

Introduction to Carbohydrates

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I. OVERVIEW

Carbohydrates are the most abundant organic molecules in nature. They have a wide range of functions, including providing a significant fraction of the dietary calories for most organisms, acting as a storage form of energy in the body, and serving as cell membrane components that mediate some forms of intercellular communication. Carbohydrates also serve as a structural component of many organisms, including the cell walls of bacteria, the exoskeleton of many insects, and the fibrous cellulose of plants. The empiric formula for many of the simpler carbohydrates is $(\text{CH}_2\text{O})_n$, hence the name “hydrate of carbon.”

II. CLASSIFICATION AND STRUCTURE OF CARBOHYDRATES

Monosaccharides (simple sugars) can be classified according to the number of carbon atoms they contain. Examples of some monosaccharides commonly found in humans are listed in Figure 7.1. Carbohydrates with an aldehyde as their most oxidized functional group are called aldoses, whereas those with a keto as their most oxidized functional group are called ketoses (Figure 7.2). For example, glyceraldehyde is an aldose, whereas dihydroxyacetone is a ketose. Carbohydrates that have a free carbonyl group have the suffix *-ose*. [Note: Ketoses (with some exceptions, for example, fructose) have an additional two letters in their suffix: *-ulose*, for example, xylulose.] Monosaccharides can be linked by glycosidic bonds to create larger structures (Figure 7.3). Disaccharides contain two monosaccharide units, oligosaccharides contain from three to about ten monosaccharide units, whereas polysaccharides contain more than ten monosaccharide units, and can be hundreds of sugar units in length.

A. Isomers and epimers

Compounds that have the same chemical formula but have different structures are called isomers. For example, fructose, glucose, mannose, and galactose are all isomers of each other, having the same chemical formula, $\text{C}_6\text{H}_{12}\text{O}_6$. Carbohydrate isomers that differ in configuration around only one specific carbon atom (with the exception of the carbonyl carbon, see “anomers” below) are defined as epimers of each other. For example, glucose and galactose are C-4

Generic names	Examples
3 Carbons: trioses	Glyceraldehyde
4 Carbons: tetroses	Erythrose
5 Carbons: pentoses	Ribose
6 Carbons: hexoses	Glucose
7 Carbons: heptoses	Sedoheptulose
9 Carbons: nonoses	Neuraminic acid

Figure 7.1

Examples of monosaccharides found in humans, classified according to the number of carbons they contain.

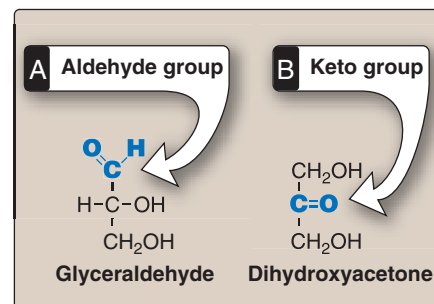


Figure 7.2

Examples of an aldose (A) and a ketose (B) sugar.

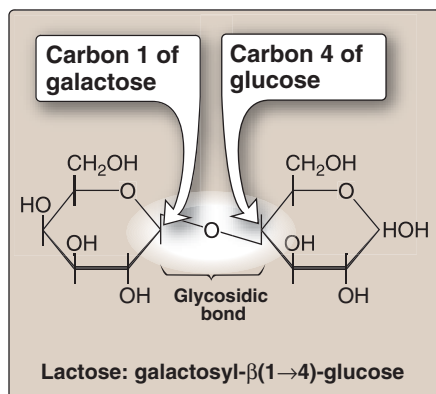


Figure 7.3

A glycosidic bond between two hexoses producing a disaccharide.

