mannuronic acid

There are other polysaccharides besides cellulose in the cell walls of plants. These are called hemicelluloses, but the name is misleading because they are unrelated to cellulose. Those that are made of pentose units (mainly xylose) are most abundant. They accumulate as wastes in the processing of agricultural

products, and on treatment with acids they yield a compound of considerable commercial importance, oxa-2,4-cyclopentadiene-2-carbaldehyde (furfural):

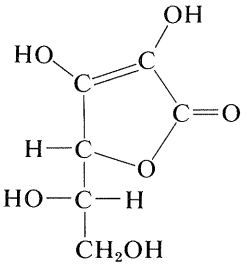


Exercise 20-15 Write Fischer projections, Haworth projections, and sawhorse conformational drawings for the following:

a. α-D-glucuronic acid **b.** β-D-iduronic acid **c.** α-D-guluronic acid

20-8 VITAMIN C

The "antiscorbutic" factor of fresh fruits, which prevents the development of the typical symptoms of scurvy in humans, is a carbohydrate derivative known as **vitamin C** or **ascorbic acid.** This substance is not a carboxylic acid, but a lactone, and owes its acidic properties (and ease of oxidation) to the presence of an enediol grouping. It belongs to the L series by the glyceraldehyde convention:



L-ascorbic acid

Most animals are able to synthesize vitamin C in their livers but, in the course of evolution, man has lost this capacity.

Exercise 20-16 Explain how you could account for the fact that ascorbic acid is most stable in the enediol form rather than having its C3 and C2 carbons arranged either as —C(=O)—CH(OH)— or as —CH(OH)—C(=O)—.

20-9 FORMATION OF CARBOHYDRATES BY PHOTOSYNTHESIS

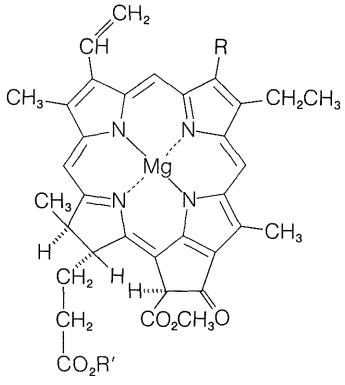
Carbohydrates are formed in green plants by **photosynthesis,** which is the chemical combination, or "fixation," of carbon dioxide and water by utilization of energy from the absorption of visible light. The overall result is the *reduction* of carbon dioxide to carbohydrate and the formation of oxygen:

$$xCO_2 + xH_2O \xrightarrow[\text{green plants}]{\text{light}} \underset{\text{carbohydrate}}{(C \cdot H_2O)_x} + xO_2 \quad \left.\begin{array}{l} \Delta G^0 \cong 686 \text{ kcal} \\ \Delta H^0 \cong 670 \text{ kcal} \end{array}\right\} \text{for } x = 6$$

If the carbohydrate formed is cellulose, then the reaction in effect is the reverse of the burning of wood, and obviously requires considerable energy input.

Because of its vital character to life as we know it, photosynthesis has been investigated intensively and the general features of the process are now rather well understood. The principal deficiencies in our knowledge include just how the light absorbed by the plants is converted to chemical energy and the details of how the many complex enzyme-induced reactions involved take place.

The ingredients in green plants that carry on the work of photosynthesis are contained in highly organized, membrane-covered units called **chloroplasts.** The specific substances that absorb the light are the plant pigments, chlorophyll *a* and chlorophyll *b*, whose structures are shown in Figure 20-6. These highly conjugated substances are very efficient light absorbers, and the energy so gained is used in two separate processes, which are represented diagrammatically in Figure 20-7.



R = CH_3 (chlorophyll *a*); —CHO (chlorophyll *b*)

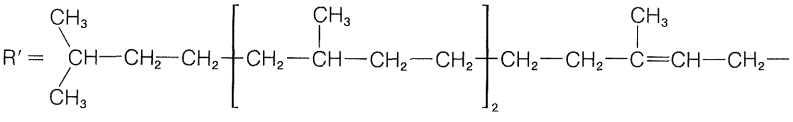


Figure 20-6 The structure of chlorophyll *a* and chlorophyll *b*, showing cis-trans relationships of the substituents

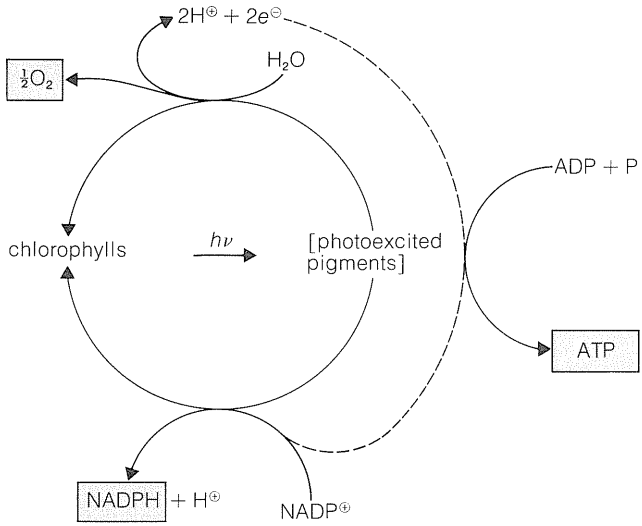
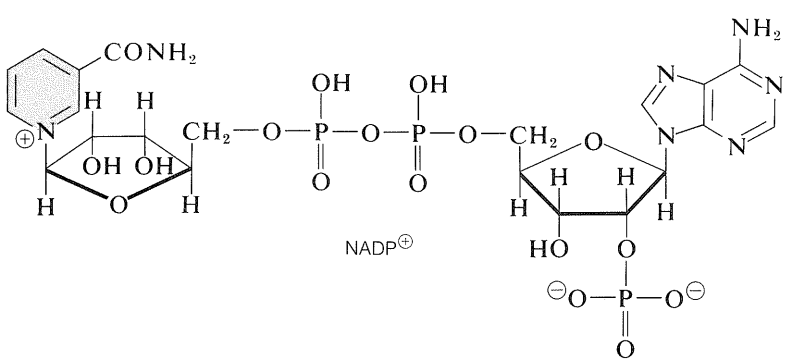
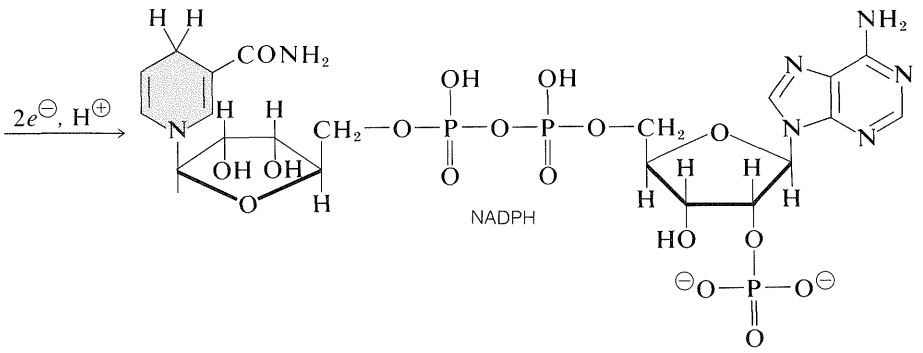


Figure 20-7 Simplified representation of the photoreactions in photosynthesis. The oxidation of water is linked to the reduction of $NADP^{\oplus}$ by an electron-transport chain (dashed line) that is coupled to ATP formation (photophosphorylation).

