Notes on Carbohydrates

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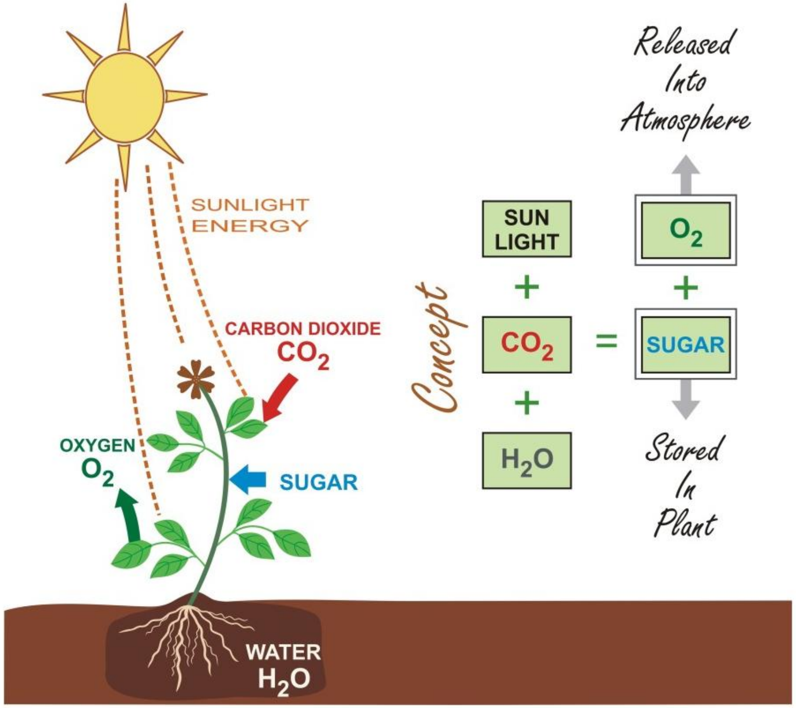
ESTD. 1962
NAGAON-ASSAM

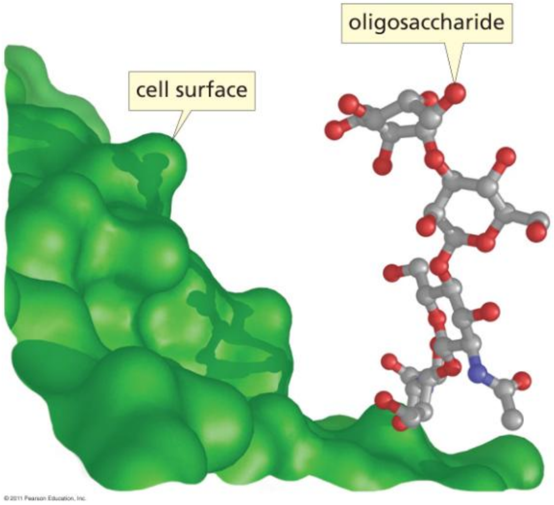
By

Dr. Gangutri Saikia

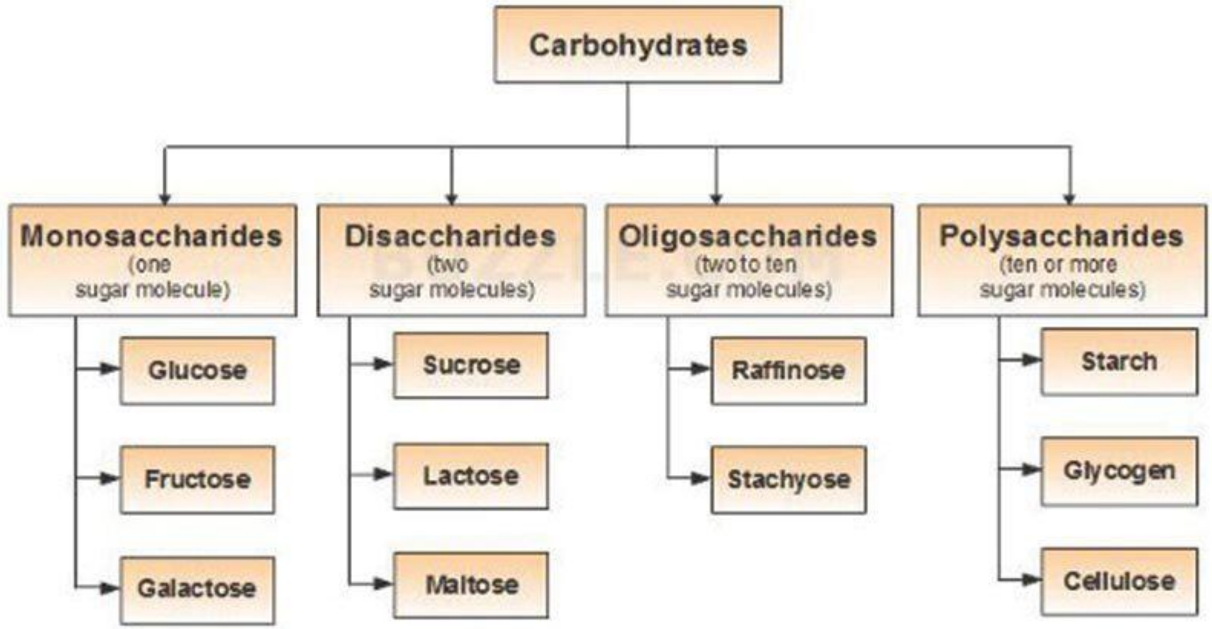
Introduction



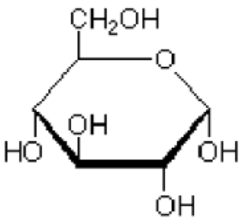
- ❖ Carbohydrates are the most abundant biomolecules on Earth.
- ❖ Each year, photosynthesis converts more than 100 billion metric tons of CO_2 and H_2O into cellulose and other plant products.
- ❖ Carbohydrates are polyhydroxy aldehydes and ketones, or substances that yield such compounds on hydrolysis.
- ❖ They have the general formula $C_n(H_2O)_n$.
- ❖ Carbohydrates are widely distributed in all life forms and serves 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.



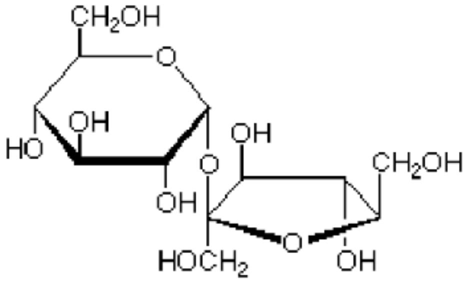
Classification of carbohydrates



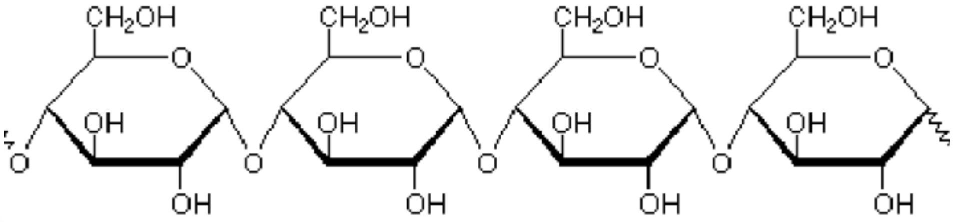
- Carbohydrates
  - Monosaccharides (one sugar molecule)
    - Glucose
    - Fructose
    - Galactose
  - Disaccharides (two sugar molecules)
    - Sucrose
    - Lactose
    - Maltose
  - Oligosaccharides (two to ten sugar molecules)
    - Raffinose
    - Stachyose
  - Polysaccharides (ten or more sugar molecules)
    - Starch
    - Glycogen
    - Cellulose



glucose (a monosaccharide)



sucrose (a disaccharide)



amylose (a polysaccharide/starch)

Monosaccharide -

fruits,vegebtables,honey, nuts

Disaccharide-

sugars,milk

Polysaccharides-

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

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

(1) Functional group

(2) Number of carbon atoms

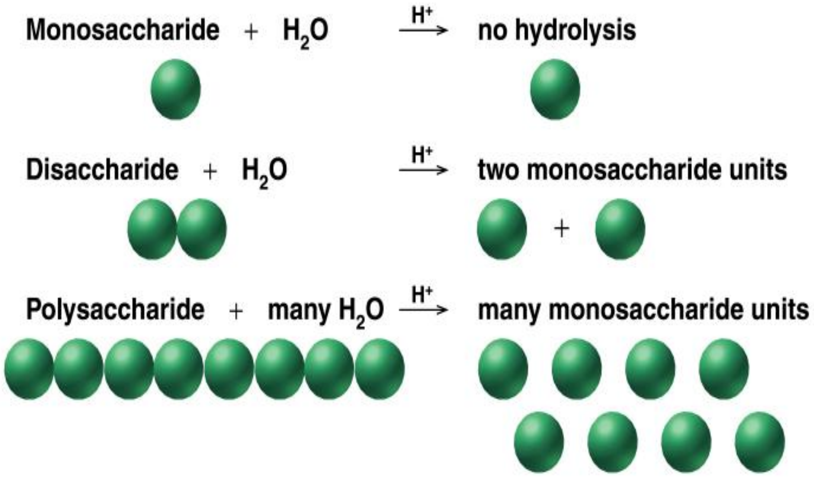
Functional group A monosaccharides can be a polyhydroxy aldehyde or ketone

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.



