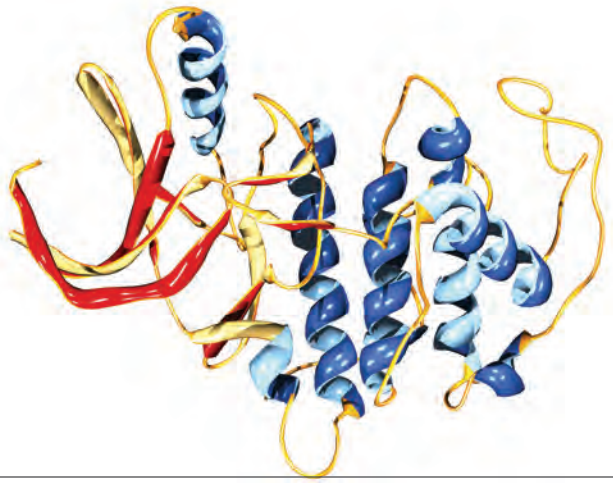


Carbohydrates

4

CHAPTER OUTLINE

Carbohydrates are most commonly encountered as the sweetener sucrose and as starch, the nutrient of bread and pasta. The carbohydrates are literally *hydrates of carbon,* having the empirical formula CH_2O. Because they posses both hydroxyl and carbonyl groups, they are a step up in complexity from lipids. Unlike lipids, carbohydrates are generally very soluble in water. The direct translation of sugar into Latin is *saccharide,* which remains in common use in the term *polysaccharides*.

Sugars are key nutrients in both animals and plants. Animals use sugars for rapid (i.e., minute-to-minute) energy production and lipids for long-term storage. Plants use sugars for energy exclusively, except at the seed stage. Because sugars are more dense than lipids (having more oxygen atoms), and often associate with water, their greater weight impairs mobility. Hence, lipids are the long-term energy source used for mobile lifestyles (i.e., animals and plant seeds), and carbohydrates are the immediate energy source for animals.

Aside from providing energy, sugars have a wide variety of roles once they are chemically modified, such as cell–cell recognition and signaling. Sugars attached to lipids comprise specific blood groups, and sugars are covalently linked to proteins secreted from cells. The basis for understanding sugars rests on the study of the simplest ones: the monosaccharides.

4.1 Monosaccharides

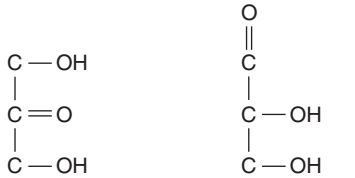
Monosaccharides have a single carbonyl group, which occurs at the first or second carbon atom. All remaining carbons have an attached hydroxyl group. There are two classes of monosaccharides, called aldoses and ketoses. **Aldoses** (aldehydes) have the carbonyl at carbon one, whereas **ketoses** (ketones) have the carbonyl at carbon two.

The "ose" suffix (as in ald*ose* and ket*ose*) is commonly used to define a compound as a sugar. The general category name for sugars is shown in **Table 4.1**, starting with the smallest, **triose**. Exceptions to this naming rule are found in the simplest monosaccharides: dihydroxyacetone and glyceraldehyde (**FIGURE 4.1**).

Dihydroxyacetone is a symmetrical molecule, because a plane of symmetry can be drawn through its central carbon atom. Glyceraldehyde, however, has an asymmetric central carbon, called **chiral** (Latin for *handedness*). Any carbon to which four distinct groups are attached is a chiral center. As drawn in two dimensions, two different forms of glyceraldehyde can be represented in a **Fischer projection**, shown in **FIGURE 4.2**. The molecule on the left is called L, whereas the one on the right is called D, an arbitrary but agreed-upon convention. The letters themselves stand for Levo and Dexter, from the Latin for "left" and "right." In three dimensions, the four groups attached to the chiral carbon are spatially as far apart from one another as possible, because the bonding electrons repel each other. Each group attached to the chiral carbon is at the corner of a virtual

TABLE 4.1 General Nomenclature of Sugars

Carbons	Sugar Category Name
3	Triose
4	Tetrose
5	Pentose
6	Hexose
7	Heptose
8	Octose



Dihydroxyacetone Glyceraldehyde

FIGURE 4.1 Triose Sugars.

tetrahedron, as shown in **FIGURE 4.3**. Note that carbon number 1 is assigned, by chemical convention, to the most oxidized carbon in the molecule. In the case of a ketose, the carbonyl becomes carbon number 2.

The two forms of glyceraldehyde are called L-glyceraldehyde and D-glyceraldehyde. They are mirror reflections or **enantiomers** (indicated in Figure 4.2) of each other. As a result, the two are not superimposable on each other, just as your left and right hands are not superimposable on each other.

Enantiomers share many chemical properties, such as identical melting and boiling points. They were first identified through their distinct interaction with polarized light. Polarized light is produced by special filters that eliminate all light rays other than those oriented in one plane. Experimentally, the interaction of a compound with polarized light is measured as degrees of rotation from a reference point, and a separate naming system is used (**BOX 4.1**). From a biochemical perspective, the greatest significance of enantiomers is their selective interaction with enzymes. For example, most living systems can metabolize D-sugars, but not L-sugars.

Larger sugar molecules (e.g., those with four or more carbon atoms) have multiple chiral carbons. **FIGURE 4.4** shows the Fischer projection of a four-carbon sugar (a tetrose). It is an aldose because it has an aldehyde group at the first carbon. The next two carbons are both chiral, as indicated with asterisks. The convention for naming such a sugar unambiguously is to first differentiate D-sugars from L-sugars. The carbon furthest from the carbonyl determines if the entire molecule is D or L. In this example, it is carbon 3. By comparing this molecule to glyceraldehyde, as indicated, the molecule is a D-sugar. All that remains is to resolve the ambiguity of the remaining chiral center. This is done by simply assigning a name to the molecule: this one is called erythrose. Our focus will be on D-sugars because they are far more common than L-sugars. The other four-carbon D-sugars are D-threose and D-erythrulose, shown in **FIGURE 4.5**. Unless we are making an explicit stereochemical point, we will usually omit the D indicator.

Sugars that differ at chiral centers other than the D and L positions are called epimers. Thus, threose (Figure 4.5) is the epimer of erythrose (Figure 4.4). Larger sugars have correspondingly greater numbers of isomers, but the naming conventions hold. After assigning the D and L forms, each molecular arrangement of the remaining chiral centers has a unique name. Examples of commonly occurring D-sugars are shown in **FIGURE 4.6**: ribose, glucose, galactose, and fructose.

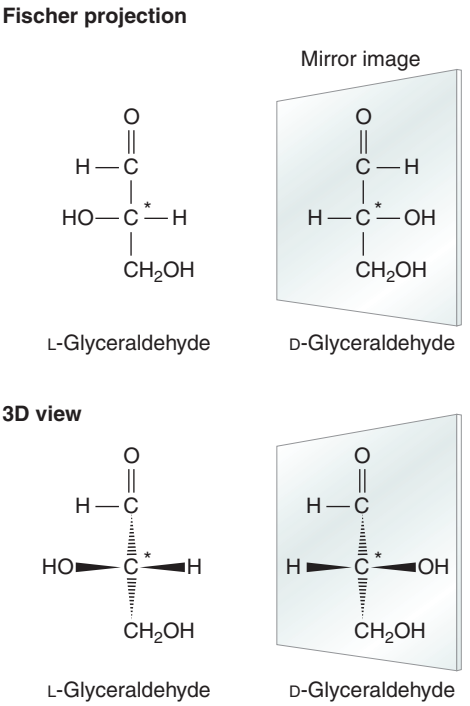


FIGURE 4.2 D- and L-Glyceraldehyde. For each form, the Fischer projection is shown above a representation of the three-dimensional view. Chiral carbons are indicated by asterisks.

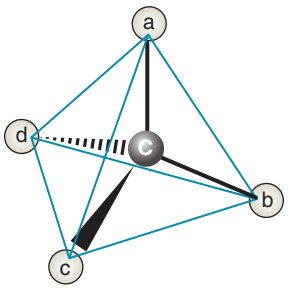


FIGURE 4.3 Tetrahedral Carbon. The carbon with four substituents, each as far apart from one another as possible, forms a tetrahedron in space.