One photoprocess reduces *nicotinamide adenine dinucleotide phosphate* ($NADP^{\oplus}$) to NADPH. These dinucleotides, shown below, differ from $NAD^{\oplus}$ and NADH (Section 15-6C) in having a phosphate group at C2 of one of the ribose units. The oxidized form, $NADP^{\oplus}$, behaves like $NAD^{\oplus}$ and receives the equivalent of $H:^{\ominus}$ at C4 of the nicotinamide ring to form NADPH:





The other important photoreaction is oxidation of water to oxygen by the reaction:

$$H_2O \longrightarrow 2H^{\oplus} + \tfrac{1}{2}O_2 + 2e^{\ominus}$$

The oxygen formed clearly comes from H_2O and not from CO_2, because photosynthesis in the presence of water labeled with ^{18}O produces oxygen labeled with ^{18}O, whereas carbon dioxide labeled with ^{18}O does not give oxygen labeled with ^{18}O. Notice that the oxidation of the water produces two electrons, and that the formation of NADPH from $NADP^{\oplus}$ requires two electrons. These reactions occur at different locations within the chloroplasts and in the process of transferring electrons from the water oxidation site to the $NADP^{\oplus}$ reduction site, adenosine diphosphate (ADP) is converted to adenosine triphosphate (ATP; see Section 15-5F for discussion of the importance of such phosphorylations). Thus electron transport between the two photoprocesses is coupled to phosphorylation. This process is called **photophosphorylation** (Figure 20-7).

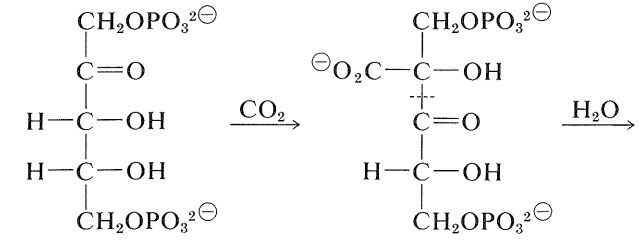
The end result of the photochemical part of photosynthesis is the formation of O_2, NADPH, and ATP. Much of the oxygen is released to the atmosphere, but the NADPH and ATP are utilized in a series of dark reactions that achieve the reduction of carbon dioxide to the level of a carbohydrate (fructose). A balanced equation is

$$6CO_2 + 12NADPH + 12H^{\oplus} \longrightarrow C_6H_{12}O_6 + 12NADP^{\oplus} + 6H_2O$$

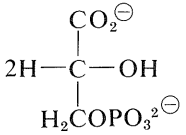
The cycle of reactions that converts carbon dioxide to carbohydrates is called the **Calvin cycle,** after M. Calvin, who received the Nobel Prize in chemistry in 1961 for his work on determining the path of carbon in photosynthesis.

Carbon enters the cycle as carbon dioxide. The key reaction by which the CO_2 is "fixed" involves enzymatic *carboxylation* of a pentose, D-ribulose 1,5-phosphate.[8]

[8]All of the reactions we will be discussing are mediated by enzymes, and we will omit henceforth explicit mention of this fact. But it should not be forgotten that these are *all* enzyme-induced processes, for which we have few, if any, laboratory reagents to duplicate on the particular compounds involved.



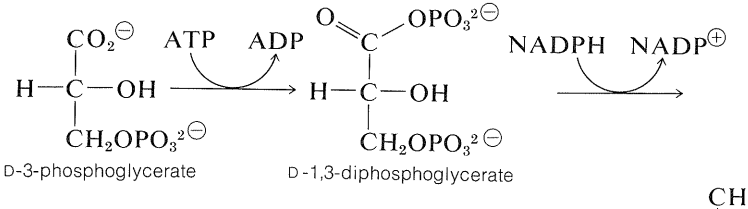
D-ribulose 1,5-diphosphate



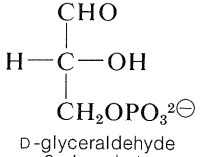
D-3-phosphoglycerate (20-4)

A subsequent hydrolytic cleavage of the C2–C3 bond of the carboxylation product (this amounts to a reverse Claisen condensation; Section 18-8B) yields two molecules of D-3-phosphoglycerate.[9]

In subsequent steps, ATP is utilized to phosphorylate the carboxylate group of 3-phosphoglycerate to create 1,3-diphosphoglycerate (a mixed anhydride of glyceric and phosphoric acids). This substance then is reduced by NADPH to glyceraldehyde 3-phosphate:



D-3-phosphoglycerate D-1,3-diphosphoglycerate

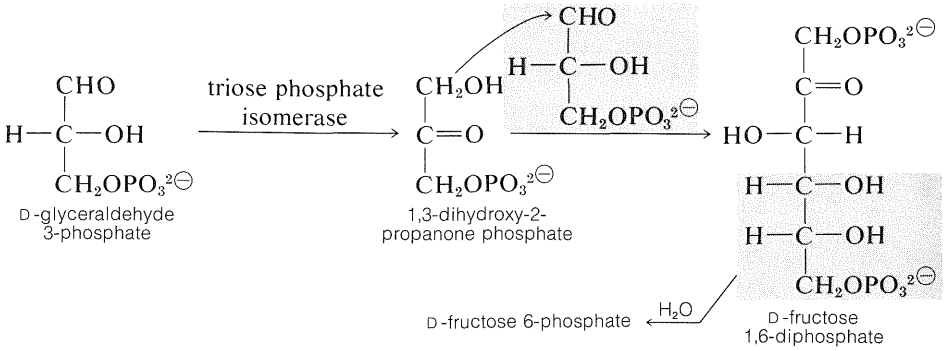


D-glyceraldehyde 3-phosphate

Two glyceraldehyde 3-phosphates are utilized to build the six-carbon chain of fructose by an aldol condensation ($C_3 + C_3 \longrightarrow C_6$), but the donor nucleophile in this reaction is the phosphate ester of dihydroxypropanone, which is an isomer of glyceraldehyde 3-phosphate. Rearrangement of the C_3 aldose to

[9]We will henceforth, in equations, designate the various acids we encounter as the phosphate and the carboxylate anions, although this is hardly reasonable at the pH values normal in living cells. Glyceric and phosphoric acids are only partially ionized at pH 7–8. However, it would be equally unrealistic to represent the acids as being wholly undissociated.

the C_3 ketose (of the type described in Section 20-2D) therefore precedes the aldol addition. (For a discussion of the mechanism of the enzymatic aldol reaction, see Section 17-3F.) The fructose 1,6-diphosphate formed is then hydrolyzed to fructose 6-phosphate:



From what we have described thus far, only one atom of carbon has been added from the atmosphere, and although we have reached fructose, five previously reduced carbons were consumed in the process. Thus the plant has to get back a five-carbon sugar from a six-carbon sugar to perpetuate the cycle. Rather than split off one carbon and use that as a building block to construct other sugars, an amazing series of transformations is carried on that can be summarized by the following equations:

$$C_6 + C_3 \xrightarrow{\text{transketolase}} C_4 + C_5$$

$$C_4 + C_3 \xrightarrow{\text{aldolase}} C_7$$

$$C_7 + C_3 \xrightarrow{\text{transketolase}} C_5 + C_5$$

These reactions have several features in common. They all involve phosphate esters of aldoses or ketoses, and they resemble aldol or reverse-aldol condensations. Their mechanisms will not be considered here, but are discussed more explicitly in Sections 20-10A, 20-10B, and 25-10. Their summation is $C_6 + 3C_3 \longrightarrow 3C_5$, which means that fructose 6-phosphate as the C_6 component reacts with a total of three C_3 units (two glyceraldehyde 3-phosphates and one dihydroxypropanone phosphate) to give, ultimately, three ribulose 5-phosphates. Although the sequence may seem complex, it avoids building up pentose or hexose chains one carbon at a time from one-carbon intermediates.

