Organic Chemistry III

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24. Carbohydrates

Take a piece of bread and place it in your mouth. After a few minutes it will begin to taste distinctly sweet, as if you had added sugar to it. The acid and enzymes in your saliva have cleaved the starch in the bread into its component units: glucose molecules. You all know glucose as dextrose or grape sugar. The polymer, starch, and its monomer, glucose, are two examples of carbohydrates.

Carbohydrates are major contributors to our daily diets, in the form of sugars, fibers, and starches, such as bread, rice, and potatoes. They function as chemical energy-storage systems, being metabolized to water, carbon dioxide, and heat or other energy. They also serve as building units of fats and nucleic acids.

Carbohydrates are considered to be **polyfunctional,** because they possess multiple functional groups. Glucose, $C_6(H_2O)_6$, and many related simple members of this compound class form the building blocks of the complex carbohydrates and have the empirical formulas $C_n(H_2O)_n$, essentially hydrated carbon. As a result, they are highly water soluble.

24-1 NAMES AND STRUCTURES OF CARBOHYDRATES

The simplest carbohydrates are the sugars, or **saccharides.** As chain length increases, the increasing number of stereocenters gives rise to a multitude of diastereomers. Fortunately for chemists, nature deals mainly with only one of the possible series of enantiomers.

Sugars are polyhydroxycarbonyl compounds and many form stable cyclic hemiacetals, which affords additional structural and chemical variety.

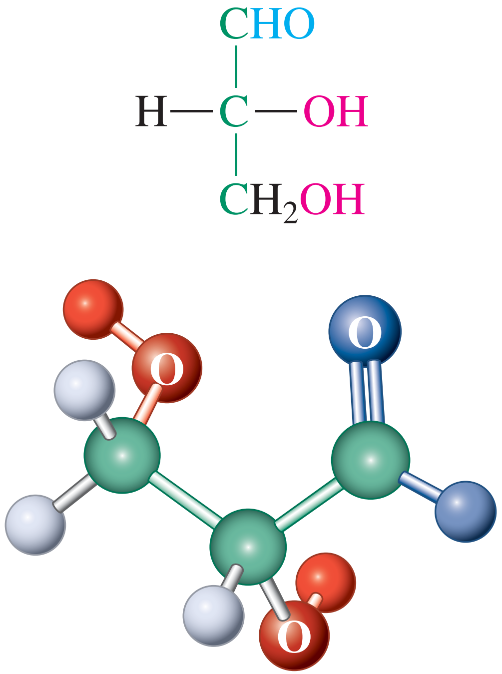
Carbohydrate is the general name for the monomeric (monosaccharides), dimeric (disaccharides), trimeric (trisaccharides), oligomeric (oligosaccharides), and polymeric (polysaccharides) forms of sugar (*saccharum,* Latin, sugar).

A **monosaccharide,** or **simple sugar,** is an aldehyde or ketone containing at least two additional hydroxy groups. Thus, the two simplest members of this class of compounds are 2,3-dihydroxypropanal (glyceraldehyde) and 1,3-dihydroxyacetone.

Complex sugars are those formed by the linkage of simple sugars through ether bridges.

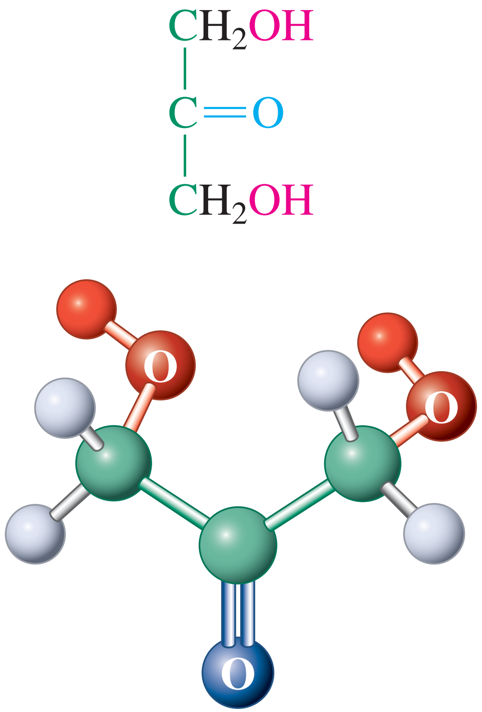
Aldehydic sugars are classified as **aldoses;** those with a ketone function are called **ketoses.** On the basis of their chain length, we call sugars **trioses** (three carbons), **tetroses** (four carbons), **pentoses** (five carbons), **hexoses** (six carbons), and so on.

Therefore, 2,3-dihydroxypropanal (glyceraldehyde) is an aldotriose, whereas 1,3-dihydroxyacetone is a ketotriose.



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

2,3-Dihydroxypropanal
(Glyceraldehyde)
(An aldotriose)



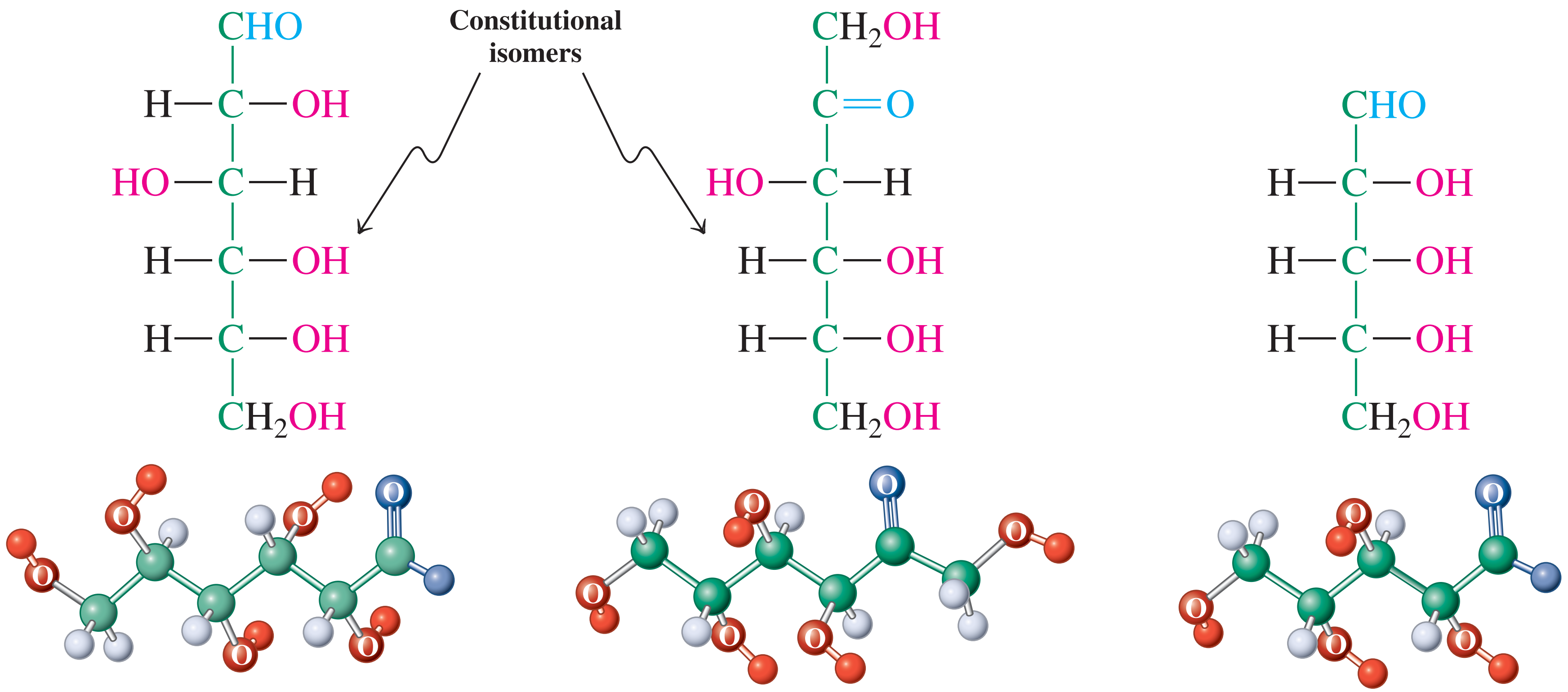
$$\begin{array}{l} \mathrm{CH_2OH} \\ | \\ \mathrm{C{=}O} \\ | \\ \mathrm{CH_2OH} \end{array}$$

1,3-Dihydroxyacetone
(A ketotriose)

Glucose, also known as dextrose, blood sugar, or grape sugar (*glykys,* Greek, sweet), is a pentahydroxyhexanal and hence belongs to the class of aldohexoses.

An isomeric ketohexose is **fructose,** the sweetest natural sugar, which is also present in many fruits (*fructus,* Latin, fruit) and in honey.

Natural sugar of aldopentose, **ribose**, is a building block of the ribonucleic acids.



Glucose
(An aldohexose)

Fructose
(A ketohexose)

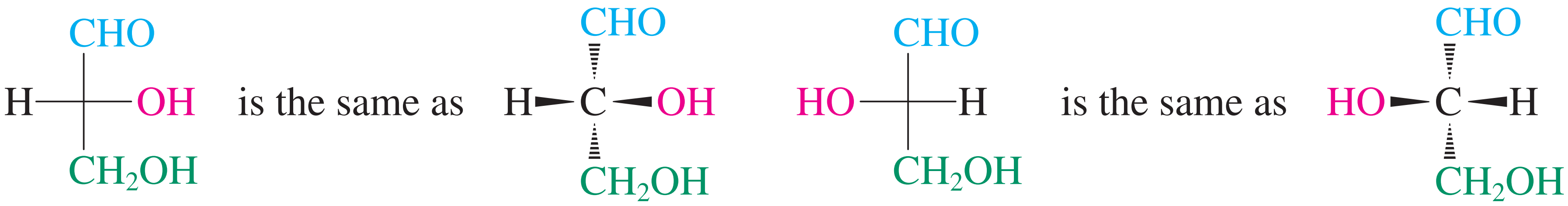
Ribose
(An aldopentose)

A **disaccharide** is derived from two monosaccharides by the formation of an ether (usually, acetal) bridge. Hydrolysis regenerates the monosaccharides. Ether formation between a mono- and a disaccharide results in a trisaccharide, and repetition of this process eventually produces a natural polymer (polysaccharide). Polysaccharides constitute the framework of cellulose and starch.