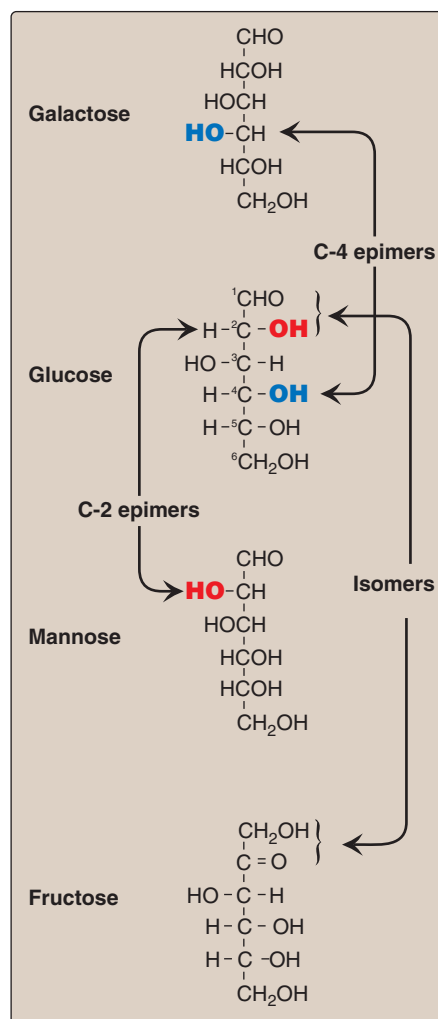


Figure 7.4

C-2 and C-4 epimers and an isomer of glucose.

epimers—their structures differ only in the position of the -OH group at carbon 4. [Note: The carbons in sugars are numbered beginning at the end that contains the carbonyl carbon—that is, the aldehyde or keto group (Figure 7.4).] Glucose and mannose are C-2 epimers. However, galactose and mannose are NOT epimers—they differ in the position of -OH groups at two carbons (2 and 4) and are, therefore, defined only as isomers (see Figure 7.4).

B. Enantiomers

A special type of isomerism is found in the pairs of structures that are mirror images of each other. These mirror images are called enantiomers, and the two members of the pair are designated as a D- and an L-sugar (Figure 7.5). The vast majority of the sugars in humans are D-sugars. In the D isomeric form, the -OH group on the asymmetric carbon (a carbon linked to four different atoms or groups) farthest from the carbonyl carbon is on the right, whereas in the L-isomer it is on the left. Enzymes known as *racemases* are able to interconvert D- and L-isomers.

C. Cyclization of monosaccharides

Less than 1% of each of the monosaccharides with five or more carbons exists in the open-chain (acyclic) form. Rather, they are predominantly found in a ring (cyclic) form, in which the aldehyde (or keto) group has reacted with an alcohol group on the same sugar, making the carbonyl carbon (carbon 1 for an aldose or carbon 2 for a ketose) asymmetric. [Note: Pyranose refers to a six-membered ring consisting of five carbons and one oxygen, for example, glucopyranose (Figure 7.6), whereas furanose denotes a five-membered ring with four carbons and one oxygen.]

1. Anomeric carbon: Cyclization creates an anomeric carbon (the former carbonyl carbon), generating the α and β configurations of the sugar, for example, α -D-glucopyranose and β -D-glucopyranose (see Figure 7.6). These two sugars are both glucose but are anomers of each other. [Note: In the α configuration, the OH on the anomeric C projects to the same side as the ring in a modified Fischer projection formula (Figure 7.6A), and is trans to the CH_2OH group in a Haworth projection formula (Figure 7.6B). Because the α and β forms are not mirror images, they are referred to as diastereomers.] Enzymes are able to distinguish between these two structures and use one or the other preferentially. For example, glycogen is synthesized from α -D-glucopyranose, whereas cellulose is synthesized from β -D-glucopyranose. The cyclic α and β anomers of a sugar in solution are in equilibrium with each other, and can be spontaneously interconverted (a process called mutarotation, see Figure 7.6).

2. Reducing sugars: If the hydroxyl group on the anomeric carbon of a cyclized sugar is not linked to another compound by a glycosidic bond, the ring can open. The sugar can act as a reducing agent, and is termed a reducing sugar. Such sugars can react with chromogenic agents (for example, Benedict's reagent or Fehling's solution) causing the reagent to be reduced and colored, with the aldehyde group of the acyclic sugar becoming oxidized. [Note:

Only the state of the oxygen in the aldehyde group determines if the sugar is reducing or nonreducing.]

||| A colorimetric test can detect a reducing sugar in urine. A positive result is indicative of an underlying pathology because sugars are not normally present in urine, and can be followed up by more specific tests to identify the reducing sugar.