The Calvin cycle is completed by the phosphorylation of D-ribulose 5-phosphate with ATP. The resulting D-ribulose 1,5-diphosphate then is used to start the cycle again by combining with carbon dioxide. There is one sixth more fructose generated per cycle than is used to reform the ribulose 1,5-diphosphate. This fructose is used to build other carbohydrates, notably glucose, starch, and cellulose.

Exercise 20-17* Write mechanisms, supported by analogy in so far as possible, for the carboxylation and cleavage reactions of Equation 20-4 as you would expect them to occur in the *absence* of an enzyme. Both reactions can be reasonably expected to be induced by $OH^{\ominus}$, and it may be helpful to review the properties of enols described in Section 17-1.

20-10 THE GENERATION OF ENERGY FROM CARBOHYDRATE METABOLISM

We will consider here the reverse process of photosynthesis, namely how carbohydrates, especially glucose, are converted to energy by being broken down into carbon dioxide and water.

A general summary of the several stages involved is shown in Figure 20-8. Initially, the storage fuels or foodstuffs (fats, carbohydrates, and proteins) are hydrolyzed into smaller components (fatty acids and glycerol, glucose and other simple sugars, and amino acids). In the next stage, these simple fuels are degraded further to two-carbon fragments that are delivered as the $CH_3\overset{|}{C}{=}O$ group (ethanoyl, or acetyl) in the form of the thioester of coenzyme A, $CH_3COSCoA$. The structure of this compound and the manner in which fatty acids are degraded has been considered in Section 18-8F, and amino acid metabolism is discussed briefly in Section 25-5C. This section is concerned mainly with the pathway by which glucose is metabolized by the process known as **glycolysis.**

In the conversion of glucose to $CH_3COSCoA$, two carbons are oxidized to carbon dioxide with consumption of the equivalent of two oxygen molecules:

$$C_6H_{12}O_6 + 2CoASH + [2O_2] \longrightarrow 2CH_3COSCoA + 4H_2O + 2CO_2 \qquad (20\text{-}5)$$

For further oxidation to occur, the $CH_3COSCoA$ must enter the next stage of metabolism, whereby the $CH_3\overset{|}{C}{=}O$ group is converted to CO_2 and H_2O. This stage is known variously as the citric acid cycle, the tricarboxylic acid cycle, or the Krebs cycle, in honor of H. A. Krebs (Nobel Prize, 1953), who first recognized its cyclic nature in 1937. We can write an equation for the process as if it involved oxygen:

$$2CH_3COSCoA + [4O_2] \longrightarrow 4CO_2 + 2H_2O + 2CoASH \qquad (20\text{-}6)$$

Notice that combination of the reactions of Equations 20-5 and 20-6, glycolysis plus the citric acid cycle, oxidizes glucose completely to CO_2 and H_2O:

$$C_6H_{12}O_6 + [6O_2] \longrightarrow 6CO_2 + 6H_2O \qquad (20\text{-}7)$$

But, as you will see, none of the steps uses molecular oxygen directly. Hence

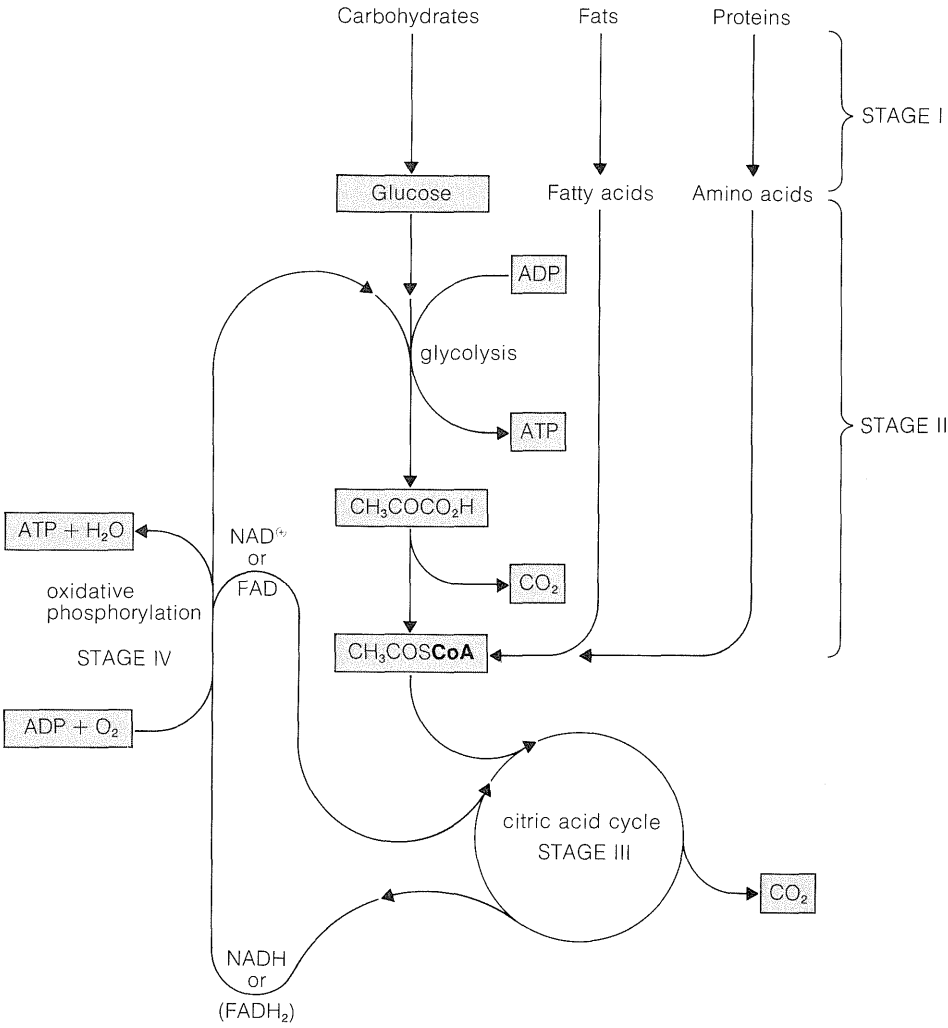


Figure 20-8 Perspective of the metabolic scheme whereby carbohydrates, fats, and proteins in foodstuffs are oxidized to CO_2, showing the link between glycolysis, the citric acid cycle, and oxidative phosphorylation

there must be a stage in metabolism whereby molecular oxygen is linked to production of oxidizing agents that are consumed in glycolysis and in the citric acid cycle.