Most sugars are chiral and optically active

With the exception of 1,3-dihydroxyacetone, all the sugars mentioned so far contain at least one stereocenter. The simplest chiral sugar is 2,3-dihydroxypropanal (glyceraldehyde), with one asymmetric carbon. Its dextrorotatory form is found to be *R* and the levorotatory enantiomer *S*.

Fischer Projections of the Two Enantiomers of 2,3-Dihydroxypropanal (Glyceraldehyde)



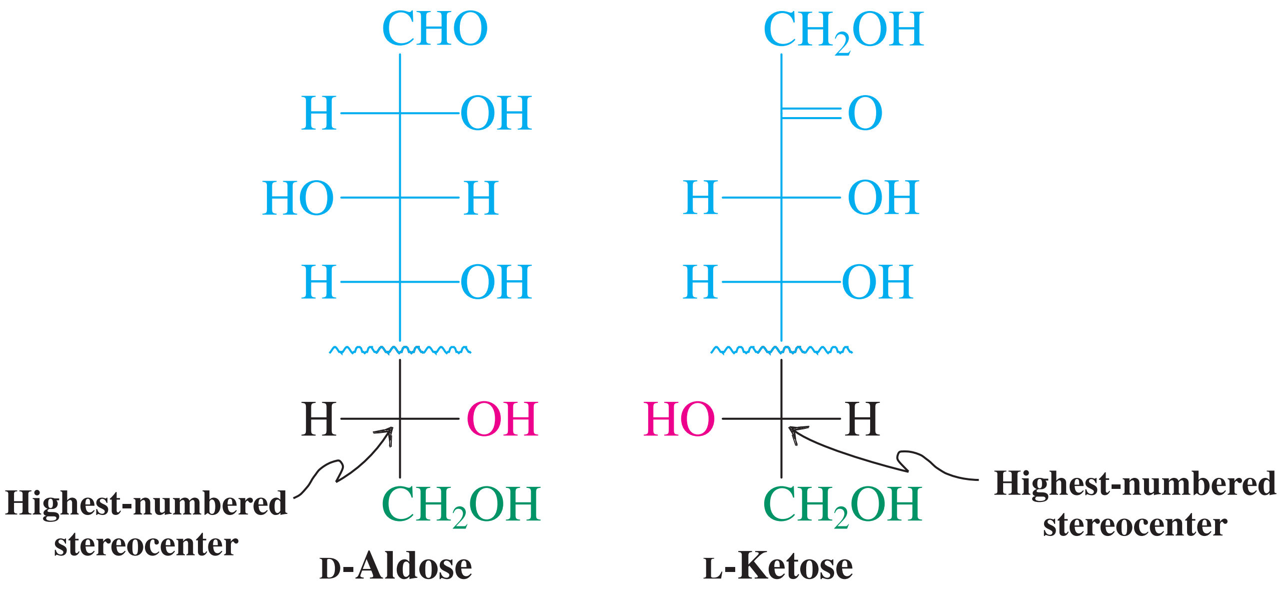
(*R*)-(+)-2,3-Dihydroxypropanal
[D-(+)-Glyceraldehyde]
($[\alpha]_D^{25°C} = +8.7$)

(*S*)-(−)-2,3-Dihydroxypropanal
[L-(−)-Glyceraldehyde]
($[\alpha]_D^{25°C} = -8.7$)

Even though *R* and *S* nomenclature is perfectly satisfactory for naming sugars, an older system is still in general use. Instead of *R* and *S*, it uses the prefixes D for the (+) enantiomer of glyceraldehyde and L for the (-) enantiomer.

Those monosaccharides whose highest-numbered stereocenter (i.e., the one farthest from the aldehyde or keto group) has the same absolute configuration as that of D-(+)-2,3-dihydroxypropanal [D-(+)-glyceraldehyde] are then labeled D; those with the opposite configuration at that stereocenter are named L.

Designation of a D and an L Sugar



Highest-numbered stereocenter

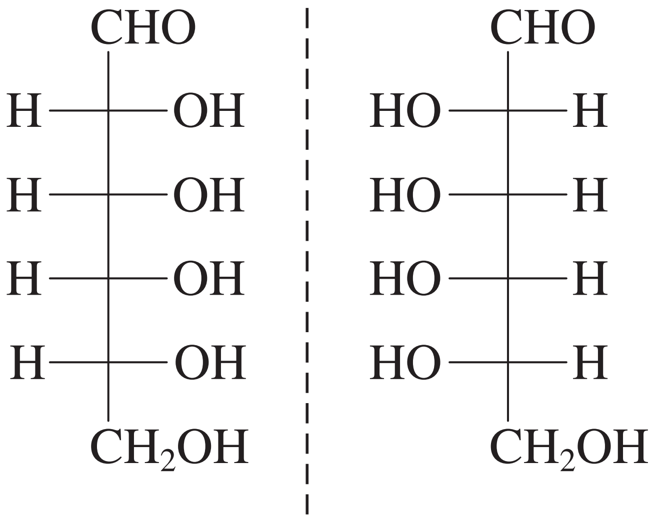
D-Aldose

L-Ketose

Highest-numbered stereocenter

Two diastereomers that differ in the stereochemistry of only one stereocenter (the same in each one) are also called **epimer**.

Enantiomers

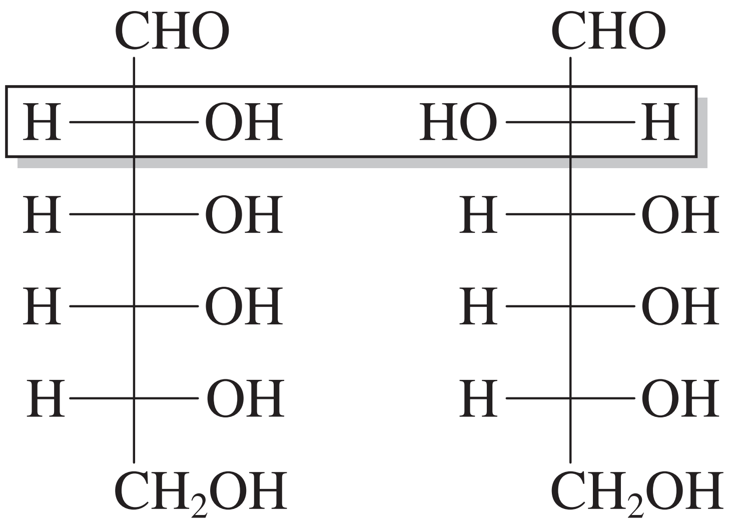


Mirror plane

All stereocenters switch configuration

D-Allose ⇌ **L-Allose**

Epimers



Only one stereocenter switches configuration

D-Allose ⇌ **D-Altrose**

The D,L nomenclature divides the sugars into two groups. As the number of stereocenters increases, so does the number of stereoisomers. For example, the aldotetrose 2,3,4-trihydroxybutanal has two stereocenters and hence may exist as four stereoisomers: two diastereomers, each as a pair of enantiomers.

The next higher homolog, 2,3,4,5-tetrahydroxypentanal, has three stereocenters, hence eight stereoisomers are possible ($2^3 = 8$): four diastereomeric pairs of enantiomers.

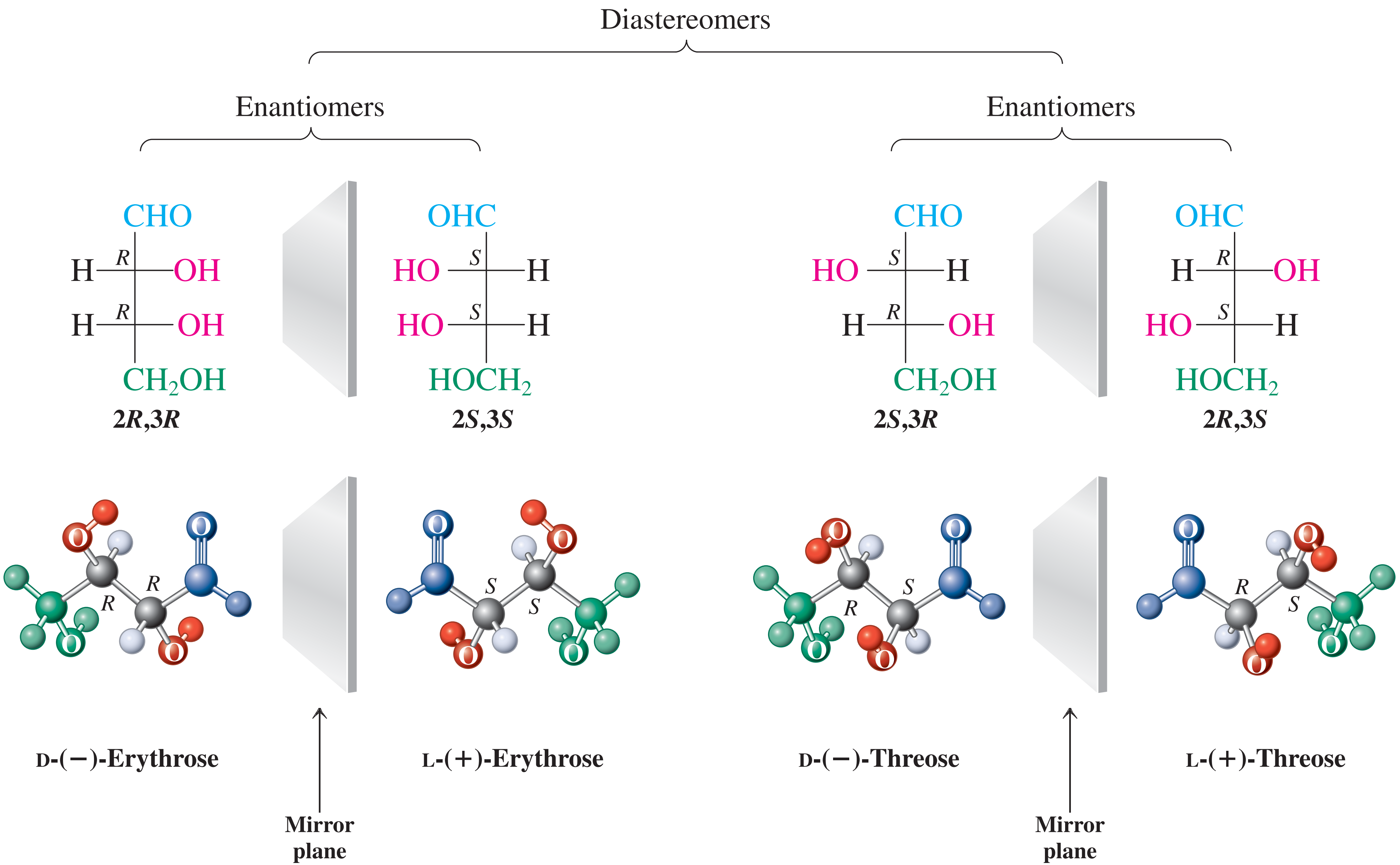
Similarly, 16 stereoisomers (as eight enantiomeric pairs) may be formulated for the corresponding pentahydroxyhexanal ($2^4 = 16$).

