

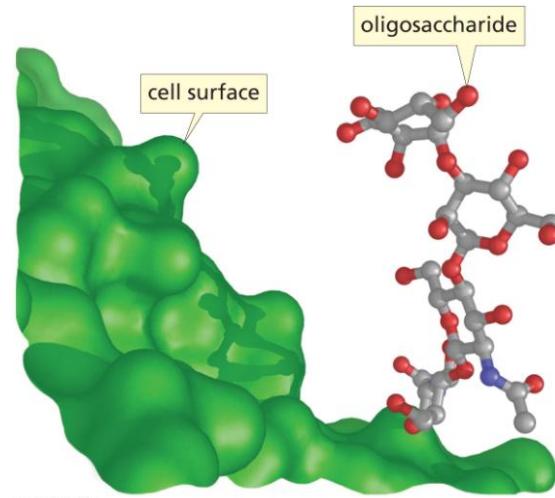
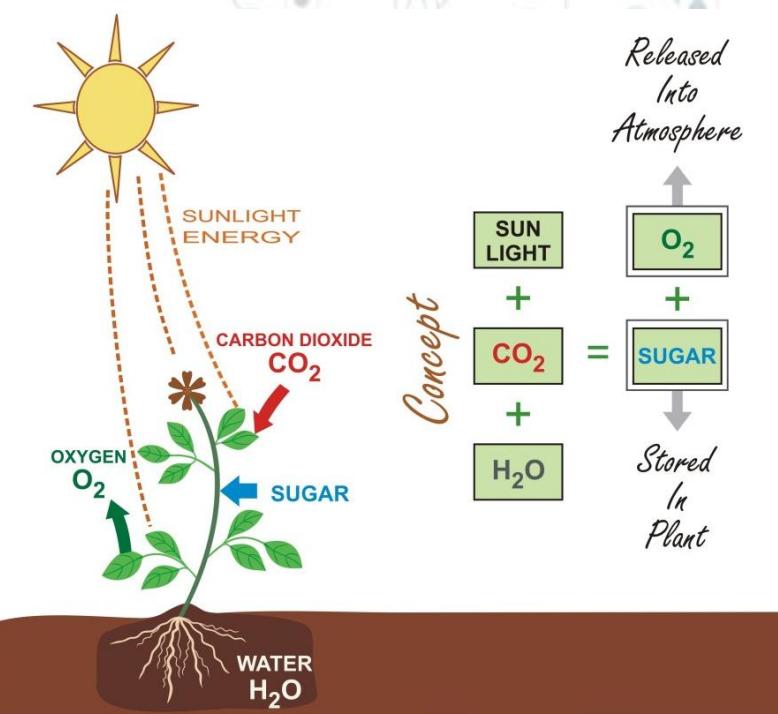
Notes on Carbohydrates



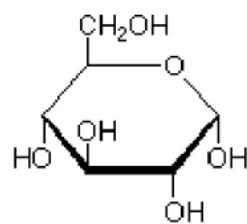
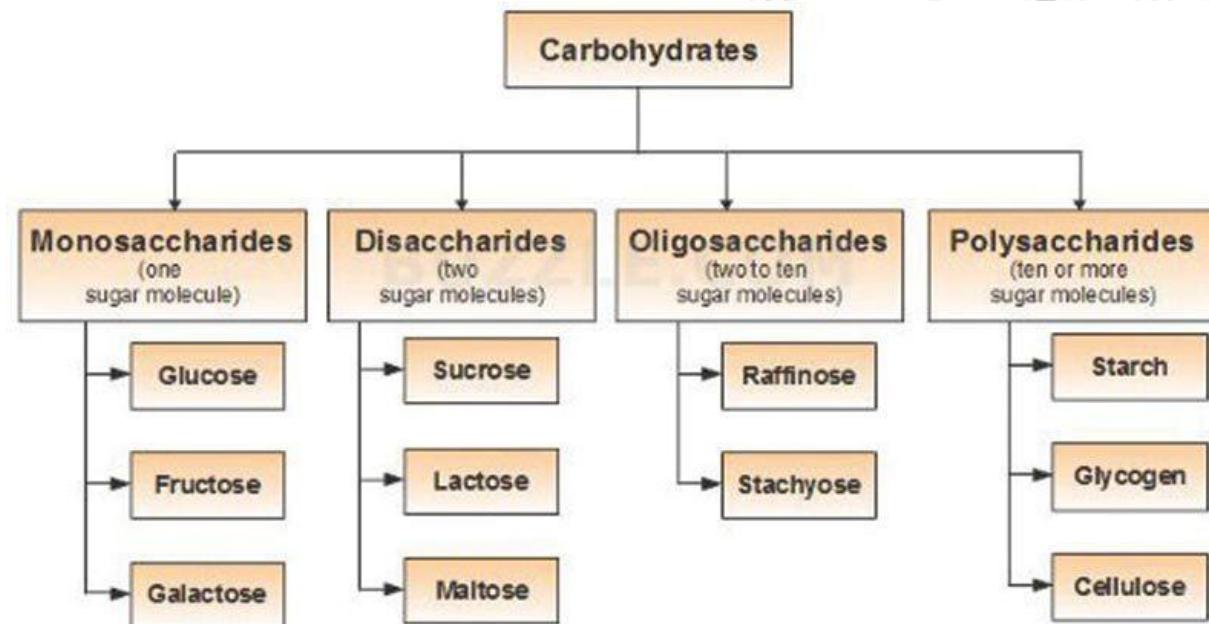
By
Dr. Gangutri Saikia

Introduction

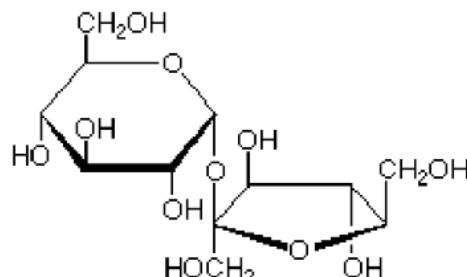
- ❖ Carbohydrates are the most abundant biomolecules on Earth.
- ❖ Each year, photosynthesis converts more than 100 billion metric tons of CO_2 and H_2O into cellulose and other plant products.
- ❖ Carbohydrates are polyhydroxy aldehydes and ketones, or substances that yield such compounds on hydrolysis.
- ❖ They have the general formula $\text{C}_n(\text{H}_2\text{O})_n$.
- ❖ Carbohydrates are widely distributed in all life forms and serve many roles such as-
 - They serve as energy stores, fuels and metabolic intermediates.
 - They are constituent of RNA and DNA backbones as ribose and deoxyribose sugars.
 - Polysaccharides are constituents of cell walls of bacteria and plants.
 - Carbohydrates are linked to surfaces of proteins and lipids where they play role as informational materials e.g. in cell-cell interaction and interaction between cells with other elements in the cellular environment.



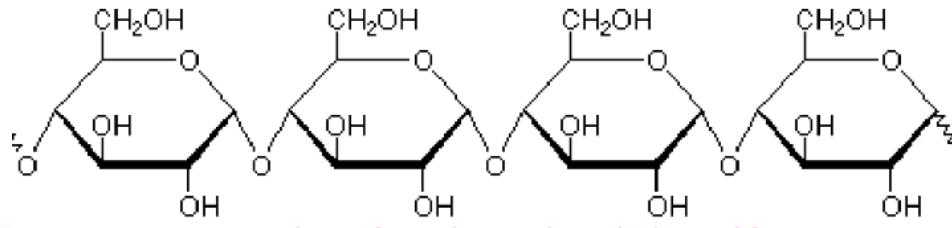
Classification of carbohydrates



glucose (a monosaccharide)



sucrose (a disaccharide)



amylose (a polysaccharide/starch)



Monosaccharide

fruits, vegetables, honey, nuts



Disaccharide-

sugars, milk



Polysaccharides

*(starchy foods)-
rice, potatoes, corn, wheat*



A monosaccharide is further sub-classified on the basis of-

- (1) Functional group
- (2) Number of carbon atoms

Functional group A monosaccharide can be a polyhydroxy aldehyde or ketone

Polyhydroxy aldehyde: aldose

Polyhydroxy ketone: ketose

Number of carbons

three carbons: triose

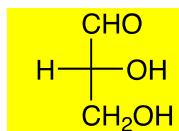
six carbons: hexose

four carbons: tetrose

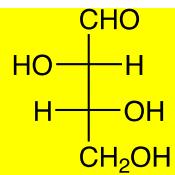
seven carbons: heptose

five carbons: pentose

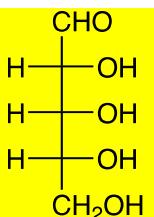
etc.



