

their isomerism: All four sugars are D-sugars because they have the same configuration as D-glyceraldehyde on the highest number chiral atom; the use of the term D has no bearing on whether these sugars are dextro- or levorotatory.

The three aldohexoses are stereoisomers—more specifically, optical isomers. Because no one of the three is an enantiomer of either of the other two, they are related as *diastereomers*. As such, they have different melting points, different boiling points, different solubilities, different specific rotations, and, in general, different chemical properties.

D(+)-Glucose may be said to be an *epimer* of D(+)-mannose because these compounds differ from each other by their configuration on a single asymmetric carbon atom. Similarly, D(+)-glucose is an epimer of D(+)-galactose. On the other hand, there is no epimeric relationship between D(+)-mannose and D(+)-galactose.

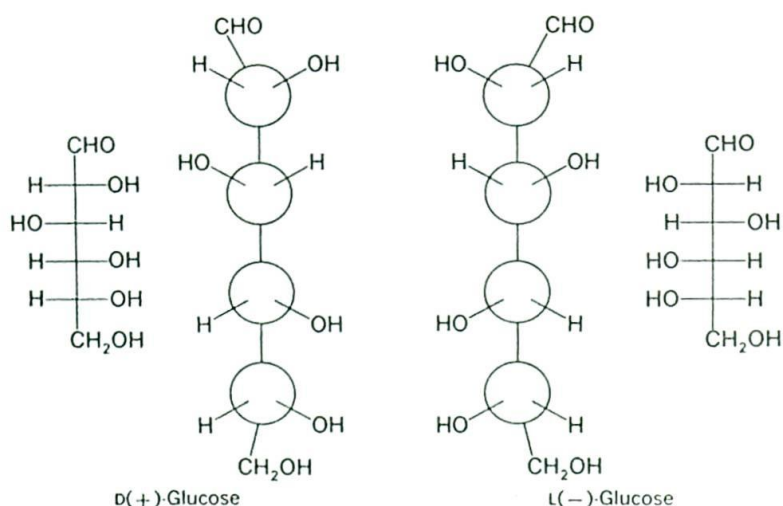
D-Fructose is a structural isomer of the other three hexoses. Although it has the same molecular formula ($\text{C}_6\text{H}_{12}\text{O}_6$), it has a different functional group; it is a ketose rather than an aldose.

2.3 THE STRUCTURE OF GLUCOSE

Emil Fischer received the Nobel Prize in Chemistry for his studies on the structure of glucose, more specifically for establishing the configuration of the four asymmetric carbon atoms in that aldohexose relative to D(+)-glyceraldehyde. From Fischer's work, chemists were able to write the projection and ball-and-stick formulas for D- and L-glucose (Structure 2.5).

If the ball-and-stick model just represented is actually constructed and the $-\text{CHO}$ and $-\text{CH}_2\text{OH}$ groups are held so that they extend away from the holder (behind the plane of the paper), the remainder of the carbon atoms will tend to form a ring extending toward the holder, and the H and OH groups will project out toward the holder.

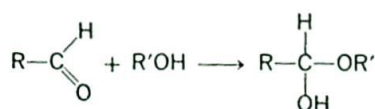
Although the aldohexoses have been considered polyhydroxy aldehydes or ketones to this point, there is abundant evidence to indicate that other forms (of glucose, e.g.) exist and, indeed, predominate both in the solid phase and solution. For instance, aldohexoses undergo the Kiliani-Fischer synthesis with difficulty, although cyanohydrin formation with simple aldehydes is usually rapid. Glucose and other aldoses fail to give the Schiff test for aldehydes. Solid glucose is quite inert to oxygen, but aldehydes are notoriously autoxidizable. Finally, it is possible to prepare two crystalline forms of D-glucose. When D-glucose is dissolved in water and allowed to crystallize out by evaporation of the water, a form designated as α -D-glucose is obtained. If glucose is crystallized



STRUCTURE 2.5

from acetic acid or pyridine, another form, β -D-glucose, is obtained. These two forms of D-glucose show the phenomenon of **mutarotation**. A freshly prepared solution of α -D-glucose has a specific rotation $[\alpha]_D^{20}$ of $+113^\circ$; when the solution is left standing, it changes to $+52.5^\circ$. A fresh solution of β -D-glucose, on the other hand, has an $[\alpha]_D^{20}$ of $+19^\circ$; on standing, it also changes to the same value, $+52.5^\circ$.