4.2 Ring Formation in Sugars

Sugars having five or more carbons exist in solution primarily in a ring form. The reaction that leads to ring formation in sugars is an *intramolecular* version of the more general one that forms **hemiacetals**

BOX 4.1: Stereochemical Conventions: Little d/l

In addition to the D/L naming convention, a separate system uses the lower case letters *d* and *l* (alternatively, + and –) to refer to the direction of rotation of plane-polarized light: *d* or + for clockwise and *l* or – for counterclockwise. To better understand the use of the *d*/*l* system, consider the following practical experiment. Suppose you take a pair of polarized sunglasses, pop out the lenses, and place them at either end of a tube filled with water (**FIGURE B4.1**). This device you have just made is a **polarimeter**. If you look through the tube, rotating one sunglass lens will entirely eliminate the light that gets through at a particular point. If you continue to rotate it, light will appear again until, with continued rotation, it darkens once again. Mark the darkest point. This is where the polarized planes in the lenses are at right angles to one another. This follows from the operation of a Polaroid filter, which allows light beams to travel only in one direction. If you now replace the water in the tube with a solution of an optically active (chiral) molecule, and start with the marked point, one lens will have to be rotated to some extent to restore the dark point. That displacement is measured in degrees, right or left (i.e., *d* or *l*). This is caused by the interaction of light with the molecules, and reveals the presence of asymmetrical interactions in the solution.

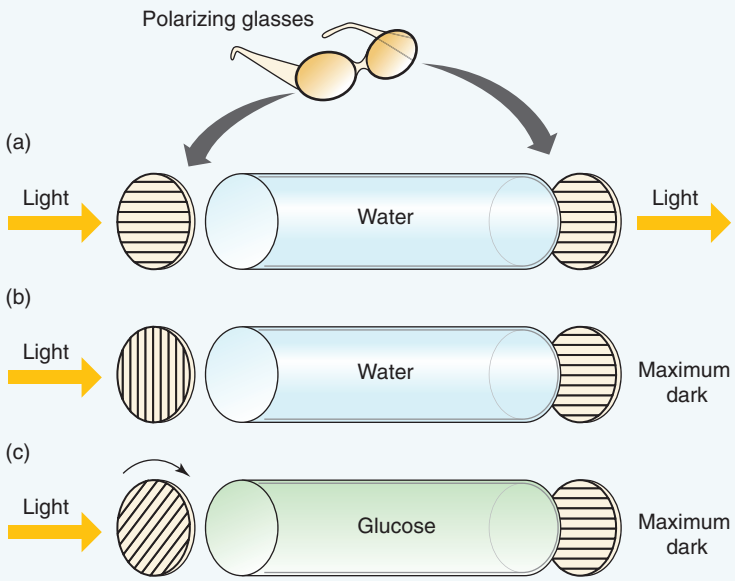


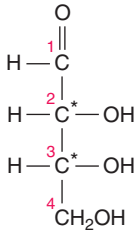
FIGURE B4.1 Polarimetry. A pair of polarizing sunglasses (or untinted polarizing glasses) can be used as polarized filters. Removing the lenses and placing each on opposite sides of a sealed tube filled with solution is the essence of a polarimeter. Its operation is shown in three situations. (a) The tube is filled with water. Both of the filters are oriented so that maximal light passes through. The polarization is indicated by lines on the filters, showing that they are in parallel. (b) Again, the tube is filled with water. The filters are oriented at 90° to one another, in which case no light passes through. (c) The tube is filled with a glucose solution. In this case, the point of maximum darkness is achieved by rotating one filter clockwise; this indicates that glucose is a *d*-sugar or, equivalently, a + sugar. Because this is independent of its D/L status, we would call this D-(+)-glucose. The same experiment performed with fructose would show that the filter would have to be rotated counterclockwise; hence, fructose is D-(–)-fructose.

or **hemiketals** (FIGURE 4.7). As described in the figure, the reaction joins a carbonyl group with a hydroxyl group (a nucleophilic substitution). Note that the carbonyl oxygen becomes a hydroxyl group in the product.

The carbonyl carbon of the straight chain form becomes the **anomeric carbon** in the ring form. Because both the carbonyl group and the alcohol group come from the same molecule, the hemiacetal or hemiketal reaction is more favorable than if the reactants were from different molecules. The other consequence of this intramolecular reaction is that the product becomes a ring. Of the different OH groups that *could* join with the carbonyl, only five- and six-membered rings are stable. Open and ring forms for the sugars fructose and glucose are shown in FIGURE 4.8.

The representation of ring forms as joined, straight-chain diagrams in Figure 4.8 is unrealistic. Most commonly, sugar rings are drawn as **Haworth projections**, as shown in the middle structure of FIGURE 4.9. When constructing this diagram, you need only place the groups appearing on the right side of the straight-chain Fischer projection below the ring in the Haworth projection to achieve the correct orientation. Note that the Haworth is a simplified representation of the more realistic chair form, also shown in Figure 4.9.

We now turn our attention to the hydroxyl group that is connected to the anomeric carbon, colored blue in these diagrams. Because the anomeric carbon has become a new chiral center in the ring form, this hydroxyl group can have two distinct stereochemical forms (FIGURE 4.10). If the hydroxyl group is on the opposite side of the ring from the position determining the D-form of the sugar, it is called the **alpha** form. If the hydroxyl group is on the same side of the ring as the position determining the D-form of the sugar, it is called the **beta** form. As drawn in the Haworth projection shown, the alpha-hydroxyl group is below the ring, and the beta-hydroxyl group is above the ring. The alpha and beta forms are in equilibrium with each other as well as with the open-chain form, so that, metabolically, any of them can be utilized in reactions. Figure 4.10 provides the full name of the sugar, with both the designation D (to identify its stereochemical similarity to D-glyceraldehyde) as well as the α and β forms resulting from ring formation.



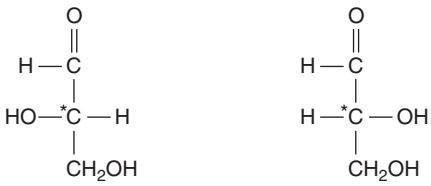


FIGURE 4.4 D-Erythrose. The configuration at carbon 2 defines this structure as erythrose; the configuration at carbon 3, the one furthest from the carbonyl, defines this as the D form. The reference compounds, L- and D-glyceraldehyde, are shown for comparison. Chiral carbons are indicated by asterisks.

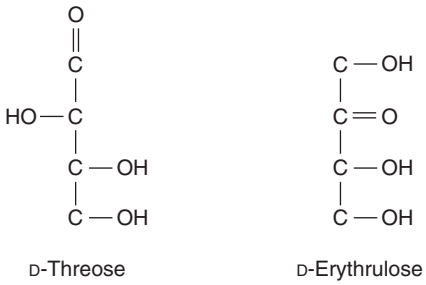


FIGURE 4.5 D-Threose and D-Erythrose.

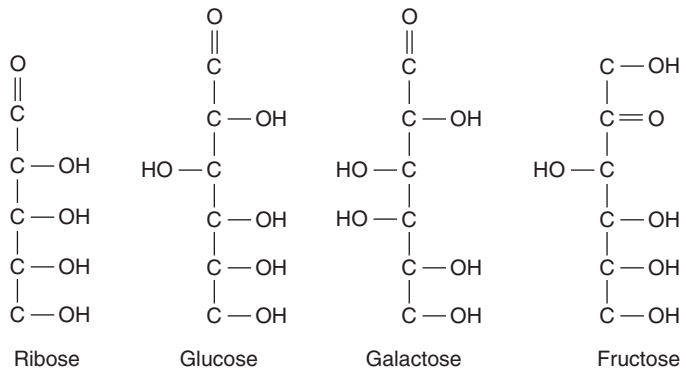


FIGURE 4.6 Common Monosaccharides. Only the D forms of these common sugars are shown, because they are the prevailing biological isomers.

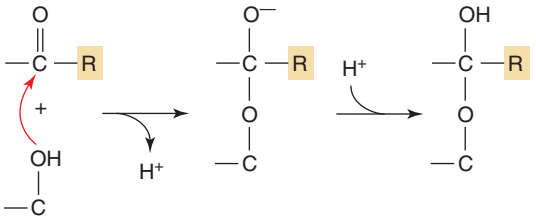


FIGURE 4.7 Hemiacetal and Hemiketal Formation. The reaction of an alcohol group with a carbonyl is one of simple nucleophilic substitution.

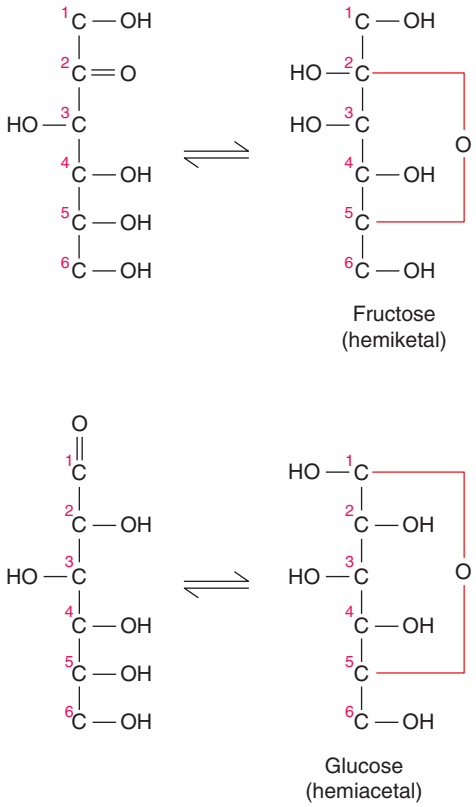


FIGURE 4.8 Ring Formation in Sugars. The reaction shown in Figure 4.7 takes place intramolecularly in sugars having at least five carbons. Because the aldehyde and alcohol are part of the same molecule, the product is a ring.

