Chapter 20
Carbohydrates

from
Organic Chemistry

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Chapter Outline of the Book

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3. Haloalkanes, Alcohols, Ethers, and Amines
4. Stereochemistry
5. Organic Spectrometry

II. Reactions, Mechanisms, Multiple Bonds

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**Note: Chapters marked with an (*) are not yet posted.*

20: Carbohydrates

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- *Monosaccharides*
- *Chemical Reactions of Monosaccharides*
- *Polysaccharides and Oligosaccharides*

Preview

Carbohydrates are molecules of enormous biological importance that have empirical formulas such as $C_n(H_2O)_n$ or $C_n(H_2O)_{n-1}$. These formulas suggest they are "hydrates of carbon" and that is why early chemists gave them the general name *carbohydrates*. We commonly call carbohydrates **sugars** and they are also known as **saccharides**.

The simplest carbohydrates are **monosaccharides**. Monosaccharides chemically bond to each other in large carbohydrate molecules called **polysaccharides**.

-MS-MS-MS-MS-MS-MS-MS-MS-MS-MS-MS-MS-MS-

Polysaccharides are Composed of
Chemically Bonded *Monosaccharides* (MS)

Cellulose is a mixture of *polysaccharides* in the cell walls of plants that serves as their structural support. Upon hydrolysis, *cellulose* breaks down into individual monosaccharide units of **D-glucose**.

cellulose	+	water	→	*D-glucose*
(polysaccharide)				(monosaccharide)

There are other polysaccharides besides *cellulose*, and many monosaccharides besides *D-glucose* that differ from it only in the stereochemical configuration at one or more chiral carbons. We will begin with an examination of structures of monosaccharides, analyze their stereochemical diversity, and then study their chemical reactions. After this we will discuss structures and biological functions of polysaccharides.

20.1 Monosaccharides

Simple monosaccharides ($C_n(H_2O)_n$) are classified according to the number of their C atoms (n) (Table 20.1) [next page]. With 4 or more C's, they are usually cyclic molecules with 5-membered (**furanose**) or 6-membered (**pyranose**) rings (Figure 20.01)[next page]

Table 20.1. General Names of Monosaccharides

Number of C's (n)	General Name
3	triose
4	tetrose
5	pentose
6	hexose
7	heptose

Figure 20.01

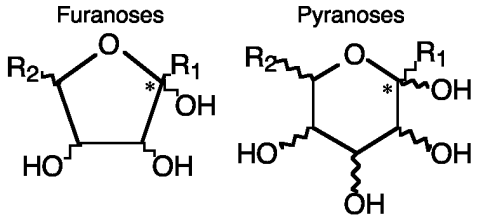
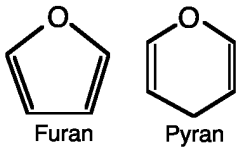


Figure 20.02



Furanoses and Pyranoses (20.1A)

Monosaccharides with 5-membered rings are called **furanoses** and those with 6 membered rings are **pyranoses** because their heterocyclic ring skeletons contain an O atom analogous to the rings of the simple cyclic ethers *furan* and *pyran* (see Figure 20.02 above).

However unlike the ethers *furan* and *pyran*, *furanoses* and *pyranoses* are cyclic **hemiacetals**. The ring O in a furanose or pyranose is attached to a carbon (C*) that also has an OH group. As a result, C* is the central carbon of a *hemiacetal* functional group (R-O-C*(OH)(R')(R")) (Chapter 16).

Figure 20.03

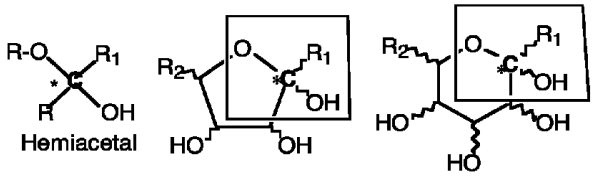
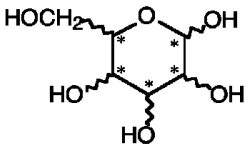


Figure 20.04



The important monosaccharide *D-glucose* is a *hexose* that primarily exists in *pyranose* ring forms. For this reason, we will first consider monosaccharides that are *hexoses* with *pyranose* rings (**pyranohexoses**), then examine 5-membered ring monosaccharides (*furanoses*), and finally look at monosaccharides with 3, 4, and 5 C's.

Glucose and Related Pyranohexoses (20.1B)

The general *pyranose* structure for *glucose* is also the general structure of many other monosaccarides (Figure 20.04 above).

Chiral C Atoms. This structure has 5 chiral carbons (C*) and no special *symmetry elements* (it has no planes, axes, or centers of symmetry) so it has the 32 different stereoisomers shown in Figure 20.05 [next page]. (The maximum number of stereoisomers of a compound with n chiral carbons is 2^n and in this case $2^n = 2^5 = 32$.)

Figures 20.05 and 20.06

Figure 20.5. The 32 Pyranohexose Stereoisomers

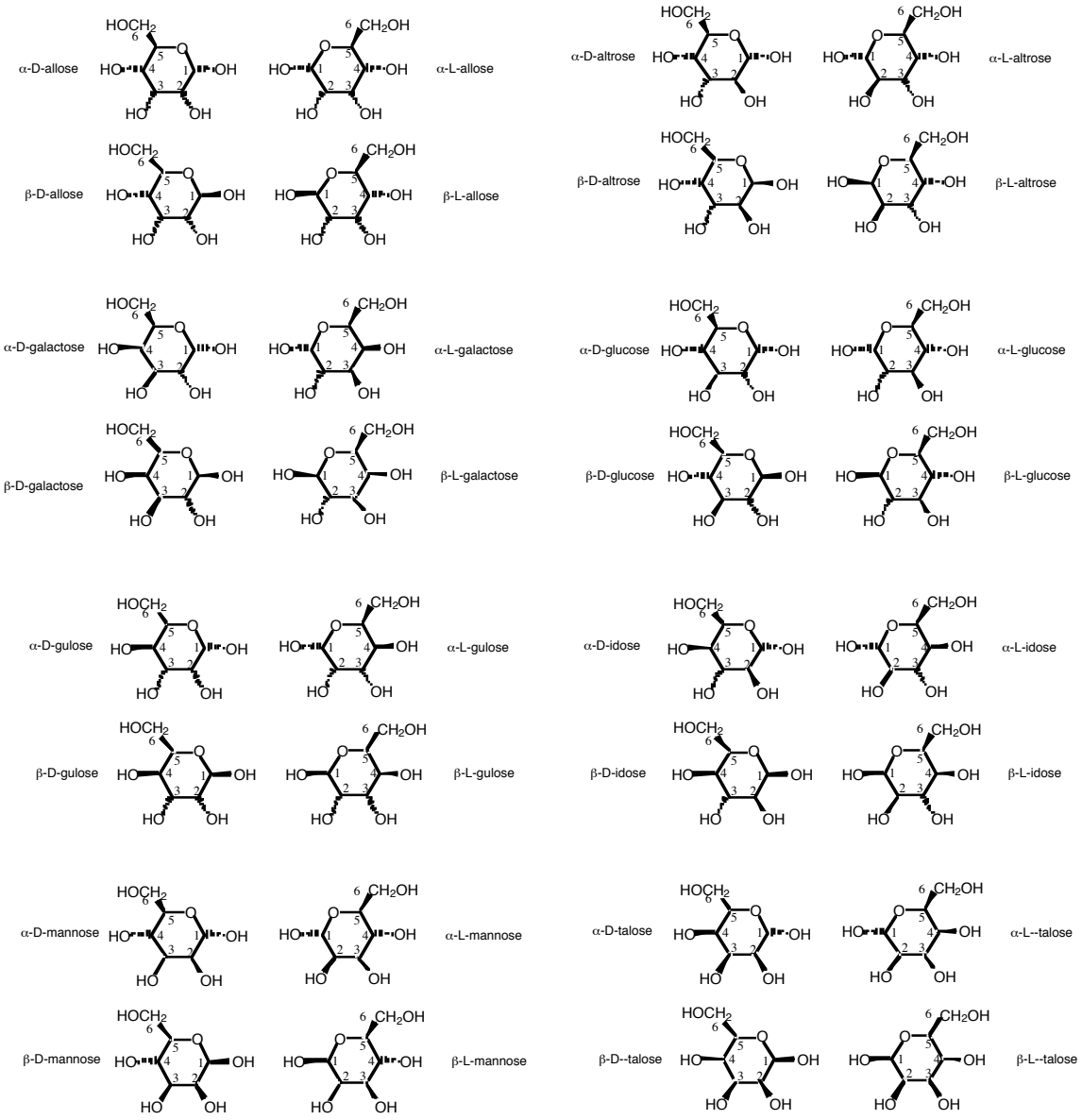
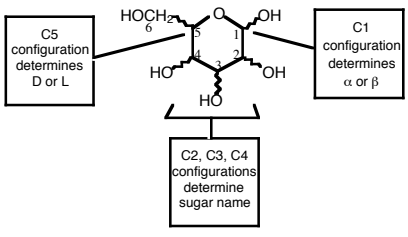


Figure 20.6



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These 32 stereoisomers are subdivided into 8 groups with the names **allose**, **altrose**, **idose**, **galactose**, **gulose**, **mannose**, and **talose** as well as *glucose*. The prefixes **α** and **β**, and **D** and **L,** in combination with these general group names, provide a unique name for each stereoisomer (see Figure 20.05 previous page).

The separate parts of these names give structural information about each stereoisomer. We will see that *α* and *β* identify the stereochemical configurations at C1, that *D* and *L* identify the configuration at C5, and that the configurations at C2, C3, and C4 determine the general group name (*allose*, *altrose*, etc.) of each stereoisomer (see Figure 20.06 previous page). Since the individual parts of each stereoisomer name describe an aspect of its stereochemistry, they help identify its structure. For this reason we will now examine the stereochemical features of these stereoisomers in detail.

Stereochemical Patterns. Look at the structures to see that all D stereoisoimers in Figure 20.05 have identical configurations at C5. The same is true for all *L* stereoisomers. In *β* stereoisomers, the C1-OH bond is a solid wedge pointing out from the paper, while C1-OH bonds for *α* stereoisomers are dash wedge bonds projecting below the plane of the paper. Finally, the pattern of configurations at C2, C3, and C4 of any particular stereoisomer (of *glucose*, for example) repeats in one other stereoisomer with the same group name, but not in any other stereoisomer with a different group name.

Enantiomers and Diastereomers. Any two stereoisomers in Figure 20.05 are either **enantiomers** or **diastereomers** of each other (Chapter 4). *Enantiomers* are non-superimposable mirror images and a close examination of Figure 20.05 shows that this is the case when two monosaccharides have names that differ only in the D or L designation. Examples of enantiomeric pairs in this figure are *α-D-glucose* and *α-L-glucose*, *β-D-glucose* and *β-L-glucose*, *α-D-mannose* and *α-L-mannose*, and so on. The stereoisomers in this figure that are not *enantiomers* of each other are *diastereomers*. Naturally occurring monosaccharides are primarily D-enantiomers.

R,S Configurations. The R,S configuration (Chapter 4) at each chiral C of one member of an *enantiomeric pair* is opposite to the configuration of the chemically identical chiral C in the other *enantiomer* (Table 20.2).

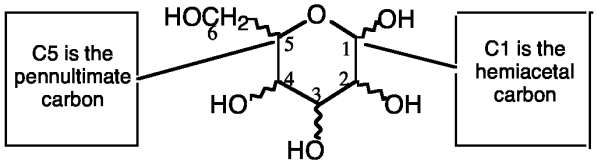
Table 20.2. R,S Configurations of Chiral C's in Glucose Enantiomeric Pairs.

Enantiomeric Pair	C1	C2	C3	C4	C5
α-D-glucose	S	R	S	R	R
α-L-glucose	R	S	R	S	S
β-D-glucose	R	R	S	R	R
β-L-glucose	S	S	R	S	S

You can determine each of the R,S configurations in Table 20.2 from the stereoisomer structures in Figure 20.05 and the R,S assignment rules (Chapter 4). You can also draw the structure of each stereoisomer from the general *pyranohexose* structure using the R,S configurations in Table 20.2. These are tedious exercises, but we will see that the definitions of *D* and *L*, as well as those of α and β, provide help in drawing or identifying these stereoisomers.

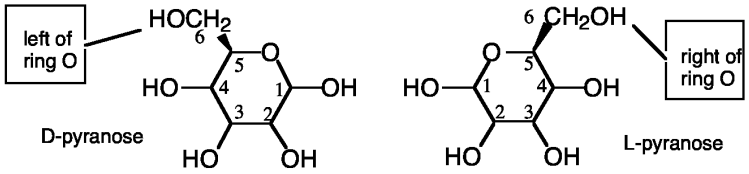
D and L. D and L define the configuration at the *highest numbered chiral C* (the **penultimate** carbon) in a monosaccharide. That C is called **penultimate** because it is "next to last" in the carbon sequence. Since we consecutively number C's in a monosaccharide so that the hemiacetal C has the lowest possible number, the hemiacetal C is C1 and the penultimate C is C5 in these pyranohexoses.

