20: Carbohydrates

- **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\(_2\)O)\(_n\) or C\(_n\)(H\(_2\)O)\(_{n-1}\). 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**.

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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**.

\[
\text{cellulose} + \text{water} \rightarrow D\text{-glucose}
\]

( polysaccharide ) \hspace{1cm} ( 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). With 4 or more C's, they are usually cyclic molecules with 5-membered \( (\text{furanose}) \) or 6-membered \( (\text{pyranose}) \) rings. [graphic 20.1]

<table>
<thead>
<tr>
<th>Number of C's (n)</th>
<th>General Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>triose</td>
</tr>
<tr>
<td>4</td>
<td>tetrose</td>
</tr>
<tr>
<td>5</td>
<td>pentose</td>
</tr>
<tr>
<td>6</td>
<td>hexose</td>
</tr>
<tr>
<td>7</td>
<td>heptose</td>
</tr>
</tbody>
</table>

**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. [graphic 20.2] However unlike the ethers furan and pyran, furanoses and pyranoses are cyclic **hemi acetals**. 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). [graphic 20.3]

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 monosaccharides. [graphic 20.4]

*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 (graphic 20.5). (The maximum number of stereoisomers of a compound with \( n \) chiral carbons is \( 2^n \) and in this case \( 2^5 = 2^5 = 32 \).) [graphic 20.5] 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 \( \alpha \) and \( \beta \), and \( D \) and \( L \), in
combination with these general group names, provide a unique name for each stereoisomer (Figure (graphic 20.5)).

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. 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 D stereoisomers in Figure (graphic 20.5) 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 particular pattern of configurations at C2, C3, and C4 for 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 (graphic 20.5) are either enantiomers or diastereomers of each other (Chapter 4). Enantiomers are non-superimposable mirror images and a close examination of Figure (graphic 20.5) 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.

<table>
<thead>
<tr>
<th>Enantiomeric Pair</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-D-glucose</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>α-L-glucose</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>β-D-glucose</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>β-L-glucose</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>
You can determine each of the R,S configurations in Table 20.2 from the stereoisomer structures in Figure (graphic 20.5) 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 \( \alpha \) and \( \beta \), 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. [graphic 20.7] With each stereoisomer oriented so that the C5-O bond is at the top of the structure and the CH\(_2\)OH group on C5 points out from the page as in Figure (graphic 20.5), the D stereoisomers have CH\(_2\)OH to the left of the ring O, while it is to the right in L stereoisomers. [graphic 20.8]

**\( \alpha \) and \( \beta \).** \( \alpha \) and \( \beta \) identify the *relative* configurations at the hemiacetal C and the penultimate C of a cyclic monosaccharide. [graphic 20.9] The OH on the hemiacetal C (C1) in \( \alpha \)-pyranohexoses is always *trans* to the CH\(_2\)OH on C5, while these two groups are *cis* in \( \beta \)-pyranohexoses (e.g., compare \( \alpha \)- and \( \beta \)-D-glucose in Figure (graphic 20.5)). The hemiacetal C (C\(^*\)) with the \( \alpha \) or \( \beta \) OH is the *anomeric* carbon, and \( \alpha \)- and \( \beta \)-D-glucose (or \( \alpha \)- and \( \beta \)-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 20.5) is glucose, mannose, or has one of the other "sugar names" mentioned earlier. The general definitions of D, L, \( \alpha \), and \( \beta \), permit you to assign those prefixes to any stereoisomer in Figure (graphic 20.5), 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 20.5)), but they appear more frequently as **Haworth projections** with flattened rings (Chapter 4). [graphic 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 20.5)) 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\textsubscript{2}OH group on C5 has the same configuration in both of these D isomers, that the C1-OH groups have opposite configurations in the α and the β anomers, that the C1-OH group and the C5-CH\textsubscript{2}OH groups are **trans** in the α anomer and **cis** in the β anomer, and that the configurations at C2, C3, and C4 are identical in both of these stereoisomers.

The generalized structures shown here emphasize the features in Haworth projections that are characteristic of α and β, and D and L. [graphic 20.11] 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.

**Chair Forms of Monosaccharides.** Wedge-bond drawings and Haworth projections show the stereochemical relationships of groups in **pyranohexoses**, but the actual 3-dimensional structures of these stereoisomers are equilibrating chair conformations as shown here for α and β-D-glucose. [graphic 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. [graphic 20.13] This causes the CH\textsubscript{2}-OH group on C5 to be **equatorial**, α C1-OH groups to be **axial**, and β C1-OH groups to be **equatorial**.

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. [graphic 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 placed in water slowly decreases at the same rate that β-D-glucose appears in the solution. [graphic 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, those of pure α-D-glucose ([α]_D +112.2°) or pure β-D-glucose ([α]_D +18.7°) change to an apparent [α]_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. [graphic 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 functional group of α-D-glucose gives an intermediate (1) with a C=O group and new OH group. [graphic 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 (graphic 20.17))!