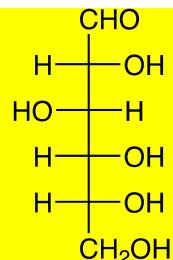
glyceraldehyde
(triose)



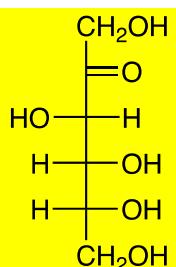
threose
(tetrose)



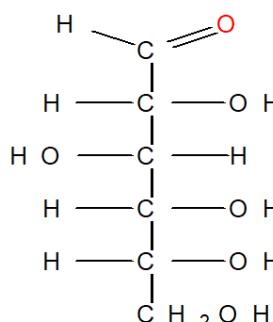
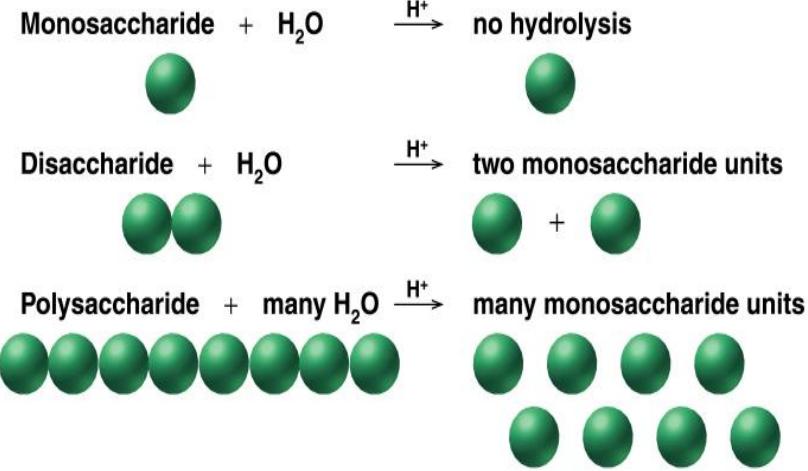
ribose
(pentose)



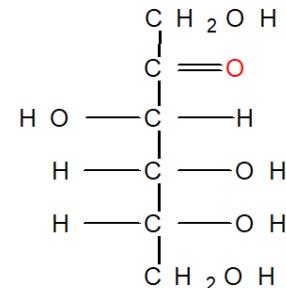
glucose
(hexose)
(alohexose)



fructose
(hexose)
(ketohexose)



D - glucose



D - fructose

Carbohydrates can be further classified as (i) reducing and (ii) non-reducing sugar. Carbohydrates that reduce Fehling's or Tollen's reagent are known as reducing sugar, while carbohydrates that do not reduce Fehling's or Tollen's reagent are known as non-reducing sugar

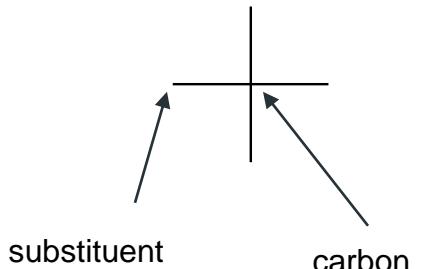
General properties of carbohydrates

Carbohydrates have the following major properties:

- They have chiral or asymmetric carbons that are generally manifested by the rotation of plane polarized light.
- They have the ability to form multiple hydrogen bonds, generally giving them the property of being water-soluble, but they also can be water-insoluble when they form intermolecular hydrogen bonds with each other to give crystals or large, high molecular weight, insoluble crystalline aggregates, granules, or fibers.
- They are generally, although not all of them, sweet-tasting (for example, D-glucose, D-glucitol, D-fructose, D-xylose, D-xylitol and sucrose are sweet-tasting) by forming specific hydrogen and hydrophobic bonds with the sweet-taste receptors on the tongue.
- When attached to proteins or cell surfaces, the structural diversity of oligosaccharides mediate a large number of biochemical and biological processes.
- Many have reactivities of aldehydes that can be oxidized to acids by reagents that are thereby reduced (e. g., reducing an oxidizing agent such as an alkaline solution of copper(II) or ferricyanide/cyanide), and they, hence, are considered to be reducing sugars, or they can themselves be reduced by reducing reagents, such as NaBH_4 , to give sugar alcohols.
- The aldehyde or ketone groups in carbohydrates with five or more carbons will react with intramolecular alcohol groups to form cyclic structures with hemiacetal and hemiketal hydroxyl groups.
- The hemiacetal or hemiketal hydroxyls are more reactive than the alcohols and can react intermolecularly with alcohols and amines to give acetals or ketals (glycosidic bonds) that are fairly stable.
- They have two kinds of alcohol groups, secondary and primary, that can undergo the usual reactions of alcohols to give esters and ethers and can be replaced, for example, by hydrogen, halogens (F, Cl, Br, and I), amino groups, *N*-acetyl amino groups, and sulfhydryl groups.

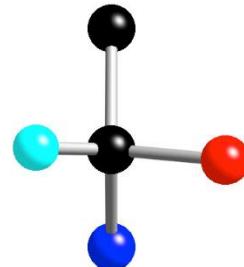
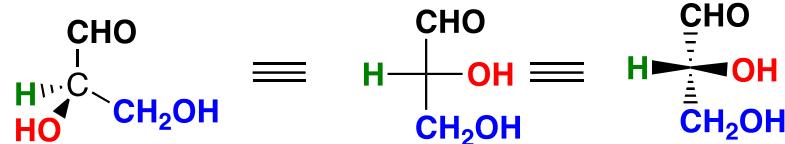
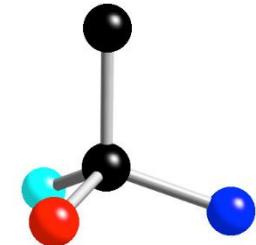
Fischer Projections and the D, L Notation. Representation of a three-dimensional molecule as a flat structure. Tetrahedral carbon represented by two crossed lines:

horizontal line is coming out of the plane of the page (toward you)

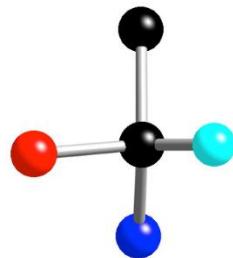
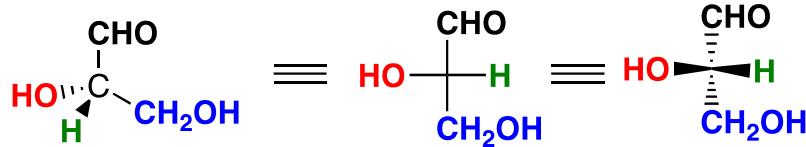
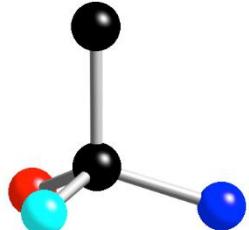