Monosaccharide + H_2O $\xrightarrow{H^+}$ no hydrolysis

Disaccharide + H_2O $\xrightarrow{H^+}$ two monosaccharide units

Polysaccharide + many H_2O $\xrightarrow{H^+}$ many monosaccharide units

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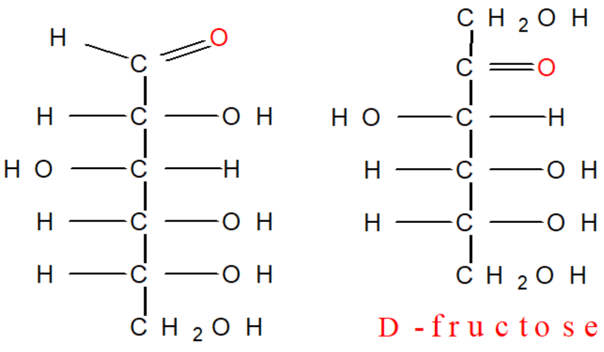
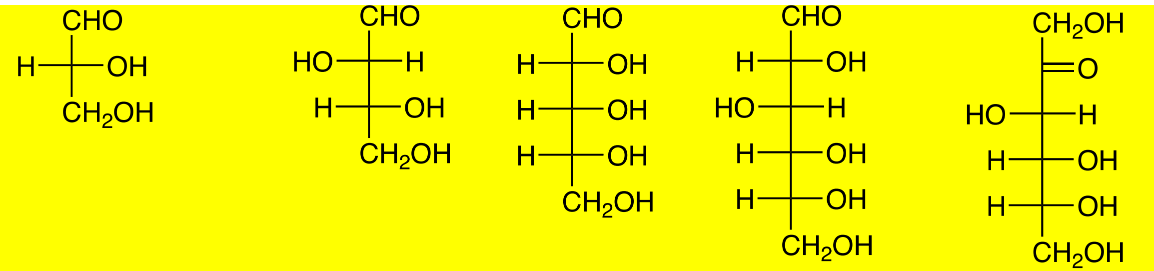


D-glucose

D-fructose



glyceraldehyde (triose)

threose (tetrose)

ribose (pentose)

glucose (hexose) (aldohexose)

fructose (hexose) (ketohexose)

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

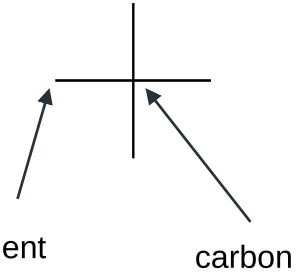
General properties of carbohydrates

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.*

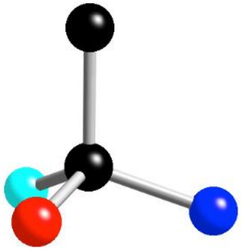
Fischer Projections and the D, L Notation. Representation of a three-dimensional molecule as a flat structure. Tetrahedral carbon represented by two crossed lines:

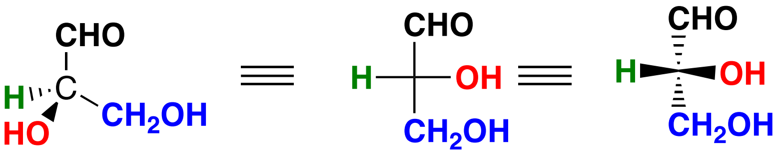
horizontal line is coming
out of the plane of the
page (toward you)

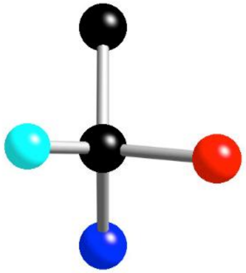


vertical line is going back
behind the plane of the
paper (away from you)

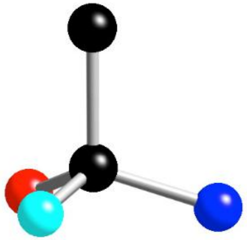
(*R*)-(+)-glyceraldehyde

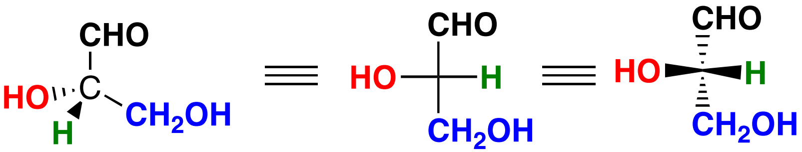


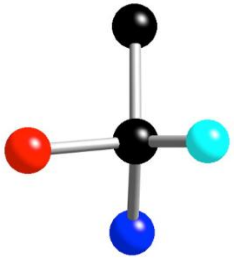




(*S*)-(-)-glyceraldehyde



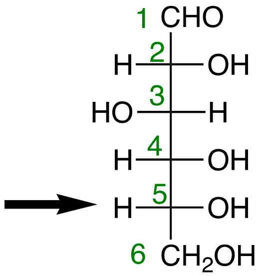




For carbohydrates, the convention is to arrange the Fischer projection with the carbonyl group at the top for aldoses and closest to the top for ketoses. The carbons are numbered from top to bottom.

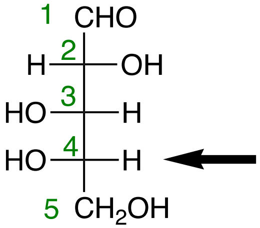
Carbohydrates are designated as D- or L- according to the stereochemistry of the highest numbered chiral carbon of the Fischer projection. If the hydroxyl group of the highest numbered chiral carbon is pointing to the right, the sugar is designated as **D** (<u>*Dextro*</u>: Latin for *on the right side*). If the hydroxyl group is pointing to the left, the sugar is designated as **L** (<u>*Levo*</u>: 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 (-).



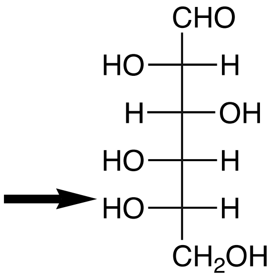
highest numbered "chiral" carbon

D-Glucose



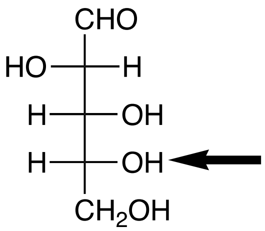
highest numbered "chiral" carbon

L-Arabinose



highest numbered "chiral" carbon

L- glucose



highest numbered "chiral" carbon

D-Arabinose

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.

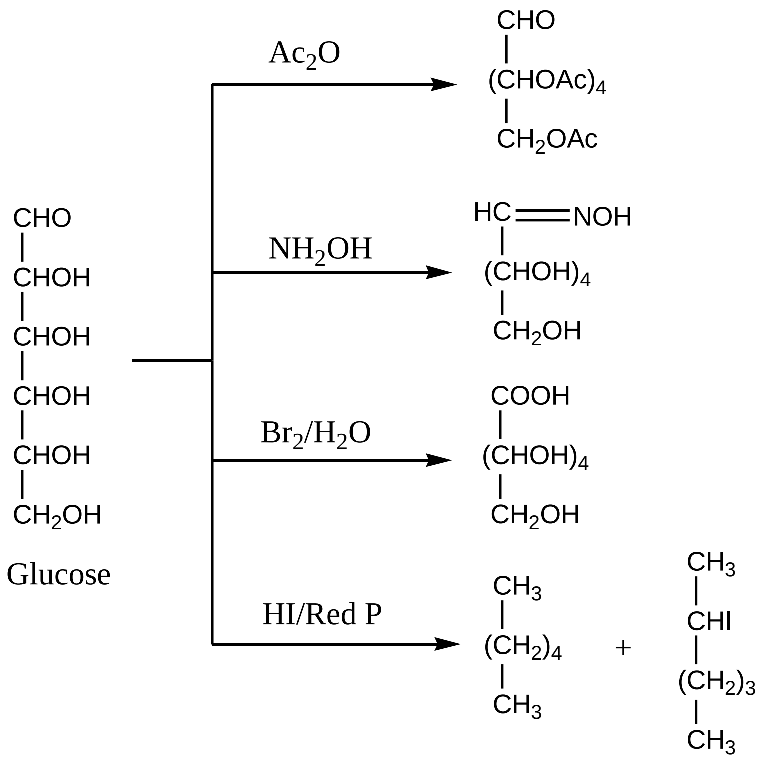
❑ When treated with hydroxylamine, it forms an oxime, suggests the presence of carbonyl group.

❑ 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 ºC, 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-

$$CHO{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CH_2OH$$



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.

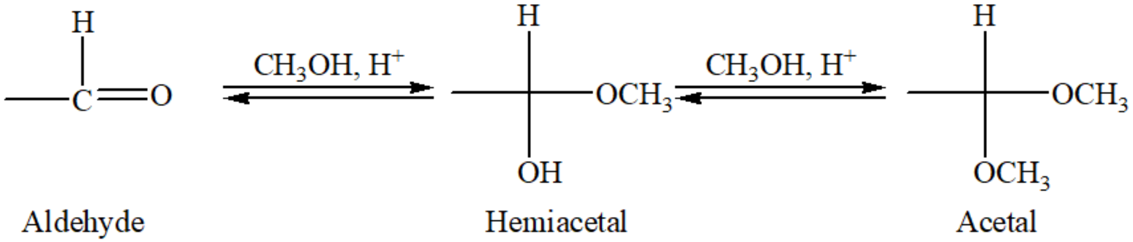
Cyclized structure of Glucose

There are certain facts which cannot be explained by open chain structure such as-

- ❖ **D-(+)-Glucose fails to undergo certain reactions typical of aldehydes**: Although it is readily oxidized, it gives a negative Schiff test and does not form a bisulfite addition product.

- ❖ **D-(+)-Glucose exists in two isomeric forms which undergo mutarotation**: When crystals of D-(+)-glucose of m.p. 146 ºC are dissolved in water, the specific rotation gradually changes from +112.2º to +52.7º. When crystals of D-(+)-glucose of m.p. 150 ºC are dissolved in water, the specific rotation gradually changes from +18.7º to +52.7º. The form with the higher positive rotation is called α-D-(+)-glucose and that with lower rotation is called β-D-(+)-glucose. This slow change in optical rotation to an equilibrium value is called mutarotation.