The coupling of oxygen into the metabolism of carbohydrates is an extremely complex process involving transport of the oxygen to the cells by an oxygen carrier such as hemoglobin, myoglobin, or hemocyanin. This is followed by a series of reactions, among which NADH is converted to $NAD^{\oplus}$ with associated formation of three moles of ATP from three moles of ADP and inorganic

phosphate. Another electron-carrier is flavin adenine dinucleotide (FAD; Section 15-6C), which is reduced to $FADH_2$ with an associated production of two moles of ATP from two moles of ADP. These processes are known as **oxidative phosphorylations** and can be expressed by the equations:

$$NADH + \tfrac{1}{2}O_2 + H^{\oplus} \xrightarrow{3ADP\ 3ATP} NAD^{\oplus} + H_2O \qquad (20\text{-}8)$$

$$FADH_2 + \tfrac{1}{2}O_2 \xrightarrow{2ADP\ 2ATP} FAD + H_2O \qquad (20\text{-}9)$$

Oxidative phosphorylation resembles photophosphorylation, discussed in Section 20-9, in that electron transport in photosynthesis also is coupled with ATP formation.

By suitably juggling Equations 20-7 through 20-9, we find that the metabolic oxidation of one mole of glucose is achieved by ten moles of $NAD^{\oplus}$ and two moles of FAD:

$$C_6H_{12}O_6 + 10\,NAD^{\oplus} + 2FAD + 6H_2O \xrightarrow{34ADP\ 34ATP} 6CO_2 + 10\,NADH + 2FADH_2 + 10\,H^{\oplus} \qquad (20\text{-}10)$$

The overall result is production of 36 moles of ATP from ADP and phosphate per mole of glucose oxidized to CO_2 and H_2O. Of these, 34 ATPs are produced according to Equation 20-10 and, as we shall see, two more come from glycolysis.

20-10A Glycolysis

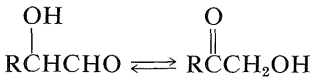
Glycolysis is the sequence of steps that converts glucose into two C_3 fragments with the production of ATP. The C_3 product of interest here is 2-oxopropanoate (pyruvate):

$$\underset{\text{glucose}}{C_6H_{12}O_6} \xrightarrow{ADP\ \ ATP} \underset{\text{pyruvate}}{2CH_3\overset{\overset{O}{\|}}{C}CO_2^{\ominus}}$$

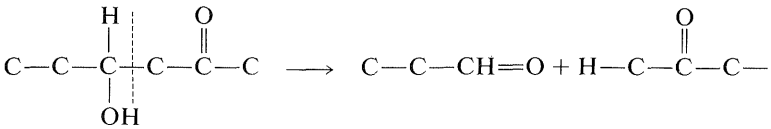
There are features in this conversion that closely resemble the dark reactions of photosynthesis, which build a C_6 chain (fructose) from C_3 chains (Section 20-9). For example, the reactants are either phosphate esters or mixed anhydrides, and the phosphorylating agent is ATP:

$$ROH + ATP \longrightarrow RO{-}PO_3^{2\ominus} + ADP + H^{\oplus}$$

Furthermore, rearrangements occur that interconvert an aldose and ketose,



and the cleavage of a C_6 chain into two C_3 chains is achieved by a reverse aldol condensation:



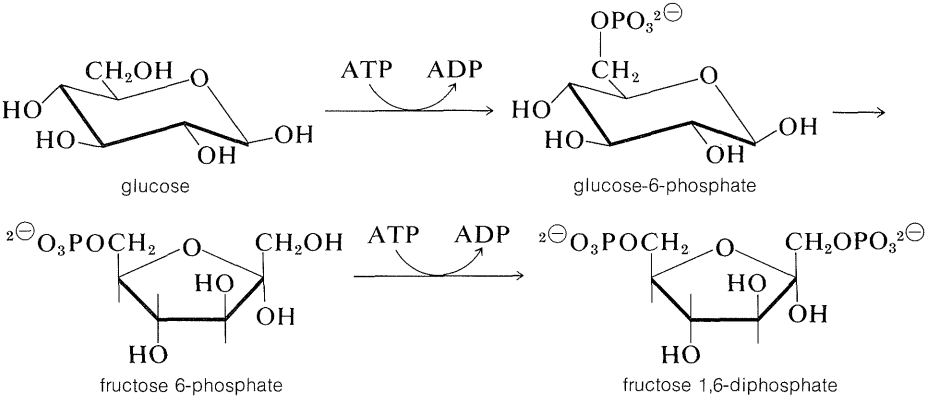
Also, oxidation of an aldehyde to an acid is accomplished with $NAD^{\oplus}$. There is a related reaction in photosynthesis (Section 20-9) that accomplishes the reduction of an acid to an aldehyde and is specific for NADPH, not NADH:

$$RCHO + NAD^{\oplus} + H_2O \xrightarrow{\text{glycolysis}} RCO_2^{\ominus} + NADH + 2H^{\oplus}$$

$$RCHO + NADP^{\oplus} + H_2O \xleftarrow{\text{photosynthesis}} RCO_2^{\ominus} + NADPH + 2H^{\oplus}$$

The detailed sequence in glycolysis is summarized in Figure 20-9 and each of the steps is identified more specifically in the ensuing discussion.

First, glucose is phosphorylated to glucose 6-phosphate with ATP. Then an aldose $\rightleftharpoons$ ketose rearrangement converts glucose 6-phosphate into fructose 6-phosphate. A second phosphorylation with ATP gives fructose 1,6-diphosphate:



At this stage the enzyme aldolase catalyzes the aldol cleavage of fructose 1,6-diphosphate. One product is glyceraldehyde 3-phosphate and the other is