To summarize, we have discussed three types of stereochemistry that allow us to unambiguously identify a sugar:

1. D or L, which refers to the configuration of the chiral carbon furthest from the carbonyl group
2. Different names for other epimers (e.g., mannose or galactose)
3. Alpha or beta, which refers to the configuration of the anomeric carbon

The ring forms of ribose and fructose, shown as **FIGURE 4.11**, are also in equilibrium with their open-chain forms. The fact that common sugars like these form rings is important not merely because this is the predominant solution form, but also because the hydroxyl group attached to the anomeric carbon is used in bonding sugars together. The first example of this kind of linkage is in the disaccharides.

4.3 Disaccharides

Two sugars bonded together are called **disaccharides**; some examples are shown in **FIGURE 4.12**. Of these, the best known is sucrose; it is what we popularly call "sugar" itself. Sucrose is widely found in plants but is heavily concentrated in just a few, such as sugar cane and sugar beets. Maltose is a product of the partial digestion of starch and is common in the production of beer. The partial digest itself is called a "malt," hence the name "malt liquor." Lactose is milk sugar, which is produced by mammals for feeding their newborn. Trehalose is uncommon in plants but found in bacteria, fungi, and invertebrates and plays a role analogous to sucrose in those organisms.

In each of these disaccharides, one of the sugar units is glucose; the other is glucose, galactose, or fructose. The linkage between the two sugars is called a **glycosidic bond**. The glycosidic bond of maltose,

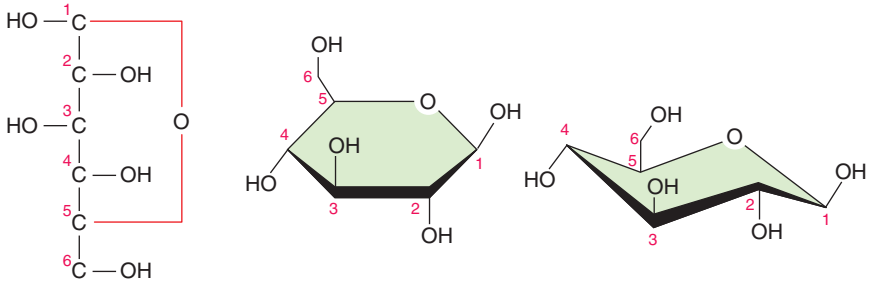


FIGURE 4.9 Views of Sugar Rings. The straight-chain form (Fischer projection) can be recast as the Hayworth projection by taking groups positioned to the right in the Fischer projection above the ring, and those to the left below it. The chair form is a solution structure that more closely represents the three-dimensional structure of the sugar molecule.

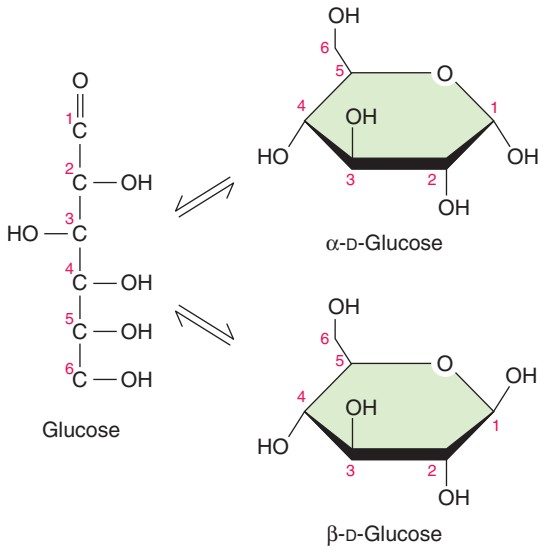


FIGURE 4.10 Multiple Ring Forms of Glucose. Two separate ring forms of glucose are possible, depending on which face of the carbonyl is attacked by the hydroxyl group attached to carbon 5.

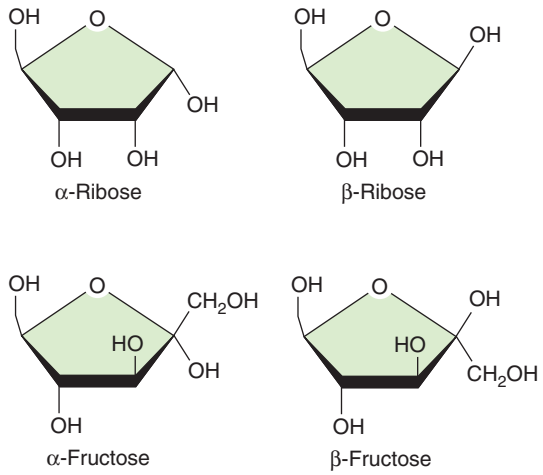


FIGURE 4.11 Ring Forms of Ribose and Fructose.

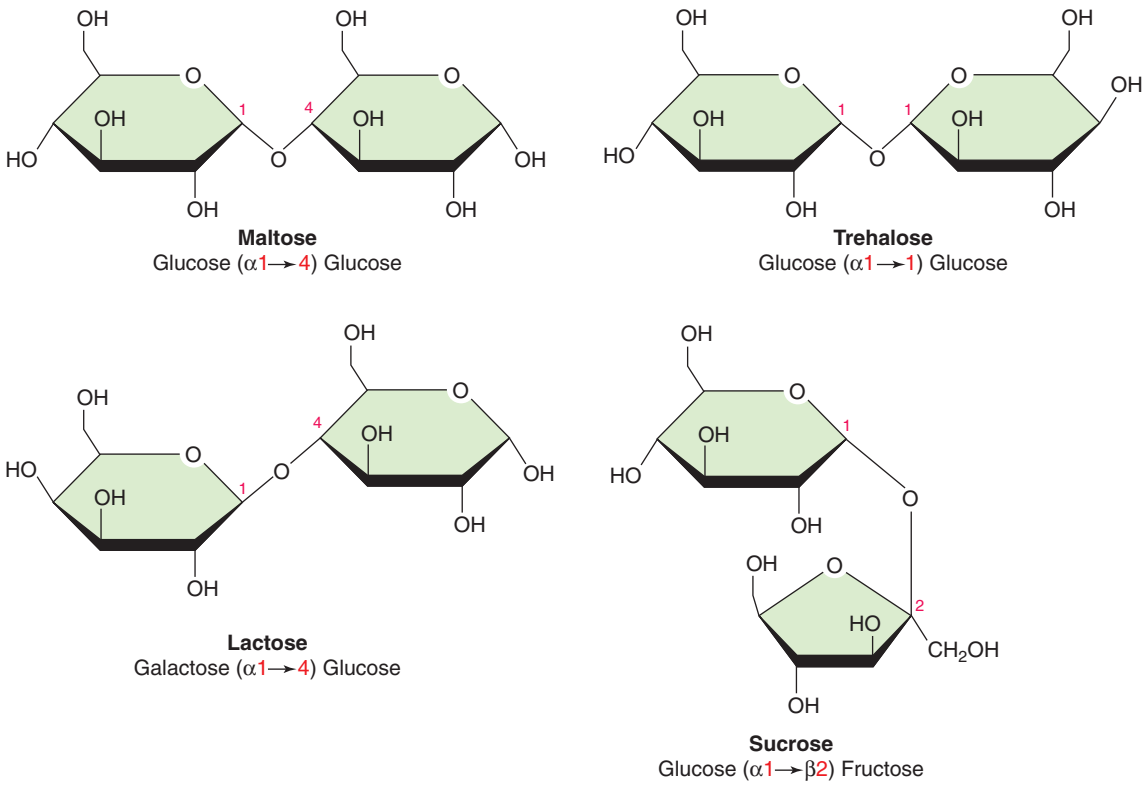


FIGURE 4.12 Disaccharides. The two sugars in the disaccharide are linked by a glycosidic bond. This locks the anomeric hydroxyl in either the alpha or the beta configuration. Either one (maltose and lactose) or both (sucrose and trehalose) sugar units have their anomeric carbons in a glycosidic bond.

for example, is *formally* a removal of water from two glucose molecules, as indicated in **FIGURE 4.13**. The metabolic route to glycoside formation involves energy input and intermediate steps.