Figure 20.07



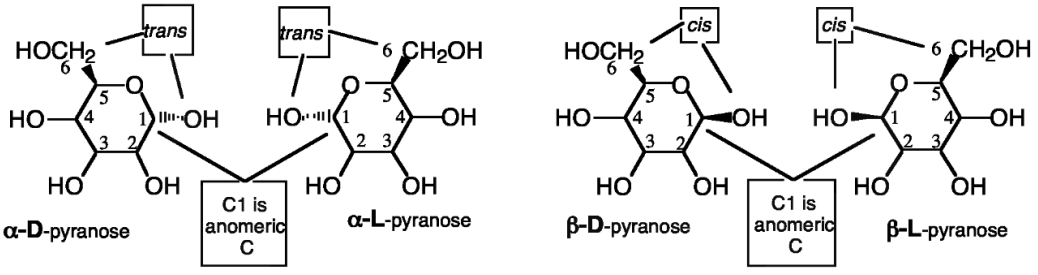
With each stereoisomer oriented so that the C5-O bond is at the top of the structure and the CH_2OH group on C5 points out from the page as in Figure 20.05, the D stereoisomers have CH_2OH to the left of the ring O, while it is to the right in L stereoisomers.

Figure 20.8



α andβ. α and β identify the relative configurations at the hemiacetal C and the penultimate C of a cyclic monosaccharide.

Figure 20.09



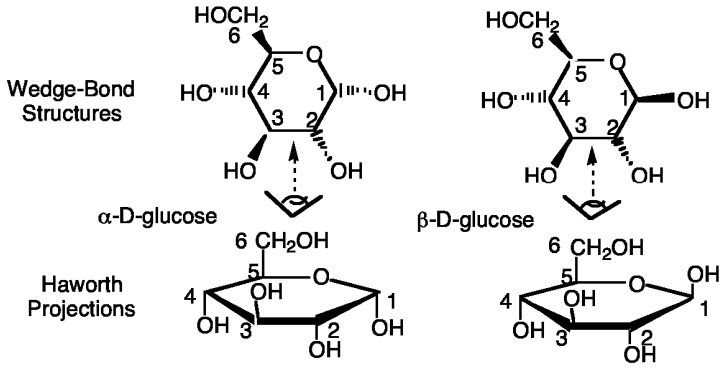
The OH on the hemiacetal C (C1) in *α-pyranohexoses* is always *trans* to the CH_2OH on C5, while these two groups are *cis* in *β-pyranohexoses* (*e.g.*, compare α– and β-D-glucose in

Figure 20.05. The hemiacetal C (C*) with the α or β OH is the **anomeric** carbon, and α- and β-D-glucose (or α- and β-L-glucose, etc.) are **anomers** of each other. *Anomers* are *diastereomers* of each other (see Table 20.2).

Configurations at the Other Chiral C's. The configurations at C2, C3, and C4 determine whether a particular stereoisomer in Figure (graphic 20.05) is *glucose*, *mannose*, or has one of the other "sugar names" mentioned earlier. The general definitions of D, L, α, and β, permit you to assign those prefixes to any stereoisomer in Figure (graphic 20.05), but the only way to know its group name or "sugar name" is from its specific configurations at C2, C3, and C4. You could memorize the R,S configurations at C2, C3, and C4 for each stereoisomer, but it is better to remember whether the C2, C3, or C4 OH groups of a monosaccharide with a particular "sugar name" are "up" or "down" in its wedge-bond drawing or in the **Haworth projections** described in the next section.

Haworth Projections. We have represented pyranose stereoisomers using wedge-bond structures (Figure (graphic 20.05)), but they appear more frequently as *Haworth projections* (Figure 20.10) with flattened rings (see Chapter 4).

Figure 20.10

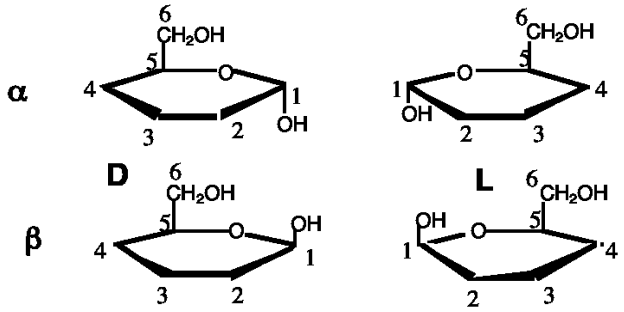


The usual Haworth projections for *α-D-glucose* and *β-D-glucose* are the views "seen by the eye-ball" looking in the plane of the paper across the *wedge-bond drawings* from the C2-C3 bond towards the ring C5-O bond. As a result, the ring O atom is "in back" and "to the right". The *wedge-bond structures* of α and β-D-glucose (Figure (graphic 20.05)) are views of the Haworth projections from above.

Haworth projections are useful for comparing stereochemical features of pyranoses. Those of *α-* and *β-D-glucose* clearly show that the CH_2OH group on C5 has the same configuration in both D isomers, that the C1-OH groups have opposite configurations in the α and the β anomers, that the C1-OH group and C5-CH_2OH groups are *trans* in the α anomer and *cis* in the β anomer, and that configurations at C2, C3, and C4 are identical in both stereoisomers.

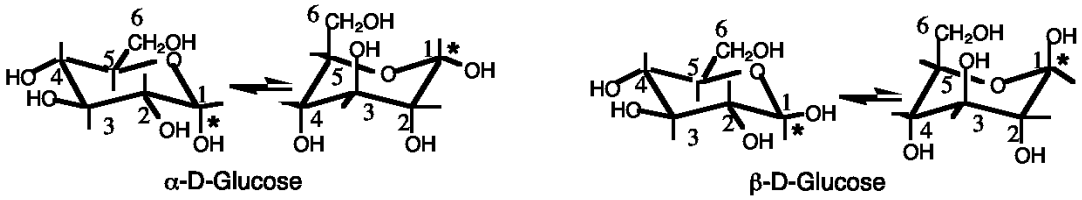
The generalized structures shown here emphasize the features in Haworth projections that are characteristic of α and β, and D and L. They serve as templates that you can use to draw Haworth projections of the individual pyranose stereoisomers if you memorize the "up"-"down" OH configurations at C2, C3, and C4 for the different sugar group names.

Figure 20.11



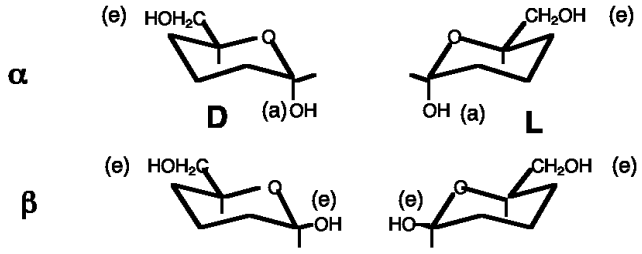
Chair Forms of Monosaccharides. Wedge-bond drawings and Haworth projections show stereochemical relationships of groups in *pyranohexoses*, but the 3-dimensional structures of these stereoisomers are equilibrating chair conformations like these for α and β-*D-glucose*.

Figure 20.12



When representing monosaccharides by chair forms, it is conventional to draw the single conformation where the C5-O ring bond is in the "back" of the structure, the ring O is "up", and the anomeric C of D-stereoisomers is on the right while that of L-stereoisomers is on the left. This causes the CH_2-OH group on C5 to be *equatorial*, α C1-OH groups to be *axial*, and β C1-OH groups to be *equatorial*.

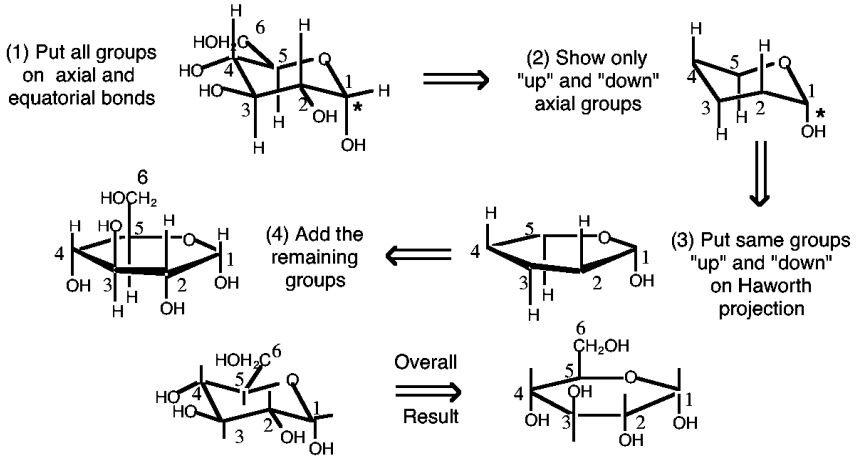
Figure 20.13



You need to be able to readily interconvert between wedge-bond structures, Haworth projections, and chair forms. We have already described wedge-bond structures and Haworth projections as different views of the same flat-ring structure. You can also imagine that a Haworth projection results from flattening a chair form.

It is easiest to see this if you include all of the axial and equatorial bonds in the chair form. You can then decide whether the groups on a particular ring C atom in a chair form go "up" or "down" in the Haworth projection by examining *axial* groups in the chair form.

Figure 20.14



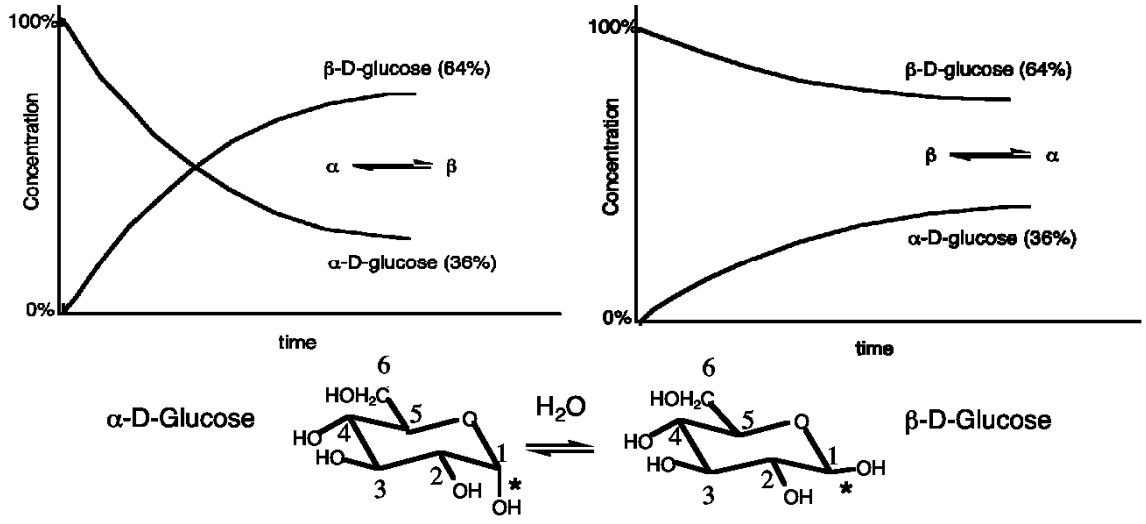
If an axial group points "up", that group will be "up" in the Haworth projection, and axial groups pointing "down" are "down" in Haworth projections. We finally add the equatorial groups of each C to the remaining unfilled bonds on the Haworth projection. In order to go from a Haworth projection to a chair form, we reverse this process.

Mutarotation (20.1C)

α and β anomers of monosaccharides slowly interconvert in aqueous solution.

α and β Anomers are in Equilibrium. The concentration of a pure sample of *α-D-glucose* in water slowly decreases at the same rate that *β-D-glucose* appears in the solution.

Figure 20.15

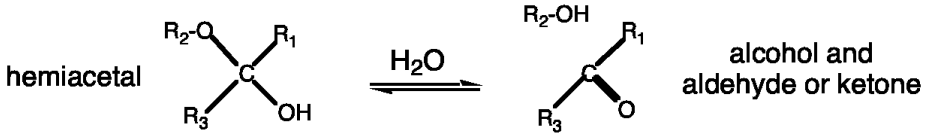


Ultimately, the solution contains an equilibrium mixture of *α-D-glucose* and *β-D-glucose* where the sum of the concentrations of the two anomers is identical to the initial concentration of *α-D-glucose*. The same equilibrium mixture arises when we place a pure sample of *β-D-glucose* in water, and analogous equilibria exist for α and β anomers of the other pyranohexoses.

This equilibration of anomers is called **mutarotation** since it causes the optical rotation of a water solution of the pure anomer to change. For example, the optical rotation of a water solution of pure α-D-glucose ($[\alpha]_D$ +112.2°), or of pure β-D-glucose ($[\alpha]_D$ +18.7°), changes to an apparent $[\alpha]_D$ of +52.7° for the equilibrium mixture of the two anomers.