**Anomerization** occurs in neutral, acidic, or basic water solutions and we will see 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 (graphic 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 (ΔΔG ≈ 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.

Acyclic Mutarotation Intermediates (20.1D)
We can call the mutarotation intermediate (1) in Figure (graphic 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 that 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). 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.
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. 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). 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.

**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. 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.

The same types of acyclic mutarotation intermediates exist for the other pyranohexoses in Figure and we show them here for the D-enantiomers. 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 clearly 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 structures for other monosaccharides and 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. 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-γ-glucose, they are more completely named α-D-glucopyranose and β-D-glucopyranose. 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 this is also the case for the configurations at C2 through C4.

α and β-D-glucofuranose are in equilibrium with the pyranose anomers and the acyclic form, but their equilibrium concentrations are very low (about 0.2 to 0.3%) indicating that the 6-membered pyranose rings are thermodynamically more stable than the 5-membered furanose rings. While formation of 4-membered or even 3-membered rings by reaction of C3-OH, or C2-OH with the C1 C=O is possible, we do not find rings of these sizes because of their inherent strain. 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 Monosaccharides.** In contrast to glucose, the relative amounts of furanose forms are much larger for some of its stereoisomers (Table 20.3) indicating that the relative thermodynamic stabilities of the four cyclic forms depends on the configurations at all of the ring C's. [Table 20.3]

<table>
<thead>
<tr>
<th>Name</th>
<th>pyranose forms</th>
<th>furanose forms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%-α</td>
<td>%-β</td>
</tr>
<tr>
<td>glucose</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>allose</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>altrose</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>galactose</td>
<td>29</td>
<td>64</td>
</tr>
<tr>
<td>gulose</td>
<td>&lt;0.1</td>
<td>78</td>
</tr>
<tr>
<td>idose</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>mannose</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>talose</td>
<td>40</td>
<td>29</td>
</tr>
</tbody>
</table>
**Other Monosaccharides** (20.1F)

All of the monosaccharides 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 [graphic 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). 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 (*). [graphic 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).
Table 20.4. Equilibrium Amounts of the Cyclic Forms of Aldopentoses

<table>
<thead>
<tr>
<th>Name</th>
<th>pyranose forms</th>
<th>furanose forms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%-α</td>
<td>%-β</td>
</tr>
<tr>
<td>ribose</td>
<td>21</td>
<td>59</td>
</tr>
<tr>
<td>arabinose</td>
<td>63</td>
<td>34</td>
</tr>
<tr>
<td>xylose</td>
<td>37</td>
<td>63</td>
</tr>
<tr>
<td>lyxose</td>
<td>70</td>
<td>28</td>
</tr>
</tbody>
</table>

These cyclic forms are of D-ribose that is the monosaccharide component of ribonucleic acids (RNA's). The aldotetroses erythrose and threose have furanose forms, but not enough C's to form pyranoses. The aldoto triose glyceraldehyde is acyclic because it cannot form either 5 or 6-membered rings.

**Ketoses.** D-fructose is a biologically important ketohexose that exists in furanose and pyranose forms. Because it is a 2-ketose, its anomic 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. A heterocyclic base (adenine, guanine, cytosine, or uracil) (B) bonds to each D-ribofuranose unit at its anomic C. DNA strands are qualitatively similar to RNA strands except that 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.

### 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 interconverts 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 [graphic 20.30]. The mechanism at neutral pH involves concerted proton transfer to and from water molecules. The base-catalyzed mechanism is similar to that shown for neutral pH solution except that −OH rather than H₂O removes the proton from the anomeric OH group.

**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 Cα gives a mixture of the two *epimeric* monosaccharides with opposite stereochemical configurations at Cα. Figure (graphic 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 Cα.

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). [graphic 20.33] 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.

We show an acid-catalyzed mechanism for these glycosidation reactions in Figure [graphic 20.34] beginning with methanol and α-D-glucofuranose. [graphic 20.34] 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. [graphic 20.35]

**Anomerization and Hydrolysis of Glycosides.** While anomic alkyl glycosides equilibrate in the alcohol/HCl solutions, each anomic 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. [graphic 20.36] Glycosides hydrolyze in aqueous acid by a mechanism that is the reverse of the one for their formation (see Figure (graphic 20.34)).

**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≡N (cyanide ion) to an aldose or a ketose. [graphic 20.37] The initial step of this Kiliani chain-lengthening method is addition of C≡N to the C=O group of an acyclic aldose (or ketose). [graphic 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. [graphic 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-NH₂) to give unusual compounds called osazones. [graphic 20.40] Because osazones are crystalline compounds, they have seen extensive use in the historical characterization and identification of monosaccharides.