The isomer of 2,3,4-trihydroxybutanal with 2*R*,3*R* configuration is called **erythrose**; its diastereomer, **threose**.

Note that each of these isomers has two enantiomers, one belonging to the family of the D sugars, its mirror image to the L sugars. The sign of the optical rotation is not correlated with the D and L label (just as in the *R*,*S* notation).

ng

Stereoisomeric 2,3,4-Trihydroxybutanals: Erythrose (2 Enantiomers) and Threose (2 Enantiomers)



D-(−)-Erythrose

L-(+)-Erythrose

D-(−)-Threose

L-(+)-Threose

Mirror plane

Mirror plane

Why then use the D,L nomenclature even though it designates the absolute configuration of only one stereocenter?

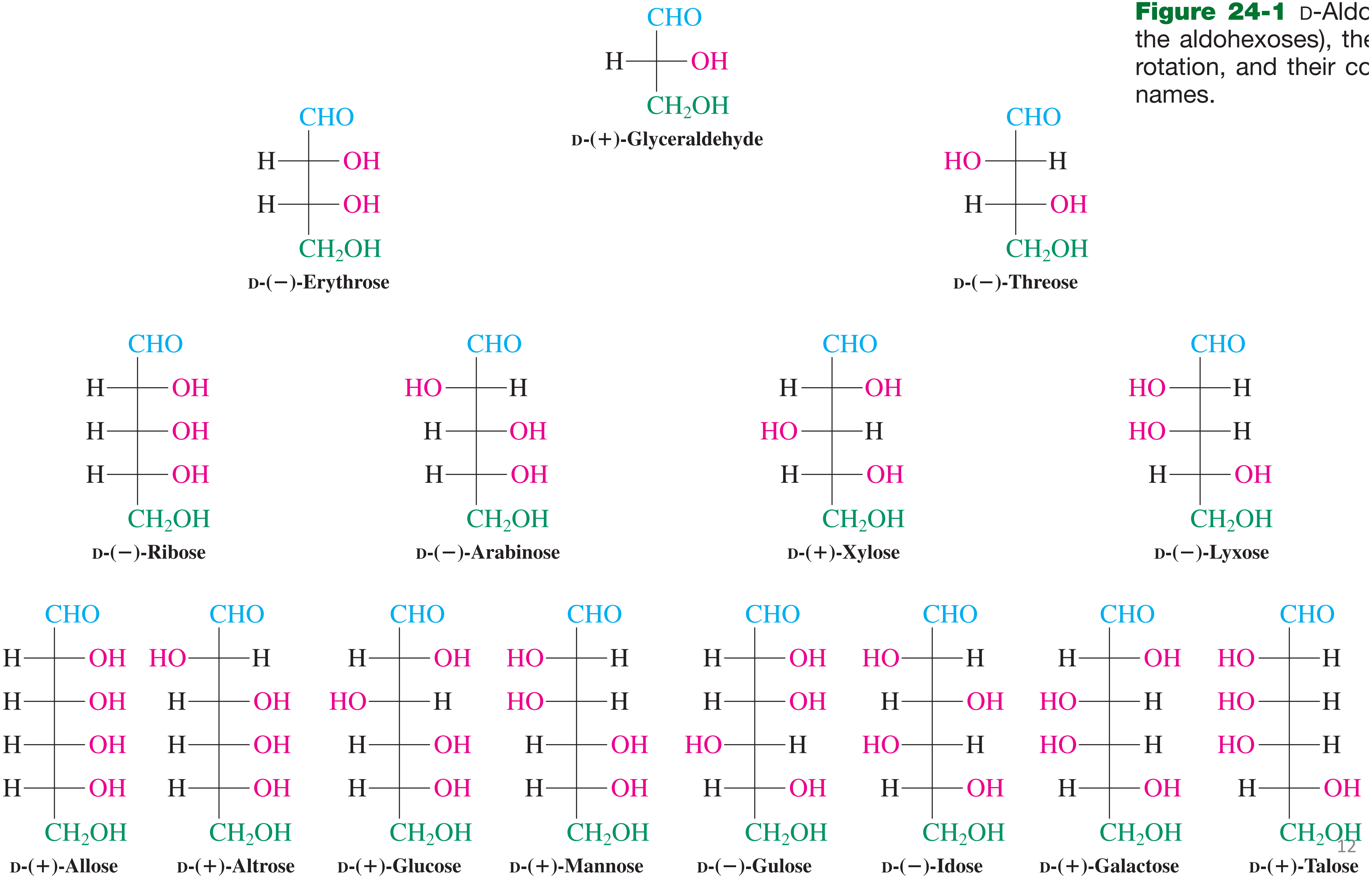
Probably because *almost all naturally occurring sugars have the D configuration*.

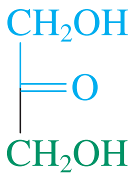
Evidently, somewhere in the structural evolution of the sugar molecules, nature “chose” only one configuration for one end of the chain. The amino acids are another example of such selectivity.

Fischer projections of the series of D-aldoses and D-ketoses:

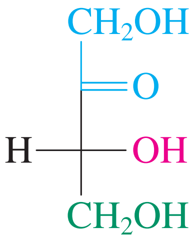
The carbon chain extends vertically and the aldehyde terminus is placed at the top. In this convention, the hydroxy group at the highest-numbered stereocenter (at the bottom) points to the right in all D sugars.

Figure 24-1 D-Aldo
the aldohexoses), the
rotation, and their co
names.

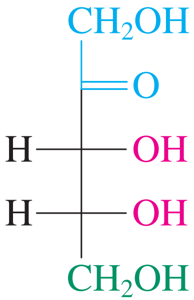




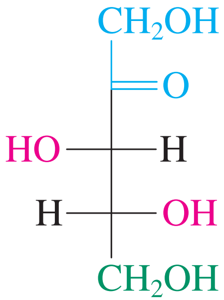
1,3-Dihydroxyacetone



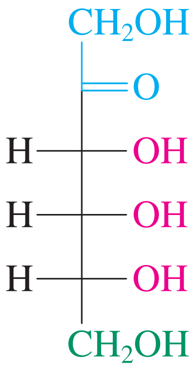
D-(−)-Erythrulose



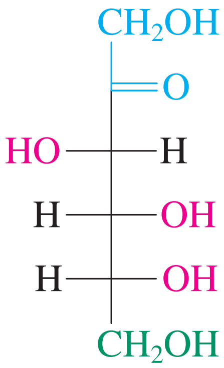
D-(+)-Ribulose



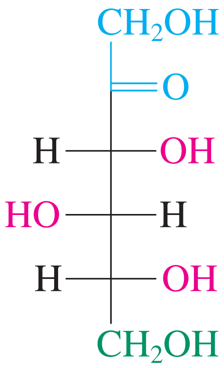
D-(+)-Xylulose



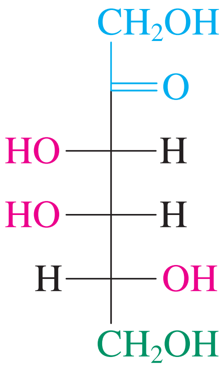
D-(+)-Psicose



D-(−)-Fructose



D-(+)-Sorbose



D-(−)-Tagatose

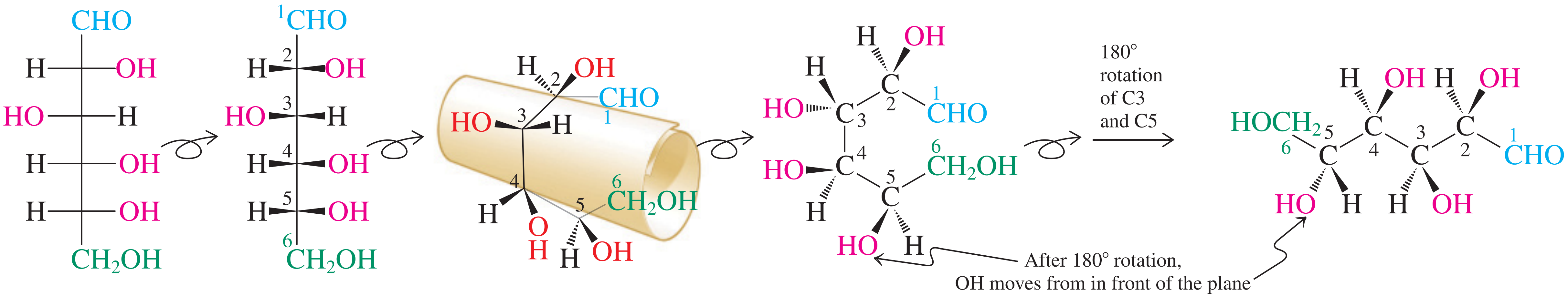
24-2 CONFORMATIONS AND CYCLIC FORMS OF SUGARS

Sugars are molecules with multiple functional groups and multiple stereocenters. This structural complexity gives rise to a variety of chemical properties.

Several ways of depicting sugars have been developed. It introduces the cyclic isomers that exist in solutions of simple sugars.

Fischer projections depict all-eclipsed conformations

Fischer Projection and Hashed-Wedged Line Structures for D-(+)-Glucose



After 180° rotation, OH moves from in front of the plane of the page to behind it.

Fischer projection

All-eclipsed hashed-wedged line structure

All-staggered hashed-wedged line structure

A molecular model, the groups on the *right* of the carbon chain in the original Fischer projection now project *upward* (wedged bonds). From this conformer, we can reach the all-staggered form by 180^o rotations of C3 and C5.