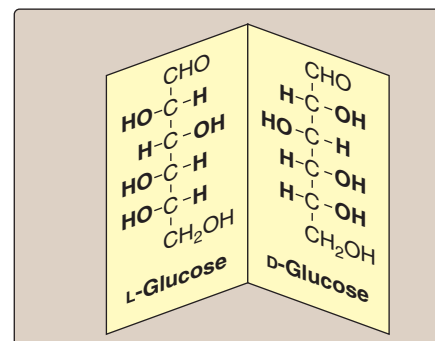


Figure 7.5

Enantiomers (mirror images) of glucose.

D. Joining of monosaccharides

Monosaccharides can be joined to form disaccharides, oligosaccharides, and polysaccharides. Important disaccharides include lactose (galactose + glucose), sucrose (glucose + fructose), and maltose (glucose + glucose). Important polysaccharides include branched glycogen (from animal sources) and starch (plant sources) and unbranched cellulose (plant sources); each is a polymer of glucose. The bonds that link sugars are called glycosidic bonds. These are formed by enzymes known as *glycosyltransferases* that use nucleotide sugars such as UDP-glucose as substrates.

1. Naming glycosidic bonds: Glycosidic bonds between sugars are named according to the numbers of the connected carbons, and with regard to the position of the anomeric hydroxyl group of the sugar involved in the bond. If this anomeric hydroxyl is in the α configuration, the linkage is an α -bond. If it is in the β configuration, the linkage is a β -bond. Lactose, for example, is synthesized by forming a glycosidic bond between carbon 1 of β -galactose and carbon 4 of glucose. The linkage is, therefore, a $\beta(1\rightarrow4)$ glycosidic bond (see Figure 7.3). [Note: Because the anomeric end of the glucose residue is not involved in the glycosidic linkage it (and, therefore, lactose) remains a reducing sugar.]

E. Complex carbohydrates

Carbohydrates can be attached by glycosidic bonds to non-carbohydrate structures, including purine and pyrimidine bases (found in

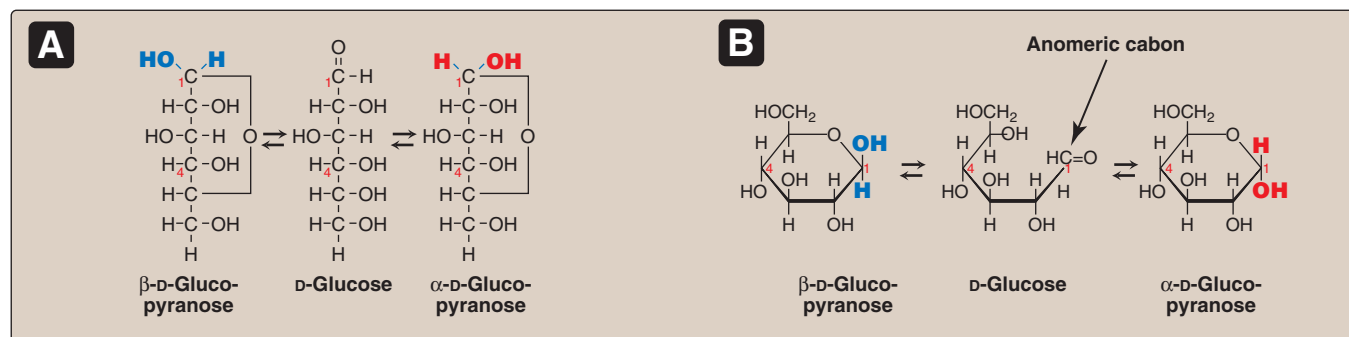
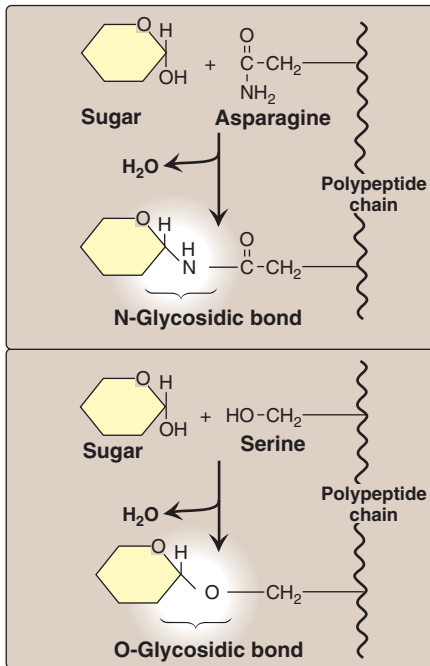
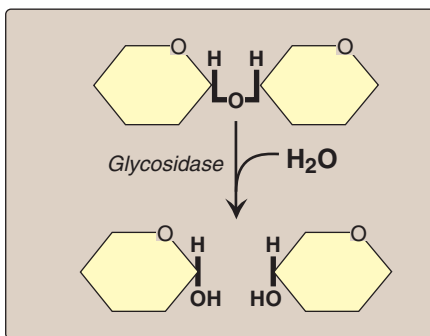