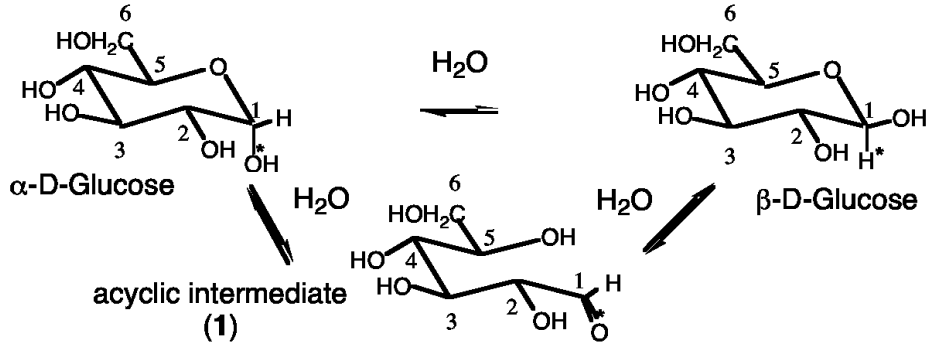
The Mutarotation Reaction. Why and how do anomers equilibrate in water? The answers come from the chemistry of hemiacetals described in Chapter 16.

Figure 20.16



Hemiacetals undergo a reaction in water to give a carbonyl compound (an aldehyde or a ketone) and an alcohol. This is the reverse of hemiacetal formation from addition of an alcohol to a carbonyl compound. The analogous reversible reaction of the hemiacetal group of α-D-glucose gives an intermediate (1) with a C=O group and new OH group.

Figure 20.17



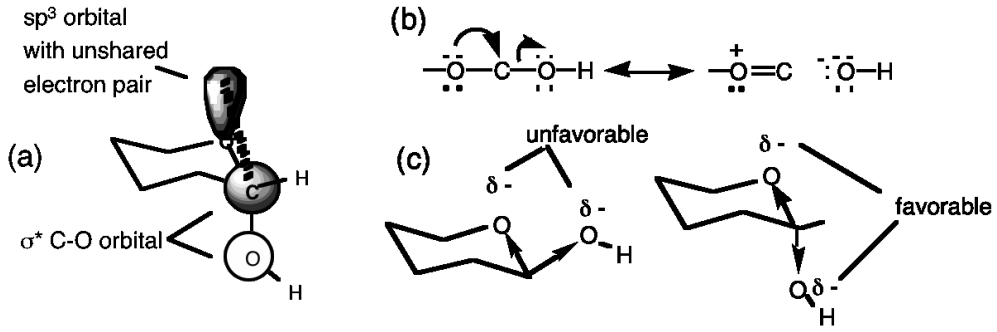
The important difference between this reaction of α-D-glucose and the general reaction of hemiacetals is that carbons C2 through C4 of the intermediate (1) connect the C=O group at C1 (an aldehyde) and the OH group at C5. As a result, the C5-OH group of (1) is in a position not only to react again with C1=O of (1) to regenerate α-D-glucose, but to also give β-D-glucose by reaction with C1=O from its opposite face (Figure 20.17). This so-called **anomerization** equilibrium occurs in neutral, acidic, or basic water solutions and we will see its mechanisms later in this chapter.

What About the Other OH Groups? You may wonder if an OH group on C2, C3, C4 or C6 of intermediate (1), can also react with the C=O group to form cyclic structures with rings of 3 atoms (C2-OH), 4 atoms (C3-OH), 5 atoms (C4-OH), and 7 atoms (C6-OH). While the highly strained 3- and 4-membered rings do not form, we will see that energetically favorable 5-membered rings do form, and there is even evidence for the presence of trace amounts of 7-membered ring cyclic sugars.

Equilibrium Concentrations of α and β-D-Glucose. The equilibrium mixture of α- and β-D-glucose is approximately 36% α and 64% β anomer (Figure 20.15), while the acyclic intermediate (1) represents only a trace of the total D-glucose. The two anomers differ in concentration because they have different stabilities ($\Delta\Delta G \approx 1.5$ kJ/mol). All substituents on the six-membered ring of *β-D-glucose* can be *equatorial*, but the C1 OH of *α-D-glucose* is *axial* when the other groups are equatorial. While the β:α ratio of 64:36 ([β]/[α] =1.78) is consistent with the expectation that substituents on cyclohexane rings want to be *equatorial*, the β:α ratio is somewhat smaller than predicted by the *equatorial preference* of OH (Chapter 2).

This higher-than-expected stability of an anomer with an *axial* anomeric OH group is a general observation called the **anomeric effect**. Explanations include (a) favorable orbital overlap between unshared electron pairs on attached O's and an anti-bonding orbital on the anomeric C, (b) an unusual type of "negative" hyperconjugation that is more favorable in the α-anomer, and (c) unfavorable dipole-dipole repulsions in the β-anomer. *[graphic 20.18]*

Figure 20.18



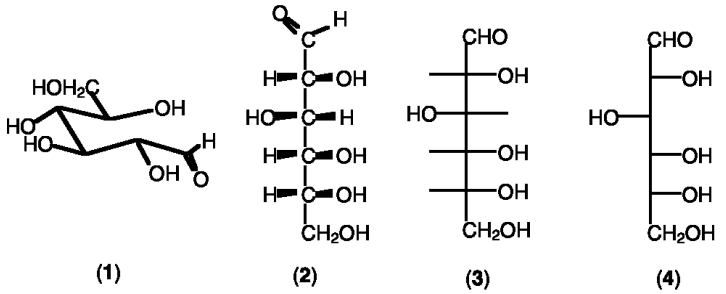
Acyclic Mutarotation Intermediates (20.1D)

We can call the mutarotation intermediate (1) in Figure 20.17 simply "D-glucose" because the terms α and β no longer apply. C1 is in the achiral C=O group so intermediate (1) has only 4 chiral C's (C2 through C5) and they retain the configuration they had in α and β-D-glucose.

Representations of the Acyclic Intermediate. You will most often see acyclic *D-glucose* written as the wedge-bond form (2), or as the *Fischer projections* (3) or (4), rather than as (1) as we show in Figure 20.19 [next page]. Since organic and biochemistry texts frequently use

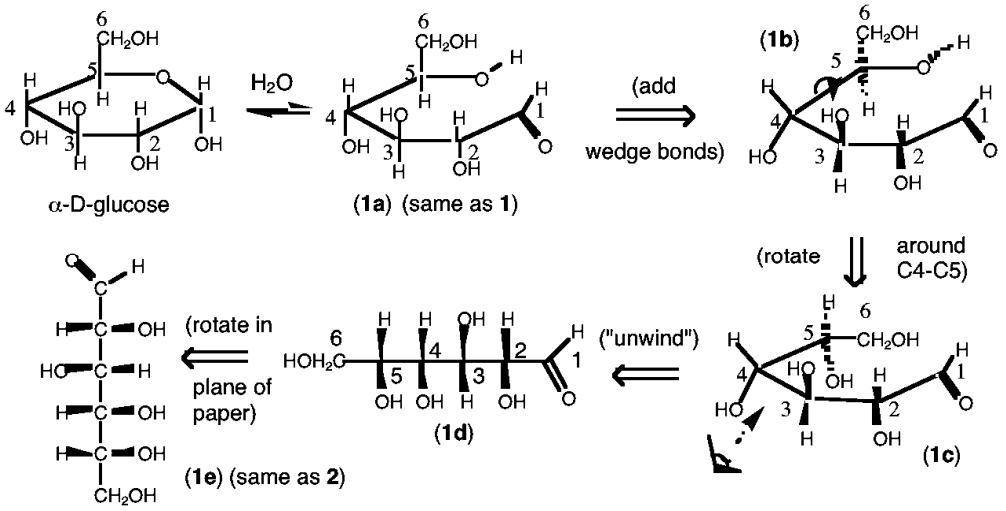
Fischer projections (Chapter 4) to represent structures of monosaccharides, it is particularly important for you to review their meaning and to remember that they usually do not specifically show the chiral C atoms in the vertical carbon skeleton.

Figure 20.19



In order to see the relationship between (1) and (2), you must rotate several C-C bonds and reorient the structure in space. You can do this with molecular models, or on paper by starting with a Haworth representation of α-D-glucose.

Figure 20.20



Structure (1a) is the "Haworth projection equivalent" of structure (1) shown earlier in the mutarotation reaction. Structure (1b) results from the addition of wedge-bonds to (1a), and (1c) is obtained by rotation about C4-C5 in (1b).

You can imagine (1d) as a stretched version of (1c) or the projection view seen by the "eyeball" looking at (1c). Finally, rotation of (1d) in the plane of the paper gives (1e) that is the same as structure (2).

In Figure 20.19, structure (3) is the Fischer projection of (2), while structure (4) is an alternate version of (3) without C-H bonds on the chiral C's. Structures (1) and (2) are not energetically favorable conformations of acyclic *D-glucose*. Structure (1) depicts the conformation first formed after the pyranohexose ring opens, while structure (2) is the

conformation that most clearly shows the configurations at the chiral C's. We would expect the six-carbon chain to preferentially adopt a fully staggered conformation.

Figure 20.21

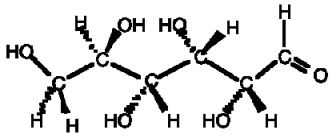
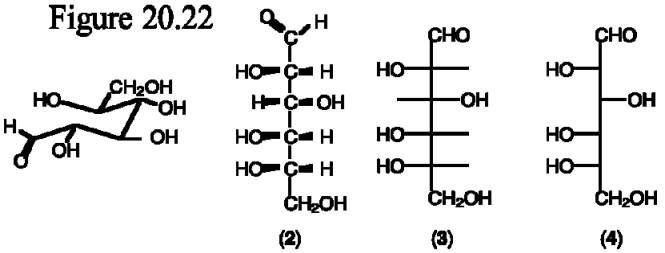


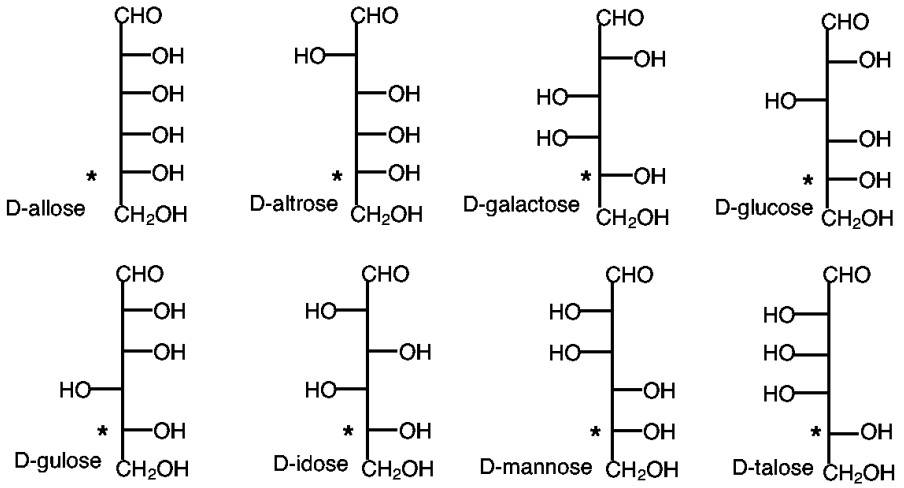
Figure 20.22



Acyclic Forms of the Other Stereoisomers. We can draw analogous structures for the acyclic intermediate *L-glucose* which forms during mutarotation of α- and β-L-glucose (Figure 20.22). L-monosaccharides have R,S configurations opposite to those of their D-enantiomers at every chiral carbon. As a result, the structures for *L-glucose* are mirror images of those shown for *D-glucose* in Figure 20.19

The same types of acyclic mutarotation intermediates exist for the other pyranohexoses in Figure (graphic 20.5) and we show them for the D-enantiomers in Figure 20.23.

Figure 20.23



They all have the same configuration at C5 (*) because they are D-enantiomers, but they have unique configurations at C2, C3, and C4 because they have different "sugar names". These Fischer projections show that C5 is the "next to the last" (the *penultimate*) C in the chain.

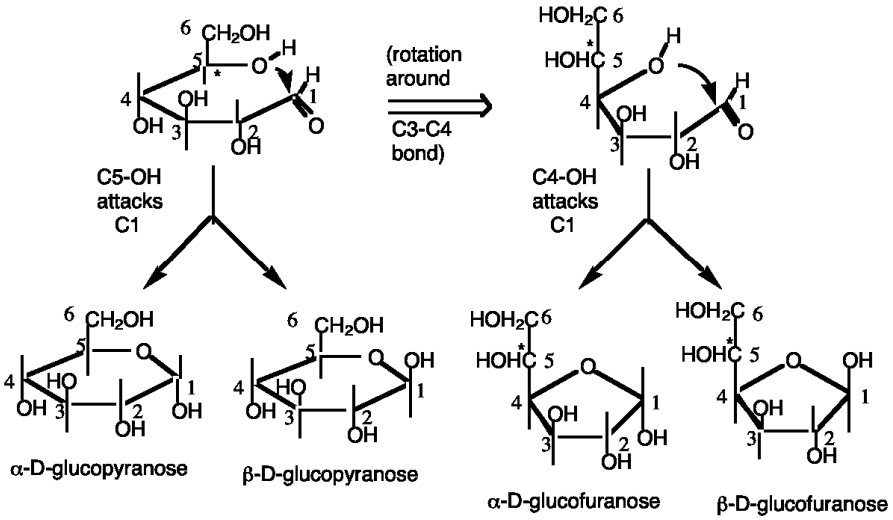
These acyclic forms are called **aldoses** because they have an aldehyde functional group and **aldohexoses** since they have 6 C's. Chemists also refer to their cyclic forms (the pyranose forms) as *aldohexoses* because their acyclic mutarotation intermediates are *aldohexoses*.