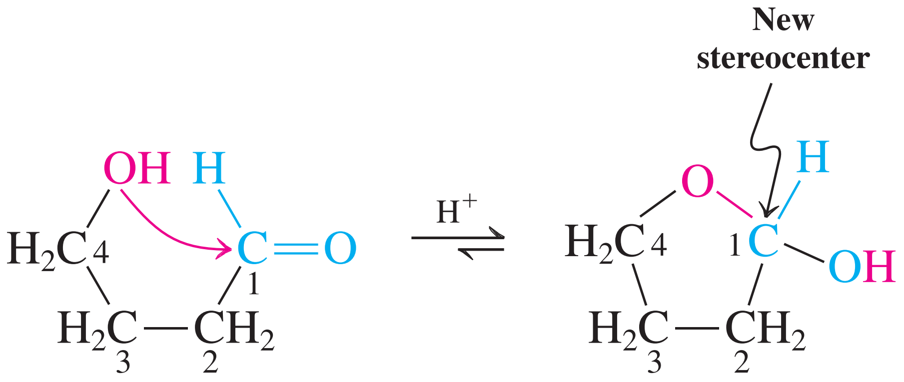
Sugars form intramolecular hemiacetals

Sugars are hydroxycarbonyl compounds that should be capable of intramolecular hemiacetal formation. Indeed, glucose and the other hexoses, as well as the pentoses, exist as an equilibrium mixture with their cyclic hemiacetal isomers, in which the hemiacetals strongly predominate.

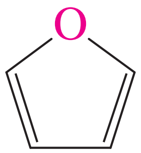
In principle, any one of the five hydroxy groups could add to the carbonyl group of the aldehyde. However, three- and four-membered rings are too strained, and five- and six-membered rings are the products.

The six-membered ring structure of a monosaccharide is called a **pyranose,** a name derived from *pyran,* a six-membered cyclic ether. Sugars in the five-membered ring form are called **furanoses,** from *furan*.

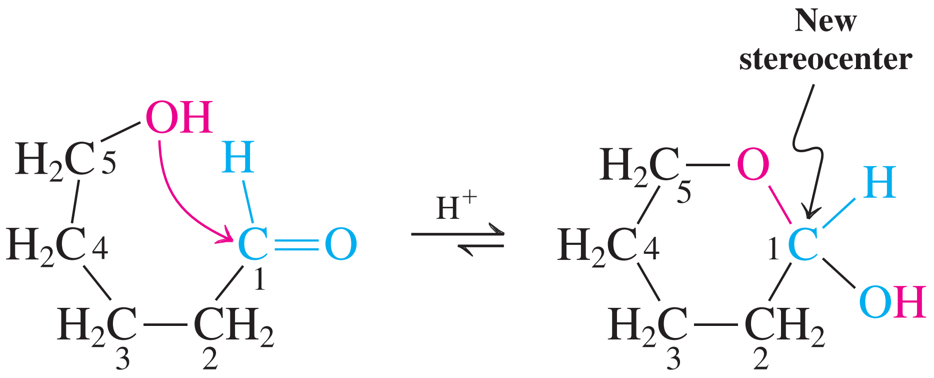
Five- and Six-Membered Cyclic Hemiacetal Formation


New stereocenter

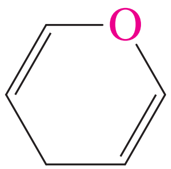
Furanose ring



Furan


New stereocenter

Pyranose ring



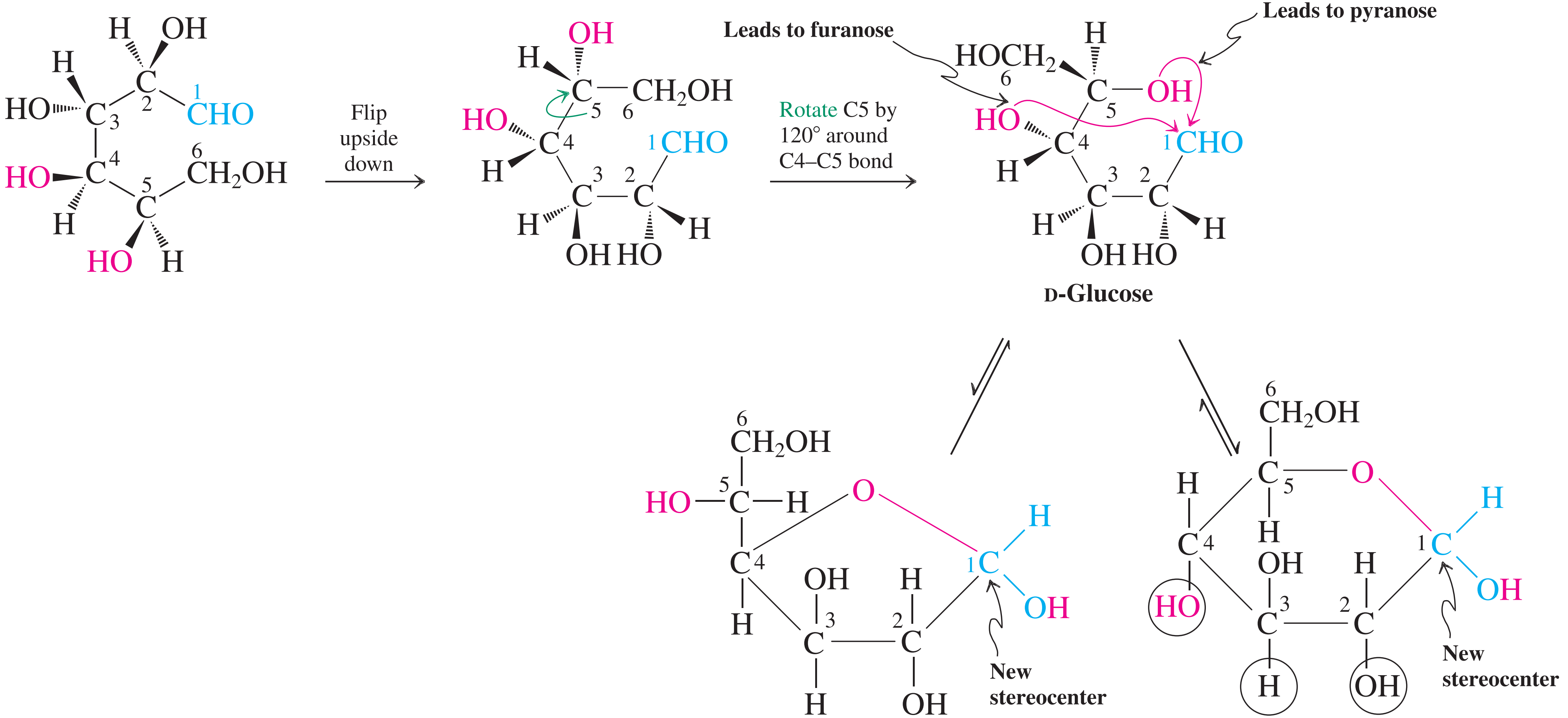
Pyran

To depict a D-series sugar correctly in its cyclic form, draw the hashed-wedged line representation of the all-eclipsed structure on the previous page and flip it upside down, as shown below.

Rotation of C5 places its hydroxy group in position to form a six-membered cyclic hemiacetal by addition to the C1 aldehyde carbon. Similarly, a five-membered ring can be made by rotation of C4 to place its OH group in position to bond to C1.

The resulting drawings depict the ring in a somewhat artificial way: It is shown as if it were planar and from a perspective in which the bottom-most ring bonds (between C2 and C3 in the structures below) are interpreted as being *in front* of the plane of the page.

Cyclic Hemiacetal Formation by Glucose



D-Glucofuranose

(Less stable, 0.4%)

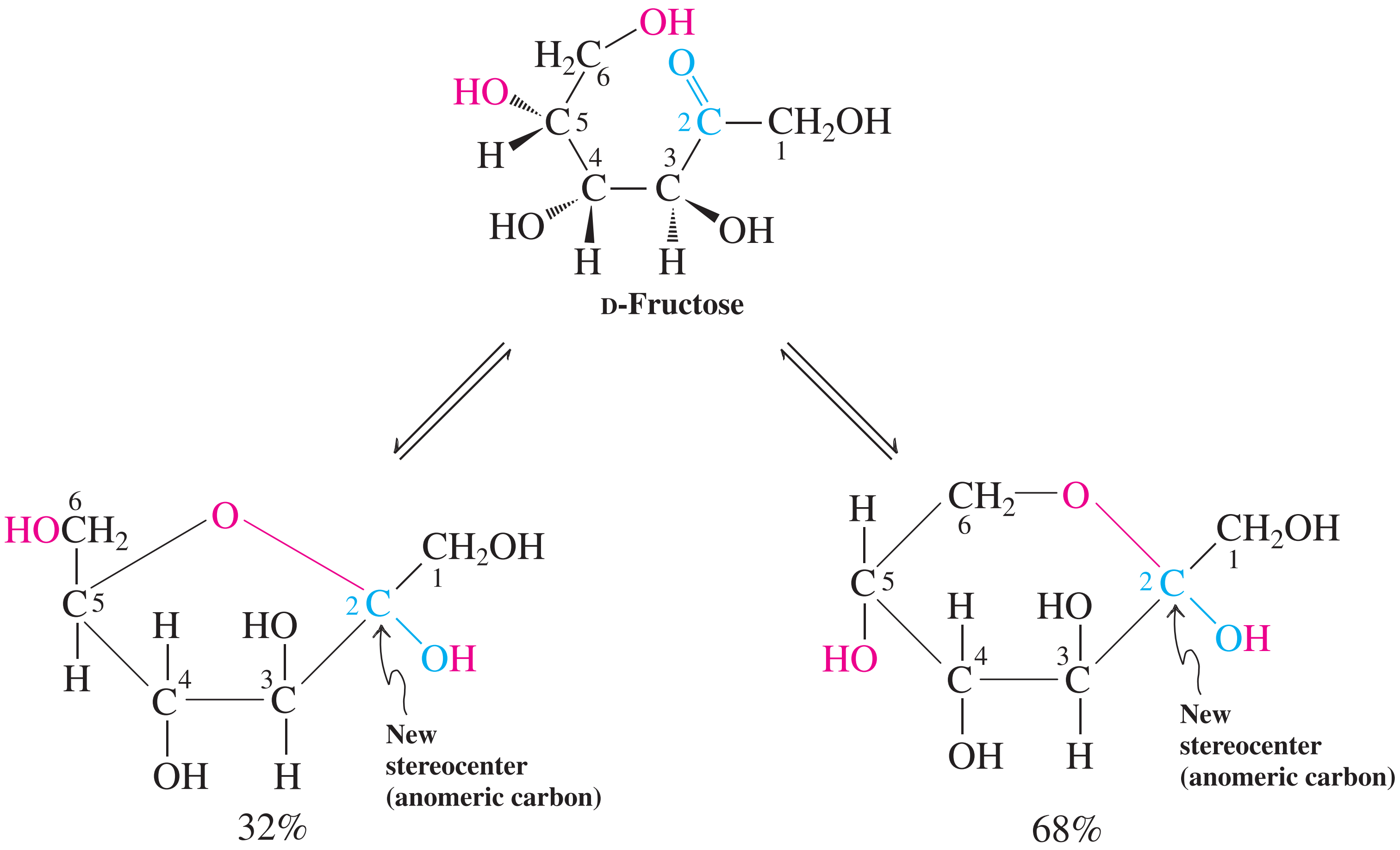
D-Glucopyranose

(More stable, 99.6%)

(Groups on the *right* in the original Fischer projection [circled] *point downward* in the cyclic hemiacetal except at C5, which has been rotated)

In contrast with glucose, which exists primarily as the pyranose, fructose forms both fructopyranose and fructofuranose in a rapidly equilibrating 68:32 mixture.