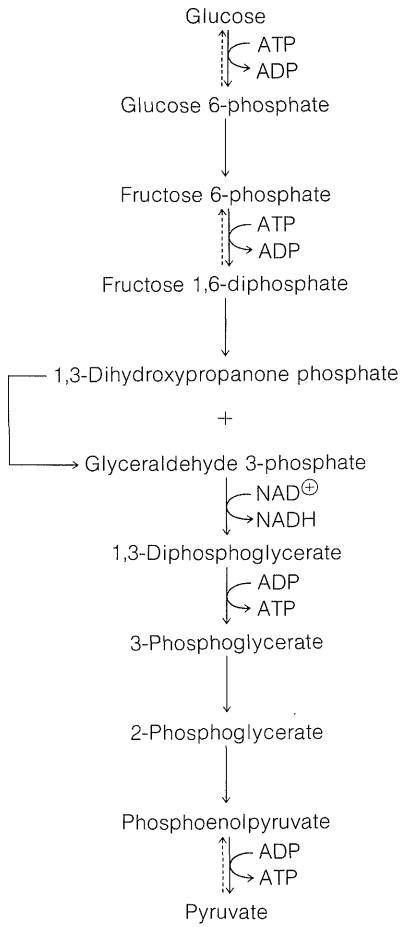
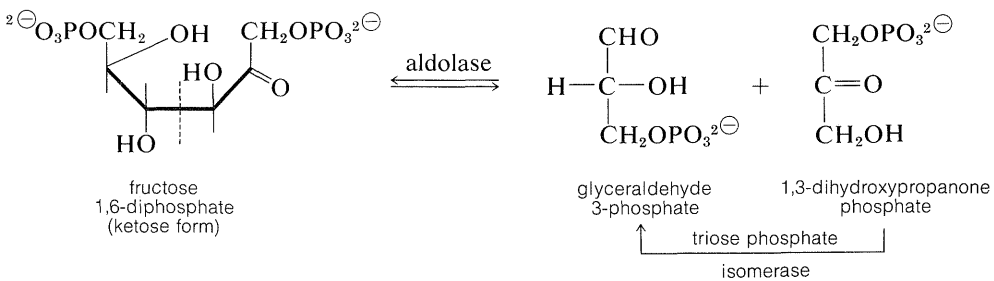
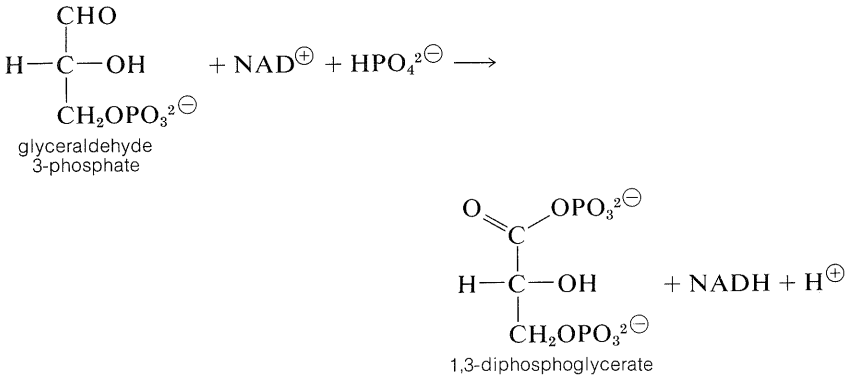


Figure 20-9 The glycolytic sequence. [The dashed arrows in the reverse direction indicate the steps in the synthesis of glucose from pyruvate (glyconeogenesis) that differ from those in glycolysis.]

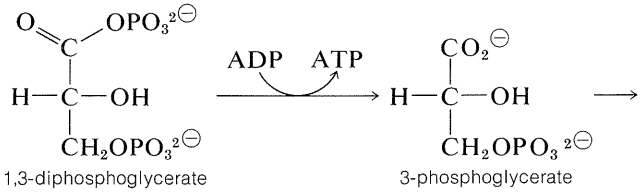
1,3-dihydroxypropanone phosphate. Another ketose $\rightleftharpoons$ aldose equilibrium converts the propanone into the glyceraldehyde derivative:

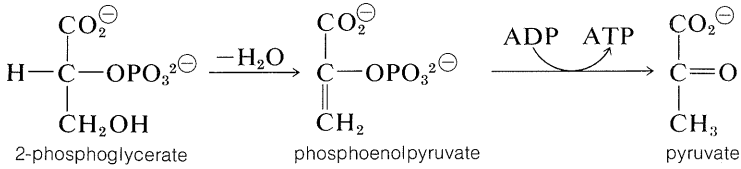


The next step oxidizes glyceraldehyde 3-phosphate with $NAD^{\oplus}$ in the presence of phosphate with the formation of 1,3-diphosphoglycerate:



The mixed anhydride of phosphoric acid and glyceric acid then is used to convert ADP to ATP and form 3-phosphoglycerate. Thereafter the sequence differs from that in photosynthesis. The next few steps accomplish the formation of pyruvate by transfer of the phosphoryl group from C3 to C2 followed by dehydration to phosphoenolpyruvate. Phosphoenolpyruvate is an effective phosphorylating agent that converts ADP to ATP and forms pyruvate:

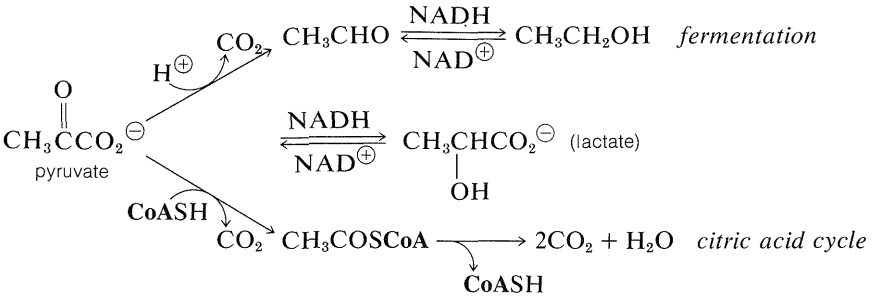




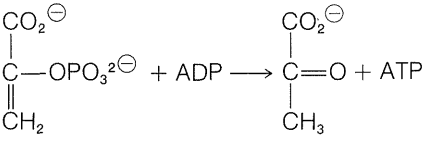
The net reaction at this point produces more ATP than is consumed in the phosphorylation of glucose and fructose (see Exercise 20-20).

What happens thereafter depends on the organism. With yeast and certain other microorganisms, pyruvate is decarboxylated and reduced to ethanol. The end result of glycolysis in this instance is *fermentation*. In higher organisms, pyruvate can be stored temporarily as a reduction product (lactate) or it can be oxidized further to give $CH_3COSCoA$ and CO_2. The $CH_3COSCoA$ then enters

the citric acid cycle to be oxidized to CO_2 and H_2O, as discussed in the next section:

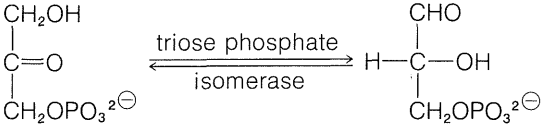


Exercise 20-18* From the discussion in Section 15-5F, it should be clear that the reaction of an alcohol phosphate with ADP to give ATP, $ROPO_3^{2\ominus} + ADP \longrightarrow ATP + ROH$, is not likely to have a favorable equilibrium constant. Explain why one might expect the following reaction to be more energetically favorable.



Exercise 20-19* The heat of combustion of glucose(*s*) to $CO_2(g)$ and $H_2O(l)$ is 670 kcal mole^{-1}, whereas that of 2-oxopropanoic acid(*l*) is 280 kcal mole^{-1}. Neglecting the heats of solution of the compounds in water, estimate the energy of glucose(*aq*) + $O_2 \longrightarrow 2CH_3COCO_2H(aq) + 2H_2O(l)$.

Exercise 20-20* The following interconversion is catalyzed by the enzyme *triose phosphate isomerase:*



Explain how you might use bond energies to estimate whether the equilibrium constant, *K*, for this reaction would be greater, or less, than unity.

Exercise 20-21* Assuming that one molecule of glucose is oxidized to two molecules of 2-oxopropanoic acid (pyruvic acid), how many moles of ATP are formed from ADP in the overall reaction by the sequence of steps given in Figure 20-9?