Furanose Forms (20.1E)

At the beginning of this chapter, we learned that monosaccharides are cyclic molecules with 5-membered (*furanose*) as well as 6-membered (*pyranose*) rings. So far we have focused exclusively on *pyranose* forms because they are the most important forms of *D-glucose*, however *furanose* forms are important for other monosaccharides so we consider them here.

Glucose has Furanose Forms. We have seen that the C5-OH of D-glucose adds to its C1 C=O group to give α and β pyranose anomers of D-glucose. In analogous reactions, the C4-OH also adds to the C1 C=O group to give low concentrations of α and β *furanose* anomers of D-glucose.

Figure 20.24



Since they are structurally different from the α and β pyranoses, these furanose forms must have unique names. While we have referred to the pyranose anomers of D-glucose as *α* and *β-D-glucose*, they are more completely named **α-D-glucopyranose** and **β-D-gluco-pyranose**. In the same way, the furanose anomers are named **α** and **β-D-glucofuranose**. We do not show the configuration at C5 (C*) in α and β-D-glucofuranose, but it is the same as in the acyclic form, and so are the configurations at C2 through C4.

α– and β-D-glucofuranose are in equilibrium with their pyranose anomers and their acyclic forms, but their equilibrium concentrations are very low (about 0.2 to 0.3%). This is because the 6-membered pyranose rings are thermodynamically more stable than 5-membered furanose rings. While reaction of the C3-OH or C2-OH with C1=O can form 4- or 3-membered rings, they do not because of the inherent strain in these small rings. However, there is evidence for minute amounts of 7-membered ring forms of D-glucose from reaction of the C6-OH with the C1 C=O.

Furanose Forms of Other Monosaccarides. In contrast to glucose, the relative amounts of furanose forms to pyranose forms for other monosaccharides are much larger (Table 20.3) indicating that the relative thermodynamic stabilities of the four cyclic forms depend on the configurations at all of the ring C's.

Table 20.3. Equilibrium Amounts of the Cyclic Forms of Aldohexoses

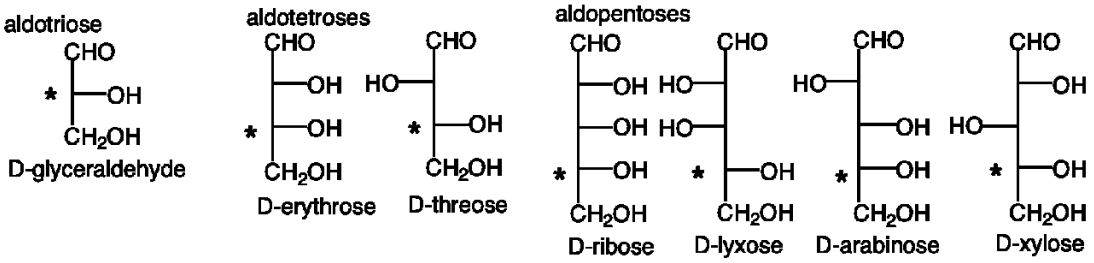
	pyranose forms		furanose forms	
Name	**%-α**	**%-β**	**%-α**	**%-β**
glucose	36	64	0.1	<0.2
allose	16	71	(4)	(5)
altrose	27	40	20	13
galactose	29	64	3	4
gulose	<0.1	78	<0.1	22
idose	39	36	11	14
mannose	66	34	(0)	(0)
talose	40	29	20	11

Other Monosaccharides (20.1F)

All of the monosaccarides that we have discussed so far are stereoisomers of the aldohexose *D-glucose*. However, there are *aldoses* that are *trioses*, *tetroses*, and *pentoses*, as well as monosaccharides with ketone functional groups (*ketoses*).

Aldotrioses, Aldotetroses, and Aldopentoses. We show the names and Fischer projections of the acyclic D-stereoisomers of aldotrioses, aldotetroses, and aldopentoses in Figure 20.25.

Figure 20.25

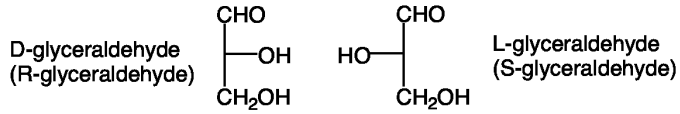


In each Fischer projection, the OH on the *penultimate* carbon (C*) has the same configuration (points in the same direction) as it did in the *D-aldohexoses* shown earlier and it is the D configuration.

As in acyclic *D-aldohexoses*, the configurations at the remaining chiral C's determine the "sugar name" of the specific monosaccharide. The number of chiral C's in each acyclic aldose determines the number of possible acyclic stereoisomers (*number of stereoisomers = 2^n* where n is the number of chiral C's). We do not show the equivalent group of L-stereoisomers.

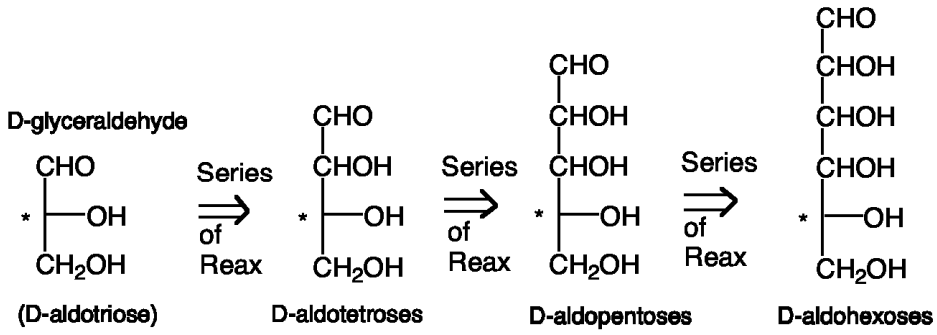
D and L-Glyceraldehyde. Glyceraldehyde has one chiral C and therefore only two stereoisomers (a pair of enantiomers).

Figure 20.26



It was resolved into its enantiomers ((+) and (-) optical isomers) in the late 1800's , but their absolute configurations were unknown until the early 1950's. Emil Fischer, in his pioneering studies of carbohydrates, recognized that glyceraldehyde was a crucial reference point for understanding stereochemistry of higher monosaccharides such as aldotetroses, aldopentoses, and aldohexoses. It is a starting point for their syntheses using reactions (described later in this chapter) that do not alter the stereochemistry at its chiral C (*).

Figure 20.27



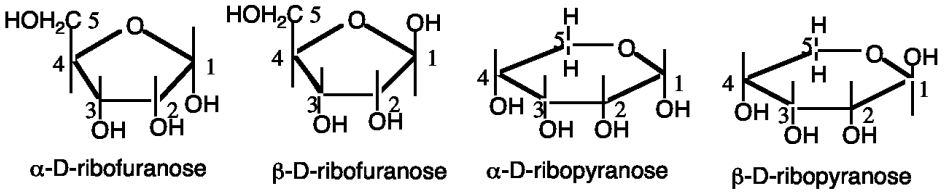
In order to draw structures illustrating the relative configurations at the chiral C's of monosaccharides, Fischer arbitrarily assigned the D-configuration to (+) glyceraldehyde and the L-configuration to (-)-glyceraldehyde. When absolute configurations of glyceraldehyde were finally experimentally determined, it turned out that Fischer's assignments of configuration had been correct so all structures of monosaccharides showing stereochemical configurations based on Fischer's assignments were valid. R,S rules show that D-glyceraldehyde is R and L-glyceraldehyde is S. (The lower case letters *d* and *l* are frequently used to designate that an enantiomer rotates light (+) (*d*), or (-) (*l*) (see Chapter 4). *d* and *l* have no connection with *D* and *L*.)

Cyclic Forms of C_3, C_4, and C_5 Aldoses. In aqueous solution, *aldopentoses* exist primarily in their 6-membered pyranose forms, but furanoses are also present in low concentrations (Table 20.4)[next page]. These cyclic forms are of D-ribose that is the monosaccharide component of ribonucleic acids (RNA's) (Figure 20.28)[next page]. The aldotetroses **erythrose** and **threose** have furanose forms, but not enough C's to form pyranoses. The aldotriose glyceraldehyde is acyclic because it cannot form either 5 or 6-membered rings.

Table 20.4. Equilibrium Amounts of the Cyclic Forms of Aldopentoses

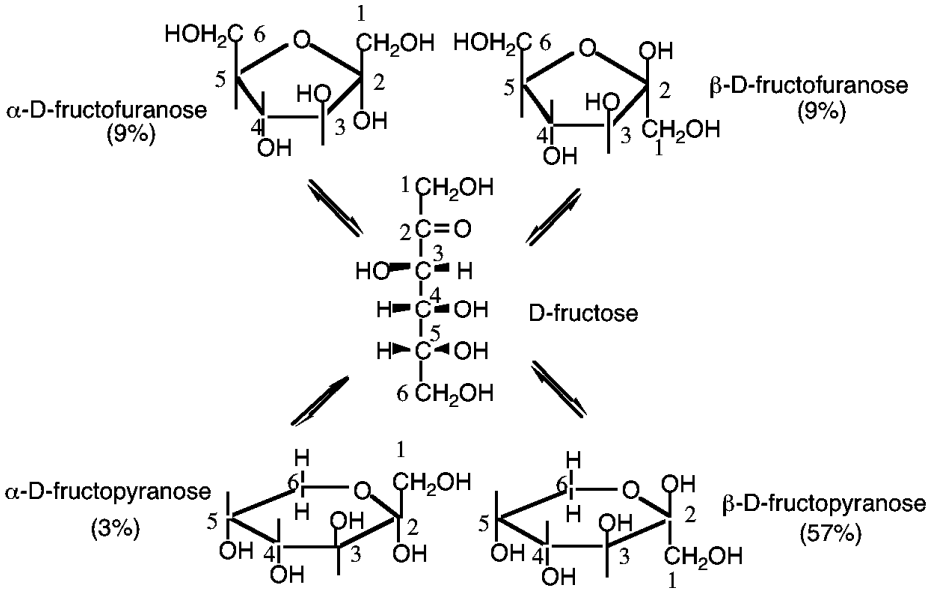
	pyranose forms		furanose forms	
Name	**%-α**	**%-β**	**%-α**	**%-β**
ribose	21	59	6	14
arabinose	63	34	(3)	(2)
xylose	37	63	<0.5	<0.5
lyxose	70	28	1.5	0.5

Figure 20.28



Ketoses. **D-fructose** is a biologically important ketohexose that exists in furanose and pyranose forms. *[graphic 20.28a]*

Figure 20.28a

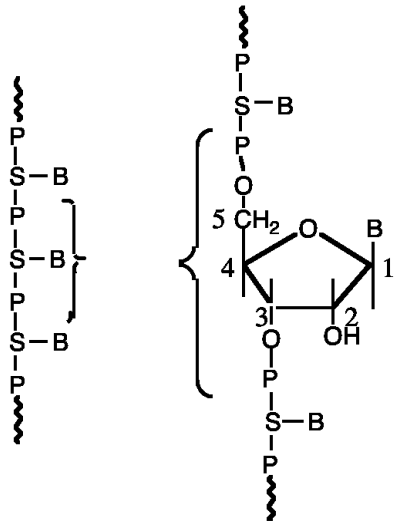


Because it is a 2-ketose, its anomeric C is C2, the ring O in its pyranose forms comes from the C6-OH, and from the C5-OH in its furanose forms. The penultimate C of D-fructose is C5 as in aldohexoses, but all of its forms have one less chiral C than aldohexoses because D-fructose has two achiral CH_2OH groups.

Cyclic Forms of Ribose. In aqueous solution, the pyranose forms of D-ribose are present in much greater concentration than the furanose forms (Table 20.4). This is not the case in RNA molecules that contain only repeating D-ribofuranose units (S) connected by phosphate groups (P) in a long strand referred to as the RNA backbone (Figure 20.29)[next page]. A heterocyclic base (*adenine*, *guanine*, *cytosine*, or *uracil*) (B) bonds to each D-ribofuranose unit at its anomeric C. DNA strands are similar

to RNA strands except they have 2-deoxyribofuranose units (H replaces OH on the C2 of ribofuranose), and *adenine* instead of *uracil*. We describe nucleic acids (DNA and RNA) in Chapter 23.

Figure 20.29



20.2 Chemical Reactions of Monosaccharides

Monosaccharides undergo a variety of chemical reactions similar to those we have studied in previous chapters for compounds with C=O and OH groups. Some of these reactions begin with the acyclic form, others require cyclic forms, and still others occur with either form. Although acyclic forms of monosaccharides are usually present in very low concentrations, they continuously regenerate from cyclic forms as they are consumed in a reaction. We broadly classify these reactions as *isomerizations*, *nucleophilic additions and substitutions*, and *oxidations* or *reductions*, although we will see that some reactions fall into more than one of these categories.