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(R)-(+)-glyceraldehyde



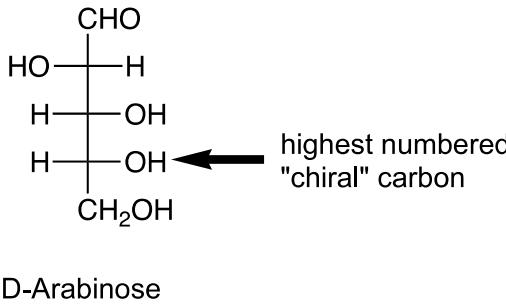
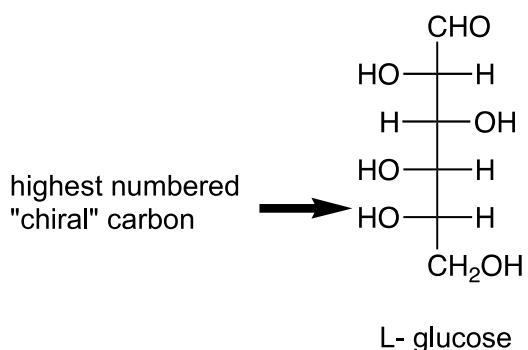
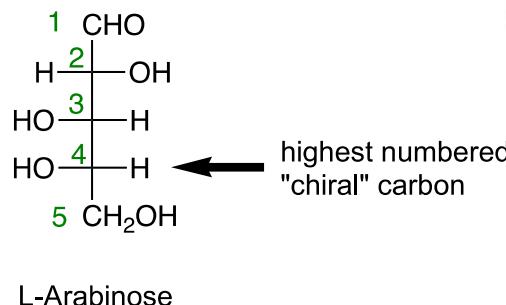
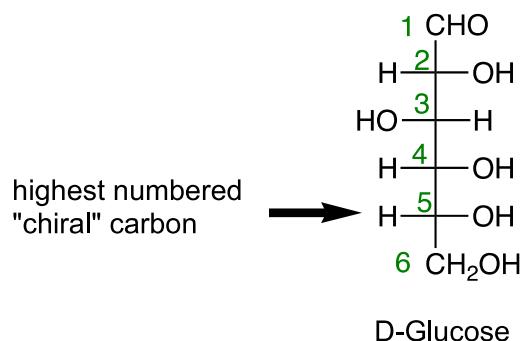
(S)-(-)-glyceraldehyde



For carbohydrates, the convention is to arrange the Fischer projection with the carbonyl group at the top for aldoses and closest to the top for ketoses. The carbons are numbered from top to bottom.

Carbohydrates are designated as D- or L- according to the stereochemistry of the highest numbered chiral carbon of the Fischer projection. If the hydroxyl group of the highest numbered chiral carbon is pointing to the right, the sugar is designated as **D** (Dextro: Latin for *on the right side*). If the hydroxyl group is pointing to the left, the sugar is designated as **L** 7 (Levo: Latin for *on the left side*). Most naturally occurring carbohydrates are of the D-configuration.

D and L, like R and S, indicate the configuration of a chirality center, but they do not indicate whether the compound rotates plane polarized light to the right (+) or to the left (-).



All of the monosaccharides except dihydroxyacetone contain one or more asymmetric (chiral) carbon atoms and thus occur in optically active isomeric forms. The simplest aldose, glyceraldehyde, contains one chiral center (the middle carbon atom) and therefore has two different optical isomers, or enantiomers. One of the two enantiomers of glyceraldehyde is, by convention, designated the D isomer and the other is the L isomer. In general, a molecule with n chiral centers can have 2^n stereoisomers. Glyceraldehyde has $2^1 = 2$; the aldohexoses with four chiral centers have $2^4 = 16$. 16 stereoisomers i.e. eight pairs of enantiomers.

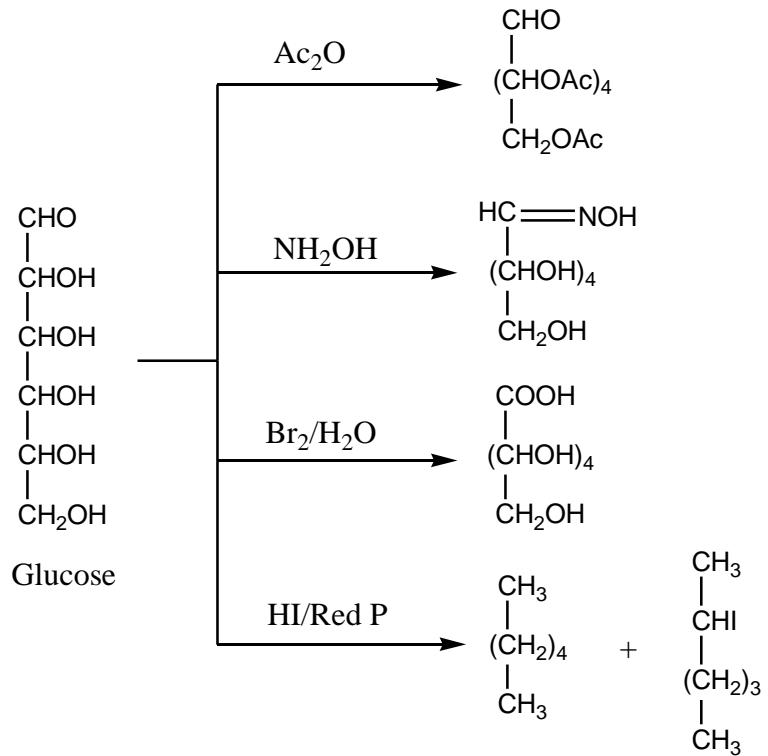
(+)-Glucose: An aldohexose

- ❖ Glucose is the most abundant monosaccharide as it is the unit of starch, cellulose and glycogen are made up.
- ❖ It is found in ripe grapes, honey and most sweet fruits.
- ❖ It is a normal constituent of blood and occurs in the urine of diabetics.

- (+)-Glucose has the molecular formula $C_6H_{12}O_6$, as shown by elemental analysis and molecular weight determinations.
- When treated with acetic anhydride, it forms penta-acetate. This indicates the presence of five hydroxyl groups, and since they are not easily dehydrated, it can be assumed that each hydroxyl group is attached to a different carbon atom.
- When treated with hydroxylamine, it forms an oxime, suggests the presence of carbonyl group.
- When it is oxidised with bromine water, a pentahydroxyacid of formula $C_6H_{12}O_7$ is obtained. This indicates that the carbonyl group is present as aldehydic group.
- When reduced with concentrated hydriodic acid and red phosphorus at $100\text{ }^{\circ}\text{C}$, it gives a mixture of 2-iodohexane and n-hexane. This indicates six carbon atoms in the compound are in straight chain.

Based on the above evidences the open chain structure of glucose is-

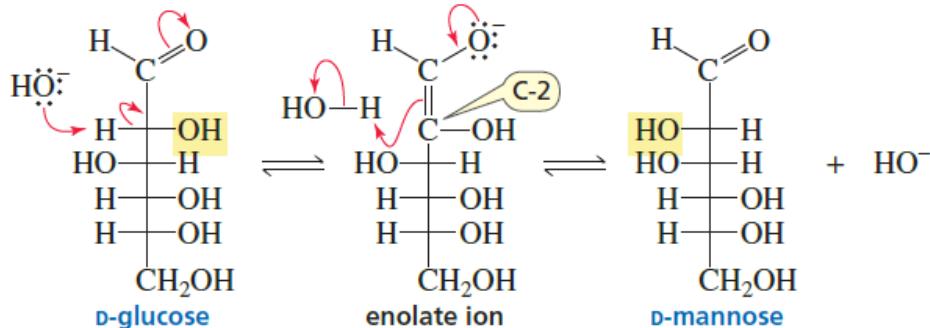




These reactions summarized the evidences about the structure of glucose: evidence consistent with the idea that (+)-glucose is a six carbon, straight chain, pentahydroxy aldehyde, i.e., (+)-glucose is an aldohexose.