Figure 7.6

A The interconversion (mutarotation) of the α and β anomeric forms of glucose shown as modified Fischer projection formulas. B. The interconversion shown as Haworth projection formulas. Carbon 1 is the anomeric carbon. [Note: Glucose is a reducing sugar.]

**Figure 7.7**

Glycosides: examples of N- and O-glycosidic bonds.

**Figure 7.8**

Hydrolysis of a glycosidic bond.

nucleic acids), aromatic rings (such as those found in steroids and bilirubin), proteins (found in glycoproteins and proteoglycans), and lipids (found in glycolipids).

- 1. N- and O-glycosides:** If the group on the non-carbohydrate molecule to which the sugar is attached is an -NH_2 group, the structure is an N-glycoside and the bond is called an N-glycosidic link. If the group is an -OH , the structure is an O-glycoside, and the bond is an O-glycosidic link (Figure 7.7). [Note: All sugar–sugar glycosidic bonds are O-type linkages.]

III. DIGESTION OF DIETARY CARBOHYDRATES

The principal sites of dietary carbohydrate digestion are the mouth and intestinal lumen. This digestion is rapid and is catalyzed by enzymes known as *glycoside hydrolases* (*glycosidases*) that hydrolyze glycosidic bonds. Because there is little monosaccharide present in diets of mixed animal and plant origin, the enzymes are primarily *endoglycosidases* that hydrolyze polysaccharides and oligosaccharides, and *disaccharidases* that hydrolyze tri- and disaccharides into their reducing sugar components (Figure 7.8). *Glycosidases* are usually specific for the structure and configuration of the glycosyl residue to be removed, as well as for the type of bond to be broken. The final products of carbohydrate digestion are the monosaccharides, glucose, galactose and fructose, which are absorbed by cells of the small intestine.

A. Digestion of carbohydrates begins in the mouth

The major dietary polysaccharides are of plant (starch, composed of amylose and amylopectin) and animal (glycogen) origin. During mastication, salivary α -*amylase* acts briefly on dietary starch and glycogen, hydrolyzing random $\alpha(1\rightarrow4)$ bonds. [Note: There are both $\alpha(1\rightarrow4)$ - and $\beta(1\rightarrow4)$ -*endoglucosidases* in nature, but humans do not produce the latter. Therefore, we are unable to digest cellulose—a carbohydrate of plant origin containing $\beta(1\rightarrow4)$ glycosidic bonds between glucose residues.] Because branched amylopectin and glycogen also contain $\alpha(1\rightarrow6)$ bonds, which α -*amylase* cannot hydrolyze, the digest resulting from its action contains a mixture of short, branched and unbranched oligosaccharides known as dextrins (Figure 7.9) [Note: Disaccharides are also present as they, too, are resistant to *amylase*.] Carbohydrate digestion halts temporarily in the stomach, because the high acidity inactivates salivary α -*amylase*.

B. Further digestion of carbohydrates by pancreatic enzymes occurs in the small intestine

When the acidic stomach contents reach the small intestine, they are neutralized by bicarbonate secreted by the pancreas, and pancreatic α -*amylase* continues the process of starch digestion.