The existence of the two forms of glucose, as well as the other anomalous properties described, was explained by the English chemist, W. N. Haworth, who showed that aldohexoses and other sugars react internally to form cyclic hemiacetals. Hemiacetal formation is a characteristic reaction between aldehydes and alcohols.



The formation of the cyclic hemiacetal structure for D-glucose is shown in Figure 2.2.

Rotation of the bond between carbon atoms 4 and 5 moves the C-5 hydroxyl group into a position where it can react with the aldehyde group on C-1. This places the $-\text{CH}_2\text{OH}$ group on C-5 above the ring. As the hemiacetal ring is formed, note that C-1 becomes a chiral center. Therefore, two diastereomeric molecules are possible. These isomers are the α and β forms of glucose; they are diastereomers, however, rather than enantiomers, for the α form differs from the β form only in the configuration at a single carbon. Since the cyclic forms of the aldohexoses have five asymmetric carbon atoms, there are 32 optical isomers of the cyclic aldohexoses consisting of 16 pairs of enantiomers.

As noted above, the angles of the tetrahedral carbon atom bend the glucose molecule into a ring. When the C-5 hydroxyl group reacts, as shown in Figure 2-2, a six-membered ring is formed. If the C-4 hydroxyl were to react, a five-membered ring would result; a seven-membered ring is too strained to permit the C-6 hydroxyl of an aldohexose to form a hemiacetal. The six-membered

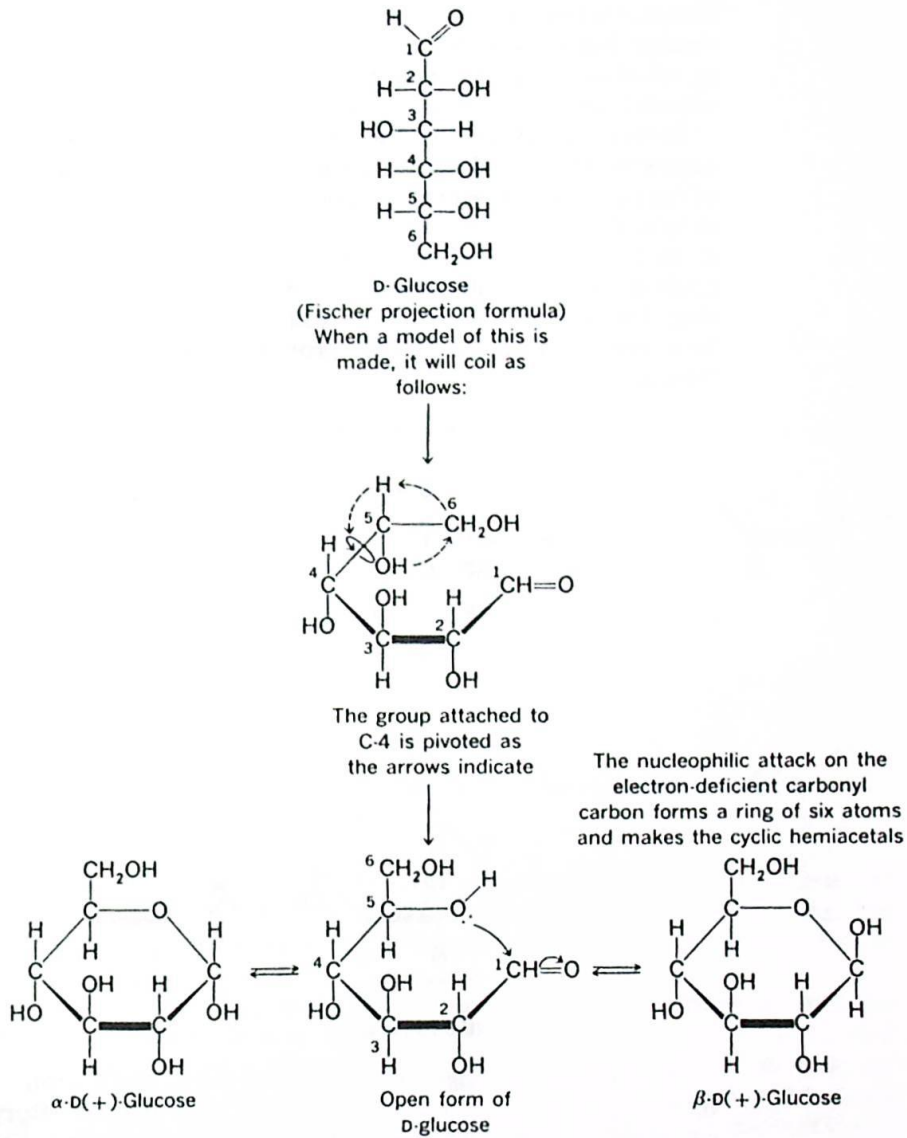
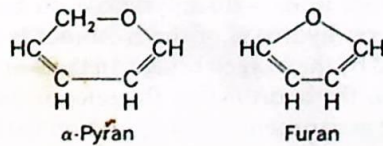