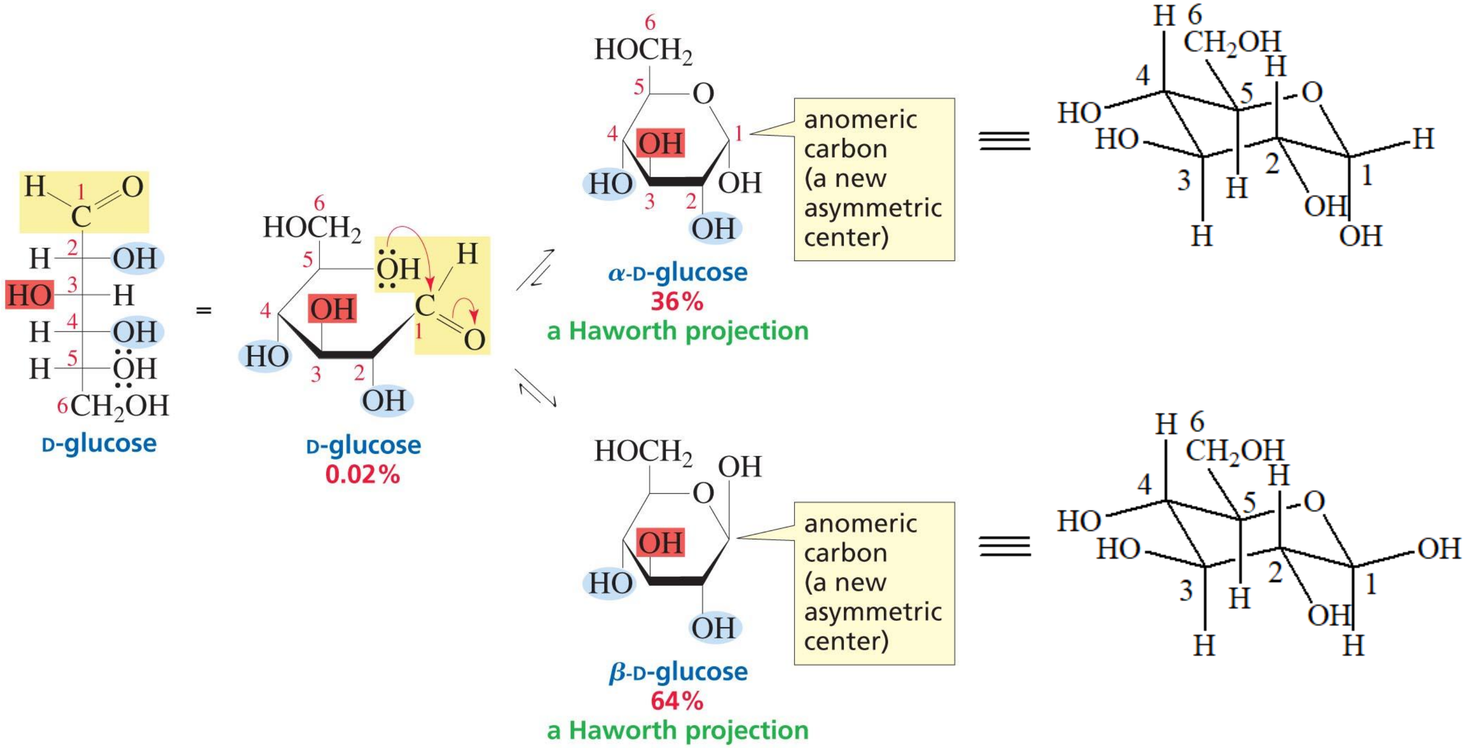
- ❖ **D-(+)-Glucose forms two isomeric methyl D-glucosides**: An aldehyde reacts with alcohols in presence of anhydrous HCl to form acetals.



When D-(+)-glucose is treated with methanol and HCl, the product methyl-D-glucoside contains only one $–CH_3$ group, but it has properties resembling those of a full acetal. It does not spontaneously revert to aldehyde and alcohol on contact with water, but requires hydrolysis by aqueous acids. Two such monomethyl derivatives of D-(+)-glucose are known, one with m.p. 165 ºC and specific rotation +158º, and the other with m.p. 107 ºC and specific rotation -33º.

The isomer of higher positive rotation is called methyl α-D-glucoside and the other is called methyl β-D-glucoside. These glucosides do not undergo mutarotation and do not reduce Tollens' or Fehling's reagent.

To fit these facts, the structure of D-(+)-glucose had to be changed. In 1895, many chemists including Fischer, Tollens, and Tanret, suggested cyclic structure for D-(+)-glucose. 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.



D-glucose

D-glucose
0.02%

α-D-glucose
36%
a Haworth projection

β-D-glucose
64%
a Haworth projection

anomeric carbon (a new asymmetric center)

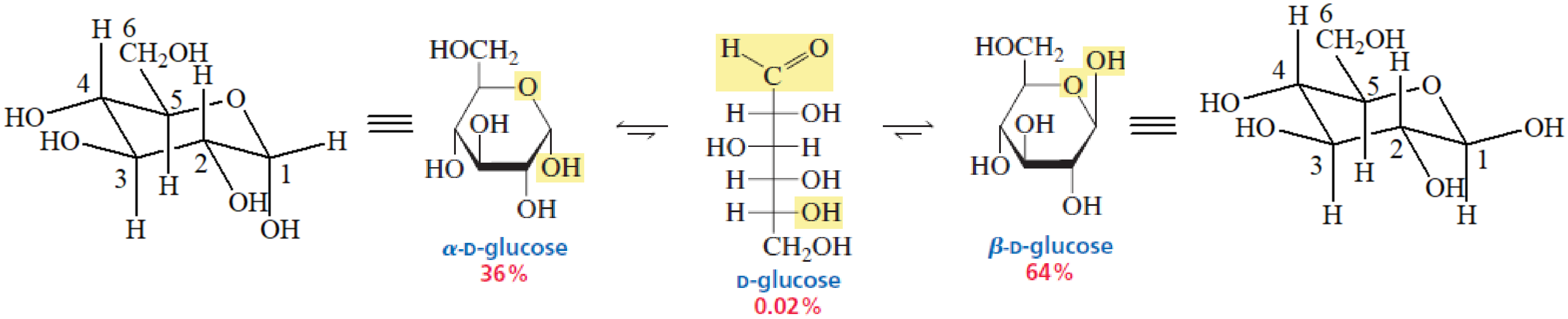
anomeric carbon (a new asymmetric center)

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.**

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.

Cyclic compounds are in equilibrium with the open chain compound



α-D-glucose 36%

D-glucose 0.02%

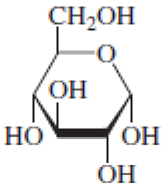
β-D-glucose 64%

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.

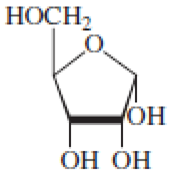
It is a general rule that the conformation which has the greatest number of large groups in equatorial orientation is the most stable form. Thus, the β-anomer will be more stable than the α-anomer and so will predominate in the equilibrium mixture.

Pyranose and furanose

Six-membered-ring sugars are called pyranoses, and five-membered-ring sugars are called furanoses. These names come from pyran and furan. Consequently, α-D-glucose is also called α-D-glucopyranose, and α-D-ribose is also called α-D-ribofuranose. The prefix “α” indicates the configuration about the anomeric carbon, and pyranose or furanose indicates the size of the ring.



α-D-glucose
α-D-glucopyranose



α-D-ribose
α-D-ribofuranose

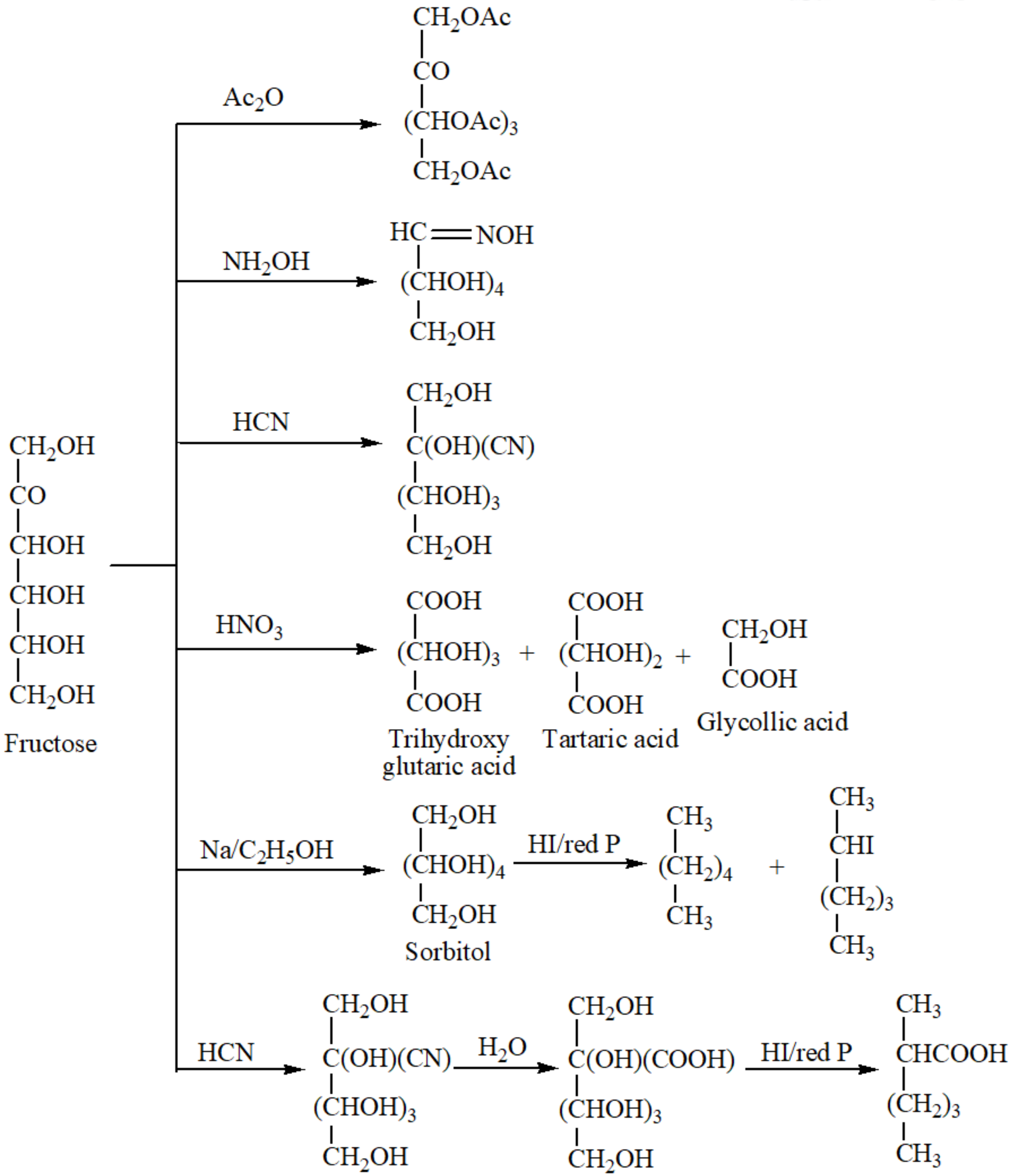
(-)-Fructose: A ketohexose

- ❖ (-)-Fructose is the most important of ketoses.
- ❖ It occurs free along with glucose in honey and sweet fruits.
- ❖ In the combined form, it is a component of disaccharides and polysaccharides.