Isomerization Reactions (20.2A)

Mutarotation of pyranoses and furanoses is an *isomerization* reaction. Another is **epimerization** that changes the stereochemistry at the C that is α to C=O groups and intercoverts aldoses and ketoses.

Mutarotation. Mutarotation occurs at room temperature in neutral aqueous solutions as well as by acid or base catalysis. We illustrate the acid-catalyzed mechanism for isomerization of α and β-pyranohexoses in Figure 20.30 [next page]. The mechanism at neutral pH involves concerted proton transfer to and from water molecules (Figure 20.31)[next page]. The base-catalyzed mechanism is similar to that shown for neutral pH solution except that $^-$OH rather than H_2O removes the proton from the anomeric OH group.

Figure 20.30

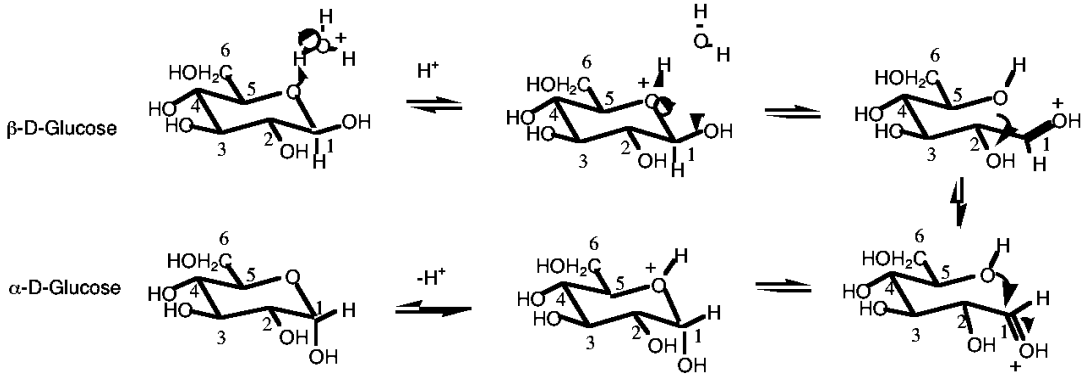
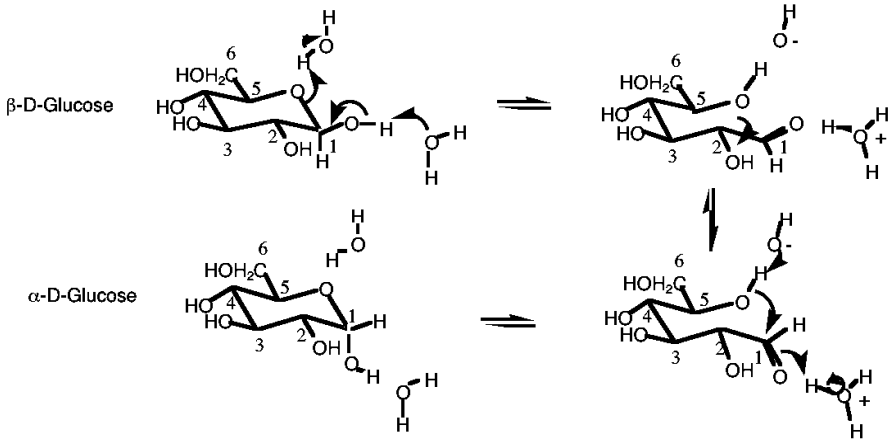
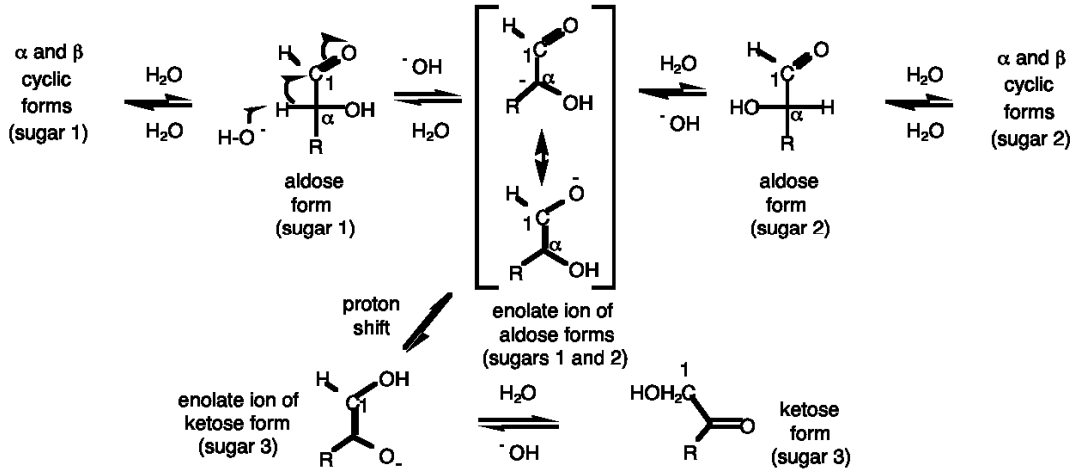


Figure 20.31



Epimerization. When we heat monosaccarides in aqueous base, there is a loss of stereochemical configuration (*epimerization*) at C's that are α to the C=O in the aldose or ketose forms. Reprotonation of the intermediate *enolate ion* on C_α gives a mixture of the two **epimeric** monosaccharides with opposite stereochemical configurations at C_α. Figure 20.32 shows this process for the transformation of one aldose (Sugar 1) into its *epimeric* stereoisomer (Sugar 2) that differs only in the stereochemical configuration at C_α.

Figure 20.32



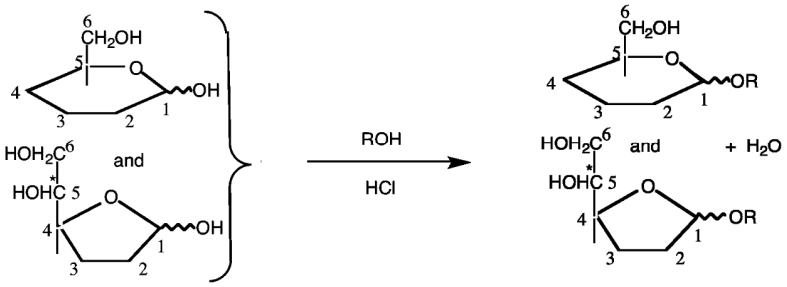
A proton shift in the enolate ion formed from Sugar 1 or 2 leads to isomerization of these aldoses to a more stable ketose form (Sugar 3). Mutarotation, epimerization, and isomerization of aldoses to ketoses, occur simultaneously when monosaccharides are heated in aqueous base.

Nucleophilic Addition and Substitution (20.2B)

Mutarotation is an *isomerization*, but we could also classify it as reversible *nucleophilic addition* at a C=O group. Related nucleophilic addition and substitution reactions are replacement of anomeric OH groups by OR groups to form **glycosides**, and *anomerization* of *glycosides*. Others are nucleophilic addition and substitution reactions by C or N nucleophiles on C=O, and nucleophilic substitutions that convert anomeric and non-anomeric OH groups to ether or ester groups.

Glycoside Formation. Heating furanoses and/or pyranoses in an alcohol (ROH) containing HCl, gives an equilibrium mixture of **alkyl glycosides** (**alkyl furanosides** and **pyranosides**). *Pyranosides* are the major products at equilibrium because they are thermodynamically more stable than furanosides. In contrast, furanosides are kinetically favored so they predominate early in the reaction.

Figure 20.33



We show an acid-catalyzed mechanism for these *glycosidation reactions* in Figure 20.34 [next page] beginning with methanol and α-D-glucofuranose. Alkyl glycosides are *acetals* and this mechanism is analogous to that for acetal formation (Chapter 16). The resulting alkyl furanosides equilibrate with alkyl pyranosides in the alcohol/HCl reaction mixture (Figure 20.35) [next page].

Anomerization and Hydrolysis of Glycosides. While anomeric alkyl glycosides equilibrate in the alcohol/HCl solutions, each anomeric alkyl glycoside is stable in aqueous solutions at basic or neutral pH. The alkyl group (R) prevents the concerted ring opening reaction involved in mutarotation of furanoses and pyranoses in neutral or basic solutions (Figure 20.36)[next page]. Glycosides hydrolyze in aqueous acid by a mechanism that is the reverse of the one for their formation (see Figure 20.34).

Figure 20.34

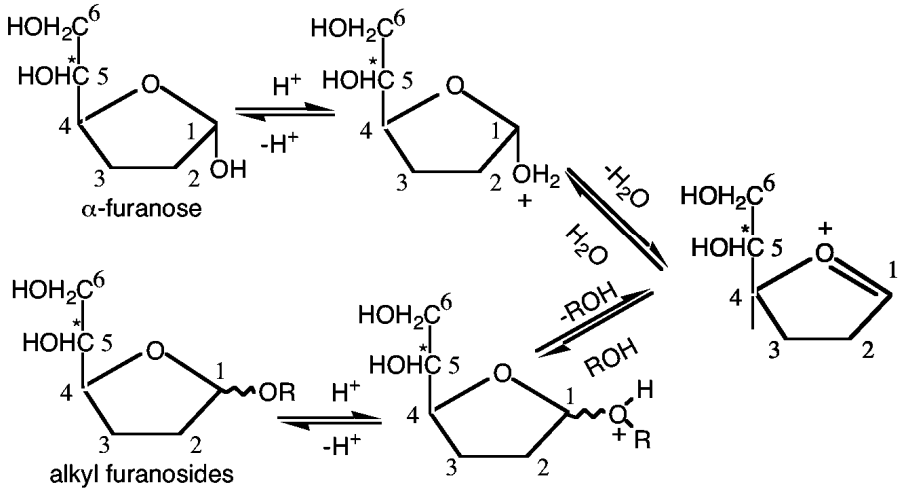


Figure 20.35

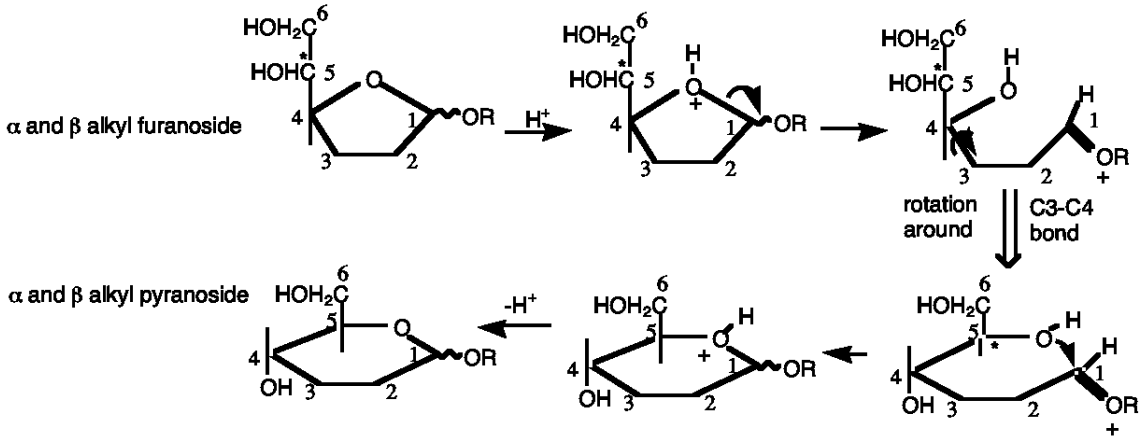
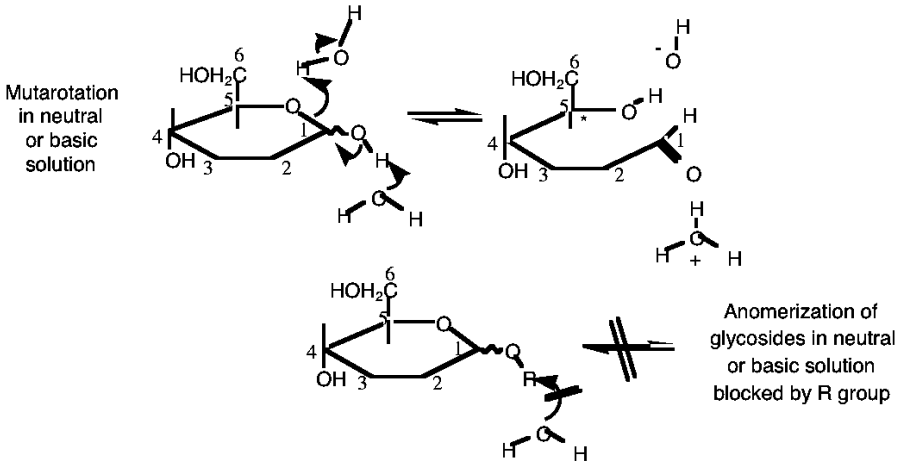
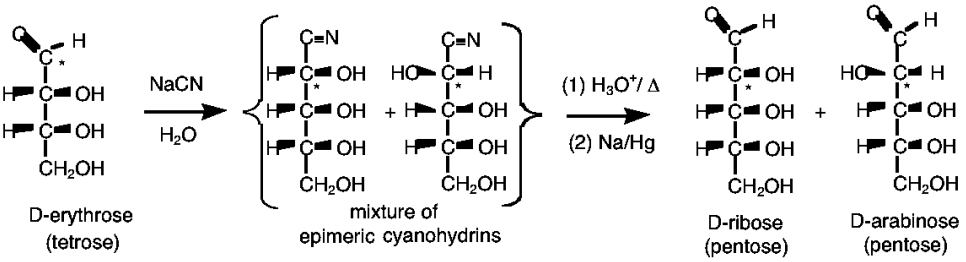


Figure 20.36



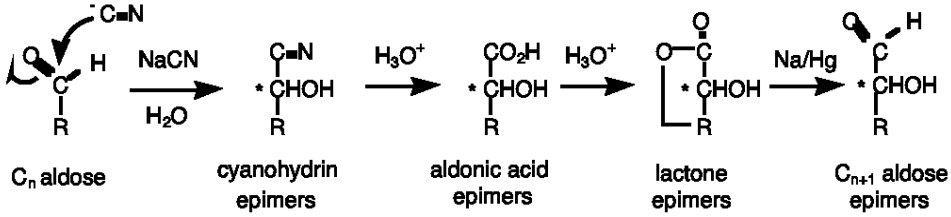
Addition of Carbon Nucleophiles. We can increase the number of carbons in a monosaccharide one C at a time by adding a carbon nucleophile such as $^-C{\equiv}N$ (cyanide ion) to an aldose or a ketose (Figure 20.37).