Cyclic Hemiacetal Formation by Fructose



D-Fructose

New stereocenter (anomeric carbon)

32%

D-Fructofuranose
(Furanose = five-membered cyclic sugar)

68%

D-Fructopyranose
(Pyranose = six-membered cyclic sugar)

Upon cyclization, the carbonyl carbon turns into a new stereocenter. As a consequence, hemiacetal formation leads to *two* new compounds, two diastereomers (epimers) differing in the configuration of the hemiacetal group.

If that configuration is *S* in a D-series sugar, that diastereomer is labeled $\boldsymbol{\alpha}$; when it is *R* in a D sugar, the isomer is called $\boldsymbol{\beta}$.

For example, D-glucose may form α- or β-D-glucopyranose or -furanose.

Because this type of diastereomer formation is unique to sugars, such isomers have been given a separate name: **anomers.** The new stereocenter is called the **anomeric carbon.**

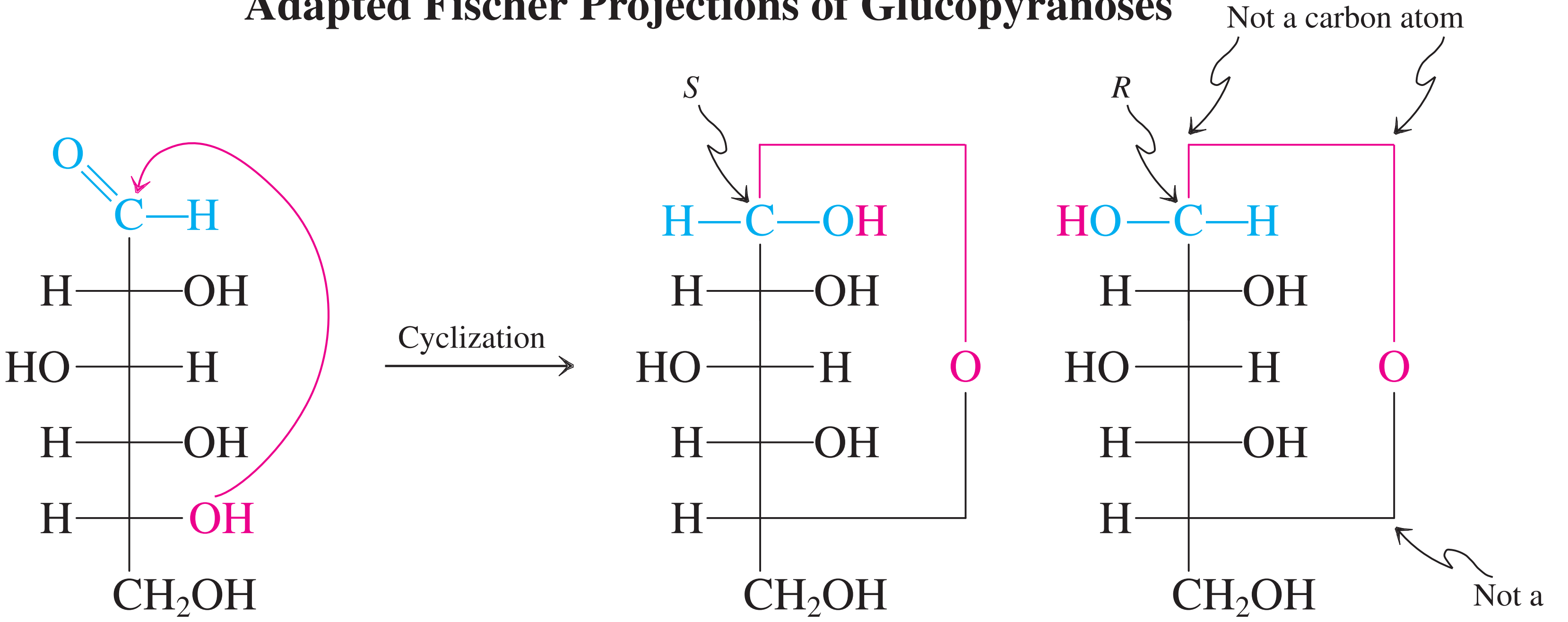
Fischer, Haworth, and chair cyclohexane projections help depict cyclic sugars

How can we represent the stereochemistry of the cyclic forms of sugars?

Fischer projections: We simply draw elongated lines to indicate the bonds formed upon cyclization, preserving the basic "grid" of the original formula.

In the Fischer projection of the α form of a D sugar, the anomeric OH points toward the *right*, while in the β form, the anomeric OH is on the *left*.

Adapted Fischer Projections of Glucopyranoses



α-D-(+)-Glucopyranose
(m.p. 146°C)

β-D-(+)-Glucopyranose
(m.p. 150°C)

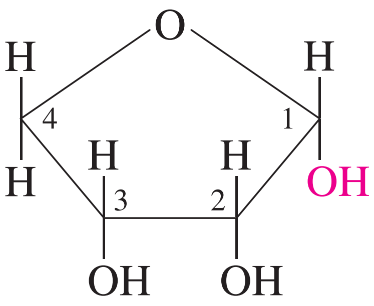
Haworth projections more accurately represent the real three-dimensional structure of the sugar molecule. The cyclic ether is written in line notation as a pentagon or a hexagon, the anomeric carbon (in a D sugar) placed on the right, and the ether oxygen put on top.

The substituents located above or below the ring are attached to vertical lines. The ring bond at the bottom (between C2 and C3) assume to be *in front* of the plane of the paper, and the ring bonds containing the oxygen are understood to be in back.

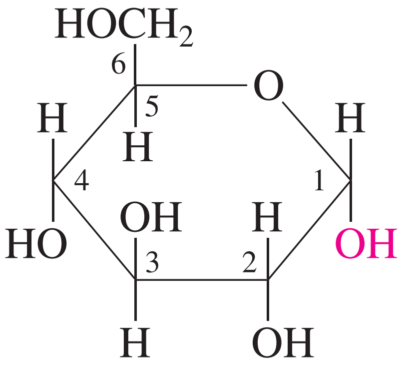
In a Haworth projection, the α anomer has the OH group at the anomeric carbon pointing down, whereas the β anomer has it pointing up.

Groups on the right in the Fischer projection point *downward* in the Haworth formula.

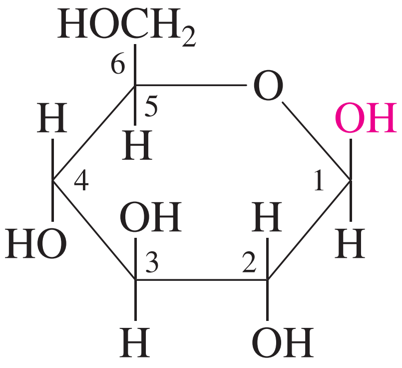
Haworth Projections



α-D-(−)-Erythrofuranose



α-D-(+)-Glucopyranose



β-D-(+)-Glucopyranose

The cyclic forms of sugars can be presented mostly as envelope (for furanoses) or chair (for pyranoses) conformations.

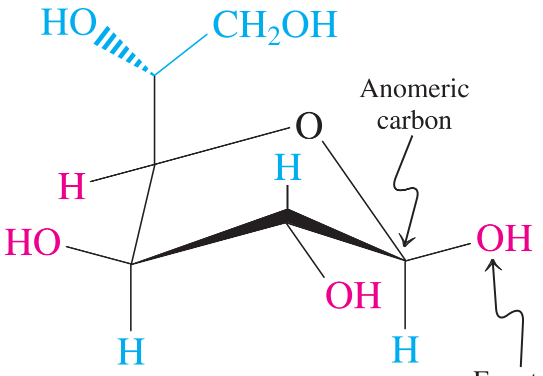
The ether oxygen will be placed usually top right and the anomeric carbon at the right vertex of the envelope or chair.

Although there are exceptions, most aldohexoses adopt the chair conformation that places the bulky hydroxymethyl group at the C5 terminus in the equatorial position.

For glucose, this preference means that, in the α form, four of the five substituents can be equatorial, and one is forced to lie axial; in the β form, *all* substituents can be equatorial.

This situation is unique for glucose; the other seven D aldohexoses contain one or more axial substituents.