Esters and Ethers. Acetic anhydride in pyridine converts all OH groups of monosaccharides into O-C(=O)CH₃ ester groups. [graphic 20.41] Methylation of OH using methylating reagents such as (a) CH₃I/AgOH, (b) (CH₃)₂SO₄, or (c) CH₃I and NaH in DMF, gives OCH₃ ether groups.

Oxidation and Reduction (20.2C)
Various reagents selectively oxidize or reduce functional groups in monosaccharides.

Halogen and Hypohalite Oxidations. Molecular bromine (Br₂) or hypohalites such as NaOBr or NaOI oxidize aldehyde groups of aldoses to carboxylic acid groups of aldonic acids. [graphic 20.42] These reagents also oxidize anomic OH groups of pyranoses and furanoses to lactones. Hydrolysis of the lactones gives the acyclic aldonic acids.

Oxidation with HNO₃ or NO₂. The more powerful oxidizing agents HNO₃ (nitric acid) or NO₂ (nitrogen dioxide) oxidize the aldehyde group, and the terminal (1°) CH₂-OH group to give dicarboxylic acids called aldaric acids. [graphic 20.43] Aldonic acids form cyclic lactones, but aldaric acids are acyclic.

Reduction with NaBH₄. Reduction with NaBH₄ under basic conditions transforms C=O groups of aldoses and ketoses to OH groups of acyclic alditols. [graphic 20.44]

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. [graphic 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.

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.

\[
\text{maltose} + \text{H}_2\text{O} \rightarrow \text{D-glucose} + \text{D-glucose}
\]

\[
\text{cellobiose} + \text{H}_2\text{O} \rightarrow \text{D-glucose} + \text{D-glucose}
\]

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

\[
\text{lactose} + \text{H}_2\text{O} \rightarrow \text{D-glucose} + \text{D-galactose}
\]

\[
\text{sucrose} + \text{H}_2\text{O} \rightarrow \text{D-glucose} + \text{D-fructose}
\]

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 (Figure (graphic 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 (Figure (graphic 20.46)) gives an equimolar mixture of D-glucose anomers and D-galactose anomers. The glycosidic monosaccharide unit (the monosaccharide unit on the left in Figure (graphic 20.46)) is a D-galactopyranoside joined by a β-glycosidic linkage to C4 of the D-glucopyranose unit on the right. As is the case for 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 (Figure (graphic 20.46)). In contrast to the other three disaccharides, 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 $\beta$ while that to the D-glucopyranoside unit is $\alpha$ (Figure (graphic 20.46)). You may sometimes have difficulty identifying the $\alpha$ or $\beta$ 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). [graphic 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.

**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. [graphic 20.48] 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 (graphic 20.46) and (graphic 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.

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

<table>
<thead>
<tr>
<th>Reducing Sugar</th>
<th>Oxidized Sugar + Ag$^0$ (or Cu$^{+1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag$^{+1}$ → (or Cu$^{+2}$)</td>
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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$_2$O. Because you can visually monitor the formation of a silver mirror or a Cu$_2$O 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. [graphic 20.49] Maltotriose is homologous with maltose and you can draw its structure by making an $\alpha$-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 $\alpha$-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-galactopyranose rings and a D-glucopyranose ring) joined by $\alpha$-glycoside bonds to C6 carbons. You can imagine its formation from a dissacharide known as melibiose by adding a third D-galactopyranose using an $\alpha$-glycoside bond.

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 $\beta$-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. 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.

**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)CH₃ groups replace the C2-OH groups. [graphic 20.51]

**Storage Polysaccharides.** Starch is a mixture of the polysaccharides amyllose and amylopectin present in the cells of plants. [graphic 20.52] 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.

Amylopectin is a branched polysaccharide composed of amyllose strands connected by α-glycosidic bonds between the anomeric C1 of one amyllose strand and C6 on another amyllose 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** is a mucopolysaccharide that serves as the lubricant in joints between bones. ![graphic 20.53] The two monosaccharide units in each disaccharide connect to each other with a 1,3-β-glycoside bond.

**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*. ![graphic 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.

**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 a specific sugar name (*glucose*, *mannose*, *ribose*, *fructose*, etc). (3) The stereochemical configuration of the penultimate carbon is D or L, that of the anomic 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 anomic 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, tetrose, 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 NH₂OH (Wohl degradation), and acylation (ester formation) and alkylation (ether formation) of all OH groups. (3) Oxidation with X₂ or NaOX gives aldonic acids (and lactones), while the oxidizing agents HNO₃ and NO₂ give aldaric acids. (4) Reduction with NaBH₄ yields alditols.
**Polysaccharides and Oligosaccharides**

(1) Oligosaccharides contain 2-10 monosaccharide units connected by glycosidic bonds while polysaccharides can contain thousands 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).