Figure 20.37



The initial step of this **Kiliani** chain-lengthening **method** is addition of $^-C{\equiv}N$ to the C=O group of an acyclic aldose (or ketose). *[graphic 20.38]*

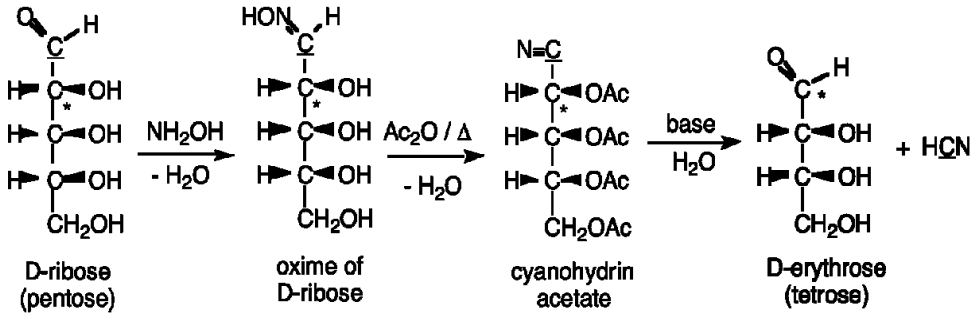
Figure 20.38



Hydrolysis of the C≡N group of the intermediate cyanohydrin and reduction of the resulting lactone gives a chain-lengthened aldose. We can resolve the mixture of epimeric cyanohydrins with the new chiral carbon (C*) into two diastereomers before C≡N hydrolysis.

Addition of Nitrogen Nucleophiles. A variety of nitrogen nucleophiles adds to C=O groups of aldoses and ketoses. Hydroxylamine (NH_2-OH) gives an oxime intermediate used to shorten the length of a monosaccharide by the **Wohl degradation**.

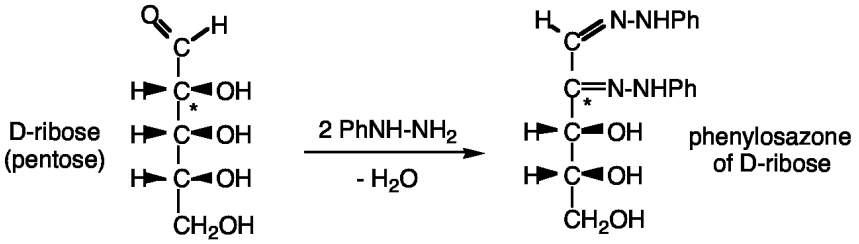
Figure 20.39



The intermediate oxime dehydrates in acetic anhydride to a cyanohydrin acetate that loses H-C≡N to regenerate a C=O group. Since the C≡N carbon was originally the C of the C(=O)H group, the loss of H-C≡N transforms the *CHOH group into an aldehyde group (*C(=O)H). The overall result is an aldose with one less C atom.

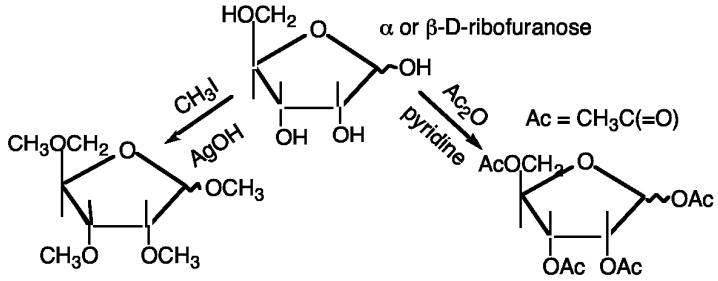
Osazones. Aldoses react with the nitrogen nucleophile phenylhydrazine (Ph-NH-NH_2) to give unusual compounds called osazones (Figure 20.40). Because osazones are crystalline compounds, they have seen extensive use in the historical characterization and identification of monosaccharides.

Figure 20.40



Esters and Ethers. Acetic anhydride in pyridine converts all OH groups of monosaccharides into O-C(=O)CH_3 ester groups. Methylation of OH using reagents such as (a) CH_3I/AgOH, (b) $(CH_3)_2SO_4$, or (c) CH_3I and NaH in DMF, gives OCH_3 ether groups.

Figure 20.41

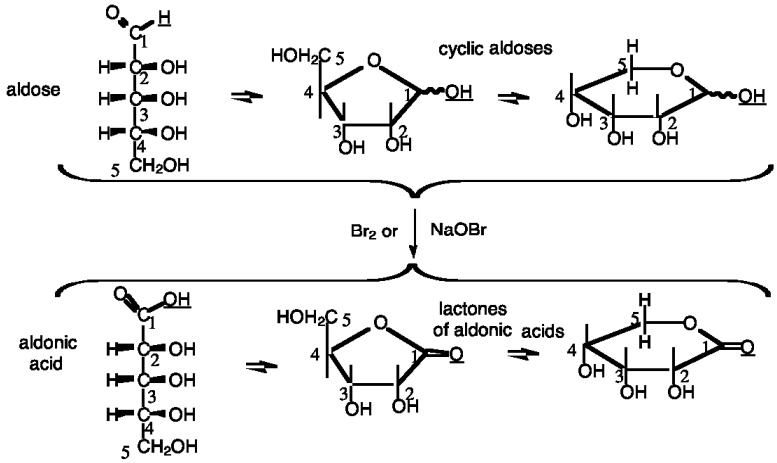


Oxidation and Reduction (20.2C)

Various reagents selectively oxidize or reduce functional groups in monosaccharides.

Halogen and Hypohalite Oxidations. Molecular bromine (Br_2) or hypohalites such as NaOBr or NaOI oxidize aldehyde groups of *aldoses* to carboxylic acid groups of **aldonic acids**. These reagents also oxidize anomeric OH groups of pyranoses and furanoses to lactones. Hydrolysis of the lactones gives the acyclic *aldonic acids*.

Figure 20.42



Oxidation with HNO_3 or NO_2. The more powerful oxidizing agents HNO_3 (nitric acid) or NO_2 (nitrogen dioxide) oxidize the aldehyde group, and the terminal (1°) CH_2-OH group to give dicarboxylic acids called **aldaric acids** (Figure 20.43). Aldonic acids form cyclic lactones, but aldaric acids are acyclic.

Figure 20.43

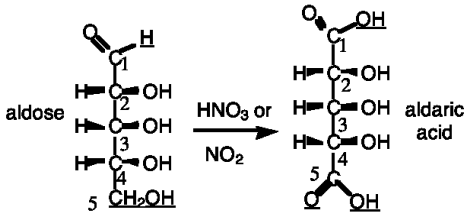
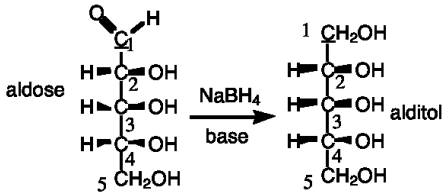


Figure 20.44

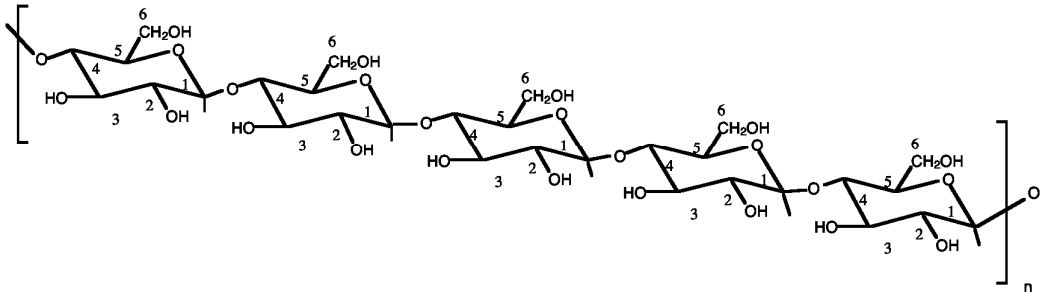


Reduction with $NaBH_4$. Reduction with $NaBH_4$ under basic conditions transforms C=O groups of aldoses and ketoses to OH groups of acyclic **alditols** (Figure 20.44 above).

20.3 Polysaccharides and Oligosaccharides

Most monosaccharides exist in nature in *polysaccharides* such as *cellulose*. Cellulose polysaccharides contain thousands of D-glucose monosaccharides chemically bonded by glycosidic linkages.

Figure 20.45



Polysaccharides with 2-10 monosaccharide units are called **oligosaccharides**. Before examining large polysaccharides, we will first learn about structural features of oligosaccharides with 2 or 3 monosaccharide units (disaccharides and trisaccharides). They provide a basis for understanding structures of large polysaccharides such as cellulose.

Disaccharides and Trisaccharides (20.3A)

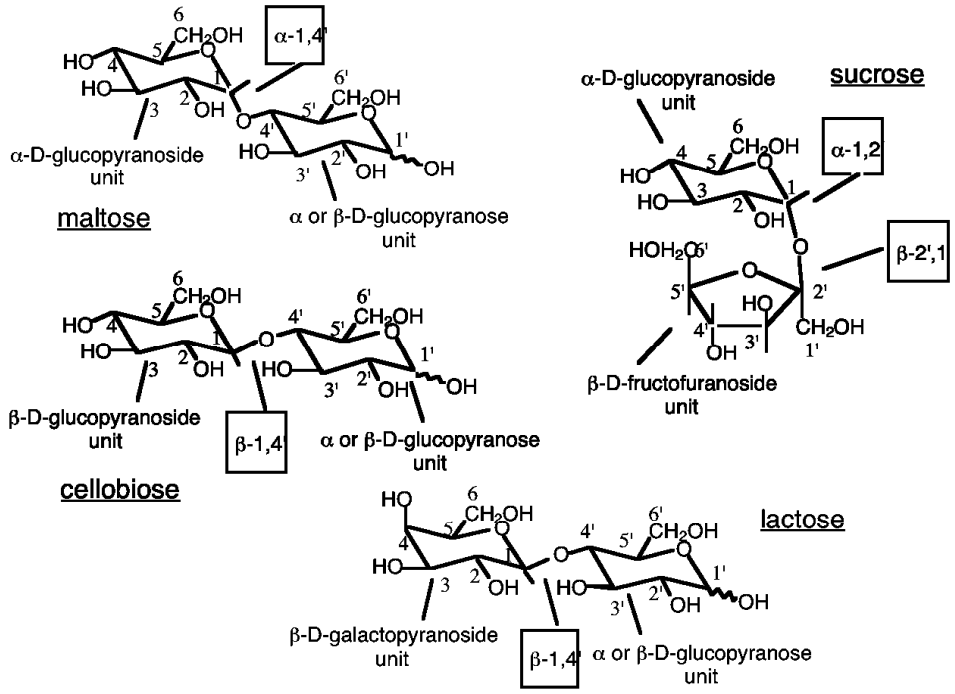
Lactose, **sucrose**, **maltose**, and **cellobiose** illustrate the structural diversity of disaccharides (Figure 20.46)[next page]. Hydrolysis of *maltose* gives an equilibrium mixture of only D-glucose anomers, so both of its monosaccharide units must be D-glucose. Since the same is true of *cellobiose*, we can classify both maltose and cellobiose as **homooligosaccharides**.