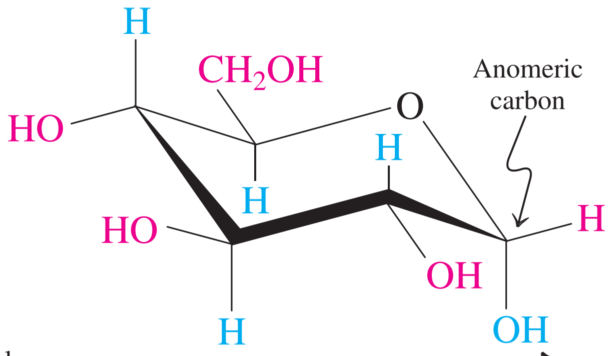
Conformational Pictures of Glucofuranose and -pyranose



Anomeric carbon

Equatorial (β)

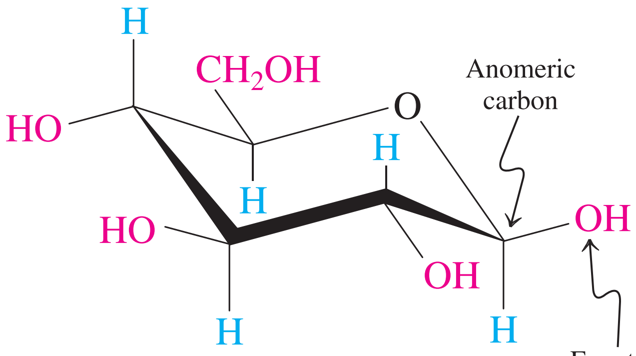
Envelope conformation



Anomeric carbon

Chair conformation

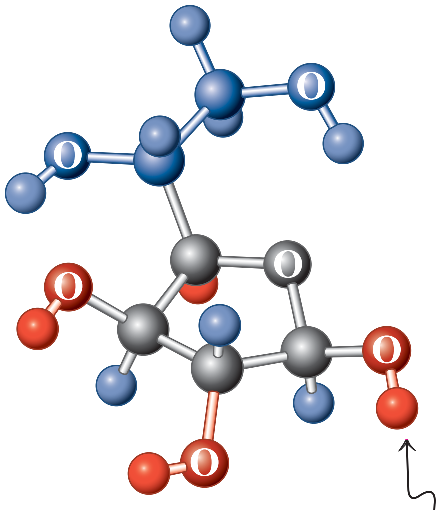
Axial (α)



Anomeric carbon

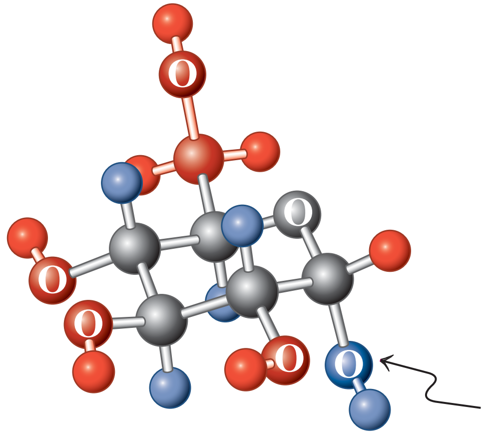
Equatorial (β)

Chair conformation



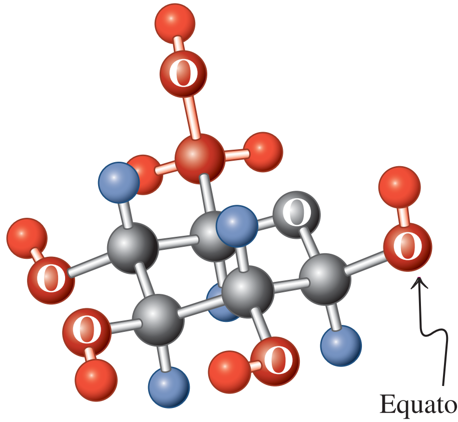
β-D-Glucofuranose

Equatorial (β)



Axial (α)

α-D-Glucopyranose
(One axial –OH group)



Equatorial (β)

β-D-Glucopyranose
(All substituents equatorial)
Most stable form

24-3 ANOMERS OF SIMPLE SUGARS: MUTAROTATION OF GLUCOSE

Glucose precipitates from concentrated solutions at room temperature to give crystals that melt at 146 ^{o}C. Structural analysis by X-ray diffraction reveals that these crystals contain only the α-D-(+)-glucopyranose anomer.

When crystalline α-D-(+)-glucopyranose is dissolved in water and its optical rotation measured immediately, a value $[a]_D^{25oC}$ = +112 is obtained. Curiously, this value decreases with time until it reaches a constant +52.7. The process that gives rise to this effect is the interconversion of the α and β anomers.

In solution, the α-pyranose rapidly establishes an equilibrium (catalyzed by acid and base) with a small amount of the open-chain aldehyde, which in turn undergoes reversible ring closure to the β anomer.

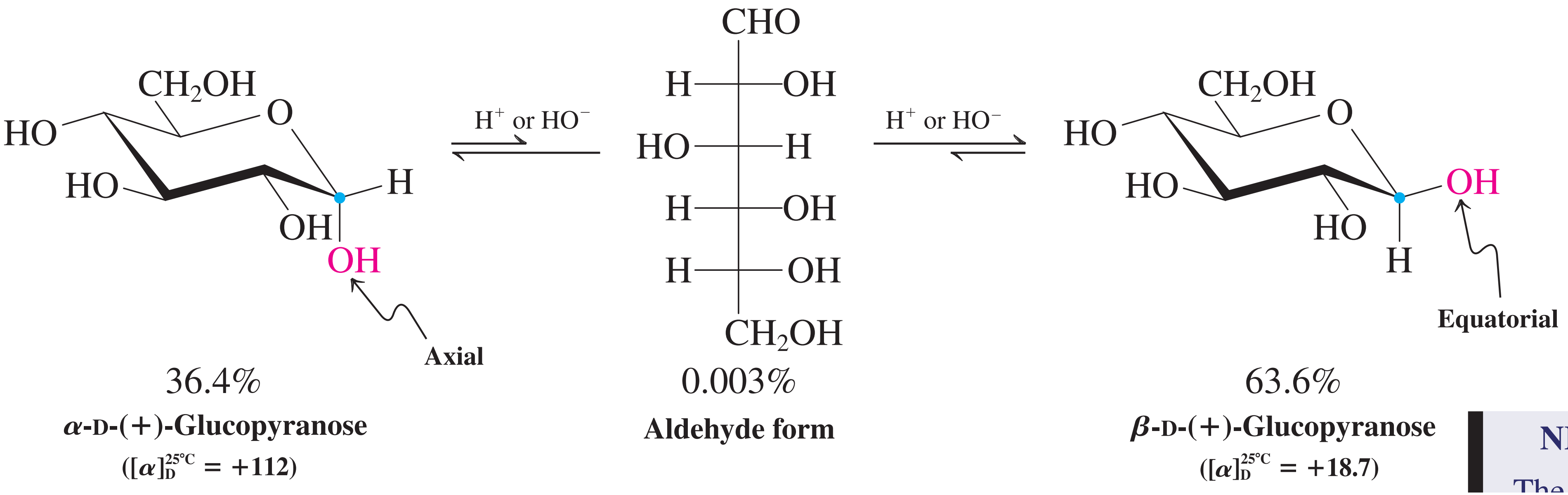
The β form has a considerably lower specific rotation (+18.7) than its anomer; therefore, the observed α value in solution decreases.

Similarly, a solution of the pure *β* anomer (m.p. 150 °C, obtainable by crystallizing glucose from acetic acid) gradually increases its specific rotation from +18.7 to +52.7. At this point, a final equilibrium has been reached, with 36.4% of the *α* anomer and 63.6% of the *β* anomer.

The change in optical rotation observed when a sugar equilibrates with its anomer is called **mutarotation** (*mutare,* Latin, to change). Interconversion of *α* and *β* anomers is a general property of sugars.

This includes all monosaccharides capable of existing as cyclic hemiacetals.

Interconversion of Open-Chain and Pyranose Forms of D-Glucose



36.4%
α-D-(+)-Glucopyranose
($[\alpha]_D^{25°C} = +112$)

0.003%
Aldehyde form

63.6%
β-D-(+)-Glucopyranose
($[\alpha]_D^{25°C} = +18.7$)

Solved Exercise 24-10

Calculate the equilibrium ratio of α- and β-glucopyranose from the specific rotations of the pure anomers and the observed specific rotation at mutarotational equilibrium.

Solution

Let's designate the mole fraction of the α form as x_α and the mole fraction of its β isomer as x_β. Their respective specific rotations are given as +112 (α) and +18.7 (β), whereas the equilibrium mixture exhibits a value of +52.7. Thus, we have

$$+52.7 = (+112)(x_\alpha) + (+18.7)(x_\beta)$$

By the definition of mole fraction, $x_\alpha + x_\beta = 1$, so we can substitute one for the other in the above equation. Solving gives $x_\alpha = 0.364$ and $x_\beta = 0.636$. Therefore the equilibrium ratio is $x_\alpha / x_\beta = (0.636)/(0.364) = 1.75$.

24-4 POLYFUNCTIONAL CHEMISTRY OF SUGARS: OXIDATION TO CARBOXYLIC ACIDS

Simple sugars exist as isomers: the open-chain structure and the α and β anomers of various cyclic forms. Because all of these isomers equilibrate rapidly, the relative rates of their individual reactions with various reagents determine the product distribution of a particular transformation.

The reactions of sugars are divided into two groups, those of the linear form and those of the cyclic forms, *because the two structures contain different functional groups*.

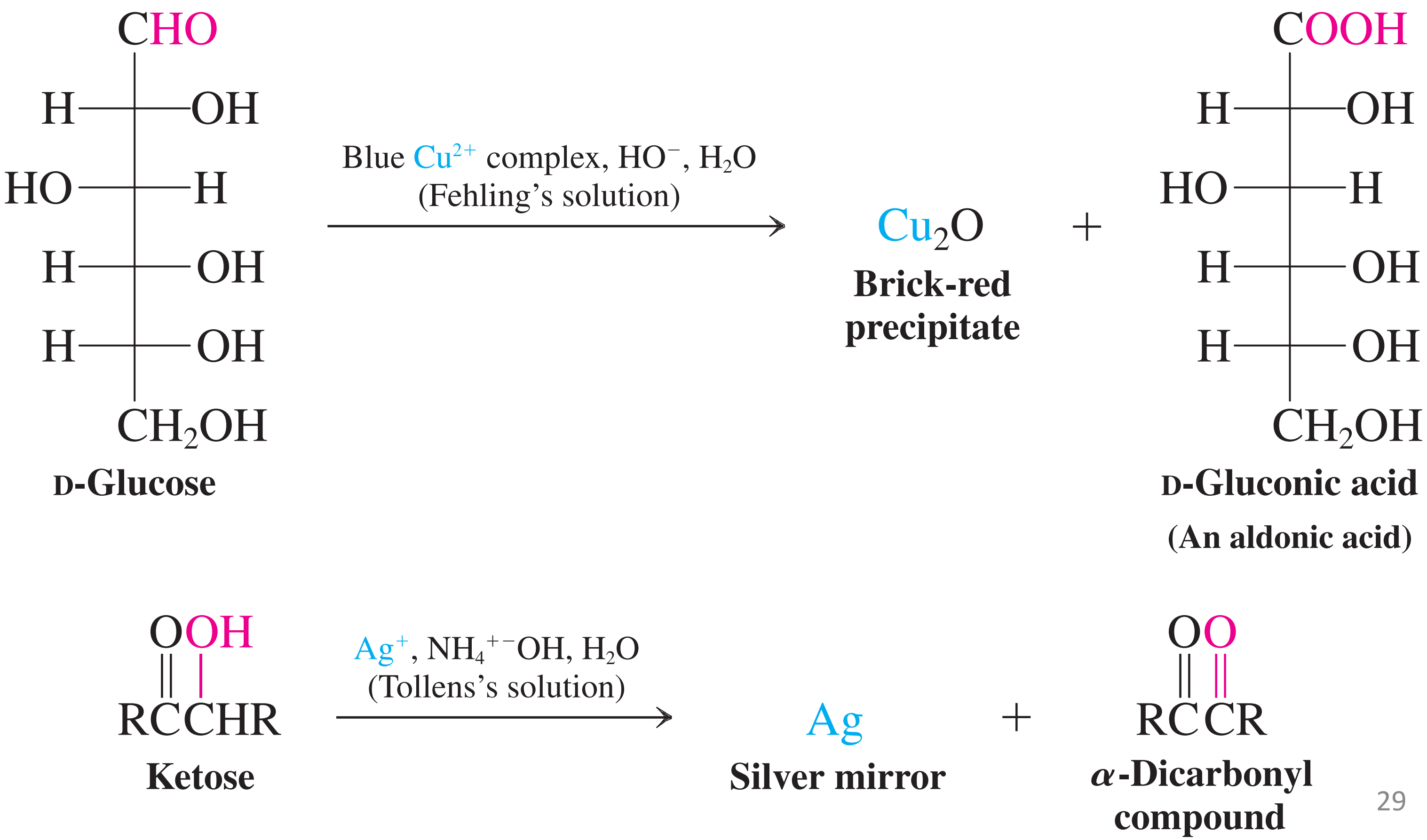
Although the two forms may sometimes react competitively, reactions of aldoses with oxidizing agents take place at the aldehyde moiety of the open-chain form, not the hemiacetal function of the cyclic isomers.