Reactions of Glucose

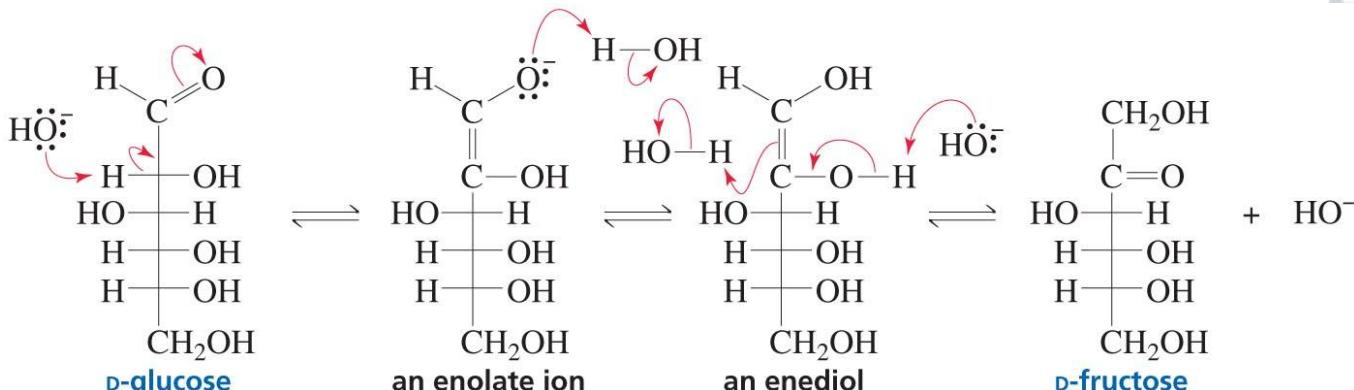
Epimerization



- The base removes a proton from the α -carbon, forming an enonate ion.
- When C-2 is reprotonated, the proton can come from top or bottom of the planar sp^2 carbon, forming both D-glucose and D-mannose (C-2 epimers).
- Because, the reaction forms a pair of epimers, it is called epimerization. It changes the configuration of a carbon by removing a proton and then reprotonating it.
- Epimers are diastereomers that contain more than one chiral center but differ from each other in absolute configuration at only one chiral center.

The Enediol rearrangement

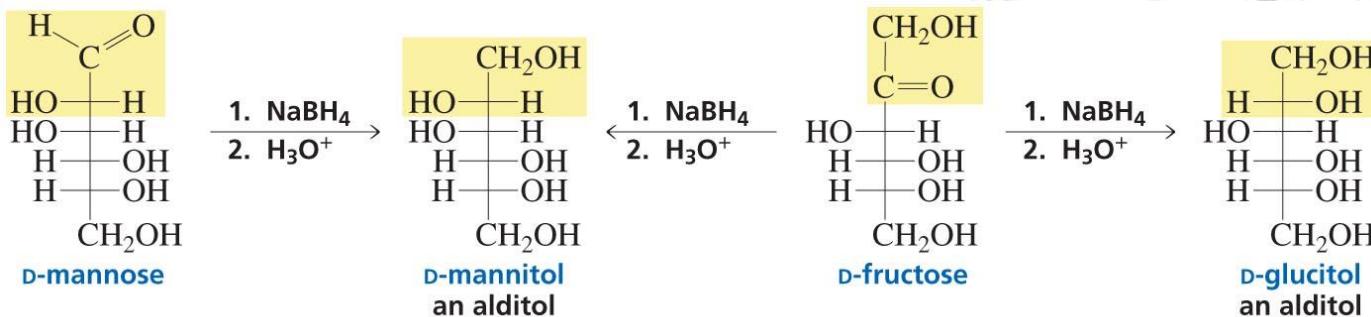
D-glucose also undergoes enediol rearrangement, which also forms D-fructose.



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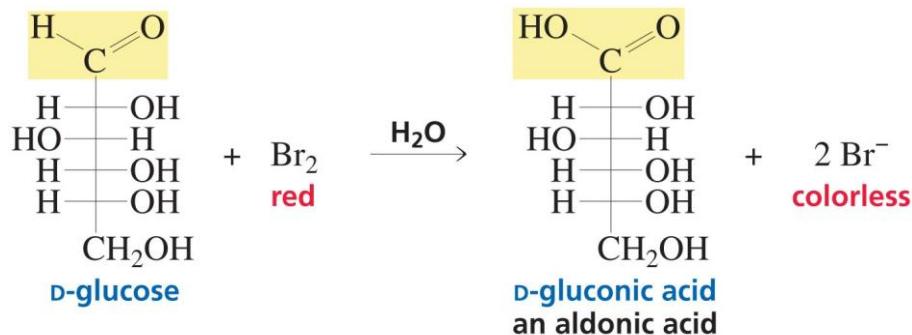
- The base removes a proton from an α -carbon, forming an enolate ion.
- Either C-2 can be protonated, or the oxygen of the enolate ion can be protonated to form an enediol.
- The enediol has two OH groups that can form a carbonyl group. Removal of a proton from the OH at C-1 followed by tautomerization re-forms D-glucose or forms D-mannose; removal of a proton from the OH group at C-2 followed by tautomerization forms D-fructose.
- Another enediol rearrangement, initiated by a base removing a proton from C-3 of D-fructose, forms an enediol that can tautomerize to give a ketose with the carbonyl group at C-2 or C-3. Thus, the carbonyl group can be moved up and down the chain.

Reduction



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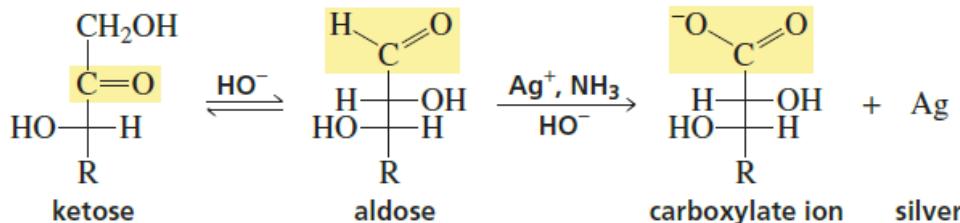
Oxidation



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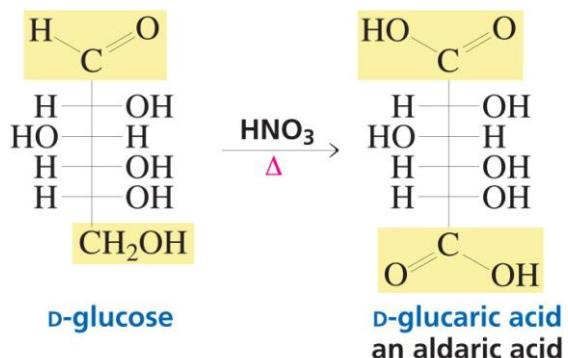
- ❖ Br₂ is a mild oxidizing agent that easily oxidizes aldehydes but cannot oxidize ketones or alcohols. Therefore, adding a small amount of an aqueous solution of Br₂ to an unknown monosaccharide can tell you whether the sugar is an aldose or a ketose.
- ❖ The reddish-brown color of Br₂ will disappear if the monosaccharide is an aldose because when Br₂ oxidizes the aldehyde, Br₂ is reduced to Br⁻, which is colorless. If the red color persists, indicating no reaction with Br₂, then the monosaccharide is a ketose. The product of the oxidation reaction is an **aldonic acid**.

Both aldoses and ketoses are oxidized to aldonic acids by Tollens reagent.



Although Tollens' reagent only oxidizes aldehydes, it cannot be used to distinguish aldoses and ketoses. The oxidation reaction is carried out in a basic solution that will convert a ketose to an aldehyde by an enediol rearrangement, and the aldehyde will then be oxidized by Tollens' reagent.

A strong oxidizing agent such as HNO_3 can oxidize both the aldehyde and the alcohol groups.