- Analysis and molecular weight determinations show that the molecular formula of fructose is $C_6H_{12}O_6$.
- When treated with acetic anhydride, fructose forms penta-acetate. This indicates the presence of five hydroxyl groups.
- Fructose reacts with hydrogen cyanide to yield a cyanohydrin, it also forms oxime on reaction with hydroxylamine. These reactions show that fructose contains carbonyl group.
- When oxidised with nitric acid, fructose is converted into a mixture of trihydroxyglutaric, tartaric and glycolic acids. Since a mixture of acids each containing fewer carbon atoms than fructose is obtained, the carbonyl group in fructose must be present as ketonic group.
- Fructose may be reduced to a hexahydric alcohol, sorbitol, which on reduction with hydriodic acid and red phosphorus at 100 ºC, gives a mixture of 2-iodohexane and n-hexane. The formation of the latter two compounds indicates that the six carbon atoms in fructose are in a straight chain.
- On ascending the series by the Kiliani reaction, and reducing the product with hydriodic acid, 2-methylhexanoic acid is obtained. This shows that the ketonic group in fructose is adjacent to one of the terminal carbon atoms.

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

$$CH_2OH\cdot CO\cdot CHOH\cdot CHOH\cdot CHOH\cdot CH_2OH$$



$$\underset{\text{Fructose}}{\begin{array}{c}CH_2OH\\ \vert\\ CO\\ \vert\\ CHOH\\ \vert\\ CHOH\\ \vert\\ CHOH\\ \vert\\ CH_2OH\end{array}}$$

$$\xrightarrow{Ac_2O}\begin{array}{c}CH_2OAc\\ \vert\\ CO\\ \vert\\ (CHOAc)_3\\ \vert\\ CH_2OAc\end{array}$$

$$\xrightarrow{NH_2OH}\begin{array}{c}HC{=}NOH\\ \vert\\ (CHOH)_4\\ \vert\\ CH_2OH\end{array}$$

$$\xrightarrow{HCN}\begin{array}{c}CH_2OH\\ \vert\\ C(OH)(CN)\\ \vert\\ (CHOH)_3\\ \vert\\ CH_2OH\end{array}$$

$$\xrightarrow{HNO_3}\underset{\begin{array}{c}\text{Trihydroxy}\\ \text{glutaric acid}\end{array}}{\begin{array}{c}COOH\\ \vert\\ (CHOH)_3\\ \vert\\ COOH\end{array}}+\underset{\text{Tartaric acid}}{\begin{array}{c}COOH\\ \vert\\ (CHOH)_2\\ \vert\\ COOH\end{array}}+\underset{\text{Glycollic acid}}{\begin{array}{c}CH_2OH\\ \vert\\ COOH\end{array}}$$

$$\xrightarrow{Na/C_2H_5OH}\underset{\text{Sorbitol}}{\begin{array}{c}CH_2OH\\ \vert\\ (CHOH)_4\\ \vert\\ CH_2OH\end{array}}\xrightarrow{\text{HI/red P}}\begin{array}{c}CH_3\\ \vert\\ (CH_2)_4\\ \vert\\ CH_3\end{array}+\begin{array}{c}CH_3\\ \vert\\ CHI\\ \vert\\ (CH_2)_3\\ \vert\\ CH_3\end{array}$$

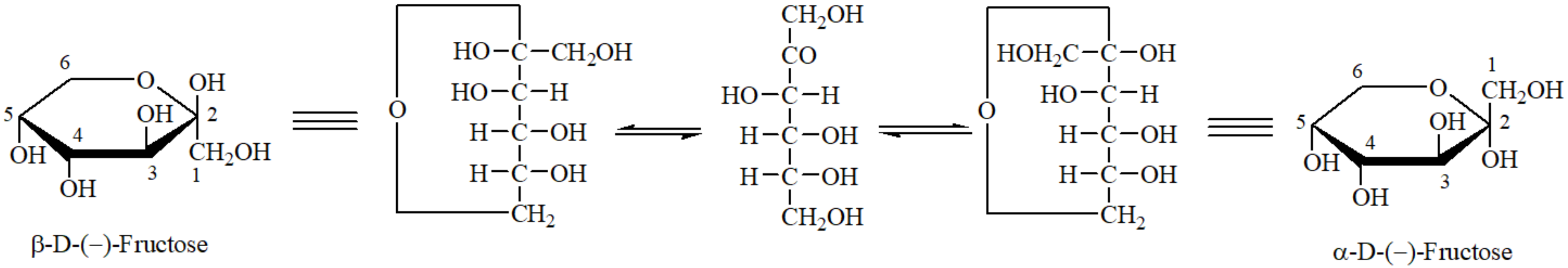
$$\xrightarrow{HCN}\begin{array}{c}CH_2OH\\ \vert\\ C(OH)(CN)\\ \vert\\ (CHOH)_3\\ \vert\\ CH_2OH\end{array}\xrightarrow{H_2O}\begin{array}{c}CH_2OH\\ \vert\\ C(OH)(COOH)\\ \vert\\ (CHOH)_3\\ \vert\\ CH_2OH\end{array}\xrightarrow{\text{HI/red P}}\begin{array}{c}CH_3\\ \vert\\ CHCOOH\\ \vert\\ (CH_2)_3\\ \vert\\ CH_3\end{array}$$

Cyclized structure of Fructose

The open chain structure assigned to fructose cannot explain certain facts:

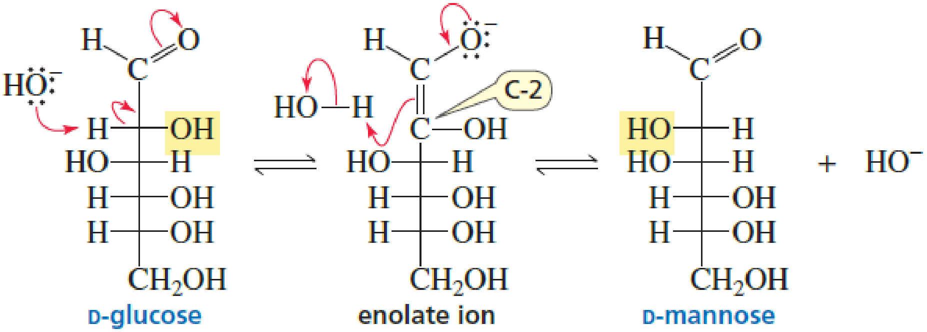
- ❖ It does not react with $NaHSO_3$ indicating that the keto group is not free in fructose.
- ❖ Like glucose, this also shows mutarotation. This indicates the ring structure of glucose. Fructose exists in α and β forms, α form has a specific rotation of -20º while β form has -133º. The equilibrium mixture has a specific rotation of -92.4º.
- ❖ When fructose is refluxed with methyl alcohol in the presence of hydrogen chloride, it forms methyl fructoside. This compound does not exhibit carbonyl properties and can exist in two isomeric forms, viz. α- and β- methyl fructoside.
- ❖ Pentaacetyl fructose does not exhibit carbonyl properties indicating that the keto group of fructose is not free.

The above facts can be best explained if fructose is assumed to have a ring structure formed by the interaction between the carbonyl and hydroxyl group as it occurs in the formation of hemiacetals.



Reactions

Epimerization



- The base removes a proton from the α-carbon, forming an enonate ion.

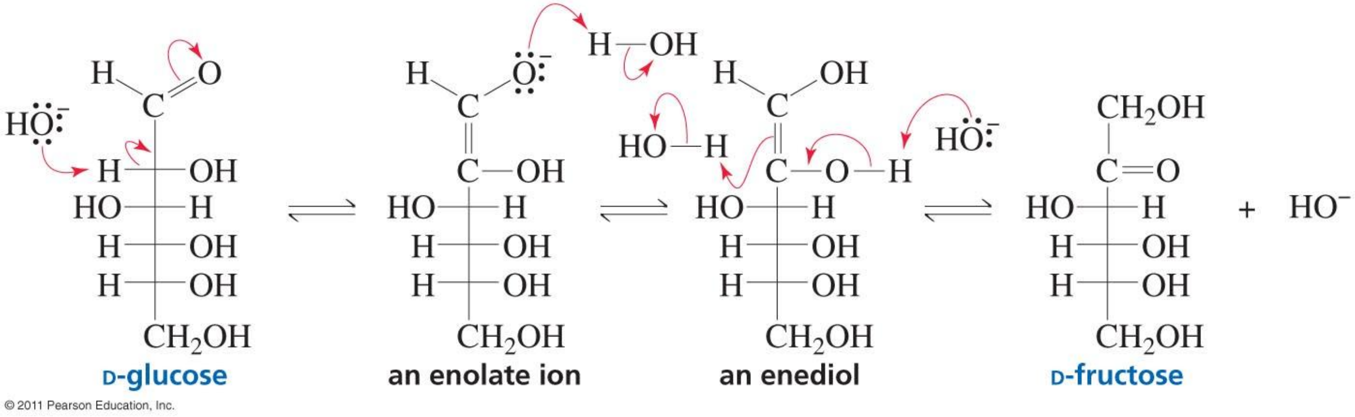
- When C-2 is reprotonated, the proton can come from top or bottom of the planar sp^2 carbon, forming both D-glucose and D-mannose (C-2 epimers).