Because they are polyfunctional compounds, the open-chain monosaccharides undergo the reactions typical of each of their functional groups.

Fehling's and Tollens's tests detect reducing sugars

Aldoses contain the oxidizable formyl group and therefore respond to the standard oxidation tests such as exposure to Fehling's or Tollens's solutions. The α-hydroxy substituent in ketoses is similarly oxidized.

Results of Fehling's and Tollens's Tests on Aldoses and Ketoses



D-Glucose

Brick-red precipitate

D-Gluconic acid (An aldonic acid)

Ketose

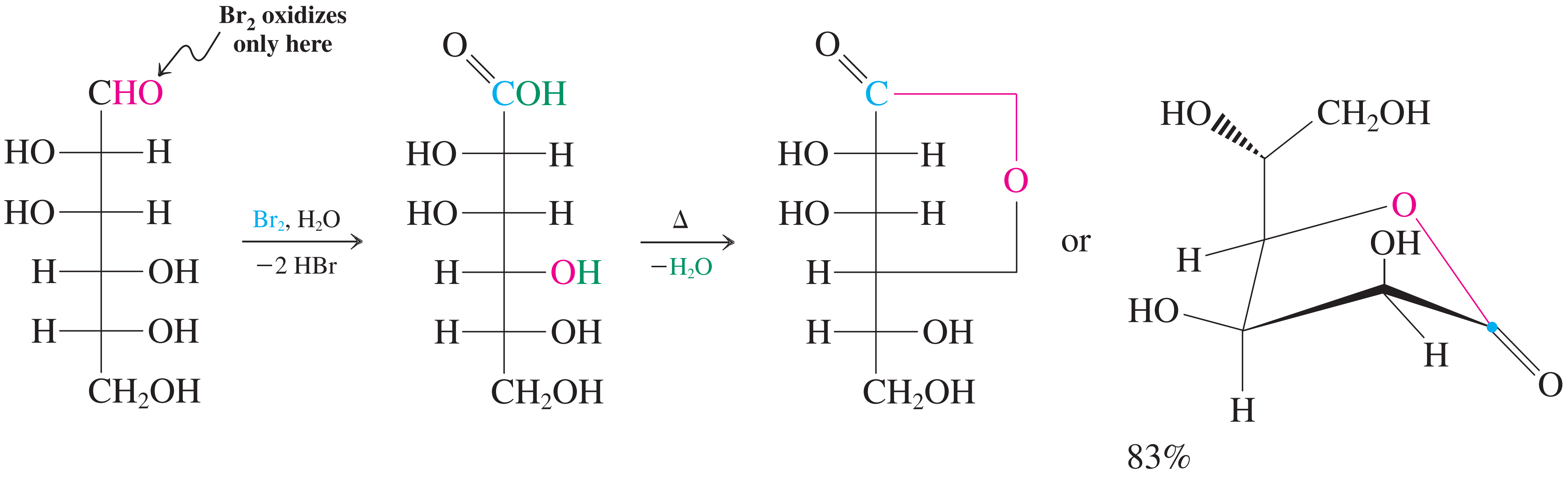
Silver mirror

α-Dicarbonyl compound

The aldoses are transformed into **aldonic acids,** ketoses into α-dicarbonyl compounds. Sugars that respond positively to these tests are called **reducing sugars.** All ordinary monosaccharides are reducing sugars.

Aldonic acids are made on a preparative scale by oxidation of aldoses with bromine in buffered aqueous solution (pH = 5-6). Upon subsequent evaporation of solvent from the aqueous solution of the aldonic acid, the γ-lactone forms spontaneously.

Aldonic Acid Preparation and Subsequent Dehydration to Give an Aldonolactone

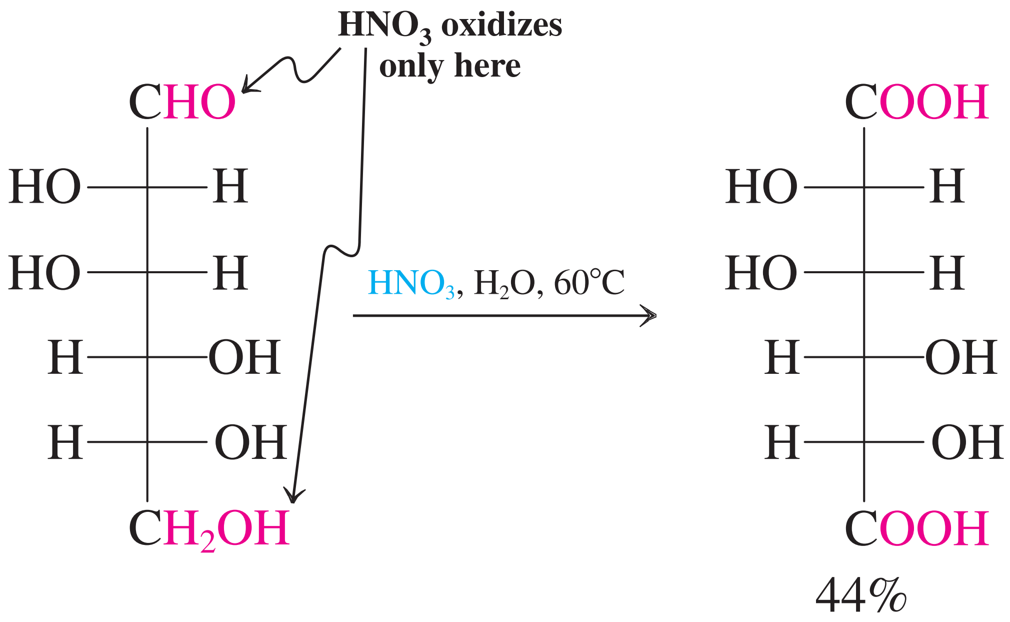


D-Mannose **D-Mannonic acid** **D-Mannono-γ-lactone**

More vigorous oxidation of an aldose leads to attack at the primary hydroxy function as well as at the formyl group. The resulting dicarboxylic acid is called an **aldaric,** or **saccharic, acid.**

This oxidation can be achieved with warm dilute aqueous nitric acid. For example, D-mannose is converted into D-mannaric acid under these conditions.

Preparation of an Aldaric Acid



D-Mannose **D-Mannaric acid**

The preceding syntheses of aldonic and aldaric acids directly from the corresponding aldoses are notable in that they occur in the presence of unprotected secondary hydroxy substituents.

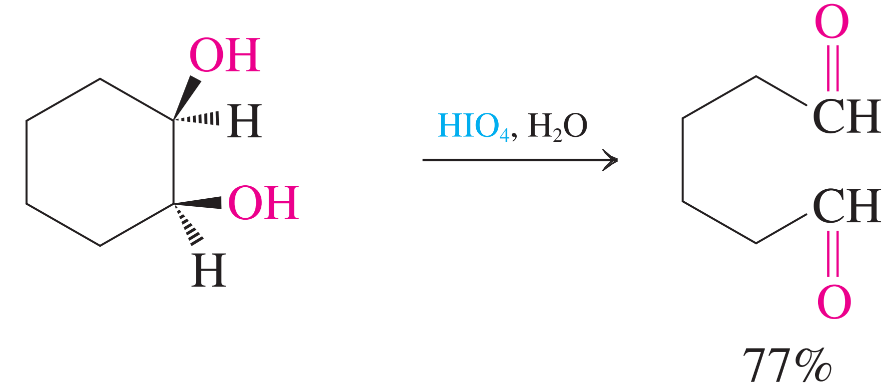
This selectivity arises from the intrinsically higher reactivity of the aldehyde function in oxidations (via the corresponding hydrates) and the lesser steric hindrance of primary versus secondary alcohols.

To achieve selective conversion of the internal hydroxy groups (leaving the remaining hydroxycarbonyl frame intact) requires more complex protecting-group strategies.

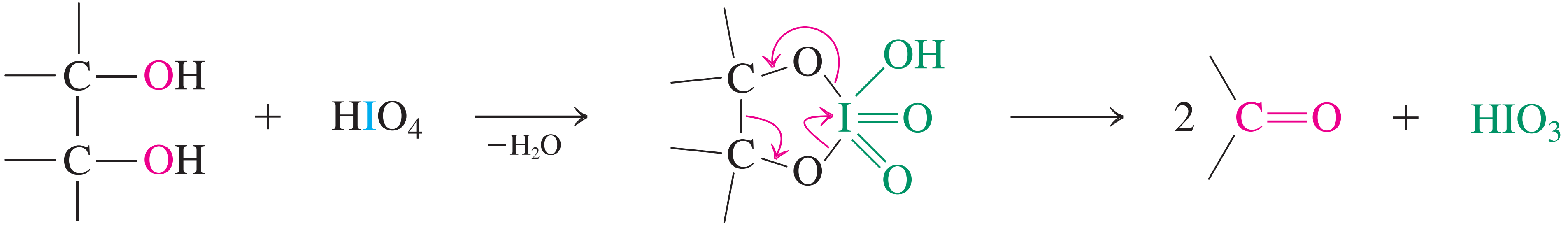
24-5 OXIDATIVE CLEAVAGE OF SUGARS

A reagent that leads to C–C bond rupture is periodic acid, HIO_4. This compound oxidatively degrades vicinal diols to give carbonyl compounds.