C. Final carbohydrate digestion by enzymes synthesized by the intestinal mucosal cells

The final digestive processes occur primarily at the mucosal lining of the upper jejunum, and include the action of several *disacchari-*

Glycosaminoglycans, Proteoglycans, and Glycoproteins

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I. OVERVIEW OF GLYCOSAMINOGLYCANS

Glycosaminoglycans are large complexes of negatively charged heteropolysaccharide chains. They are generally associated with a small amount of protein, forming proteoglycans, which typically consist of over 95% carbohydrate. [Note: This is in comparison to the glycoproteins, which consist primarily of protein with a small amount of carbohydrate (see p. 165).] Glycosaminoglycans have the special ability to bind large amounts of water, thereby producing the gel-like matrix that forms the basis of the body's ground substance, which, along with fibrous structural proteins such as collagen and elastin, and adhesive proteins such as fibronectin, make up the extracellular matrix (ECM). The hydrated glycosaminoglycans serve as a flexible support for the ECM, interacting with the structural and adhesive proteins, and as a molecular sieve, influencing movement of materials through the ECM. The viscous, lubricating properties of mucous secretions also result from the presence of glycosaminoglycans, which led to the original naming of these compounds as mucopolysaccharides.

II. STRUCTURE OF GLYCOSAMINOGLYCANS

Glycosaminoglycans (GAGs) are long, unbranched, heteropolysaccharide chains generally composed of a repeating disaccharide unit [acidic sugar–amino sugar]_n (Figure 14.1). The amino sugar is either D-glucosamine or D-galactosamine, in which the amino group is usually acetylated, thus eliminating its positive charge. The amino sugar may also be sulfated on carbon 4 or 6 or on a nonacetylated nitrogen. The acidic sugar is either D-glucuronic acid or its C-5 epimer, L-iduronic acid (Figure 14.2). [Note: A single exception is keratan sulfate, in which galactose rather than an acidic sugar is present.] These acidic sugars contain carboxyl groups that are negatively charged at physiologic pH and, together with the sulfate groups, give GAGs their strongly negative nature.

A. Relationship between glycosaminoglycan structure and function

Because of their large number of negative charges, these heteropolysaccharide chains tend to be extended in solution. They repel each other, and are surrounded by a shell of water molecules. When brought together, they “slip” past each other, much as two magnets

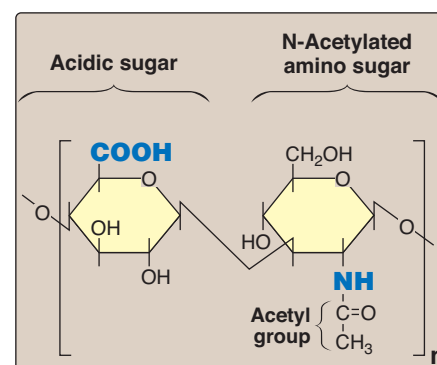


Figure 14.1
Repeating disaccharide unit.

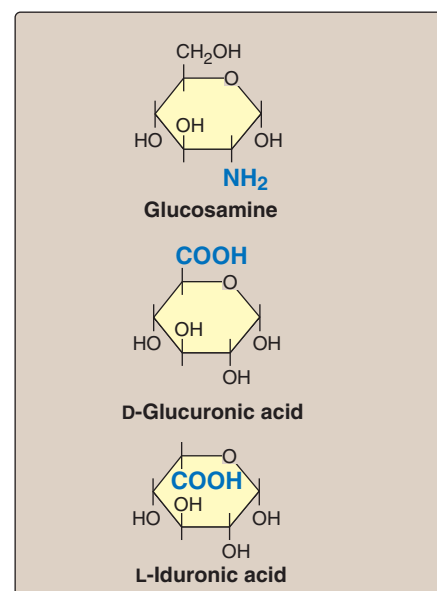


Figure 14.2
Some monosaccharide units found in glycosaminoglycans.