FIGURE 2.2 Scheme depicting the formation of the hemiacetal forms of D-glucose. Note that an equilibrium exists between the α and β forms and the open-chain form.

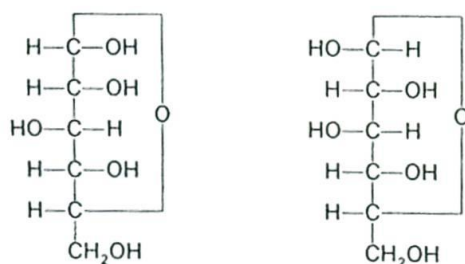
ring sugars may be considered derivatives of pyran, whereas the five-membered rings are considered relatives to furan.



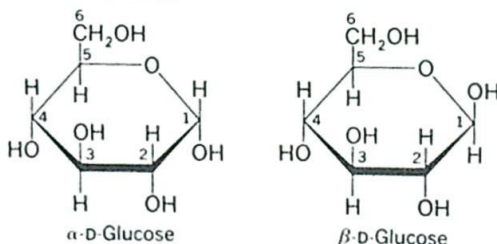
Hence, it is customary to refer to the **pyranose** or **furanose** form of the monosaccharide. Furanose forms of the hexoses are less stable than the pyranose forms in solution; combined forms of furanose sugars (as in the fructose unit of sucrose) are found in nature, however.

Haworth proposed that these cyclic hemiacetal forms of glucose and other sugars be represented as a hexagonal ring in a plane perpendicular to the plane of the paper. The side of the hexagon that is nearer to the reader would then be indicated by a thickened line. When this is done, the substituents on the carbon atom then will extend above or below the plane of the six-membered ring. Carbon atom 6, a substituent on C-5, will therefore be above the plane of the ring. The Haworth formulas for α -D(+)-glucose and β -D(+)-glucose may then be compared with the Fischer projection formulas for these diastereomers (Structure 2.6).

Fischer projection formulas



Haworth formulas



STRUCTURE 2.6

With respect to assigning structures to the α - and β -anomers, Fischer originally suggested that, in the D-series, the more dextrorotatory compound be called the α -anomer whereas, in the L series, the α -anomer would be the more levorotatory substance. Later, Freudenberg proposed that the α - and β -anomers be classified with respect to their configuration rather than sign or magnitude of rotation. The relationship of the anomeric hydroxyl to the reference carbon atom is easy to see when Fischer projection formulas for the ring structures are used. In these projections, the α -anomer is the isomer in which the anomeric hydroxyl is on the same side (*cis*) of the carbon chain as the hydroxyl group on the reference carbon atom. If the reference hydroxyl group happens, as it does in α -D-glucopyranose, to be involved in ring formation, then the anomeric hydroxyl of the α -isomer is on the same side as the ring structure formed by the oxygen bridge. In the β -anomer, the hemiacetal hydroxyl group is *trans* to the hydroxyl on the reference carbon atom.

The assignment of configuration to the anomeric carbon atom is less readily