- 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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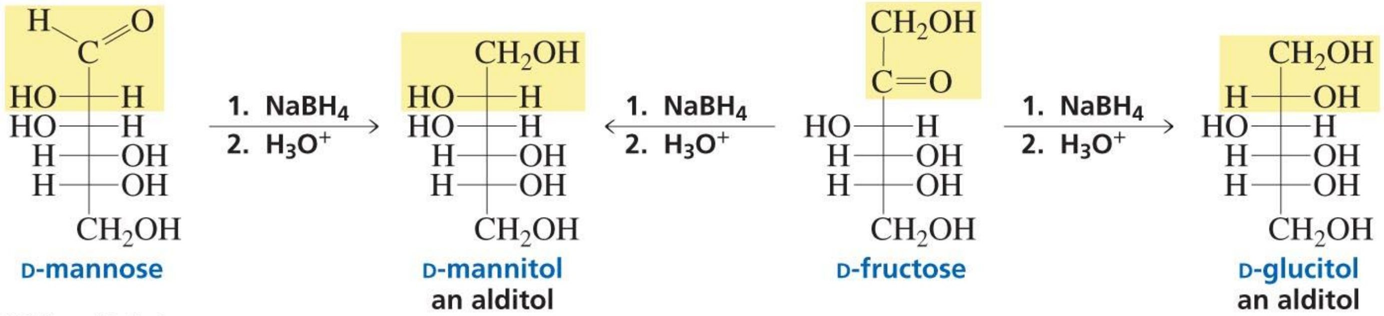
- ❑ The base removes a proton from an α-carbon, forming an enolate ion.
- ❑ Either C-2 can be protonated, or the oxygen of the enolate ion can be protonated to form an enediol.
- ❑ The enediol has two OH groups that can form a carbonyl group. Removal of a proton from the OH at C-1 followed by tautomerization 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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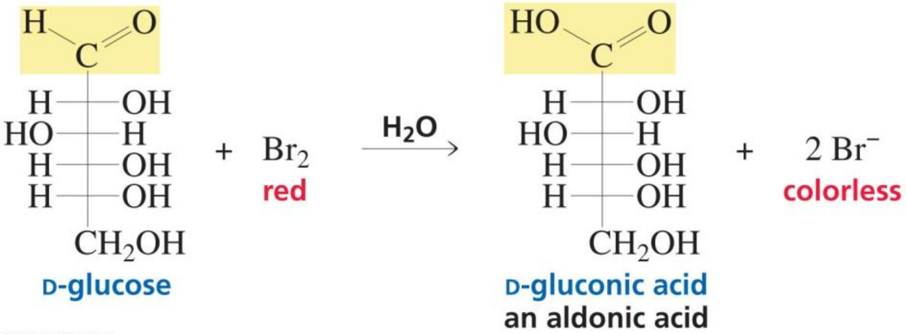
Oxidation



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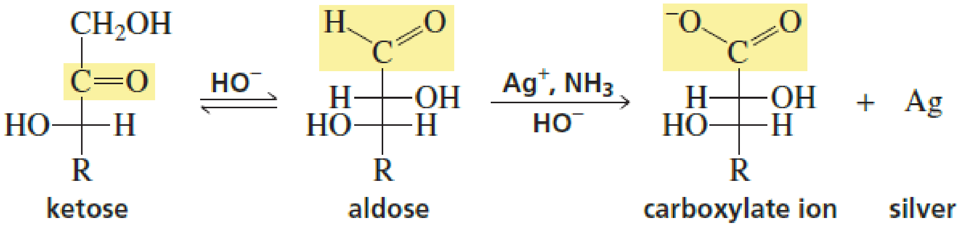
❖ Br_2 is a mild oxidizing agent that easily oxidizes aldehydes but cannot oxidize ketones or alcohols. Therefore, adding a small amount of an aqueous solution of Br_2 to an unknown monosaccharide can tell you whether the sugar is an aldose or a ketose.

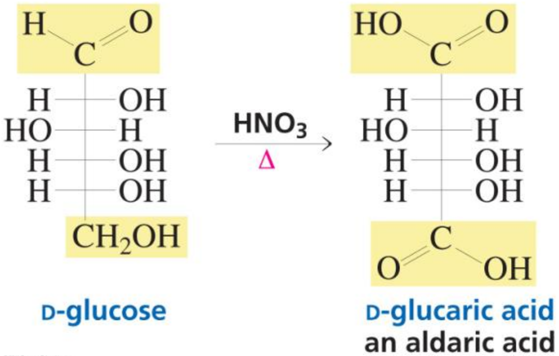
❖ The reddish-brown color of Br_2 will disappear if the monosaccharide is an aldose because when Br_2 oxidizes the aldehyde, Br_2 is reduced to Br^-, which is colorless. If the red color persists, indicating no reaction with Br_2, then the monosaccharide is a ketose. The product of the oxidation reaction 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 aldose by an enediol rearrangement, and the aldose will then be oxidized by Tollens' reagent.

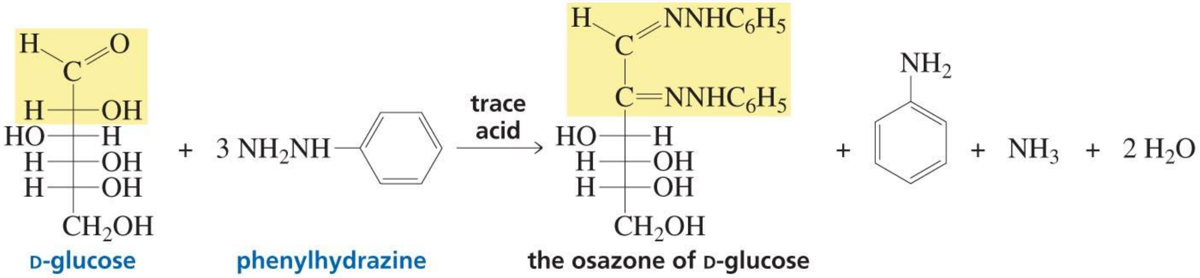
A strong oxidizing agent such as HNO_3 can oxidize both the aldehyde and the alcohol groups.



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 aldaric acid.

Osazone formation

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



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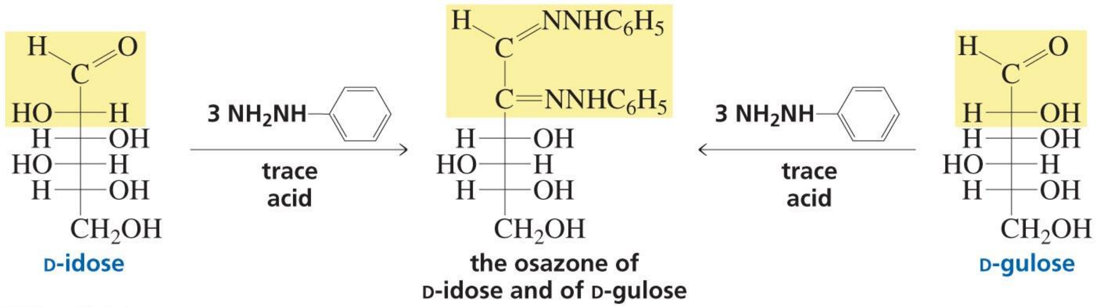
The C-2 epimers of aldoses form identical osazones… …because the configuration of the C-2 carbon is lost during osazone formation, does not affect the configuration of the rest of the molecule. This is useful not only in identifying carbohydrates, but also in determining their configuration. Treatment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



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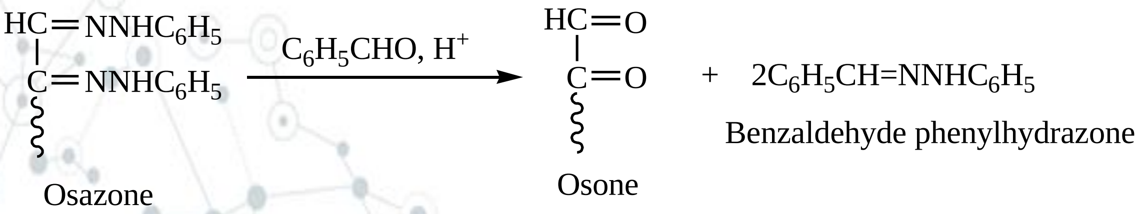
Removal of phenylhydrazine yields dicarbonyl compounds known as osones.

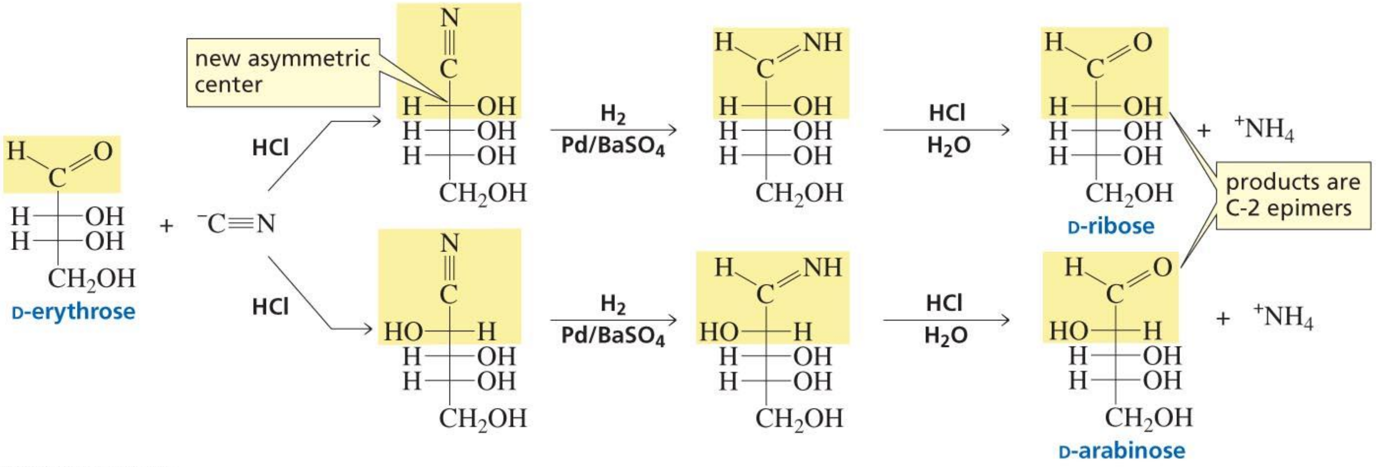


Interconversions of monosaccharides

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.

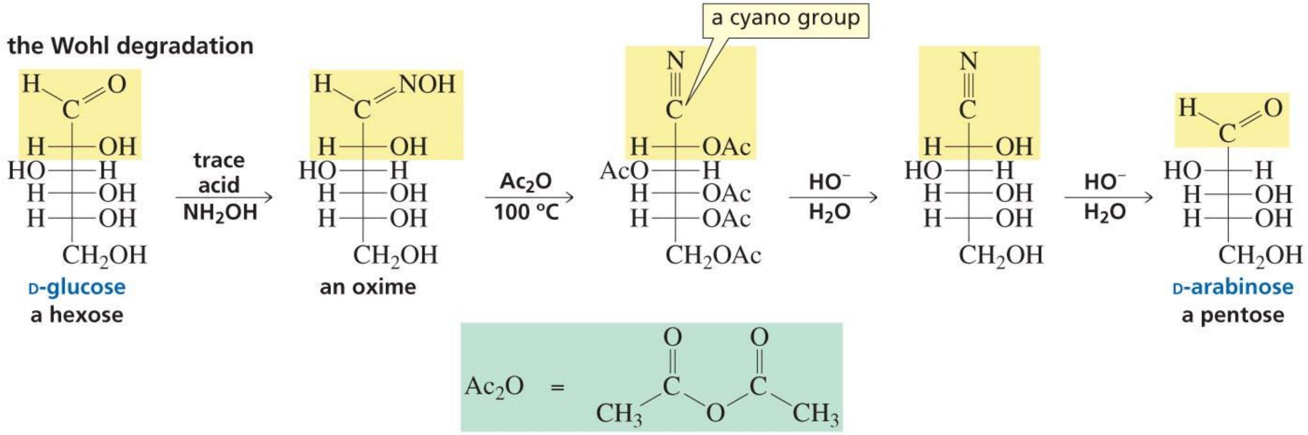
- The C≡N bond is reduced to an imine, using a partially deactivated catalyst so that the imine is not further reduced to an amine .