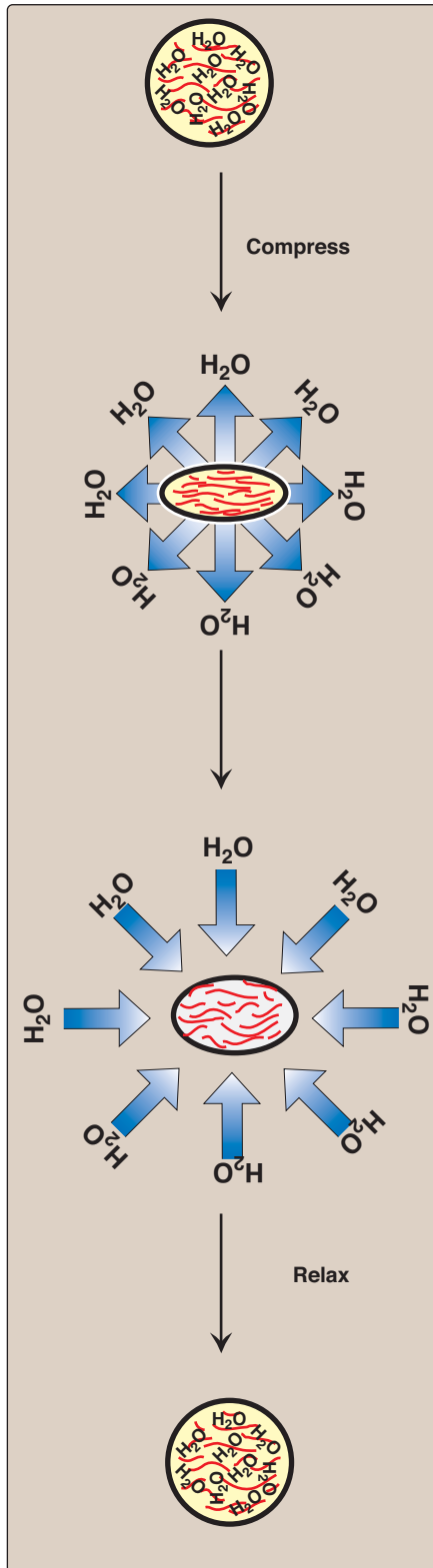


Figure 14.3
Resilience of glycosaminoglycans.

with the same polarity seem to slip past each other. This produces the “slippery” consistency of mucous secretions and synovial fluid. When a solution of glycosaminoglycans is compressed, the water is “squeezed out” and the glycosaminoglycans are forced to occupy a smaller volume. When the compression is released, the glycosaminoglycans spring back to their original, hydrated volume because of the repulsion of their negative charges. This property contributes to the resilience of synovial fluid and the vitreous humor of the eye (Figure 14.3).

B. Classification of the glycosaminoglycans

The six major classes of glycosaminoglycans are divided according to monomeric composition, type of glycosidic linkages, and degree and location of sulfate units. The structure of the glycosaminoglycans and their distribution in the body is illustrated in Figure 14.4.

C. Structure of proteoglycans

All of the glycosaminoglycans, except hyaluronic acid, are found covalently attached to protein, forming proteoglycan monomers.

- 1. Structure of proteoglycan monomers:** A proteoglycan monomer found in cartilage consists of a core protein to which the linear glycosaminoglycan chains are covalently attached. These chains, which may each be composed of more than 100 monosaccharides, extend out from the core protein, and remain separated from each other because of charge repulsion. The resulting structure resembles a “bottle brush” (Figure 14.5). In cartilage proteoglycan, the species of glycosaminoglycans include chondroitin sulfate and keratan sulfate. [Note: Proteoglycans are now grouped into gene families that code for core proteins with common structural features. The aggrecan family (aggrecan, versican, neurocan, and brevican), abundant in cartilage, is an example.]
- 2. Linkage between the carbohydrate chain and the protein:** This linkage is most commonly through a trihexoside (galactose-galactose-xylose) and a serine residue, respectively. An O-glycosidic bond is formed between the xylose and the hydroxyl group of the serine (Figure 14.6).
- 3. Proteoglycan aggregates:** The proteoglycan monomers associate with a molecule of hyaluronic acid to form proteoglycan aggregates. The association is not covalent, but occurs primarily through ionic interactions between the core protein and the hyaluronic acid. The association is stabilized by additional small proteins called link proteins (Figure 14.7).

III. SYNTHESIS OF GLYCOSAMINOGLYCANS

The polysaccharide chains are elongated by the sequential addition of alternating acidic and amino sugars donated by their UDP-derivatives. The reactions are catalyzed by a family of specific *glycosyltransferases*. The synthesis of the glycosaminoglycans is analogous to that of glycogen (see p. 126) except that the glycosaminoglycans are produced for export from the cell. Their synthesis occurs, therefore, primarily in the Golgi, rather than in the cytosol.