Once a disaccharide has formed, the stereochemistry of the anomeric carbon involved in the glycosidic bond is fixed: it is either α or β, as indicated in Figure 4.12. The notation for the glycosidic bond between the sugars provides the number of the anomeric carbon (with its α or β oxygen position indicated) separated by an arrow from the number of the connected carbon on the other sugar. Only one of the anomeric carbons is involved in the glycosidic bonds of maltose and lactose, whereas both anomeric carbons are involved in the glycosidic bonds in sucrose and trehalose.

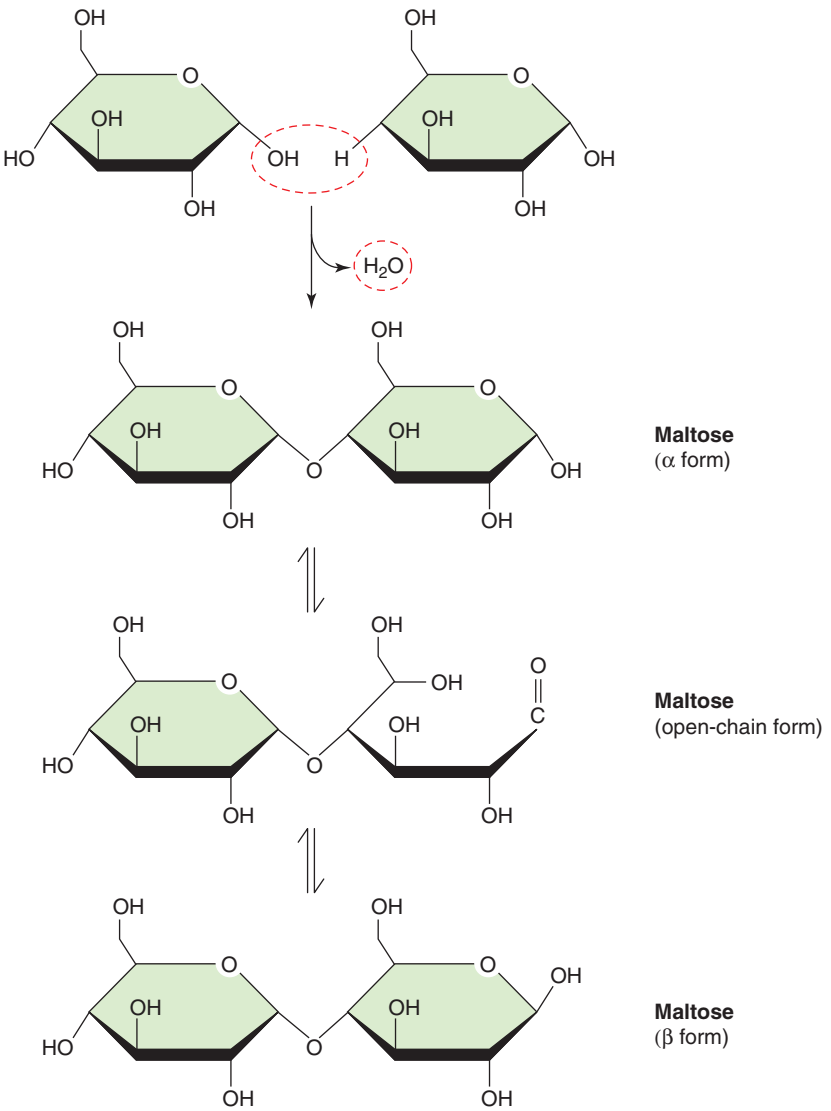


FIGURE 4.13 Maltose as a Reducing Sugar. Maltose consists of a glucose bearing an alpha anomeric carbon locked to a second glucose molecule. The second glucose molecule is in equilibrium with an open-chain form the alpha form, and the beta form. The presence of the carbonyl makes the entire maltose molecule a reducing sugar.

When just one anomeric carbon is involved in glycoside formation, as in the maltose and lactose, a free anomeric carbon remains in equilibrium with an open-chain form (see Figure 4.13 for maltose). Because at least a small amount of this open-chain form exists in solution, its carbonyl group can reduce certain metal ions in diagnostic tests. Any saccharide that has at least one free anomeric carbon (i.e., an anomeric carbon *not* involved in a glycosidic bond) is therefore called a **reducing sugar**. Maltose and lactose are reducing sugars. By contrast, sucrose and trehalose are **nonreducing sugars** because they have no free anomeric carbon atoms. To better understand the chemical meaning of the word *reducing*, see **BOX 4.2**.

4.4 Polysaccharides

When more than two sugars are linked via glycosidic bonds, they are said to be either **oligosaccharides** (meaning "a few") or **polysaccharides** (meaning "many"). The distinction is inexact; some consider chains of up to a dozen or so linked sugars to be oligosaccharides. Commonly, polysaccharides have thousands of monosaccharide residues bound together. Such molecules have extremely large molecular weights, which leads to properties distinct from smaller molecules. In general, large molecules that are constructed from small, repeating units are called **polymers**. The polysaccharides are our first example of biological polymers; the other two major classes are proteins and nucleic acids. While lipids can form large aggregates with new properties, they are not biological polymers, because they consist of noncovalently associated small molecules. Nonbiological polymers, such as nylon, were discovered and studied at the same time as biological polymers. Nonbiological and biological polymers share some properties, including the methods used for their analysis.

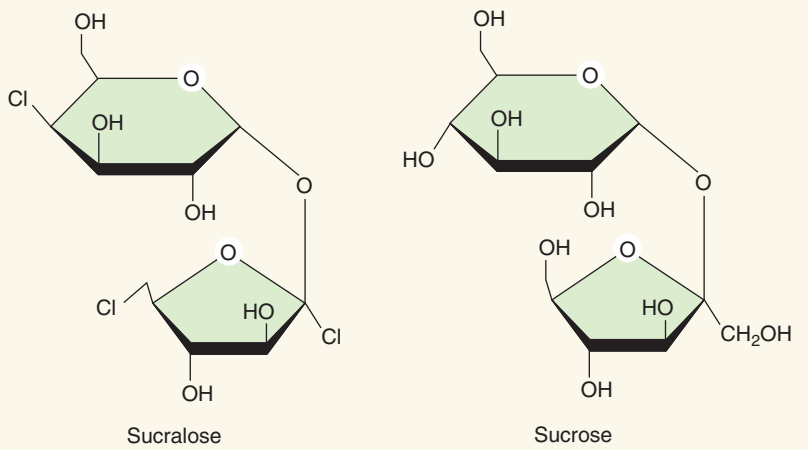


FIGURE B4.2 Sucralose and Sucrose.

BOX 4.2: WORD ORIGINS

Reducing

When a word with rich meanings such as *reducing* is applied to sugar chemistry, its interpretation may be obscured. There are distinct sociological, mathematical, biological, and chemical definitions for this word. In the everyday sense, the word originally meant to bring back, or to restore, an original condition. A later use was related to conquest, and subsequently, a general sociological meaning of *lowering*.

Mathematically, the term refers to the factor-label method of manipulating units algebraically in a separate way from the numbers they label. In biology, meiosis involves a reductive division, in which the number of chromosomes is halved. In chemistry, reduction is the decrease in oxidation number for an atom. A compound is reduced if it gains electrons, so the term *reduction* is somewhat misleading as a description of the chemical process. Reducing sugars transfer electrons from the carbonyl group to copper or silver ions. In most cases, a further electron transfer is present to produce a color reaction, confirming the result visually.

None of these definitions describes the dieter's dream molecule: a truly reducing sugar. Still, there is a long history of artificial sweeteners. Sucralose, for example, is a modern artificial sweetener made by chlorinating sucrose (**FIGURE B4.2**). As a result, sucralose can attach itself to the taste receptors (the sweet receptors in cells of the tongue), but is metabolically inert. Thus, sucralose provides the sweetness of sucrose, but none of the calories.

Sucrose itself is the standard of sweeteners for both artificial and natural sugars. The measurement scale is less objective than others, because it requires human tasters. This is especially troublesome for the discovery of new sweeteners that, unlike sucralose, may bear no structural similarity at all to sugars, making it impossible to predict in advance whether a compound is a potential candidate. Typically, a sweetener is discovered by accident; someone working with a chemical product has actually tasted it (and survived!).