20-10B The Citric Acid (Krebs) Cycle

Glycolysis to the pyruvate or lactate stage liberates heat, which can help keep the organism warm and produce ATP from ADP for future conversion into energy. However, glycolysis does not directly involve oxygen and does not liberate CO_2, as we might expect from the overall process of the metabolic conversion of glucose to carbon dioxide and water (Equation 20-10). The liberation of CO_2 occurs subsequent to pyruvate formation in a process called variously, the citric acid cycle, the Krebs cycle, or the tricarboxylic acid (TCA) cycle.

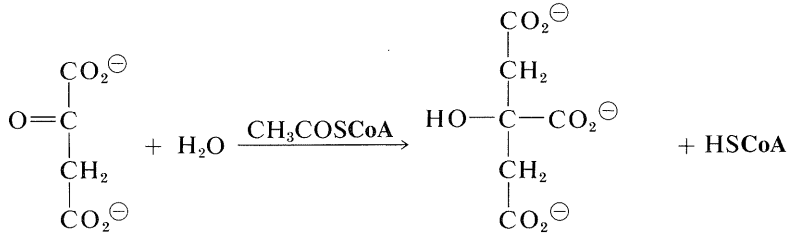
The initial step, which is not really part of the cycle, is conversion of pyruvate to ethanoyl **CoA** (acetyl **CoA**):

$$CH_3COCO_2^{\ominus} + HSCoA + NAD^{\oplus} \longrightarrow CH_3\overset{\overset{O}{\|}}{C}SCoA + CO_2 + NADH$$

This reaction looks simple but actually occurs in four discrete steps that involve a complex of enzymes having a molecular weight of about 4,500,000. We shall pass over this interesting and rather well-studied reaction as we describe the citric acid cycle. A simplified representation of the citric acid cycle is shown in Figure 20-10, and it will help to refer to this diagram as each of the steps in it are discussed in more detail.

To achieve the oxidation of acetyl **CoA** on a continuing basis, intermediates consumed in certain steps must be regenerated in others. Thus we have a situation similar to that in the Calvin cycle (Section 20-9), whereby the first stage of the cycle achieves the desired reaction (CO_2 formation) and the second stage is designed to regenerate intermediates necessary to perpetuate the cycle.

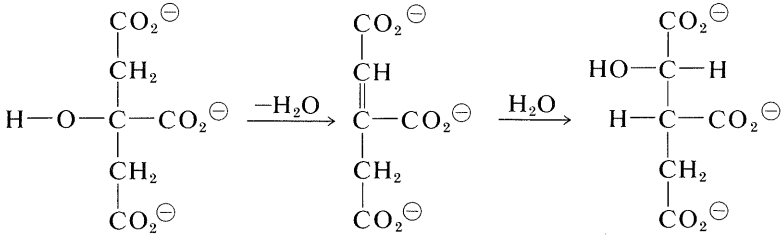
The entry point is the reaction between acetyl **CoA** and a four-carbon unit, 2-oxobutanedioic acid. An aldol-type addition of the CH_3CO group to this C_4 keto acid extends the chain to a branched C_6 acid (as citric acid):



2-oxobutanedioate (oxaloacetate)

3-hydroxy-3-carboxypentanedioate (citrate)

Dehydration-rehydration of citrate converts it to isocitrate:



2-hydroxy-3-carboxypentanedioate (isocitrate)

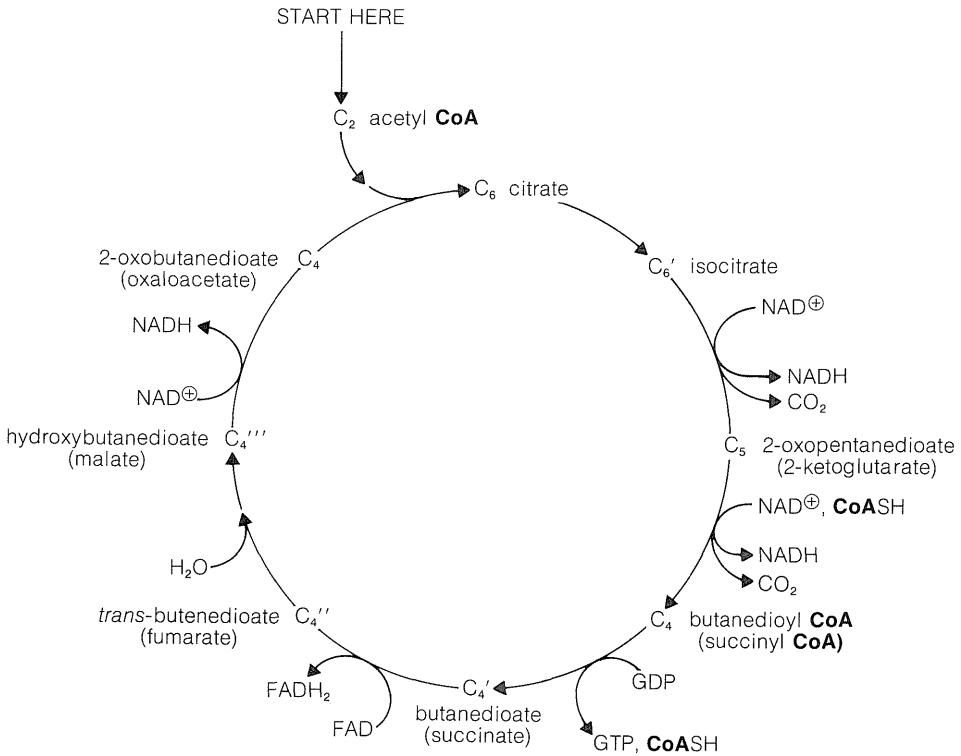
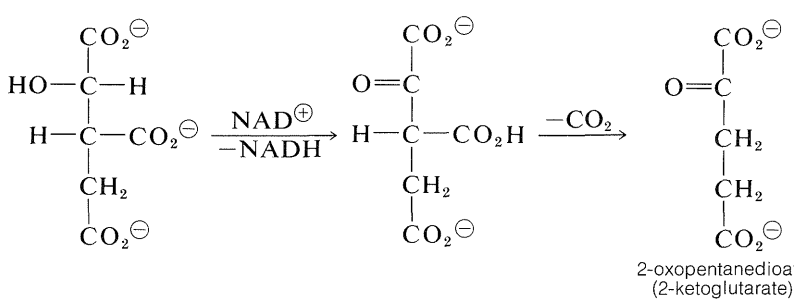
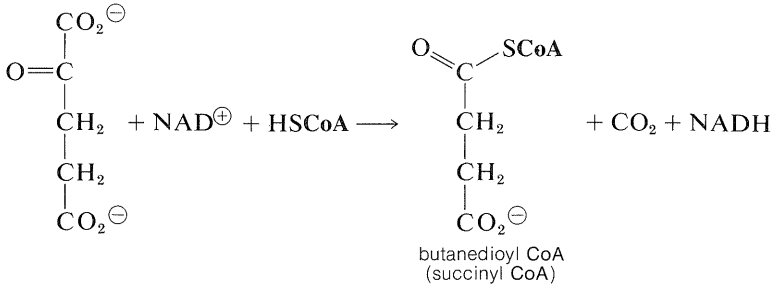