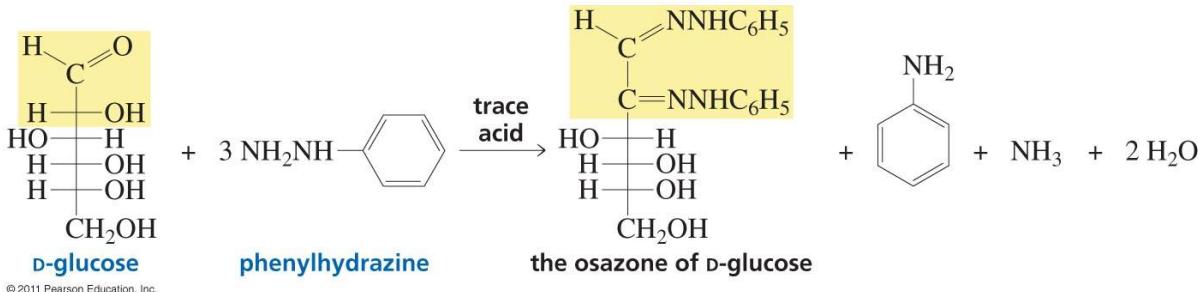


It oxidizes aldehydes and primary alcohols, but it does not oxidize secondary alcohols. The product obtained when both the aldehyde and the primary alcohol groups of an aldose are oxidized is called an aldarcic acid.

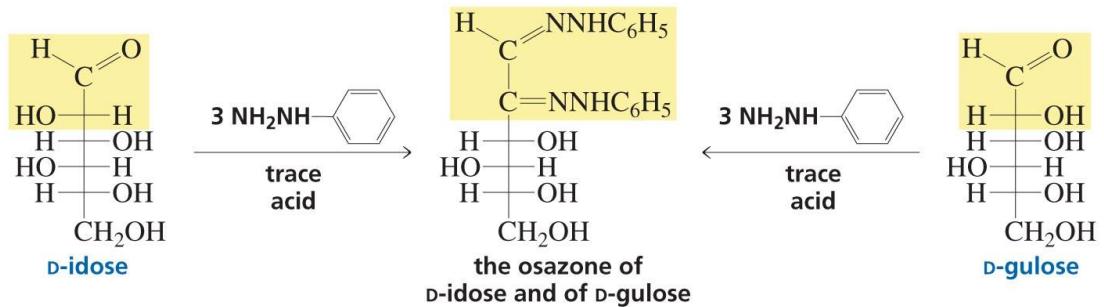
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Osazone formation

Aldoses and ketoses react with three equivalents of phenylhydrazine to form osazones.

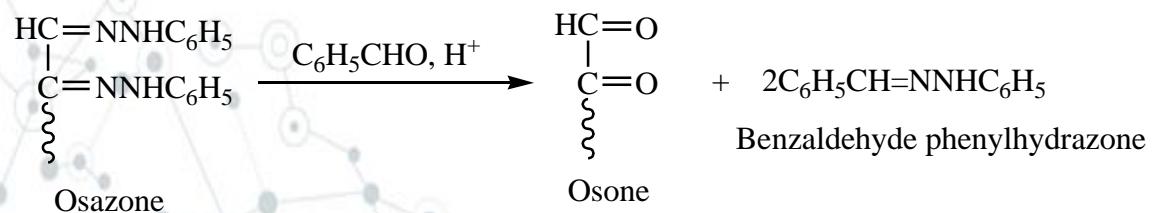


The C-2 epimers of aldoses form identical osazones...



...because the configuration of the C-2 carbon is lost during osazone formation, does not affect the configuration of the rest of the molecule. This is useful not only in identifying carbohydrates, but also in determining their configuration. Treatment with phenylhydrazine converts carbohydrates into solid osazones, which are readily isolated and purified, and can be identified by their characteristic crystalline forms.

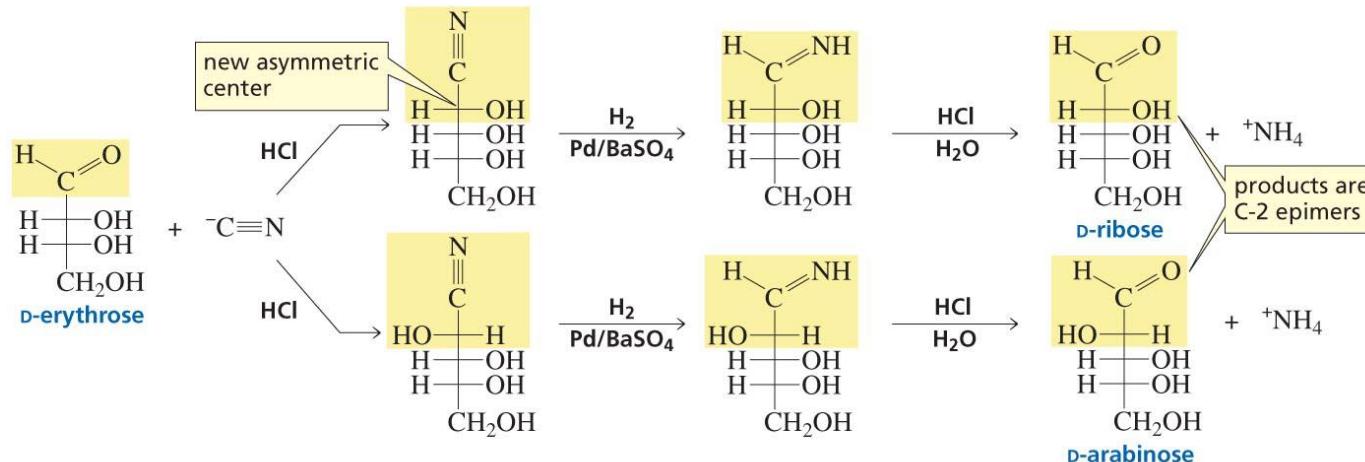
Removal of phenylhydrazine yields dicarbonyl compounds known as osones.



Lengthening the chain: The Kiliani–Fischer synthesis

The carbon chain of an aldose can be increased by one carbon by a modified **Kiliani–Fischer synthesis**. Thus, tetroses can be converted to pentoses, and pentoses can be converted to hexoses.

the modified Kiliani–Fischer synthesis



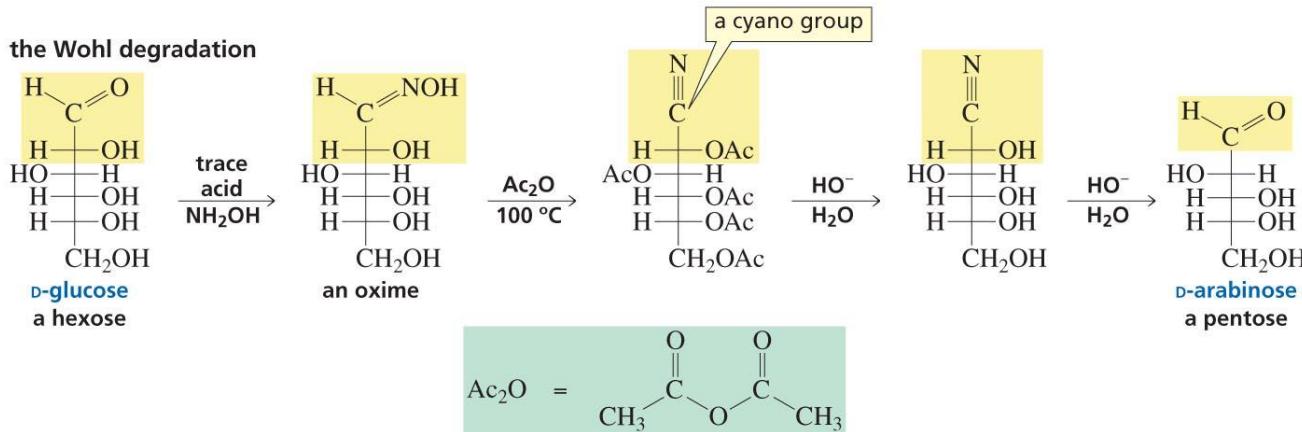
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- In the first step, hydrogen cyanide adds to the carbonyl group. This reaction converts the carbonyl carbon in the starting material to an asymmetric center. Consequently, two products are formed that differ only in their configuration at C-2. The configurations of the other asymmetric centers do not change because no bond to any of the asymmetric centers is broken during the course of the reaction.
- The $\text{C}\equiv\text{N}$ bond is reduced to an imine, using a partially deactivated catalyst so that the imine is not further reduced to an amine.
- The two imines are hydrolyzed to two aldoses.
- The modified Kiliani–Fischer synthesis leads to a pair of C-2 epimers. The two epimers are not obtained in equal amounts because they are diastereomers.