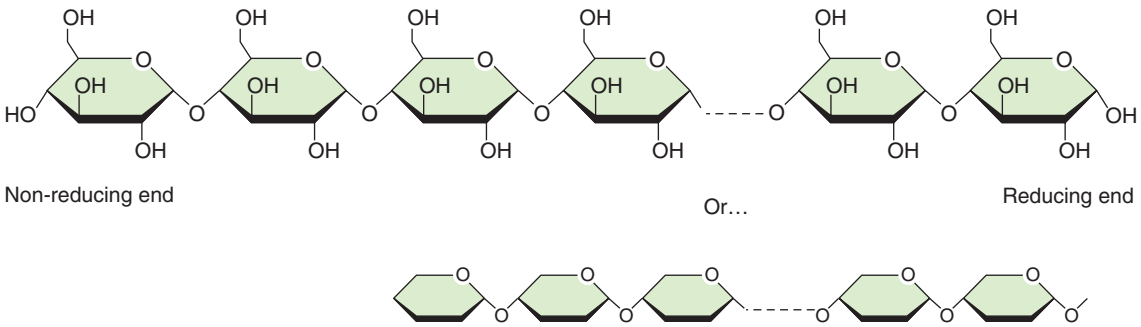


FIGURE 4.14 Amylose Has Distinct Ends. The straight-chain glucose polymer amylose has α1→4 bonds. At the left-end residue, the anomeric carbon is engaged in a glycosidic bond, and thus is nonreducing. At the right end residue, the anomeric carbon is free and, thus is reducing. All polysaccharides have these distinctive ends.

Linear Polysaccharides

Amylose is a biological polysaccharide composed of glucose molecules linked via α1→4 glycosidic bonds (**FIGURE 4.14**). Like all linear polymers, the amylose chains have distinctive ends, called the **reducing end** and the **nonreducing end**. This property of dissimilar ends also applies to disaccharides. Maltose also has a reducing end and a nonreducing end, albeit a chain of just two monosaccharide units. All unbranched polysaccharides have exactly one reducing end and one nonreducing end. In solution, amylose forms hydrogen bonds between water molecules and the free hydroxyl groups at positions 2, 3, and 6. This makes it an extended polymer with considerable flexibility.

Cellulose, another linear polymer of glucose, has β1→4 linkages, and assumes the very regular three-dimensional solution structure shown in **FIGURE 4.15**. The specific arrangement results from the

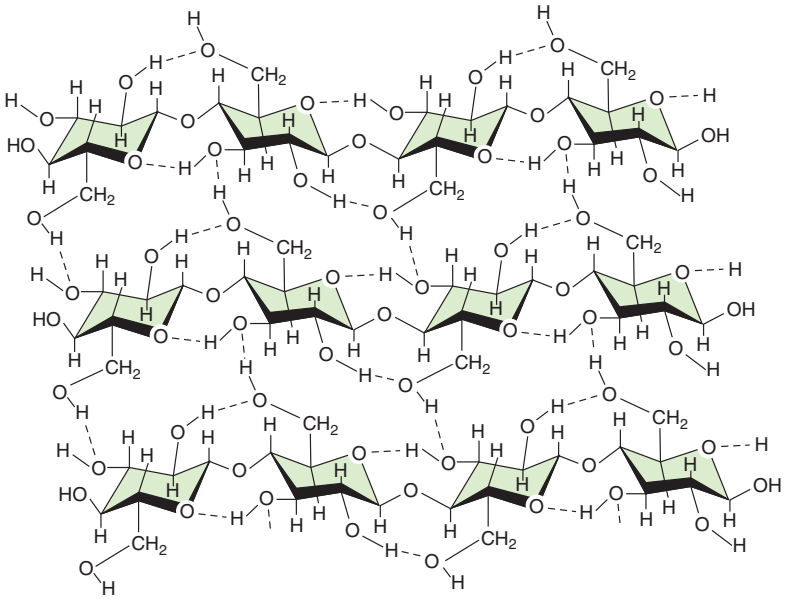


FIGURE 4.15 Cellulose. Cellulose does not interact with water because all of its hydroxyl groups are engaged in intracellular hydrogen bonding. As a result, cellulose is completely insoluble in water.

glycosidic bond being placed above the plane of the glucosyl residue. All of the hydroxyl groups in the chain interior are engaged in hydrogen bonds *with each other*. The resulting intramolecular hydrogen bonding gives the molecule enormous internal strength, but it also renders cellulose unable to bind to water. Cellulose, therefore, is entirely *insoluble* in water, despite the existence of multiple hydroxyl groups (**BOX 4.3**). Cellulose is the most abundant molecule in the world, principally found in plant cell walls; it is the major component of wood.

An important reason for using polysaccharides as energy storage molecules in animals has to do with osmosis. Osmolarity depends only on the number, rather than the size (or other qualities) of molecules. Thus, having multiple glucose molecules covalently linked greatly reduces the osmolarity within the cell compared to individual molecules, thereby minimizing osmotic pressure while maintaining a virtual glucose reservoir within the cell. This is critically important for animal cells, which must maintain the same osmolarity on either side of the plasma membrane. By contrast, plants simply have a cell wall—for which cellulose is a key structural component—allowing plant cells to maintain very high internal osmotic pressures without bursting.

Branched Polysaccharides

Amylopectin is a branched polysaccharide that occurs in plants. In addition to α1→4 linkages, amylopectin also has α1→6 linkages commonly called **branch points**. **FIGURE 4.16** shows how a single α1→6 glycosidic bond creates a branch in the overall structure. Branched polysaccharides have a more compact three-dimensional structure than linear chains.

BOX 4.3: Irony of Intramolecular Hydrogen Bonds

Hydrogen bonding is a key feature that makes certain compounds soluble in water. However, when the groups responsible for hydrogen bonding are linked to a group other than water, they lose their solubility. This commonly occurs when hydrogen bonding exists within the same molecule; that is, the hydrogen bonding is intramolecular. Cellulose, a polymer of glucose found in plants, is a perfect example of a compound that is insoluble in water due to intramolecular hydrogen bonds. These kinds of interactions exist in all biological polymers, however, including nucleic acids and proteins.

A practical application of this property is the development of synthetic molecules called **methylcelluloses**. These are formed in the laboratory by creating methyl esters with some of the hydroxyl groups of cellulose. Partial methylation prevents the remaining free hydroxyl groups from forming internal hydrogen bonds, creating new polymers whose partial solubility in water can be controlled. These polymers can be used as solvents for lipid-soluble drugs. The glucose molecules in cellulose are connected by beta linkages, for which humans have no enzymes to break down, so methylcellulose is biologically inert.

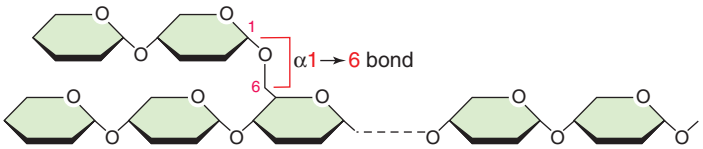


FIGURE 4.16 A Polysaccharide Branch Point. The α1→6 bond, found in glycogen and amylopectin, creates a branch point in the polysaccharide structure. With one branch point, there are now *two* nonreducing ends and still one reducing end.

Starch is a mixture of amylose and amylopectin that occurs in plants. Different plants have various proportions of the two polysaccharides, with different polymer lengths and different degrees of branching accounting for the distinctive qualities of corn starch, potato starch, and wheat starch (flour).

A purely branched polysaccharide is **glycogen**, the major form of carbohydrate storage in animal cells. Molecules of glycogen are more branched than amylopectin and are much larger, having hundreds of thousands of glucose residues. While glycogen exists in a variety of animal cells, it is found in large amounts in just two: liver and muscle. Liver stores glycogen in the fed state and releases glucose units from it to the blood during times of fasting. By contrast, muscle takes up blood glucose and uses the glucose residues of glycogen for its own metabolism during active contraction. Thus, the liver's role in glucose balance is *altruistic*, providing for the entire body, whereas the muscle's role is *selfish*, being used only for muscle metabolism. Most of the glycogen molecules in the human body are found in muscle, which has about 1% of its weight as glycogen. Liver can have up to 10% of its weight as glycogen (during the fed state), but represents less of the total body glycogen due to its relatively small total mass.

4.5 Carbohydrate Derivatives

A large number of molecules have many of the qualities of carbohydrates, because they are metabolically derived from them. We will consider two categories of such derivatives: simple modifications and substituted carbohydrates. The simple modifications consist of only slightly modified monosaccharides and polysaccharides. In the more heavily substituted carbohydrates, the sugar portion is no longer the dominant chemical property.

Simple Modifications

The modification of hydroxyl groups by a phosphate ester occurs in many of the metabolic intermediates we will encounter in later chapters. For example, glucose-6-P (the phosphate group is abbreviated as P) is glucose with a single phosphate ester and fructose-1,6-*bis*-P_2 has

two phosphate esters (FIGURE 4.17). Another simple modification is to change the oxidation state of one of the carbons. Reduction of the carbonyl carbon results in a sugar alcohol, or polyalcohol, such as glycerol (FIGURE 4.18). Glycerol is a product of fat breakdown and a major additive in prepared foods and drugs. Conversely, oxidation of the carbonyl group produces a **sugar acid**, such as glyceric acid. Oxidation can also occur at other carbons, leaving the carbonyl group intact, as in glucuronic acid. Glucuronic acid is compared to the carbonyl-oxidized gluconic acid in FIGURE 4.19. Note that gluconic acid cannot exist in a ring form.