Figure 20-10 The citric acid cycle

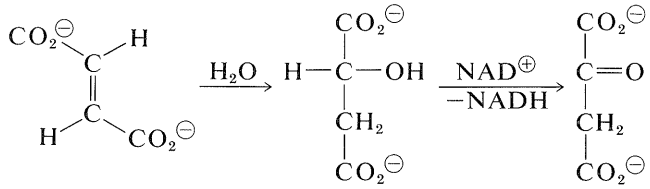
From here, oxidation of the hydroxyl function with NAD⊕ gives a keto acid, which loses CO_2 readily (Section 18-4) and affords 2-oxopentanedioate:



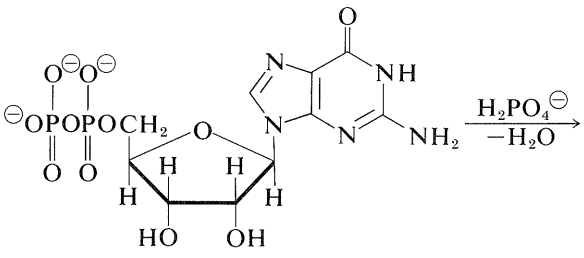
We now have a C_5 keto acid that can be oxidized in the same way as the C_3 keto acid, pyruvic acid, to give a butanedioyl **CoA**:

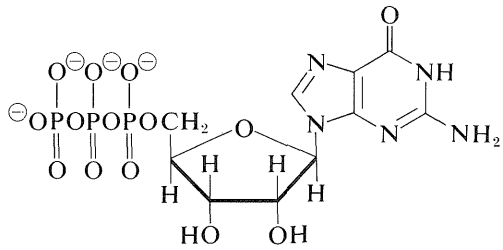


Two molecules of CO_2 now have been produced and the remaining part of the citric acid cycle is concerned with regeneration of the **CoA** for forming acetyl **CoA** from 2-oxopropanoate, and also with regenerating the 2-oxobutanedioate, which is the precursor of citrate. The steps involved are



The hydrolysis of the acyl **CoA** in the first step is used for energy storage by conversion of guanosine diphosphate (GDP) to guanosine triphosphate (GTP):





guanosine triphosphate
(GTP)

The hydration of the *trans*-butenedioate (Section 10-3G) and the final oxidation reaction (Section 15-6C) have been discussed previously.

Exercise 20-22* The reaction ADP + $RC(=O)—SR' + PO_4^{3\ominus} \longrightarrow$ ATP + RCO_2H + HSR' is substantially more favorable than the corresponding reaction with $R—C(=O)—OR$. On the basis of the valence-bond treatment, explain why this should be so.

Exercise 20-23* Citric acid is prochiral. Nonetheless, if one were to introduce acetyl CoA labeled with ^{14}C (radioactive carbon) at the carboxyl group, $CH_3—^{14}C(=O)—SCoA$, into the citric acid cycle, the 2-oxopentanedioate acid (2-ketoglutarate) formed in the fourth step of the cycle would have *all* of the ^{14}C in the carboxylate group *farthest* away from the ketone carbonyl group. For some years, this result was used to argue that citric acid itself could not be an intermediate in the formation of 2-oxopentanedioate. Review Section 19-8 and explain how, in stereospecific enzyme-induced reactions, citric acid could be an intermediate in the formation of 2-oxopentanedioate even if the ^{14}C would *not* appear equally in both carboxylic carbons of the product.

Exercise 20-24* What analogy can you draw from reactions studied in previous chapters to the cleavage $RCOCH_2COSCoA + HSCoA \longrightarrow RCOSCoA + CH_3COSCoA$? What reagents would you expect to cause this reaction to occur in water solution?

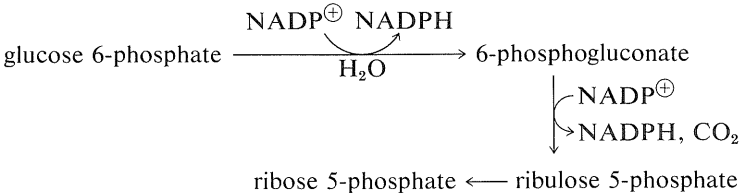
Exercise 20-25* A first step in unravelling the mechanism of the metabolism of fatty acids was made in 1904 by F. Knoop, who found that dogs metabolized 4-phenylbutanoic acid to phenylethanoic acid and 3-phenylpropionic acid to benzoic acid. What does this pattern of results indicate about the mechanism of degradation of fatty acids? Give your reasoning.

Exercise 20-26* A very strong man can lift 225 kg (500 lb) 2 meters (6.5 ft). Muscle action gets its energy from the reaction ATP + $H_2O \longrightarrow$ ADP + $H_2PO_4^{\ominus}$, a process with a ΔG^0 of −7 kcal.

a. Assuming 50% efficiency in the use of the hydrolysis free energy, how many grams of ATP (MW 507) would have to be hydrolyzed to achieve this lifting of the weight? (One kg raised one meter requires 2.3 cal of energy.)
b. How many grams of glucose would have to be oxidized to CO_2 and water to replenish the ATP used in Part a on the basis of a 40% conversion of the energy of combustion to ATP? (ΔG^0 for combustion of glucose is −686 kcal.)

20-10C Alternative Routes in Carbohydrate Metabolism

There is an alternative route, called the *pentose phosphate pathway,* by which glucose enters the glycolytic sequence to pyruvate. This route achieves the oxidative decarboxylation of glucose to give ribose, as the 5-phosphate ester. The essential steps are



One purpose of this oxidative route is to generate NADPH, which is the reducing agent required by the organism for biosynthesis. The other purpose is to produce ribose, which is needed for the biosynthesis of ATP, CoA, $NAD^{\oplus}$, FAD, RNA, DNA, and so on. However, the demand for NADPH is higher than the demand for ribose, so there must be a way of channelling the excess ribose back into the metabolic cycle. This is accomplished by the conversion of ribose into glycolysis intermediates, fructose 1,6-diphosphate and glyceraldehyde 3-phosphate (see Figure 20-11). The reactions that accomplish this are very similar to those of the Calvin cycle (Section 20-9), only in reverse. They may be summarized as

$$C_5 + C_5 \xrightarrow{\text{transketolase}} C_3 + C_7$$

$$C_7 + C_3 \xrightarrow{\text{transaldolase}} C_4 + C_6$$

$$C_5 + C_4 \xrightarrow{\text{transketolase}} C_3 + C_6$$

The net result is that three pentoses are converted into two molecules of fructose and one of glyceraldehyde ($3C_5 \longrightarrow 2C_6 + C_3$).