- 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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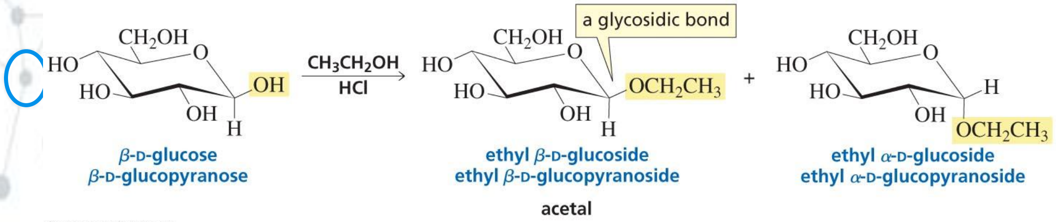
❑ In the first step, the aldehyde reacts with hydroxylamine to form an oxime.

❑ 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.

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.



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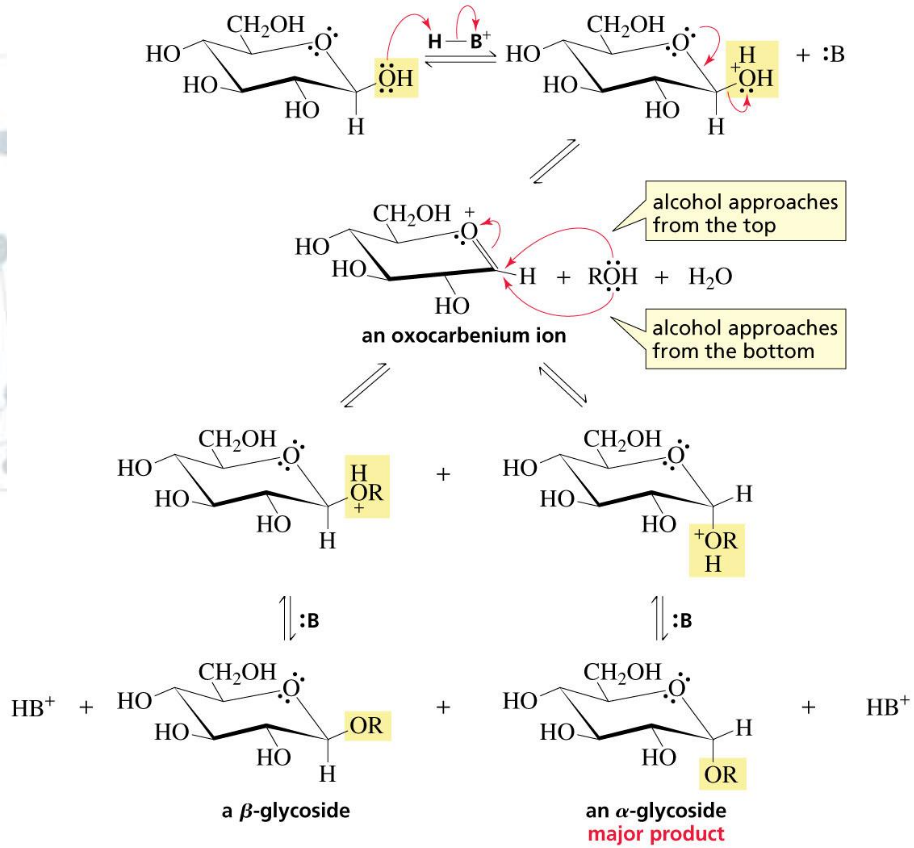
The acetal of a sugar is called a glycoside, and the bond between the anomeric carbon and the alkoxy oxygen is called a glycosidic bond.

Mechanism for glycoside formation



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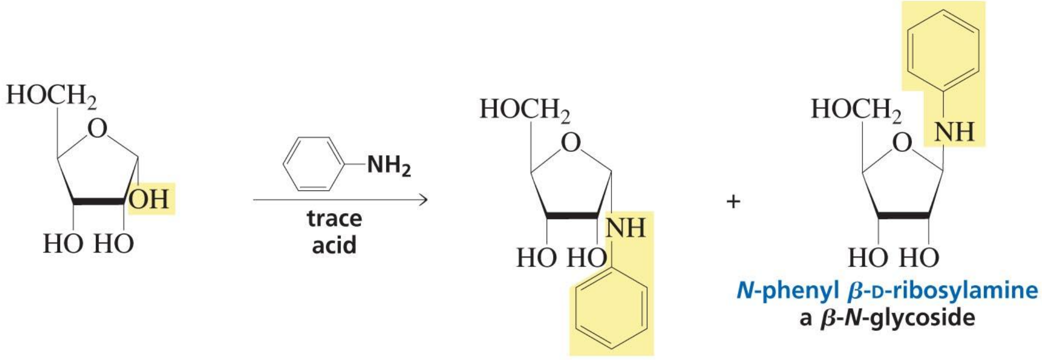
✓The acid protonates the OH group bonded to the anomeric carbon.

✓ 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 b-*N-glycosides.*



***N*-phenyl *β*-D-ribosylamine**
a *β*-*N*-glycoside

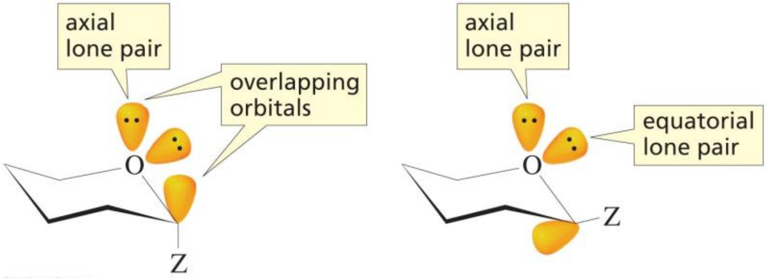
***N*-phenyl *α*-D-ribosylamine**
an *α*-*N*-glycoside

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.

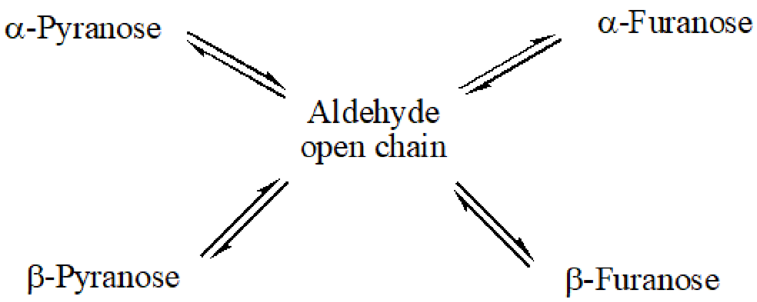


Mutarotation

When a monosaccharide is dissolved in water, the optical rotatory power of the solution gradually chages until it reaches a constant value. The final stage can be reached more rapidly either by heating the solution or by adding some catalyst which may be an acid or a base. This change in specific rotation is known as mutarotation.

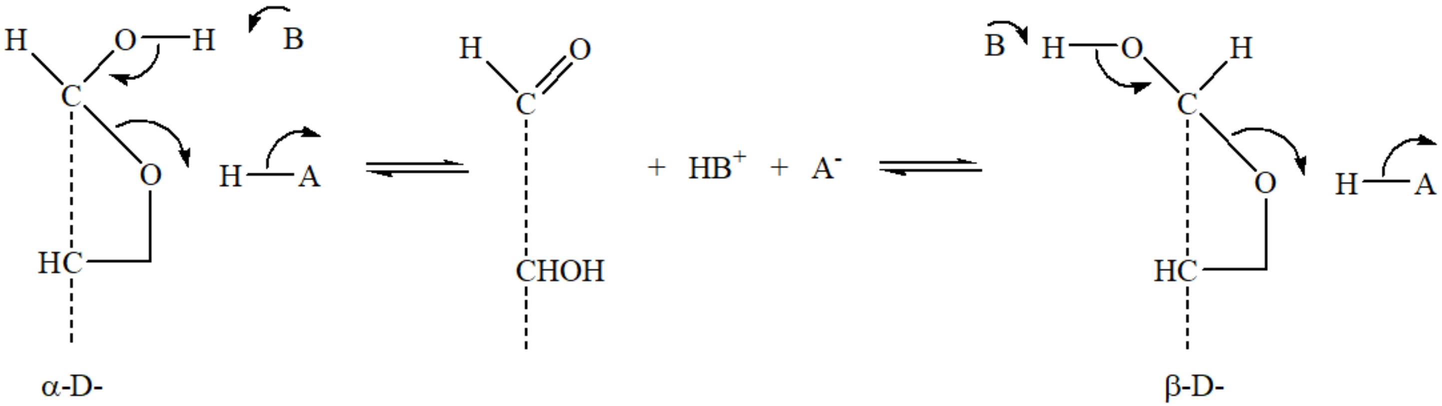
All reducing sugars undergo mutarotation. In addition to change in optical rotation, mutarotation may be followed by changes in i.r. and NMR spectra.

Mechanism of mutarotation: The accepted mechanism of mutarotation is that it arises from the complex equilibrium set up on dissolution of monosaccharides. The equilibria is shown below:



The proportion of five possible forms at equilibrium will vary widely from sugar to sugar depending on thermodynamic stabilities of each. Generally, the acyclic (aldehyde) form is present to a very small extent and of the ring forms, pyranoses are present in greater amount. For D-glucose in aqueous solution, the equilibrium mixture is essentially a mixture of α- and β-pyranose forms. For other sugars, furanoses form a significant proportion.

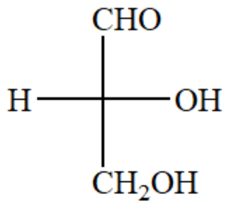
Lowry suggested the mechanism of formation of the open chain form from the ring form. It occurred by the simultaneous addition and elimination of a proton, since both an acid and a base must be present in the sugar solution.