Replacing an oxygen atom with a nitrogen atom forms another derivative, exemplified by glucosamine (FIGURE 4.20), which is found as a subunit of secreted proteins and in connective tissue. Derivatives in which one of the hydroxyl groups is replaced with a hydrogen atom, as in deoxyribose (Figure 4.20) are called deoxy sugars.

Polysaccharides can also be modified to produce derivatives with altered properties. For example, the molecule **agarose** (found in certain seaweeds) has a repeating D-galactosyl unit linked with a β1→4 glycosidic bond to an L-galactosyl residue that is modified by having an additional internal bridge oxygen between carbons 3 and 6 and a sulfate group esterified to carbon 2 (FIGURE 4.21). Agarose is a linear molecule of this repeating unit, although not all of its L-galactosyl groups are sulfated. A similar polysaccharide is **agaropectin**, which has branch points. Together, the mixture of agarose and agaropectin is known as **agar**.

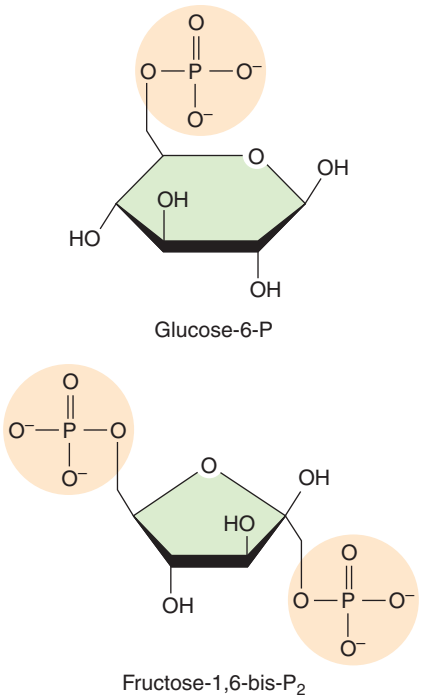


FIGURE 4.17 Phosphorylated Sugars.

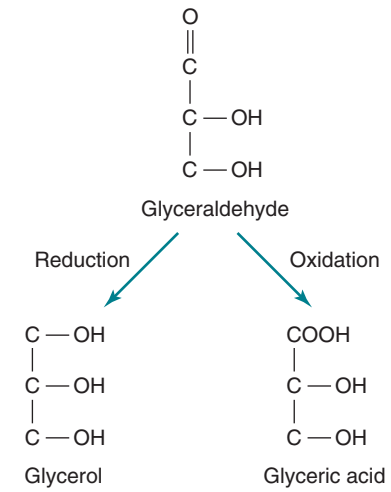


FIGURE 4.18 Redox Derivatives of Sugar.

Substituted Carbohydrates

Nucleotides, lipopolysaccharides, and proteoglycans all contain sugar molecules, but they are so heavily modified by other groups that their chemical features greatly diverge from less substituted sugars.

Nucleotides are modified sugar molecules that contain a nitrogenous base and at least one phosphate ester. The bases are either pyrimidines or purines, as shown in FIGURE 4.22. Nucleosides have bases joined to either a ribose or a deoxyribose sugar in an N-glycosidic link, as shown in FIGURE 4.23. Note that the nitrogen attached to the sugar is the 1-position of the pyrimidines but the 9-position of the purines. The sugar portion is further substituted in nucleotides: a phosphate is esterified to one of the available hydroxyl groups. These can be monophosphates or chains of phosphates. FIGURE 4.24 shows the three common nucleotides known as AMP, ADP, and ATP.

Nucleotides are key energy transfer molecules that are widely used in metabolic reactions in cells. Additionally, nucleotides are joined together to form the polymers DNA and RNA, where the sugar component of DNA is deoxyribose and the sugar component of RNA is ribose. DNA exists as two strands noncovalently linked by hydrogen bonds between the bases (FIGURE 4.25). The sugar component of DNA (i.e., deoxyribose) has no remaining free hydroxyl groups. The 2′ position is substituted by a hydrogen atom and all others are involved

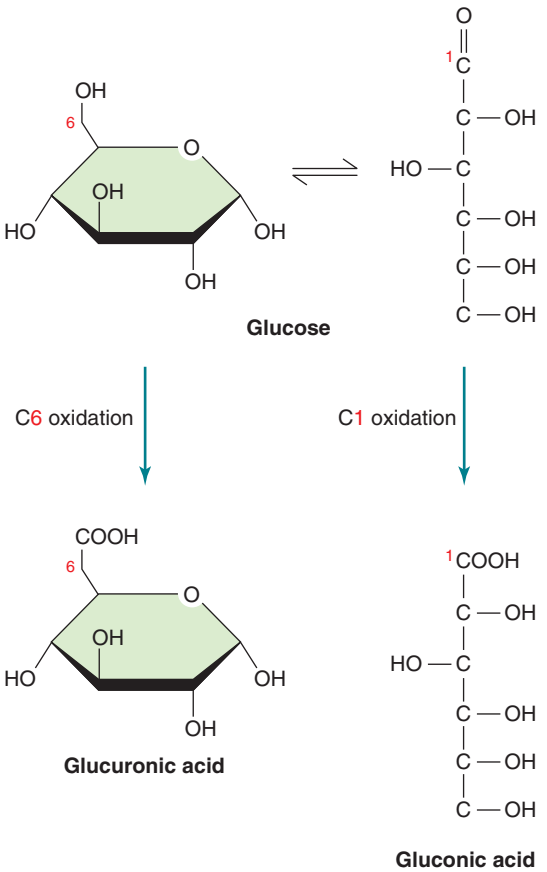


FIGURE 4.19 Different Oxidized Glucose Molecules. Oxidizing glucose at the anomeric carbon forms gluconic acid, which can no longer form a ring or become polymerized. If any other carbon in glucose is oxidized, yielding a compound such as glucuronic acid, it can still form a glycosidic bond and thus be part of a polysaccharide.

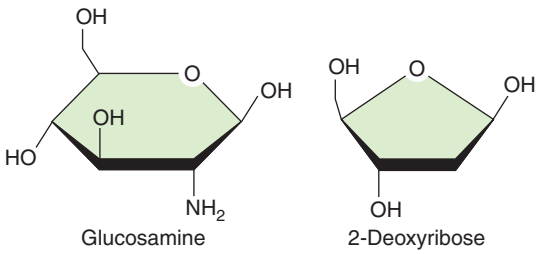


FIGURE 4.20 Sugar Derivatives Replacing Hydroxyl Groups.

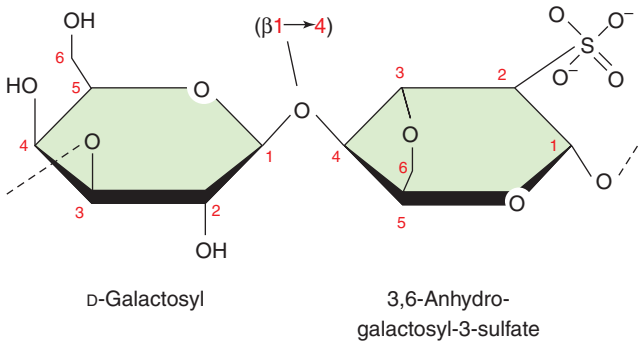


FIGURE 4.21 Agarose. The repeating unit of the polysaccharide agarose, a linear modified polysaccharide. The two residues shown are a galactosyl unit and a modified galactose in a β1→4 linkage.

in the linkages that bind the nucleotides together. RNA, unlike DNA, is usually a single-stranded polymer (**FIGURE 4.26**).

DNA provides a template for two cellular processes. First, the molecule can duplicate itself in preparation for cell division, an activity known as **replication**. Second, small regions of DNA can serve as a template for messenger RNA (mRNA) formation, an activity known as **transcription**. In turn, mRNA provides a template for protein synthesis (**translation**). These processes are critical to the formation of new cells or of new expression for cells.