Shortening the chain: The Wohl degradation

The **Wohl degradation**—the opposite of the Kiliani–Fischer synthesis—shortens an aldose chain by one carbon.

Thus, hexoses are converted to pentoses, and pentoses are converted to tetroses.

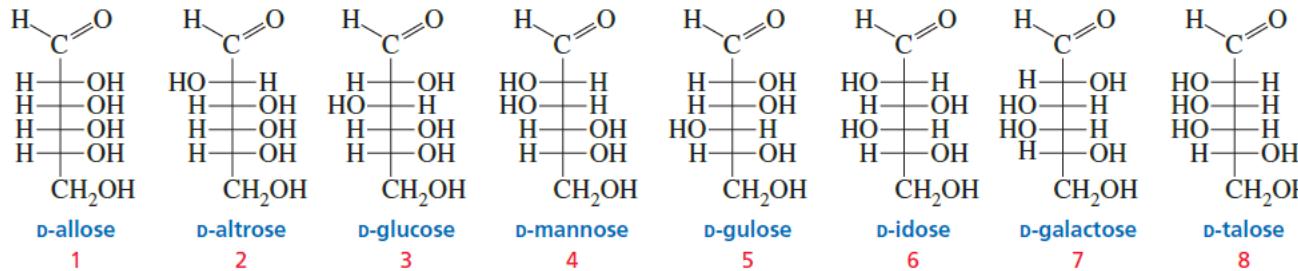


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- In the first step, the aldehyde reacts with hydroxylamine to form an oxime.
- Heating with acetic anhydride dehydrates the oxime, forming a cyano group; in addition, all the OH groups are converted to esters as a result of reacting with acetic anhydride.
- In a basic aqueous solution, all the ester groups are hydrolyzed and the cyano group is eliminated.

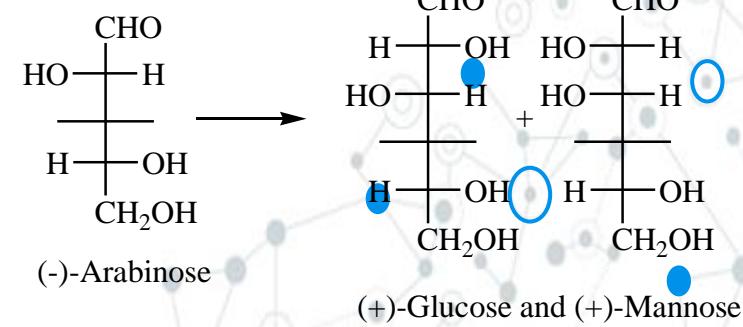
Configuration of Glucose

- Emil Fischer's determined the stereochemistry of glucose, done in 1891.
- Fischer knew that (+)-glucose is an aldohexose, but 16 different structures can be written for an aldohexose. Which of them represents the structure of (+)-glucose?
- The 16 stereoisomers of an aldohexose are actually eight pairs of enantiomers, so if the structures of one set of eight can be known, then automatically the structures of the other set of eight can be determined. Therefore, Fischer needed to consider only one set of eight.
- He considered the eight stereoisomers that have their C-5 OH group on the right in the Fischer projection (the stereoisomers shown here, which we now call the D-aldoses). One of these is (+)-glucose and its mirror image is (-)-glucose.

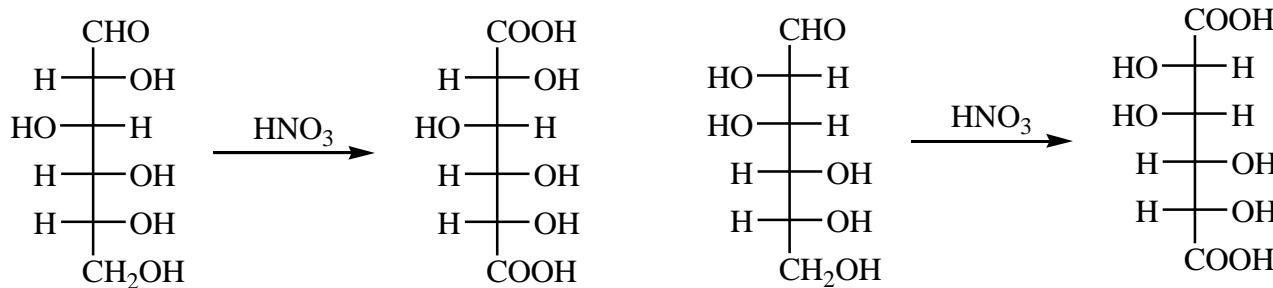


Fischer used the following information to determine glucose's stereochemistry—that is, to determine the configuration of each of its asymmetric centers.

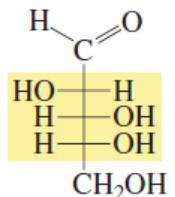
- When the Kiliani–Fischer synthesis is performed on the sugar known as (-)-arabinose, the two sugars known as (+)-glucose and (+)-mannose are obtained. This means that (+)-glucose and (+)-mannose are C-2 epimers. Consequently, (+)-glucose and (+)-mannose have to be one of the following pairs: sugars 1 and 2, 3 and 4, 5 and 6, or 7 and 8.



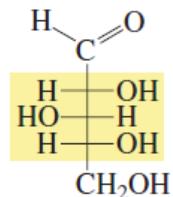
2. (+)-Glucose and (+)-mannose are both oxidized by nitric acid to optically active aldaric acids. The aldaric acids of sugars 1 and 7 would not be optically active because each has a plane of symmetry (a compound containing a plane of symmetry is achiral). Excluding sugars 1 and 7 means that (+)-glucose and (+)-mannose must be sugars 3 and 4 or 5 and 6.



3. Because (+)-glucose and (+)-mannose are the products obtained when the Kiliani–Fischer synthesis is carried out on (-)-arabinose, Fischer knew that if (-)-arabinose has the structure shown below on the left, then (+)-glucose and (+)-mannose are sugars 3 and 4. On the other hand, if (-)-arabinose has the structure shown on the right, then (+)-glucose and (+)-mannose are sugars 5 and 6:



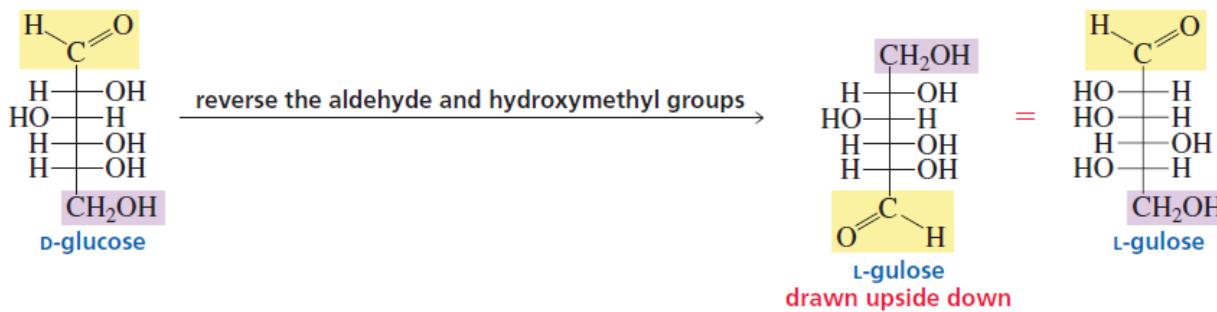
the structure of (-)-arabinose if
(+)-glucose and (+)-mannose
are sugars 3 and 4