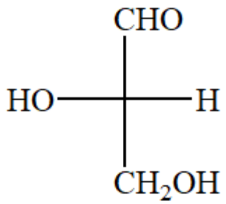
This concerted mechanism would conform to a third order reaction. Swain et al. (1952) have shown that the mutarotation of tetramethylglucose, catalysed by phenol and pyridine in benzene solution, is a third order reaction; this supports the above mechanism.

Determination of configuration of monosaccharides

- **Aldotrioses:** The structural formula of aldotriose is $OCHCHOHCH_2OH$. Since this contains only one chiral centre, there are two optically active forms (one pair of enantiomer).



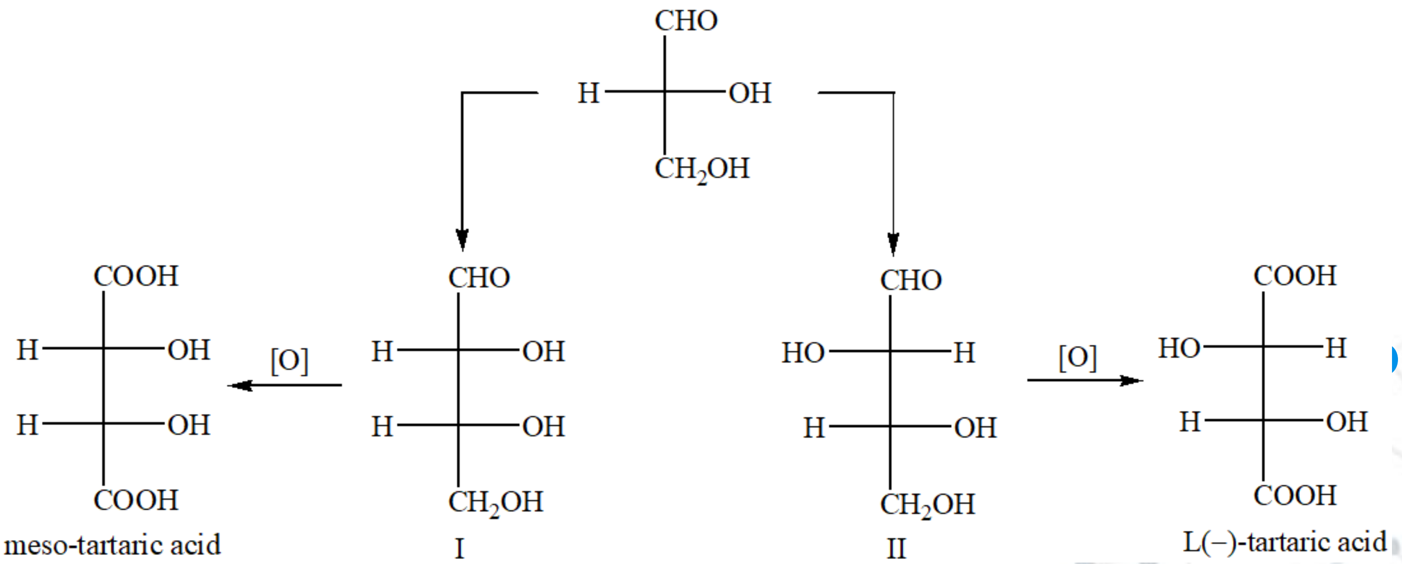
D(+)-glyceraldehyde



L(-)-glyceraldehyde

Aldotetroses: The structural formula of aldotetrose is $HOCH_2CHOHCHOHCHO$. Since this contains two chiral centres, there are four optically active forms (two pairs of enantiomers): D- and L-threose and D- and L-erythrose.

- D(+)-glyceraldehyde may be stepped up by Killiani reaction to give D(-)-erythrose and D(-)-threose.



meso-tartaric acid

I
D(–)-erythrose

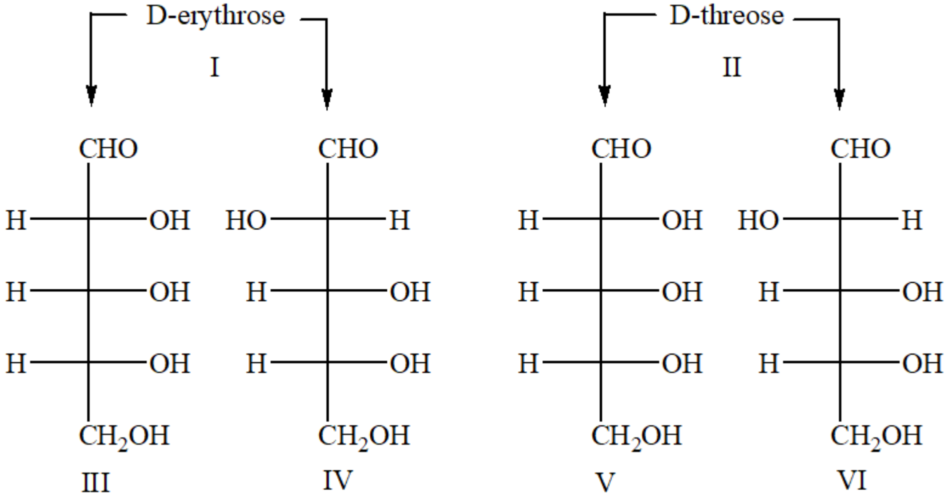
II
D(–)-threose

L(–)-tartaric acid

- On oxidation, D-erythose gives meso tartaric acid and on reduction gives meso-erythritol. Therefore D-erythrose is I and consequently II must be D-threose. The configuration of the latter is confirmed by the fact that on oxidation, D-threose gives L(-)-tartaric acid.

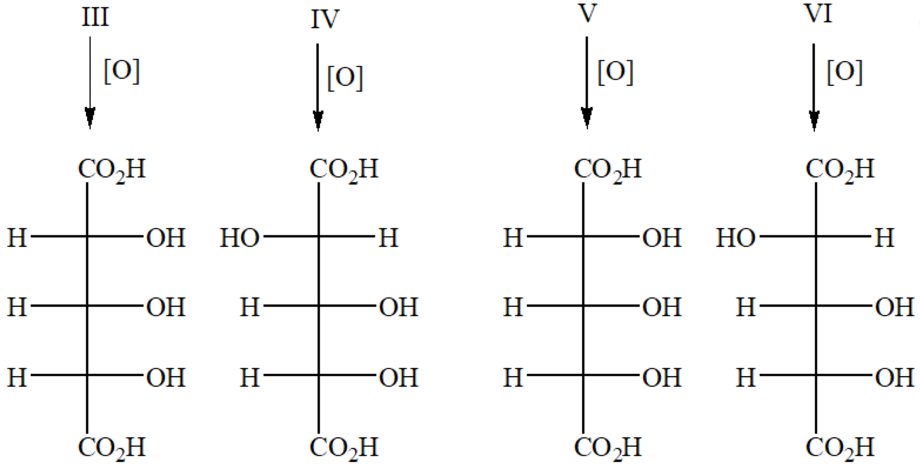
Aldopentoses: The structural formula of aldotetrose is $OCHCHOHCHOHCHOHCH_2OH$. Since this contains three chiral centres, there are eight optically active forms (four pairs of enantiomers): D- and L- forms of ribose, arabinose, xylose and lyxose.

- To ascertain the configurations of the stereoisomers, the aldotetroses- D-erythrose and D-threose may be stepped up by the Killiani reaction.



- D-erythrose gives D(-)-ribose and D(-)-arabinose; similarly, D-threose gives D(+)-xylose and D(-)-lyxose. III and IV must be ribose and arabinose.

- To determine which stereoisomer III or IV is ribose or arabinose, an oxidation reaction with nitric acid is carried out.

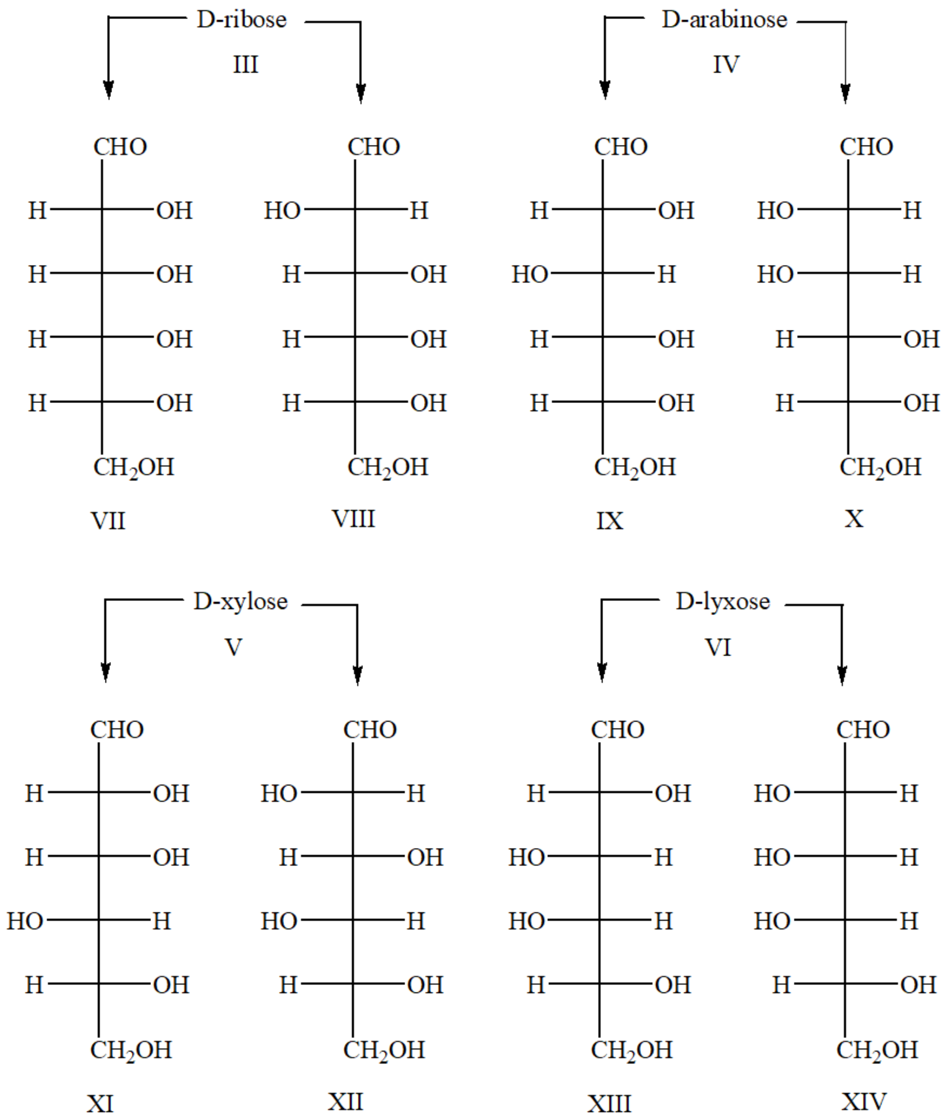


inactive IIIa   active IVa   inactive Va   active VIa

- On oxidation with nitric acid, arabinose gives an optically active dicarboxylic acid, whereas ribose gives an optically inactive dicarboxylic acid. Thus, III is D-ribose and IV is D-arabinose.