Sugars form conjugates with other biological molecules. For example, some phospholipids are sugar-lipid derivatives such as phosphatidylglycerol and phosphatidylinositol (**FIGURE 4.27**). Sugar–protein conjugates (called *glycoproteins*) are usually divided into two classes: O-linked and N-linked (**FIGURE 4.28**a and b). In the O-linked example, a glycosidic bond is formed between the sugar (the modified sugar N-acetylgalactosamine is shown) and a hydroxyl group from a

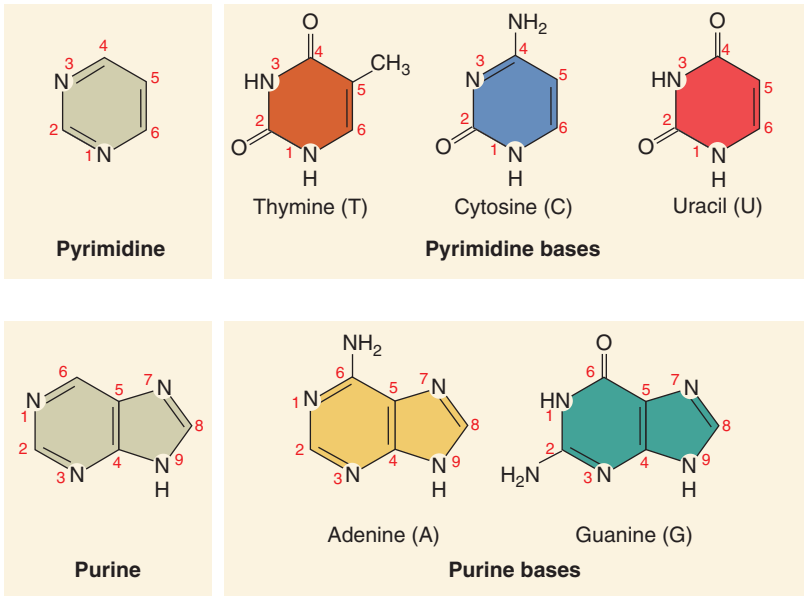


FIGURE 4.22 Purines and Pyrimidines.

protein, here contributed from the side group of an amino acid called serine. The N-linked example in Figure 4.28b shows an N-glycosidic bond, similar to those found in nucleotides. Here, the nitrogen is contributed by the side group of an amino acid called asparagine. An additional protein–sugar conjugate arises when an amine from a lysine side chain in hemoglobin reacts with glucose, followed by rearrangement to the stable ketone shown (Figure 4.28c). This relatively slow reaction produces a form of hemoglobin abbreviated as HbA_{1C}. Measuring HbA_{1C} levels provides a measure of the average blood glucose over a period of weeks. HbA_{1C}, therefore, is of considerable importance in monitoring diabetics.

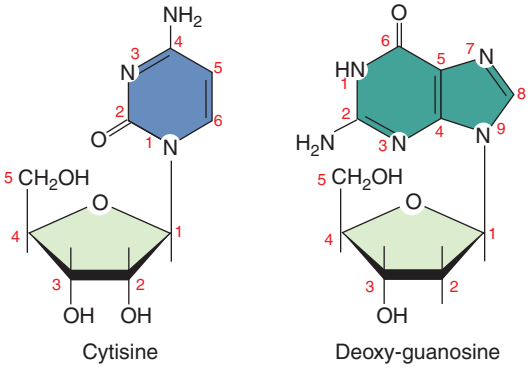


FIGURE 4.23 Nucleosides. A base from those shown in Figure 4.22 is attached to a ribose sugar or a deoxyribose sugar. A large number of other combinations are possible, with two exceptions: uracil is not found attached to deoxyribose, and thymine is not found attached to ribose.

Summary

Sugars have an empirical formula of CH_2O, with multiple hydroxyl groups and one carbonyl group in the simple sugars. The smallest monosaccharides are the trioses glyceraldehyde and dihydroxyacetone.

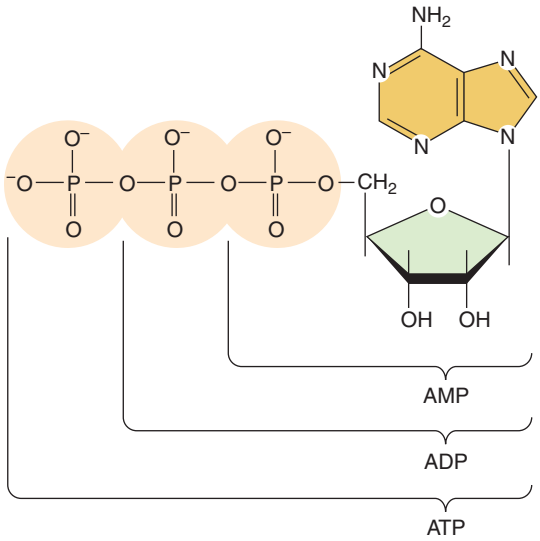


FIGURE 4.24 AMP, ADP, and ATP. A nucleotide is a phosphorylated nucleoside. The three examples shown here are the most common nucleotide forms of adenine, used in energy transfer reactions.

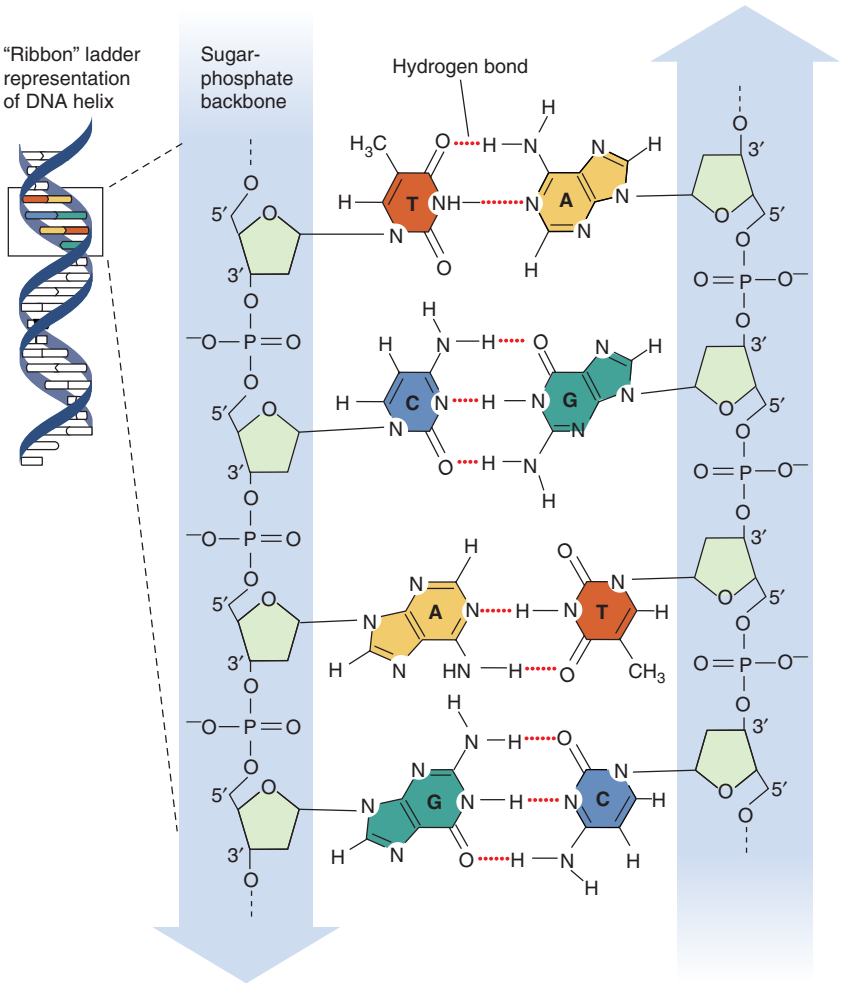


FIGURE 4.25 DNA. The two strands of the double-stranded DNA molecule are linked by hydrogen bonding. Within each strand, the sugars are covalently linked via phosphate diester bonds.

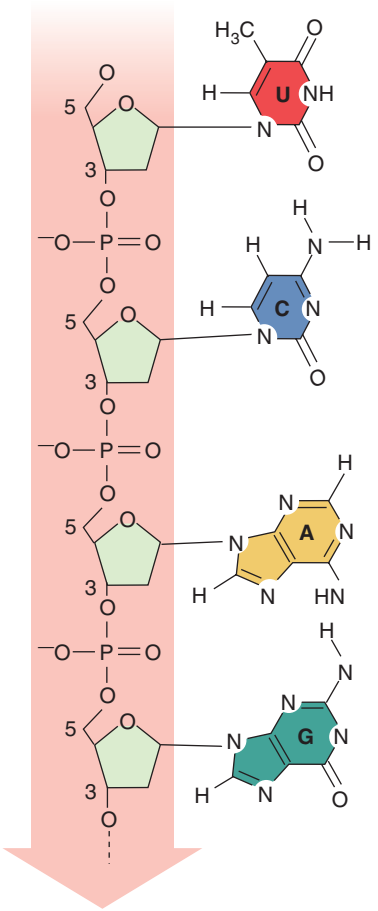


FIGURE 4.26 RNA. Like DNA, the sugar portion of RNA binds the chain together, using phosphate diester bonds as shown. The purine and pyrimidine bases also are attached to the sugars of RNA like those of DNA. Unlike DNA, the RNA molecule is typically a single chain.