maltose	+	H_2O	→	D-glucose + D-glucose
cellobiose	+	H_2O	→	D-glucose + D-glucose

In contrast, *lactose* and *sucrose* are called **heterooligosaccharides** because each gives a mixture of two different monosaccharides upon hydrolysis.

lactose + H_2O → D-glucose + D-galactose
sucrose + H_2O → D-glucose + D-fructose

Figure 20.46

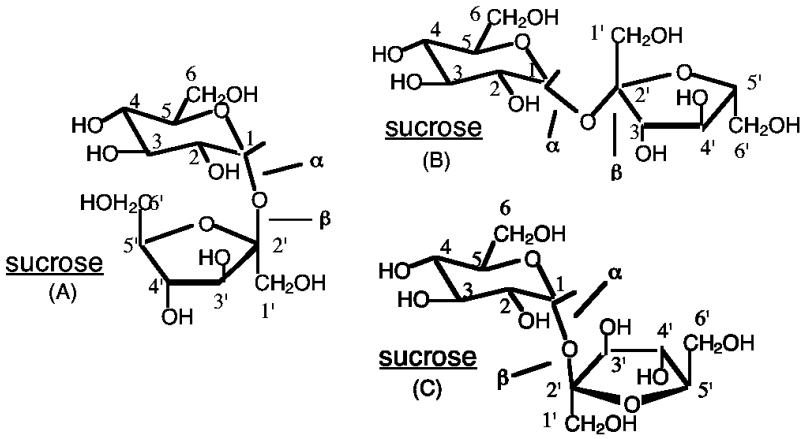


Maltose and Cellobiose. Although *maltose* and *cellobiose* give identical mixtures of α and β-D-glucose on hydrolysis, they are structurally different. While there is a glycosidic bond in both of these disaccharides between C4'-OH of the D-glucopyranose on the right and the anomeric carbon (C1) of the D-glucopyranose on the left, the C1 anomeric carbons have different configurations (see Figure 20.46). The glycosidic bond is β in *cellobiose*, while it is α in *maltose* and each is configurationally stable at neutral or basic pH as expected for a glycoside bond. In contrast, mutarotation freely occurs at the anomeric carbon (C1') in the right-hand monosaccharide units of both maltose and cellobiose.

Lactose. Hydrolysis of *lactose* (shown in Figure 20.46) gives an equimolar mixture of *D-glucose* anomers and *D-galactose* anomers. The glycosidic monosaccharide unit (the monosaccharide unit on the left of the *lactose* structure, is a D-galactopyranoside joined by a β-glycosidic linkage to C4 of the D-glucopyranose unit on the right. As in *cellulose* and *maltose*, the β-glycosidic bond of *lactose* does not mutarotate in neutral pH solutions, but mutarotation freely occurs at the anomeric carbon (C1') of its *D-glucopyranose* unit.

Sucrose. *Sucrose* hydrolyzes to an equimolar mixture of *D-fructose* and *D-glucose* anomers upon hydrolysis because it is a heterooligosaccharide composed of a *D-fructofuranoside* and a *D-glucopyranoside* (see Figure 20.46). In contrast to the other three disaccharides in that figure, mutarotation does not occur at either anomeric carbon of *sucrose* because both anomeric carbons have glycoside bonds. The glycoside bond to the *D-fructofuranoside* unit is β while that to the *D-glucopyranoside* unit is α (see Figure 20.46). You may sometimes have difficulty identifying the α or β character of glycosidic bonds in *sucrose* because it is often drawn with its D-fructofuranoside ring "upside down" or "rotated" as in structures (B) or (C) in Figure 20.47. The configurations of the anomeric C's are easiest to identify in structure (A) where you see both rings in their usual orientation.

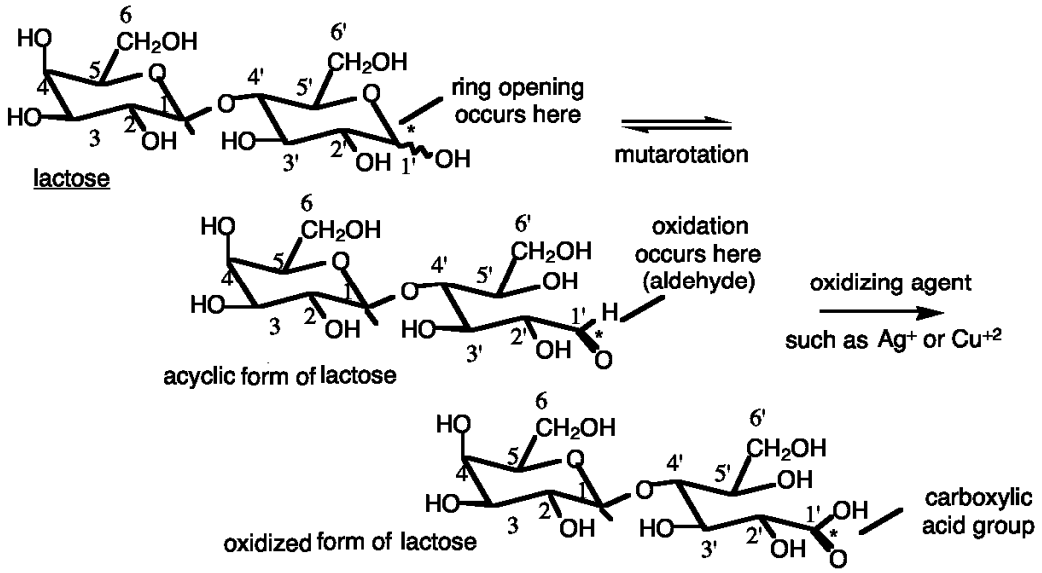
Figure 20.47



Inversion of Sucrose and Invert Sugar. An aqueous solution of sucrose has a (+) optical rotation. Upon hydrolysis of the sucrose, the optical rotation of the solution becomes (-). This occurs because the equilibrium mixture of D-fructose anomers formed during hydrolysis has a (-) optical rotation that is much greater than the (+) optical rotation of D-glucose anomers also formed during hydrolysis. This change in sign of rotation of a sucrose solution upon hydrolysis is referred to as the "inversion of sucrose". The resulting mixture of D-glucose and D-fructose anomers is called "invert sugar".

Reducing Sugars. Because *cellobiose*, *maltose*, and *lactose* each have an anomeric carbon (C*) which mutarotates, they have mutarotation intermediates where the right hand monosaccharide unit is acyclic with an aldehyde functional group as shown for lactose (Figure 20.48) [next page]. Mild oxidizing agents oxidize this aldehyde group and in the process those oxidizing agents are *reduced*. For this reason, *cellobiose*, *maltose*, and *lactose* are called **reducing sugars**. In contrast, both anomeric C's in *sucrose* (Figures 20.46 and 20.47) have glycosidic bonds, so formation of an acyclic intermediate with an oxidizable aldehyde group is impossible. As a result, *sucrose* does not reduce the mild oxidizing agents that oxidize cellobiose, maltose, and lactose, so it is a **non-reducing** sugar.

Figure 20.48



Silver ions (Ag^{+}) and cupric ions (Cu^{+2}) are mild oxidants that oxidize reducing sugars but do not oxidize non-reducing sugars.

Reducing Sugar	$\xrightarrow[\text{(or } Cu^{+2}\text{)}]{Ag^{+1}}$	Oxidized Sugar + Ag^{0} (or Cu^{+1})
Non-reducing Sugar	$\xrightarrow[\text{(or } Cu^{+2}\text{)}]{Ag^{+1}}$	No Reaction

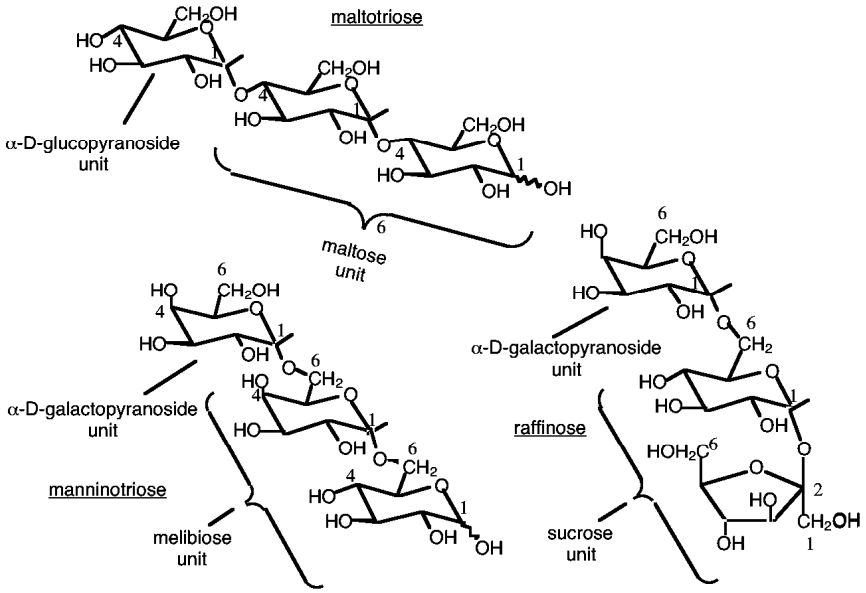
Reducing sugars reduce Ag^{+} to elemental silver (Ag^{0}) that deposits on the sides of the reaction vessel as a shiny "silver mirror". Similarly, they reduce Cu^{+2} to Cu^{+1} that precipitates from basic aqueous solutions as the brick-red solid Cu_2O. Because you can visually monitor the formation of a silver mirror or a Cu_2O precipitate, these oxidizing agents provide diagnostic tests for the presence or absence of a reducing sugar. The Cu^{+2} reagent is called **Fehling's solution** and it is prepared by dissolving $CuSO_4$ in aqueous base. Ag^{+} is in **Tollen's reagent** that is prepared by dissolving $AgNO_3$ and a small amount of ammonia in aqueous base.

Trisaccharides. The carbohydrates **maltotriose**, **manninotriose**, and **raffinose** are naturally occurring trisaccharides (Figure 20.49) [next page]. *Maltotriose* is homologous with *maltose* and you can draw its structure by making an α-glycoside bond between the anomeric C of a new D-glucopyranose unit and the unsubstituted C4-OH of *maltose*.

In a similar way you can obtain the structure of *raffinose* from that of *sucrose* by forming an α-glycoside bond between the anomeric C of *D-galactopyranose* and the C6-OH on the D-

glucopyranoside unit of sucrose. *Manninotriose* has its three pyranose rings (two D-galctopyraonose rings and a D-glucopyranose ring) joined by α-glycoside bonds to C6 carbons. You can imagine its formation from a dissacharide known as **melibiose** by adding a third D-galactopyranose using an α-glycoside bond.

Figure 20.49



Maltotriose is a *homooligosaccharide*, while manninotriose and raffinose are *heterooligosaccharides*. Raffinose is a *non-reducing sugar*, while both maltotriose and manninotriose are *reducing sugars*.

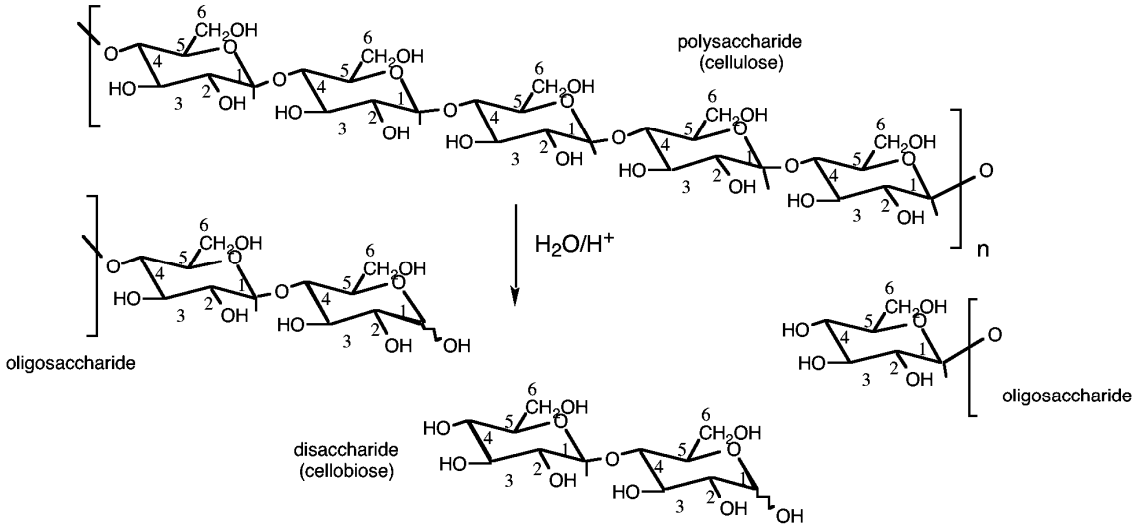
Polysaccharides (20.3B)

We began this chapter by introducing the polysaccharide *cellulose* found in all plants. It and other polysaccarides are high molecular mass carbohydrates composed of many monosaccharide units joined by glycosidic bonds. Polysaccharides serve a number of crucial biological functions in organisms such as cell wall support (**structural** polysaccharides), food (energy) storage (**storage** polysaccharides), and as the extra-cellular matrix surrounding connective tissue (**mucopolysaccharides**). Polysaccharides are also present in many *proteins* called **glycoproteins.**

Structural Polysaccharides. *Cellulose* is a mixture of polysaccharides with as many as 15,000 D-glucopyranose units joined by β-glycosidic bonds between their C1 and C4 carbons. The majority of carbon atoms in all biological systems are in cellulose molecules. Hydrolysis of cellulose in aqueous acid cleaves the glycosidic links to give smaller oligosaccharides with the same general structure as cellulose (Figure 20.50) [next page]. These further hydrolyze to α and β-D-glucose. The enzyme mixture **cellulase**, present in

the digestive systems of termites and animals that eat plants, also cleaves cellulose into smaller oligosaccharides, cellobiose, and α and β-D-glucose.