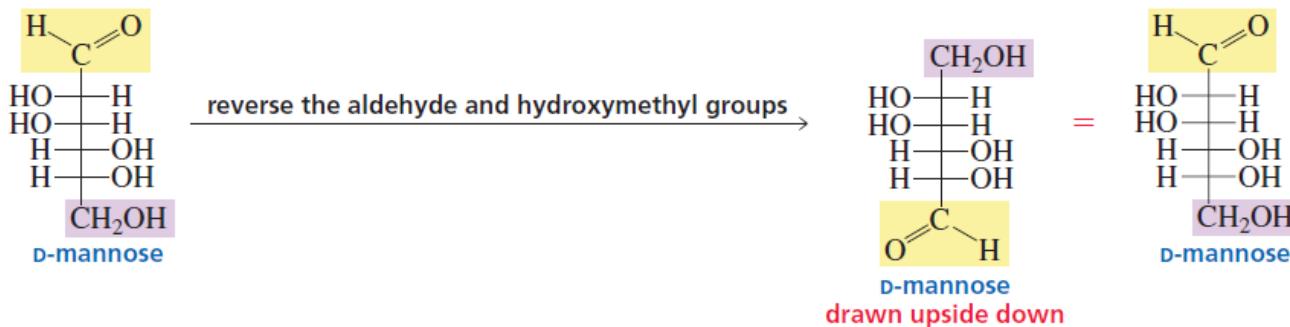
the structure of (-)-arabinose if
(+)-glucose and (+)-mannose
are sugars 5 and 6

When (-)-arabinose is oxidized with nitric acid, it forms an optically active aldaric acid. This means that the aldaric acid does *not have a plane of symmetry*. Therefore, (-)-arabinose *must have* the structure shown above on the left because the aldaric acid of the sugar on the right would have a plane of symmetry. Thus, (+)-glucose and (+)-mannose are represented by sugars 3 and 4.

4. Now the only question is whether (+)-glucose is sugar 3 or sugar 4. For this, Fischer had to develop a chemical method for interchanging the aldehyde and primary alcohol groups of an aldohexose. When he chemically interchanged those groups on the sugar known as (+)-glucose, he obtained an aldohexose that was different from (+)-glucose, but when he interchanged those groups on (+)-mannose, he still had (+)-mannose. Therefore, he was able to conclude that (+)-glucose is sugar 3 because interchanging its aldehyde and primary alcohol groups leads to a different sugar (L-gulose).



If (+)-glucose is sugar 3, then (+)-mannose must be sugar 4. As predicted, when the aldehyde and hydroxymethyl groups of sugar 4 are interchanged, the same sugar is obtained.

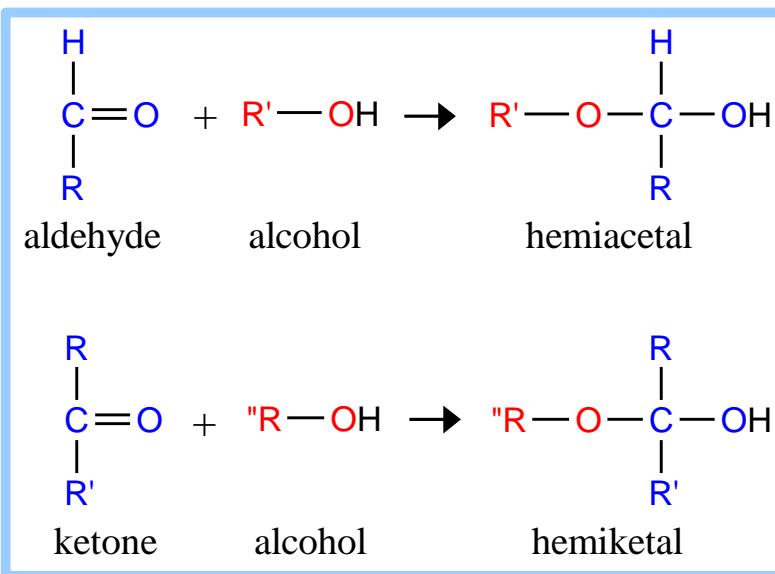


Cyclized structure of Glucose

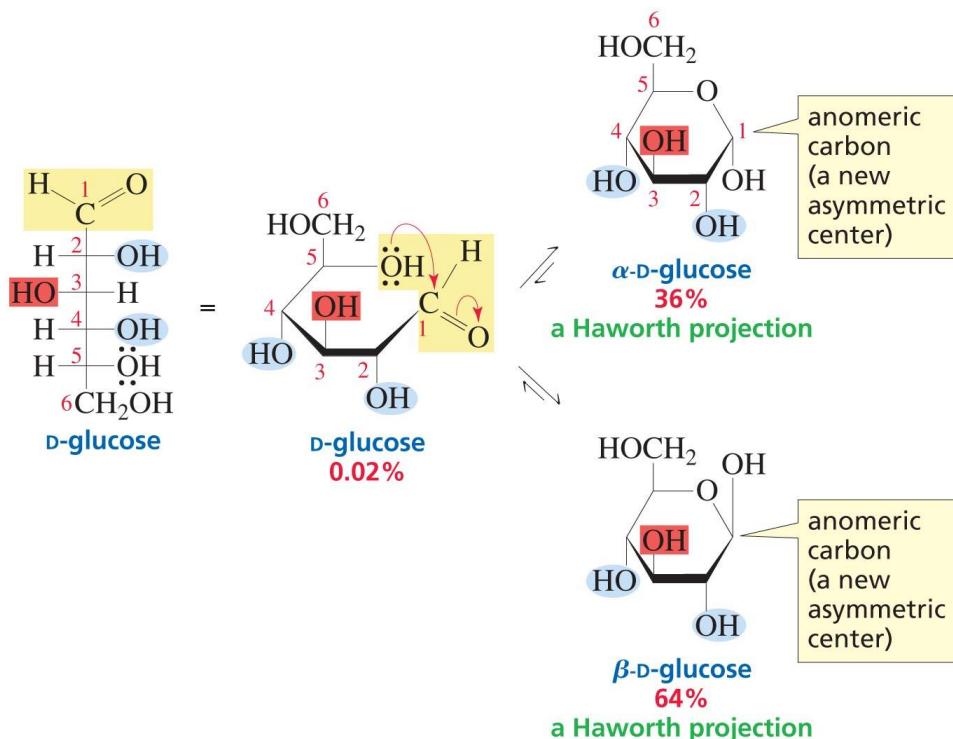
D-glucose exists in three different forms- open chain form and two cyclic forms- α -D-glucose and β -D-glucose. The cyclic forms are different because they have different physical properties: α -D-glucose melts at 146 °C, whereas β -D-glucose melts at 150 °C; α -D-glucose has a specific rotation of +112.2 °, and β -D-glucose has a specific rotation of +18.7°.

How can D-glucose exist in a cyclic form?

- An aldehyde reacts with an equivalent of an alcohol to form a hemiacetal.



A monosaccharide such as D-glucose has an aldehyde group and several alcohol groups. The alcohol group bonded to C-5 of D-glucose reacts intramolecularly with the aldehyde group, forming a six membered ring hemiacetal.



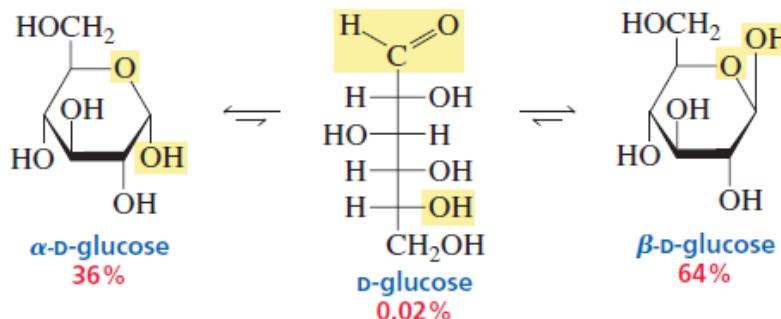
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Two different hemiacetals are formed because the carbonyl carbon of the open chain sugar becomes a new chirality center in the hemiacetal. If the OH group bonded to the new chirality center is on the right, it is α -D-glucose; if the OH group is on the left, it is β -D-glucose.