- Xylose on oxidation gives optically inactive dicarboxylic acid and lyxose gives optically active dicarboxylic acid. Therefore, V is D-xylose and VI is D-lyxose.

Aldohexoses: The structural formula of these compounds is OCHCHOHCHOHCHOHCHOHCH$_2$OH. Since this contains four chiral centres, there are sixteen optically active forms (eight pairs of enantiomers). All are known and may be prepared by stepping up the aldopentoses: D-ribose gives D(+)-allose and D(+)-altrose; D-arabinose gives D(+)-glucose and D(+)-mannose; D-xylose gives D(-)-glucose and D(-)-idose; and D-lyxose gives D(+)-galactose and D(+)-talose.



- On oxidation with nitric acid, allose gives an optically inactive and altrose gives an optically active dicarboxylic acid. Therefore, VII is allose and VIII is altrose..

- On oxidation with nitric acid, galactose gives an optically inactive and talose gives an optically active dicarboxylic acid. Therefore, XIII is galactose and XIV is talose.

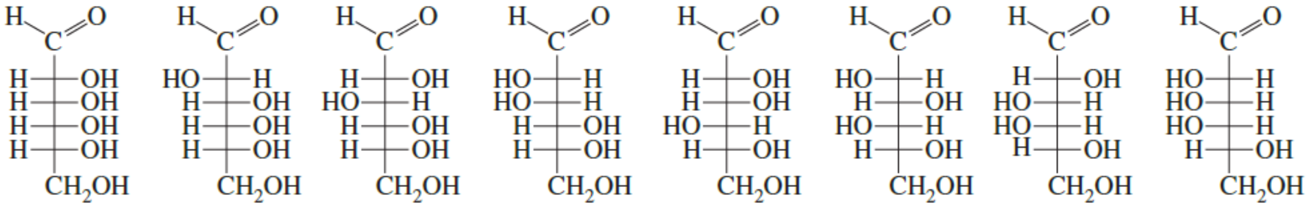
- On oxidation with nitric acid, all the other four configurations, viz., glucose, mannose, gulose and iodose give optically active dicarboxylic acid. Therefore, it is difficult to elucidate their configuration by nitric acid oxidation.

- It has been found that the dicarboxylic acid from glucose (saccharic acid) is the same as that obtained from gulose. D-glucose gives D-saccharic acid and D-gulose gives L-saccharic acid.

- Saccharic acid is produced by the oxidation of the terminal groups with rest of the molecule unaffected. Inspection of formulae IX, X, XI, and XII shows that only IX and XI have the rest of the molecule the same. By interchanging CHO and CH_2OH groups of IX, the enantiomer of XI, i.e. L-gulose is obtained. Therefore, IX must be glucose and XI must be gulose. Consequently, X is mannose and XII is idose.

Absolute Configuration of Glucose

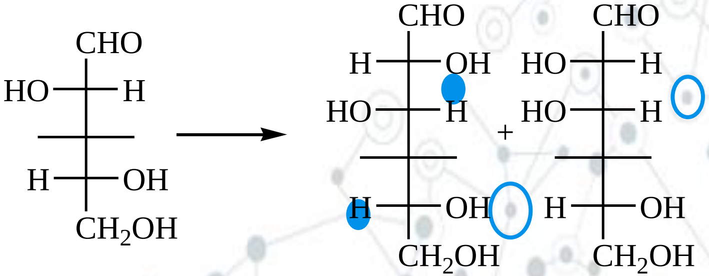
- Emil Fischer's determined the stereochemistry of glucose, done in 1891.
- Fischer knew that (+)-glucose is an aldohexose, but 16 different structures can be written for an aldohexose. Which of them represents the structure of (+)-glucose?
- The 16 stereoisomers of an aldohexose are actually eight pairs 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.



D-allose 1 | D-altrose 2 | D-glucose 3 | D-mannose 4 | D-gulose 5 | D-idose 6 | D-galactose 7 | D-talose 8

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

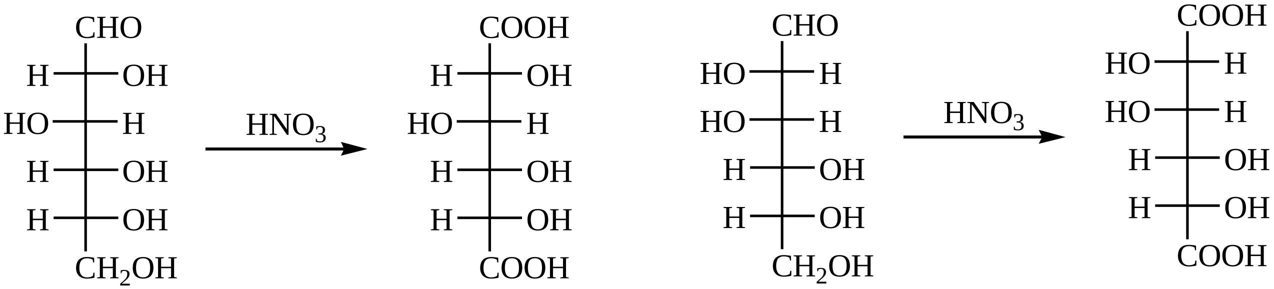
1. When the Kiliani–Fischer synthesis is performed on the sugar known as (-)-arabinose, the two sugars known as (+)-glucose and (+)-mannose are obtained. This means that (+)-glucose and (+)-mannose are C-2 epimers. Consequently, (+)-glucose and (+)-mannose have to be one of the following pairs: sugars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



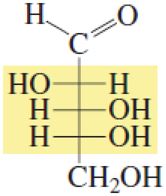
(-)-Arabinose

(+)-Glucose and (+)-Mannose

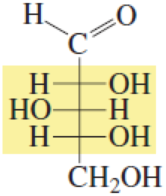
2. (+)-Glucose and (+)-mannose are both oxidized by nitric acid to optically active aldaric acids. The aldaric acids of sugars 1 and 7 would not be optically active because each has a plane of symmetry (a compound containing a plane of symmetry is achiral). Excluding sugars 1 and 7 means that (+)-glucose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



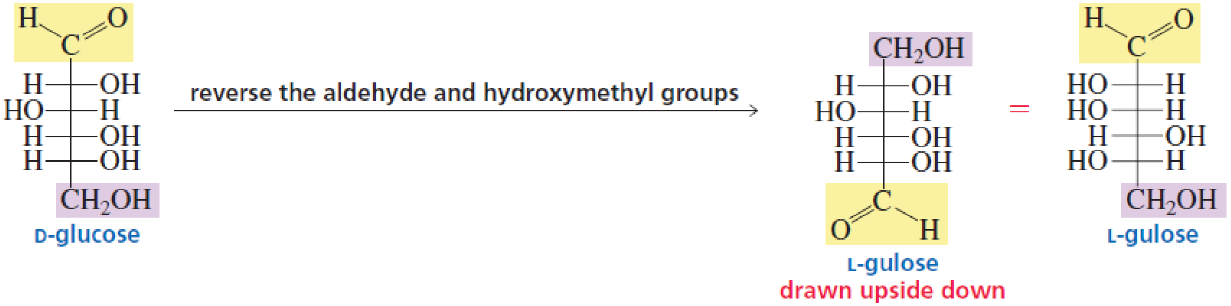
the structure of (–)-arabinose if (+)-glucose and (+)-mannose are sugars 3 and 4



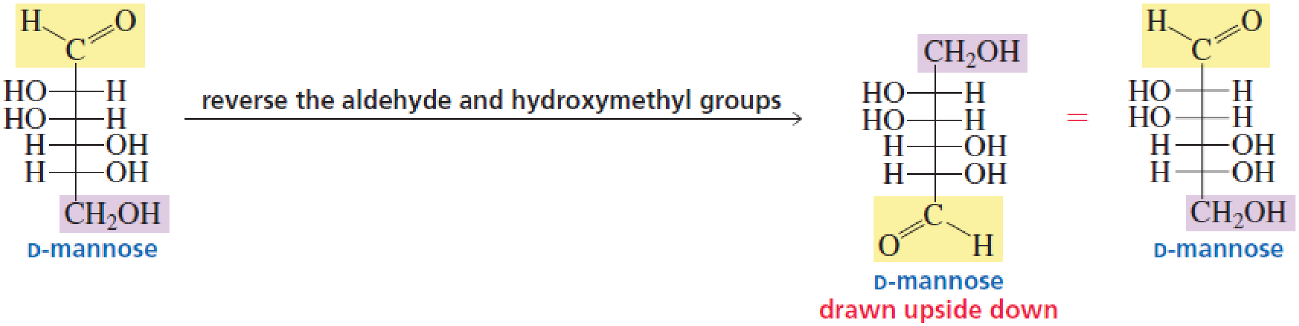
the structure of (–)-arabinose if (+)-glucose and (+)-mannose are sugars 5 and 6

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.



Absolute configuration of Fructose

- The structure of fructose contains three chiral centres, i.e., it must have eight optically active forms (four pairs of enantiomers).
- Out of these, the following six are known: D(-)- and L(+)-fructose, D(+)- and L(-)-sorbose, D(+)-tagatose and L(-)-psicose. Only D(-)-fructose, L-(-)-sorbose and D(+)-tagatose occur naturally.
- The configuration of fructose can be deduced by the osazone formation reaction. We know that natural fructose is laevorotatory which yields the same osazone as D-glucose. This indicates that natural fructose must be D(-)-fructose.
- Osazone formation involves only the first two carbon atoms in a sugar. This means that the configuration of the remaining four carbon atoms in glucose and fructose must be same. This fact confirms that the configuration of D(-)-fructose is I.