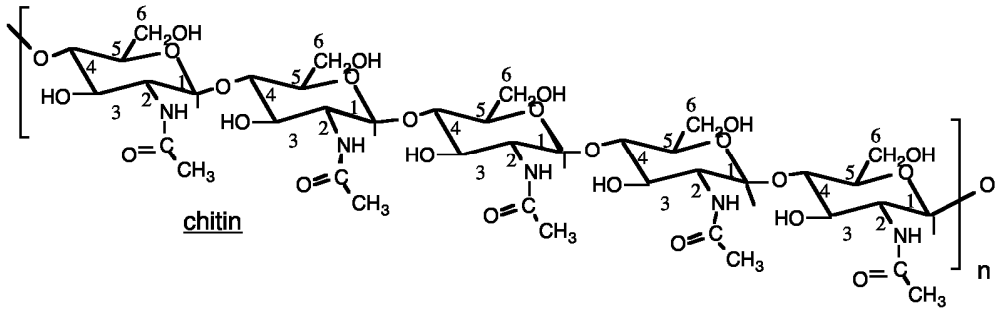
Figure 20.50



Enzymes. Enzymes are proteins that catalyze specific types of reactions *in vivo* and we discuss them in the protein chapter (Chapter 22). The names of enzymes end with "ase" and often begin with all or part of the name of the type of molecule or process on which they act. You have probably realized by now that the names of most carbohydrates end in "ose".

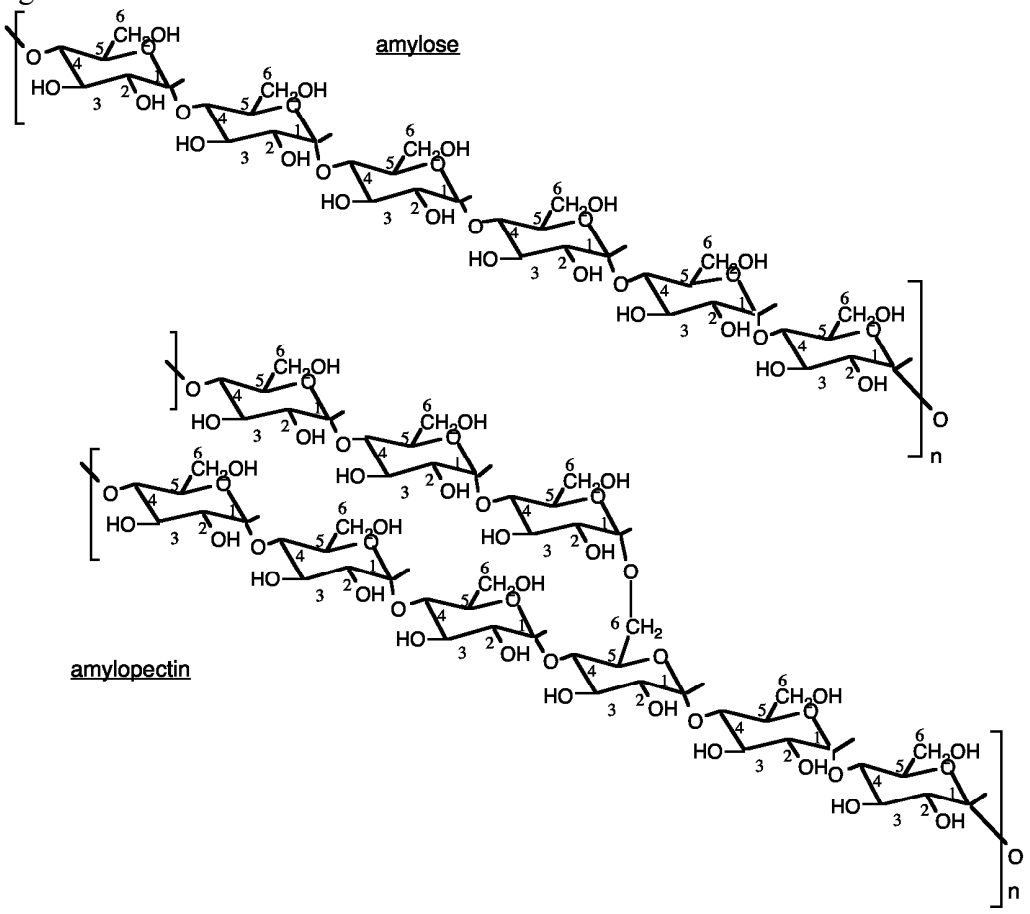
Chitin is a polysaccharide that makes up the exoskeleton of spiders, insects, and crustaceans. Its overall structure is the same as cellulose except that C2-NH(C=O)CH_3 groups replace the C2-OH groups.

Figure 20.51



Storage Polysaccharides. **Starch** is a mixture of the polysaccharides **amylose** and **amylopectin** present in the cells of plants (Figure 20.52) [next page]. *Amylose*, like cellulose, is a linear homopolysaccharide of several thousand D-glucopyranose units, however its connecting glycosidic linkages are α. It hydrolyzes in aqueous acid to give α and β-D-glucopyranose. The enzyme **α-amylase**, present in saliva and in the small intestine, also cleaves it into oligosaccharides, and ultimately into maltose and maltotriose.

Figure 20.52



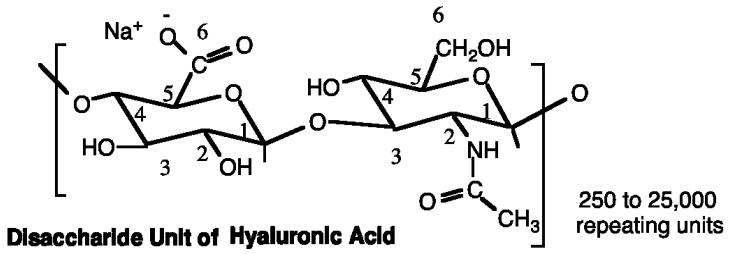
Amylopectin is a branched polysaccharide composed of *amylose* strands connected by α-glycosidic bonds between the anomeric C1 of one amylose strand and C6 on another amylose strand. Branches occur every 23-30 D-glucose units and amylopectins can contain on the order of a million D-glucose units. Amylopectin hydrolyzes in aqueous acid and *α-amylase* also cleaves it into oligosaccharides. Since α-amylase does not cleave 1,6-glycosidic linkages, oligosaccharides that contain them (**α-dextrins**) ultimately break down in the intestine into α and β-D-glucopyranose with the assistance of the enzyme *α-dextrinase* .

Glycogen is a storage polysaccharide present in cells of humans and animals. It is structurally similar to amylopectin except that its branches occur every 8 to 12 monosaccharide units. Enzymes break it down into α and β-D-glucopyranose as needed by the metabolic requirements of the organism.

Mucopolysaccharides. **Mucopolysaccharides,** also known as **glycosaminoglycans** (the term **glycan** means polysaccharide), are present in extracellular spaces surrounding connective tissue. They have a number of structural variations, but in all cases they are large

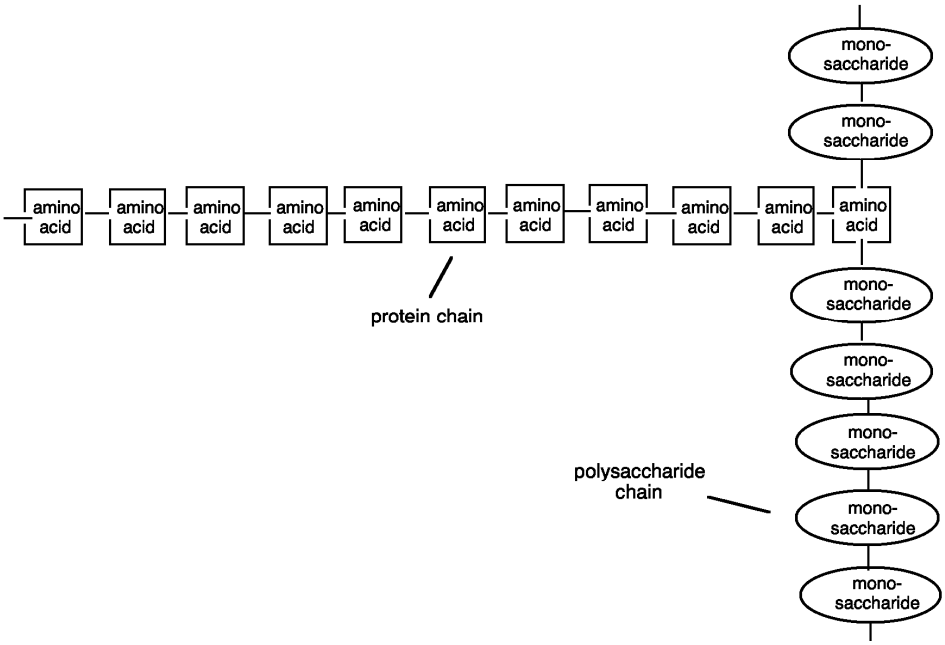
molecules made up of hundreds or thousands of repeating disaccharide units connected by 1,4-β-glycosidic bonds. **Hyaluronic acid** (see Figure 20.53) is a mucopolysaccharide that serves as the lubricant in joints between bones. The two monosaccharide units in each disaccharide unit connect to each other with a 1,3-β-glycoside bond.

Figure 20.53



Glycoproteins. Proteins are large molecules containing 100's of *amino acids* joined by *amide* bonds (Chapter 22). Those with attached carbohydrate chains are called *glycoproteins* (Figure 20.54). *Glycoproteins* are present in extra-cellular material such as cartilage (**proteoglycans**), and they also make up the walls of cells (**peptidoglycans**). The carbohydrate chains of glycoproteins have great variability in their length and in their monosaccharide composition.

Figure 20.54



Chapter Review

Monosaccharides

(1) Monosaccharides are stereoisomeric polyhydroxy cyclic hemiacetals with five-membered (furanose) and six-membered (pyranose) rings. (2) Each complete monosaccharide name contains (a) α or β, (b) D or L, (c) *pyranose* or *furanose*, and (d) the underlined part of its sugar name (*glucose*, *mannose*, *ribose*, *fructose*, *etc.*).

(3) The stereochemical configuration of the penultimate carbon is D or L, that of the anomeric carbon is α or β, those of the remaining chiral carbons determine the sugar name, and *pyranose* or *furanose* indicate the ring size. (4) α and β anomers equilibrate (mutarotate) by way of an intermediate acyclic form in which the anomeric C loses chirality and becomes C=O of an aldehyde or ketone group. (5) Pyranose forms equilibrate with the less stable furanose forms by way of the acyclic intermediate. (6) Common monosaccharides include hexoses, pentoses, tetroses, and a triose, as well as aldoses and ketoses.

Chemical Reactions of Monosaccharides

(1) Isomerization reactions include mutarotation (acid, base, or neutral water solutions), and base catalyzed epimerization and aldose/ketose interconversion. (2) Nucleophilic addition and substitution reactions include acid catalyzed glycoside formation (monosaccharide + alcohol), acid catalyzed anomerization (during glycosidation) and hydrolysis, addition of cyanide ion (Kiliani chain lengthening), addition of NH_2OH (Wohl degradation), and acylation (ester formation) and alkylation (ether formation) of all OH groups. (3) Oxidation with X_2 or NaOX gives aldonic acids (and lactones), while the oxidizing agents HNO_3 and NO_2 give aldaric acids. (4) Reduction with $NaBH_4$ yields alditols.

Polysaccharides and Oligosaccharides

(1) Oligosaccharides contain 2-10 monosaccharide units connected by glycosidic bonds while polysaccharides can contain 1000's of glycosidically bonded monosaccharide units. (2) Maltose (α-glycosidic linkage) and cellobiose (β-glycosidic linkage) are homodisaccharides of D-glucose, while lactose (galactose-β–1,4-glucose), and sucrose (glucose-α-1,2'-β-fructose) are heterodisaccharides. (3) Reducing sugars must have one non-glycosidic anomeric C. (4) Cellulose (β-glycosidic linkages) and amylose (α-glycosidic linkages) are homopolysaccharides of D-glucose, while amylopectin has branching amylose chains connected by α-1,6-glycosidic linkages. (5) In organisms, polysaccharides provide structural support (structural polysaccharides), energy storage (storage polysaccharides), serve as extracellular matrix components (mucopolysaccharides), and are bonded to proteins (glycoproteins).