The mechanism of this transformation proceeds through a cyclic **periodate ester,** which decomposes to give two carbonyl groups.



cis-**1,2-Cyclohexanediol** **Hexanedial**



Cyclic periodate ester

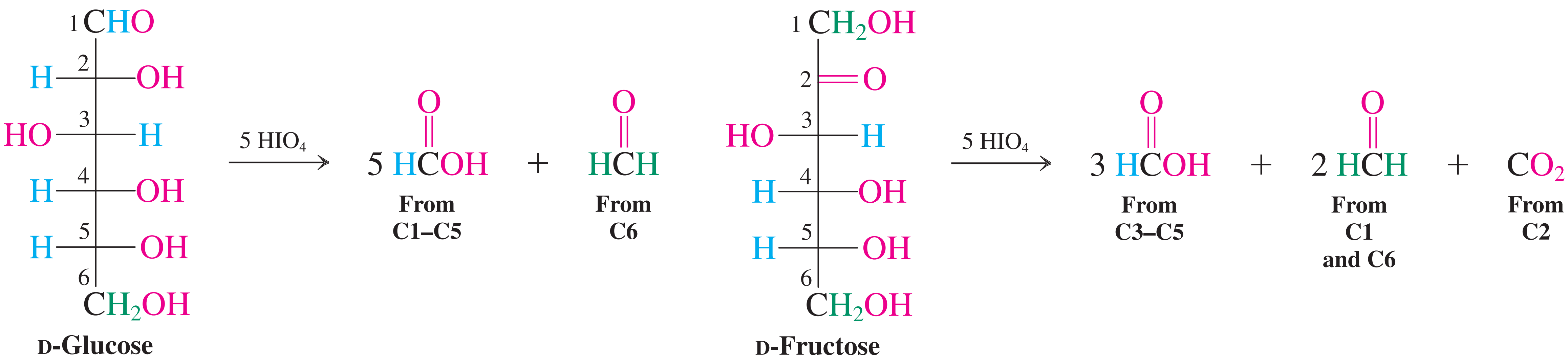
Because most sugars contain several pairs of vicinal diols, oxidation with HIO_4 can give complex mixtures. Sufficient oxidizing agent causes complete degradation of the chain to one-carbon compounds.

Treatment of glucose with five equivalents of HIO_4 results in the formation of five equivalents of formic acid and one of formaldehyde.

Similar degradation of the isomeric fructose consumes an equal amount of oxidizing agent, but the products are three equivalents of the acid, two of the aldehyde, and one of carbon dioxide.

It is found that (1) the breaking of each C–C bond in the sugar consumes one molecule of HIO_4, (2) each aldehyde and secondary alcohol unit furnishes an equivalent of formic acid, and (3) the primary hydroxy function gives formaldehyde. The carbonyl group in ketoses gives CO_2.

Periodic Acid Degradation of Sugars



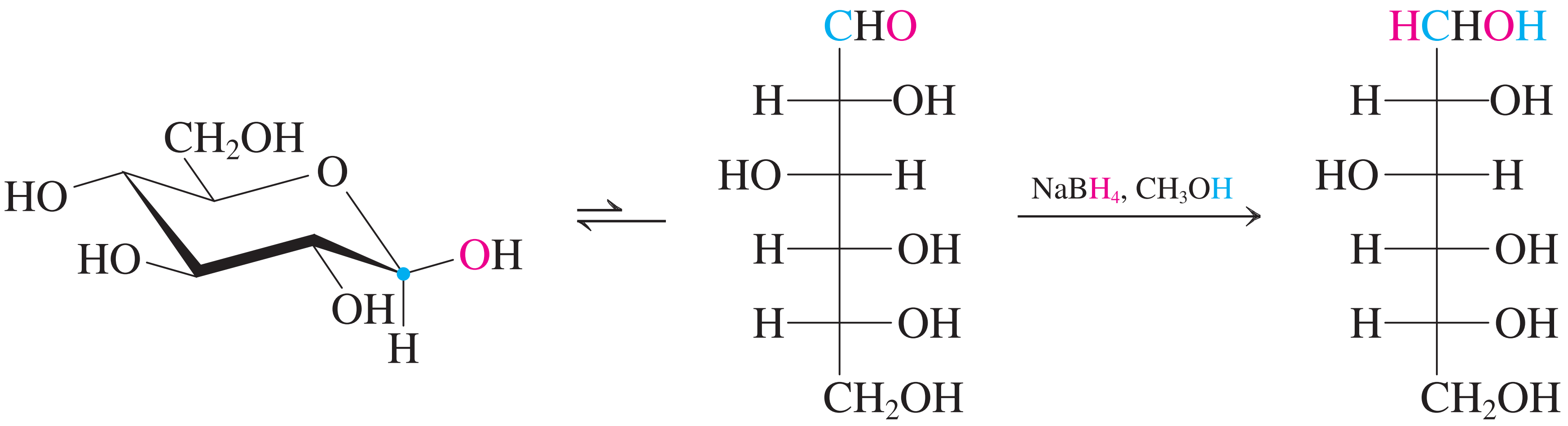
The number of equivalents of HIO_4 consumed reveals the size of the sugar molecule, and the ratios of products are important clues to the number and arrangement of hydroxy and carbonyl functions.

After degradation, each carbon fragment retains the same number of attached hydrogen atoms as were present in the original sugar.

24-6 REDUCTION OF MONOSACCHARIDES TO ALDITOLS

Aldoses and ketoses are reduced by the same types of reducing agents that convert aldehydes and ketones into alcohols. The resulting polyhydroxy compounds are called **alditols.** D-glucose gives D-glucitol (older name, D-sorbitol) when treated with sodium borohydride.

The hydride reducing agent traps the small amount of the open-chain form of the sugar, in this way shifting the equilibrium from the unreactive cyclic hemiacetal to the product.



D-Glucose

D-Glucitol
(D-Sorbitol)

Many alditols are found in nature. D-Glucitol is present in red seaweed in concentrations as high as 14%, as well as in many berries (but not in grapes), in cherries, in plums, in pears, and in apples.

It is prepared commercially from D-glucose by high-pressure hydrogenation or by electrochemical reduction.

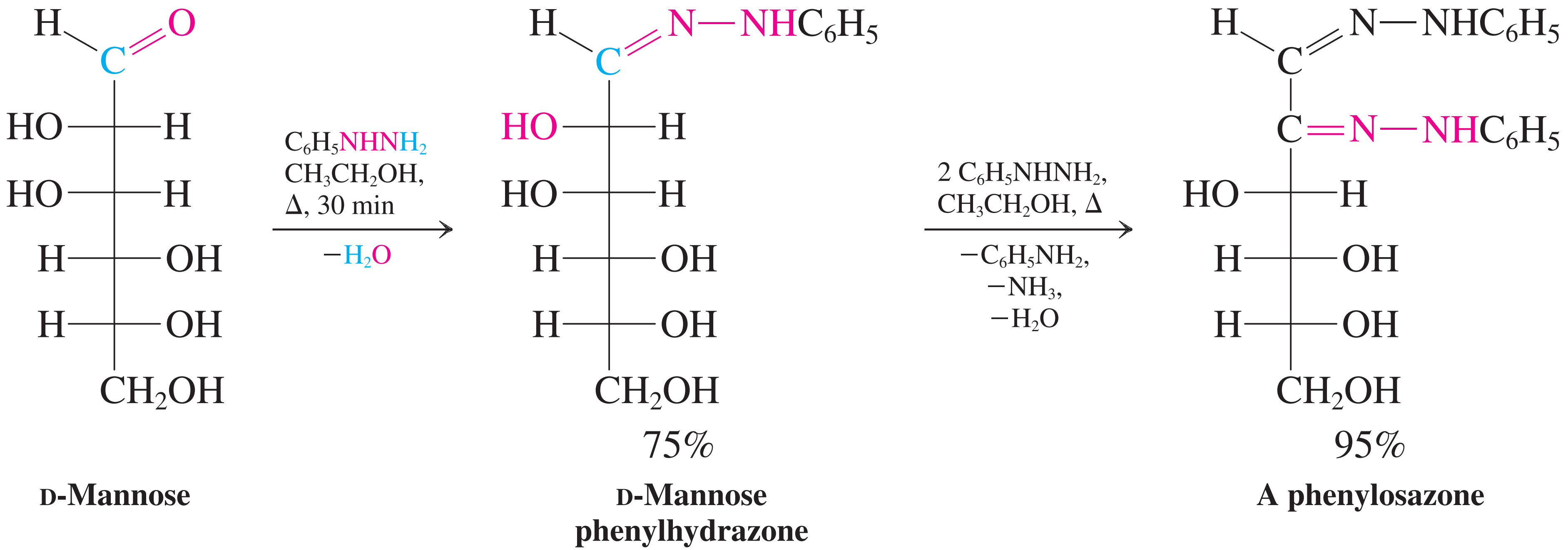
Glucitol is widely used as a sweetener in products such as mints, cough drops, mouthwashes, and chewing gum, where it is often identified by its alternative name, sorbitol.

Glucitol is similar in caloric content to glucose. However, the types of bacteria present in the mouth that cause dental caries are less capable of metabolizing glucitol than glucose.

24-7 CARBONYL CONDENSATIONS WITH AMINE DERIVATIVES

The carbonyl function in aldoses and ketoses undergoes condensation reactions with amine derivatives. Treatment of D-mannose with phenylhydrazine gives the corresponding **hydrazone,** D-mannose phenylhydrazone.

Surprisingly, the reaction does not stop at this stage but can be induced to continue with additional phenylhydrazine (two extra equivalents). The final product is a double phenylhydrazone, also called an **osazone** (here, phenylosazone).



The mechanism of osazone synthesis is complex and it constitutes an oxidation at C2 by one equivalent of phenylhydrazine, which in turn is reduced by N–N bond rupture to the component amines.

Once they are formed, the osazones do not continue to react with excess phenylhydrazine but are stable under the conditions of the reaction.

Sugars are well known for their reluctance to crystallize from syrups. Their osazones readily form yellow crystals with sharp melting points, thus simplifying the isolation and characterization of many sugars, particularly if they have been formed as mixtures or are impure.