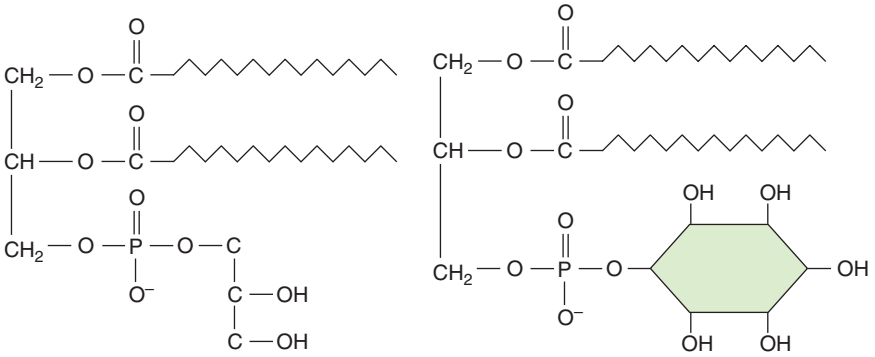


FIGURE 4.27 Phosphatidylglycerol and Phosphatidylinositol.

There are two stereochemical forms of glyceraldehyde because it has a chiral center. These are denoted D and L, but biological sugars are overwhelmingly in the D form. Sugars containing more carbon atoms have correspondingly larger numbers of stereoisomers, which are identified by assigning unique names. For example, one six-carbon sugar is glucose; another, differing in configuration at the 4-carbon, is galactose, equivalently expressed as the 4-epimer of glucose. All sugars having at least five carbon atoms form rings in a reaction between a carbonyl group and a hydroxyl group. The formation of rings produces a new chiral center, because a new hydroxyl group emerges from the

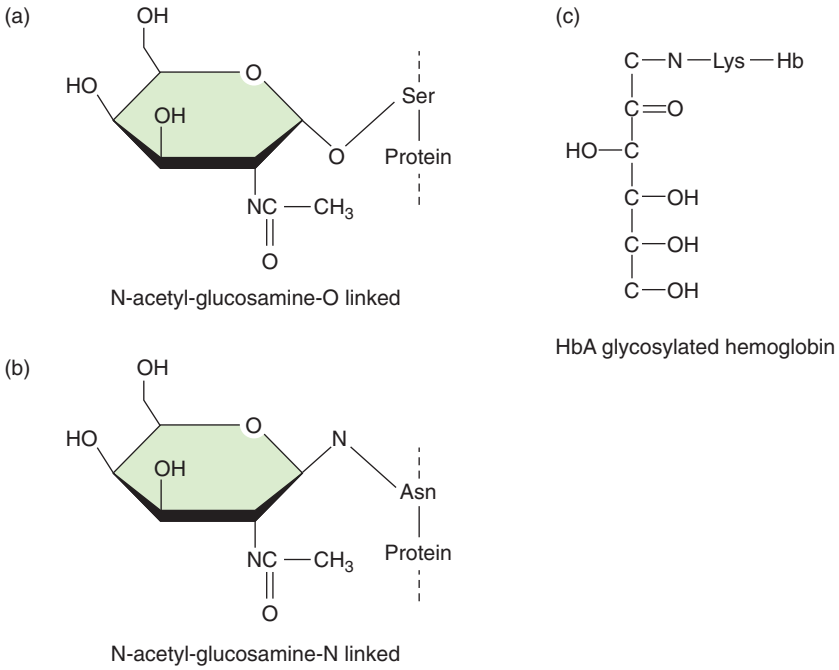


FIGURE 4.28 Sugar-Modified Proteins. The most common modifications are (a) O-linked and (b) N-linked polysaccharides; these are glycosidic and N-glycosidic bonds, respectively. (c) A nonenzymatic reaction of glucose with hemoglobin produces a specially modified glycosylated hemoglobin.

BOX 4.4: Medical Connections: Sugars and Digestion

Sugars are normally absorbed by the small intestine. If appreciable amounts are not removed by the time they reach the large intestine, they are metabolized there by the resident bacteria. The bacterial end products include gases which cause distension of the colon, bloating, and pain. Two of the most common causes of this bloating are **lactose intolerance** and **raffinose.** Lactose intolerance is a common genetic deficiency of lactase, an enzyme that breaks down the sugar lactose. Lactase is present in abundance in infants and less so in adults. Because lactose is only present in milk and milk products, and milk is a normal component of the diet only in infancy in all animals but humans, lactose intolerance is strictly a human problem.

A common intestinal disturbance is caused by the presence of raffinose, a sugar found in foods such as cabbage and beans. Raffinose is poorly digested due to the presence of the galactose-α1$\rightarrow$6-glucose bond in the first two sugar moieties of the trisaccharide. As a result, it is also metabolized in the large intestine, with attendant gas production. However, due to the far smaller amounts of raffinose in those foods, the clinical symptoms of raffinose digestion are less severe than those in lactose intolerance.

carbonyl group. The carbon at this locus is called the anomeric carbon and is always involved in joining sugar moieties together, either as disaccharides like sucrose and maltose, or in polysaccharides, such as glycogen and cellulose. The link between sugars is called a glycosidic bond, and it locks the position of the anomeric hydroxyl into two separate stereochemical forms (α and β). The three-dimensional structure that results from this distinctive orientation is the difference between glycogen, the water-soluble storage carbohydrate in animals, and cellulose, the water-insoluble storage carbohydrate that is abundant in plants. Any sugar that contains an anomeric carbon that is not connected via a glycosidic bond can equilibrate with the open-chain form. Because it can react with a test solution containing an ion that can be reduced to produce a color reaction, it is called a reducing sugar. This describes all monosaccharides and polysaccharides and some disaccharides such as maltose. Both of the anomeric carbons of the bound sugars forming sucrose are engaged in a glycosidic bond, making this disaccharide a nonreducing sugar. Polysaccharides have at least one end—more if there are branches—in which the anomeric carbon is engaged in a glycosidic bond. This is called a nonreducing end. A myriad of carbohydrate derivatives exist in biology, both of the simple monosaccharides (such as phosphorylated sugars and deoxy sugars) and the polysaccharides (such as the sulfated polymer agarose). More elaborate substitutions produce molecules where the properties of the sugar itself are lost, and the sugar merely becomes a connecting molecule, such as the role deoxyribose plays in the structure of DNA. Finally, sugars form conjugates with other biological molecules, as in lipopolysaccharides and proteoglycans.

Key Terms

agar
agaropectin
agarose
aldoses
alpha (form)
anomeric carbon
beta (form)
branch points
cellulose
chiral
disaccharides
enantiomers
epimers
galactose
glycogen
glycosidic bond
Fischer projection
Haworth projections
hemiacetals
hemiketals
ketoses
lactose intolerance
methylcelluloses
nonreducing end
nonreducing sugars
nucleotides
oligosaccharides
polymers
polysaccharides
polarimeter
raffinose
reducing end
reducing sugar
replication
sugar acid
transcription
translation
trehalose
triose

Review Questions

1. Raffinose is a sugar that, upon hydrolysis of its glycosidic bonds, yields galactose, glucose, and fructose. The galactose–glucose bond is an $\alpha 1 \rightarrow 6$ linkage, and the trisaccharide is a nonreducing sugar. Draw the structure of raffinose.
2. In the DNA structure, the sugar is completely modified. List each modification and identify an analogous, simpler substitution that exists in another sugar molecule. What sugar properties remain in the DNA molecule?
3. Glucose in solution has two ring forms and one open-chain form. How many structures exist in equilibrium for a polysaccharide of glucose that has multiple $\alpha 1 \rightarrow 4$ bonds and three $\alpha 1 \rightarrow 6$ bonds?
4. Reducing sugars are a mixture of alpha and beta forms. Why does one predominate over another in different sugars?
5. Related to the previous question, suppose you have equal concentrations of glucose and fructose at room temperature. In both cases, beta-ring forms predominate, but with different percentages. In each case, however, when a reducing sugar measurement is made, the same amount of indicator ion is reduced in each case. Moreover, the amount of directly reacting species for the indicator ion is far less than 1% of the total forms. Explain these findings.
6. One indication of the distinction in physical properties between simple sugars (like monosaccharides and disaccharides) and polysaccharides is their observed behavior in solution. For example, only starch can form a paste in water. Speculate on how that can be explained from the structural differences between these types of molecules.

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   This is a more chemically oriented description of carbohydrates.