The relationship of the pentose–phosphate pathway to glycolysis is shown in Figure 20-11. The steps involved in the pentose shunt are readily reversible, but there are several steps in glycolysis that are not. These are the phosphorylation steps (see Figure 20-9). Yet, there has to be a return route from pyruvate to glucose. This route is called **gluconeogenesis** and, in animals, takes place in

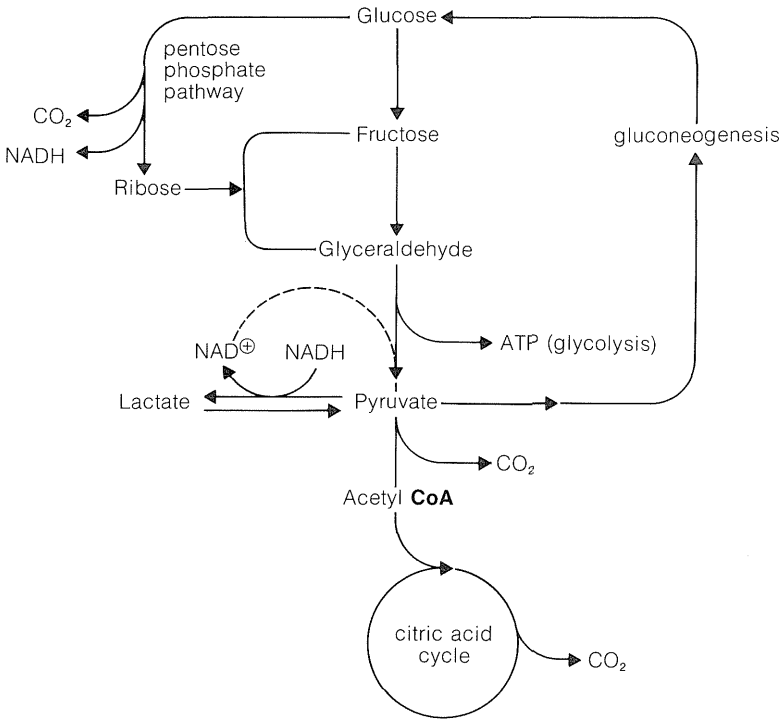


Figure 20-11 Schematic representation of metabolism of glucose by way of glycolysis and citric acid cycle, and the pentose phosphate, lactate, and gluconeogenesis links.

the liver. We shall not discuss the steps in gluconeogenesis except to indicate again that they are not all the reverse of glycolysis. For comparison, the steps that differ are indicated in Figure 20-9 by dashed lines.

Why is lactate formed from pyruvate in the metabolism of glucose? Pyruvate + NADH + $H^{\oplus}$ ⟶ lactate + $NAD^{\oplus}$ is a dead-end path, but it does furnish the $NAD^{\oplus}$ needed for glycolysis in active muscle. This route for forming $NAD^{\oplus}$ is important, because in circumstances of physical exertion, the rate of production of $NAD^{\oplus}$ from oxidative phosphorylation may be slower than the demand for $NAD^{\oplus}$, in which case a temporary supply is available from the pyruvate ⟶ lactate reduction. The lactate so formed builds up in muscle tissue under conditions of physical exertion and is apt to cause muscles to "cramp." The excess lactate so formed ultimately is removed by being converted back to pyruvate by oxidation with $NAD^{\oplus}$.

The beauty of the metabolic cycle through pyruvate, shown in summary in Figure 20-11, is the way it can be tapped at various points according to whether the organism requires ATP (from glycolysis), NADH (from pentose shunt), or $NAD^{\oplus}$ (from the lactate siding).

Additional Reading

W. W. Pigman and D. Horton (Eds.), *The Carbohydrates, Chemistry and Biochemistry,* Academic Press, New York, 1972.

L. Stryer, *Biochemistry,* W. H. Freeman and Company, San Francisco, 1975, Chapters 11–13.

Supplementary Exercises

20-27 A naturally occurring optically active pentose ($C_5H_{10}O_5$) reduces Tollen's reagent and forms a tetraethanoate with ethanoic anhydride. It gives an optically *inactive* phenylosazone. Write all the possible structures for this pentose that are in accord with each of the experimental observations.

20-28 A hexose, $C_6H_{12}O_6$, which we shall call X-ose, on reduction with sodium amalgam gives pure D-sorbitol, and upon treatment with phenylhydrazine gives an osazone different from that of D-glucose. Write a projection formula for X-ose and equations for its reactions.

20-29 Compound *A*, $C_5H_{10}O_4$, is optically active, forms a diethanoate ester with ethanoic anhydride, but does not give a silver mirror with $Ag^{\oplus}(NH_3)_2$. When treated with dilute acid, *A* yields methanol and *B*, $C_4H_8O_4$. *B* is optically active, reduces $Ag^{\oplus}(NH_3)_2$, and forms a triethanoate ester with ethanoic anhydride. On reduction, *B* gives optically inactive *C*, $C_4H_{10}O_4$. Mild oxidation of *B* gives *D*, a carboxylic acid, $C_4H_8O_5$. Treatment of the amide of *D* with dilute sodium hypochlorite solution gives (+)-glyceraldehyde ($C_3H_6O_3$). (For a description of this reaction see Section 23-12E.) Use these facts to derive structures and stereochemical configurations for *A*, *B*, *C*, and *D*. Write equations for all the reactions involved.

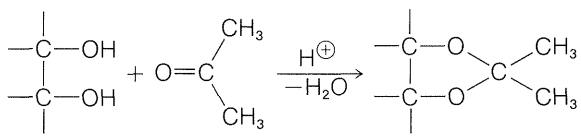
20-30 Draw Haworth- and conformation-type formulas for each of the following:

a. methyl 2,3,4,6-O-tetramethyl-α-D-glucopyranoside

b. β-D-arabinofuranosyl α-L-arabinofuranoside

c. L-sucrose

20-31 Sugars condense with anhydrous 2-propanone in the presence of an acid catalyst to form cyclic ketals known as isopropylidene derivatives:



The reaction of D-glucose with 2-propanone and an acid catalyst produces a mono- and a diisopropylidene derivative. Acid hydrolysis of the diisopropylidene derivative gives the monoisopropylidene compound. O-Methylation of the diketal derivative (Section 20-4A) followed by hydrolysis of the ketal groups forms 3-*O*-methyl-D-glucose. O-Methylation of the monoketal derivative followed by hydrolysis of the ketal function forms a tri-*O*-methyl-D-glucose. This tri-*O*-methyl-D-glucose when O-methylated forms an isomer of penta-*O*-methyl-D-glucopyranose. This isomer when subjected to hydrolysis in dilute acid yields an isomer of 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (**20**, Figure 20-4). Write structures for these cyclic ketals which agree with the experimental evidence. Give your reasoning. (Review Sections 20-2C and 20-4A.)

20-32 Complete the following sequence of reactions, writing structures for all the products, *A–I*.

a. α-D-glucofuranose $\xrightarrow[\text{HCl}]{\text{2-propanone (1 mole)}}$ *A* (see Exercise 20-31)

b. $A \xrightarrow{NaIO_4} B$

c. $B \xrightarrow{Na^{14}CN} C + D$

d. $C + D \xrightarrow[2.\ H^{\oplus},\ H_2O]{1.\ H_2O,\ OH^{\ominus}} E + F + \text{2-propanone}$

e. $E + F \xrightarrow[-H_2O]{\text{heat}} G + H$

f. $G + H \xrightarrow[H_2O]{NaBH_4} I + \text{D-glucose-6-}^{14}\text{C}$

20-33 Write a mechanism for the interconversion of an aldohexose and a ketohexose that is catalyzed by hydroxide ion. What products would you expect starting with D-glucose?

20-34 The glycoside amygdalin ($C_{20}H_{27}O_{11}N$) is hydrolyzed with the aid of the enzyme emulsin (but not with the enzyme maltase) to give D-glucose, HCN, and benzenecarbaldehyde. O-Methylation of amygdalin, followed by acid hydrolysis, gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-D-glucose. Write a structure for amygdalin that fits with these observations.