α -D-glucose and β -D-glucose are called anomers. **Anomers** are two sugars that differ in configuration only at the carbon that was the carbonyl carbon in the open chain form. This is called the anomeric carbon.

In Haworth projection, the six membered ring is represented as being flat and is viewed edge on. The ring oxygen is always placed in the back right hand corner of the ring, with the anomeric carbon (C-1) on the right hand side and the primary alcohol group drawn up from the back left hand corner (C-5). **Groups on the right in Fischer projection are down in Haworth projection. Groups on the left in Fischer projection are up in Haworth projection.**

Cyclic compounds are in equilibrium with the open chain compound



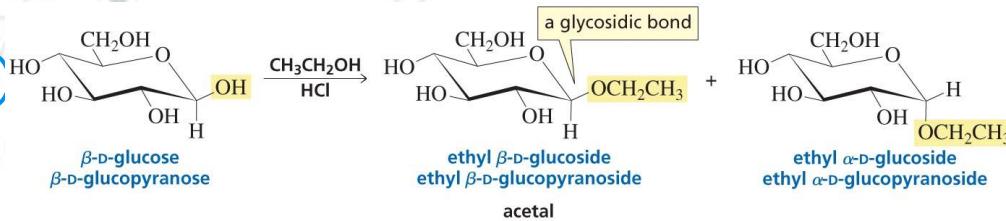
In aqueous solution, the open chain form of glucose is in equilibrium with the two cyclic hemiacetals. Formation of six membered ring cyclic hemiacetals proceeds nearly to completion, so very little glucose exists in the open chain form. At equilibrium, there is almost twice as much β-D-glucose as α-D-glucose. Glucose still undergoes the reactions due to the aldehydic group such as oxidation, reduction, and osazone formation etc. Because, the reagents can react with the small amount of open chain aldehyde that is present. As the aldehyde reacts, the equilibrium shifts to form more aldehyde, which can then undergo reaction. Eventually, all the glucose molecules react by way of the open chain aldehyde.

Mutarotation

When crystals of α-D-glucose are dissolved in water, the specific rotation gradually changes from +112.2° to +52.7°. When crystals of β-D-glucose are dissolved in water, the specific rotation gradually changes from +18.7° to +52.7°. This change of rotation occurs, because, in water, the hemiacetal opens to form the aldehyde, and when the aldehyde recycles, both α-D-glucose and β-D-glucose can be formed. Eventually, all three forms of glucose reach equilibrium concentration. The specific rotation of the equilibrium mixture is +52.7°. This is why, the same specific rotation results whether the crystals originally dissolved in water are α-D-glucose or β-D-glucose or any mixture of the two. A slow change in optical rotation to an equilibrium value is called mutarotation.

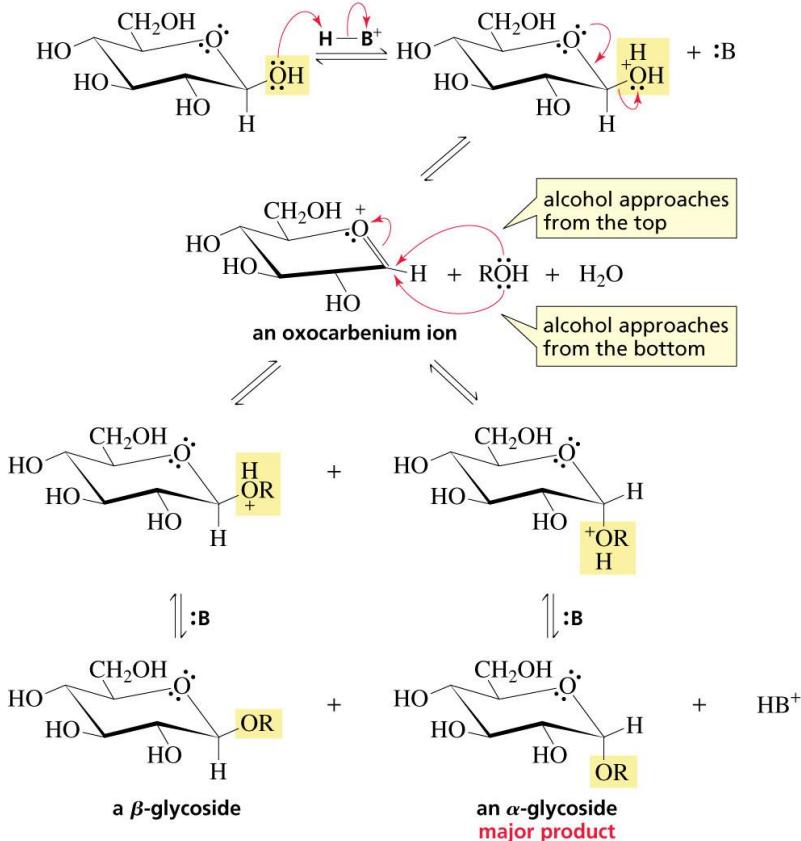
Formation of glycosides

In the same way that a hemiacetal reacts with an alcohol to form an acetal, the cyclic hemiacetal formed by a monosaccharide can react with an alcohol to form two acetals.



The acetal of a sugar is called a glycoside, and the bond between the anomeric carbon and the alkoxy oxygen is called a glycosidic bond.

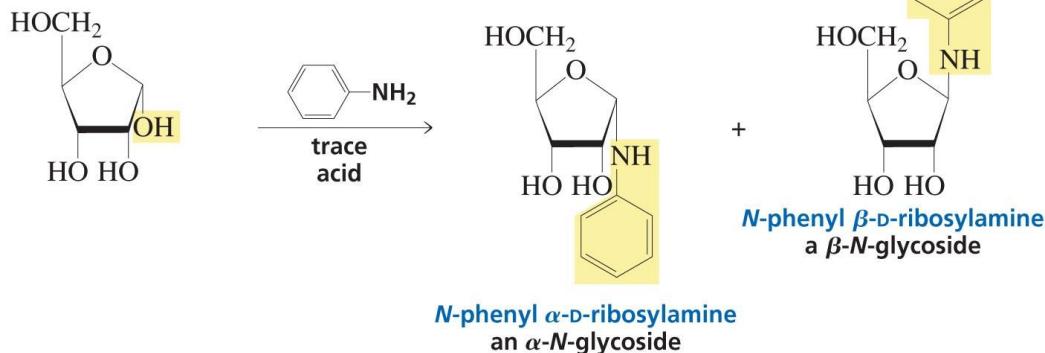
Mechanism for glycoside formation



- ✓ The acid protonates the OH group bonded to the anomeric carbon.
- ✓ A lone pair on the ring oxygen helps eliminate a molecule of water. The anomeric carbon in the resulting oxocarbenium ion is *sp*² hybridized, so that part of the molecule is planar. (**An oxocarbenium ion has a positive charge that is shared by a carbon and an oxygen.**)
- ✓ When the alcohol approaches from the top of the plane, the β -glycoside is formed; when the alcohol approaches from the bottom of the plane, the α -glycoside is formed.

Formation of an *N*-Glycoside

The reaction of a monosaccharide with an amine is similar to the reaction of a monosaccharide with an alcohol. The product of the reaction is an *N*-glycoside. An ***N*-glycoside has a nitrogen in** place of the oxygen at the glycosidic linkage. The subunits of DNA and RNA are β -*N*-glycosides.



The Anomeric effect

When glucose reacts with an alcohol to form a glucoside, the major product is the α -glucoside. Because acetal formation is reversible, the α -glucoside must be more stable than the β -glucoside. The preference of certain substituents bonded to the anomeric carbon for the axial position is called the **anomeric effect**.

What is responsible for the anomeric effect?

If the substituent is axial, one of the ring oxygen's lone pairs is in an orbital that is parallel to the σ^* antibonding orbital of the C–Z bond. The molecule then can be stabilized by hyperconjugation—some of the electron density moves from the *sp*³ orbital of oxygen into the σ^* antibonding orbital. If the substituent is equatorial, neither of the orbitals that contain a lone pair is aligned correctly for overlap.

