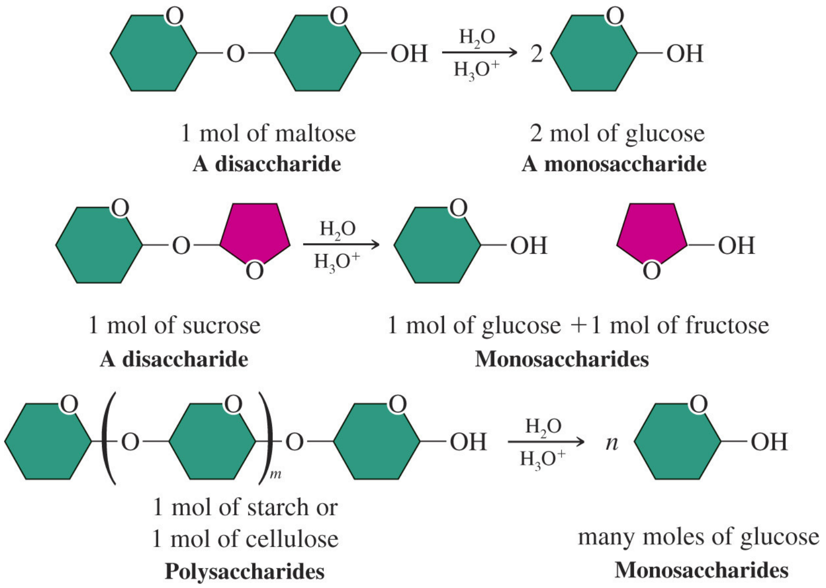
Chapter 22
Carbohydrates

♦ Introduction

Classification of Carbohydrates

- Carbohydrates have the general formula $C_x(H_2O)_y$
- Carbohydrates are defined as polyhydroxy aldehydes or ketones or substances that hydrolyze to yield polyhydroxy aldehydes and ketones
- Monosaccharides are carbohydrates that cannot be hydrolyzed to simpler carbohydrates
  - Disaccharides can be hydrolyzed to two monosaccharides
  - Oligosaccharides yield 2 to 10 monosaccharides
  - Polysacccharides yield >10 monosaccharides



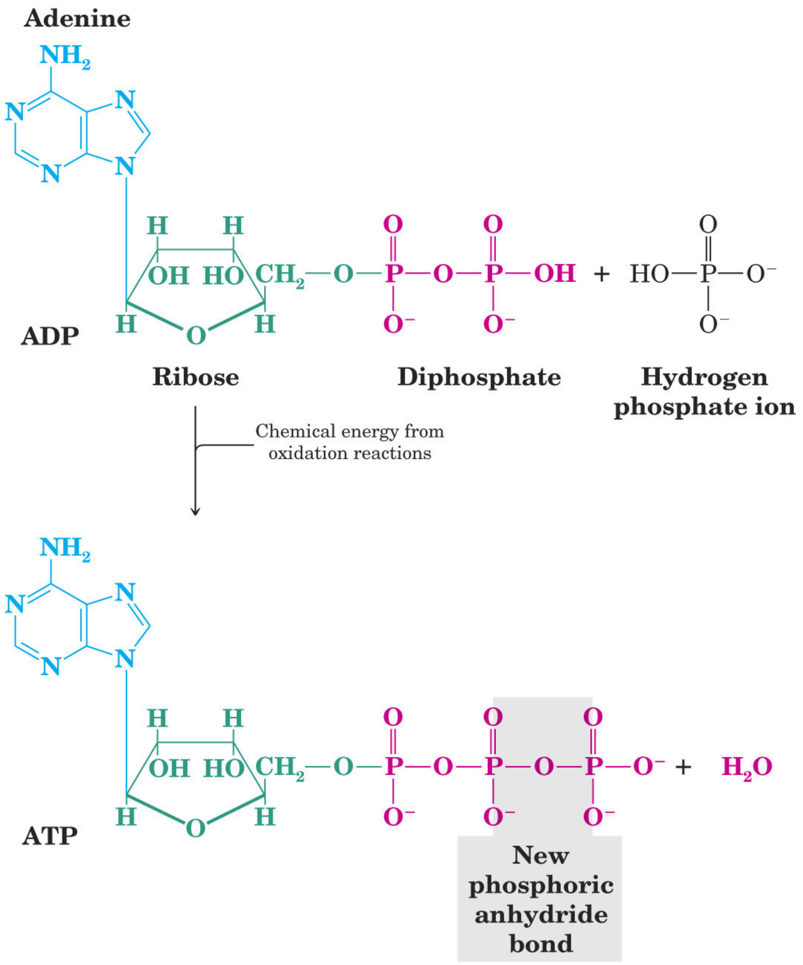
- **Photosynthesis and Carbohydrate Metabolism**
  - ➔ **Carbohydrates are synthesized in plants by photosynthesis**
    - **Light from the sun is absorbed by chlorophyll and this is converted to the energy necessary to biosynthesize carbohydrates**

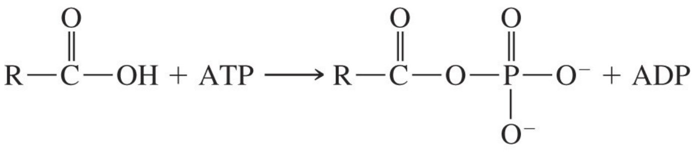
$$x\,CO_2 + y\,H_2O + \text{solar energy} \longrightarrow \underset{\textbf{Carbohydrate}}{C_x(H_2O)_y} + x\,O_2$$

  - ➔ **Carbohydrates act as a repository of solar energy**
    - **The energy is released when animals or plants metabolize carbohydrates**

$$C_x(H_2O)_y + x\,O_2 \longrightarrow x\,CO_2 + y\,H_2O + \text{energy}$$

  - ➔ **Much of the energy released by oxidation of glucose is trapped in the molecule adenosine triphosphate (ATP)**
    - **The phosphoric anhydride bond formed when adenosine triphosphate (ADP) is phosphorylated to make ATP is the repository of this energy**
    - **This chemical energy is released when ATP is hydrolyzed or a new anhydride linkage is created**





$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH + ATP \longrightarrow R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}\underset{\underset{\displaystyle O^-}{|}}{\overset{\overset{\displaystyle O}{\|}}{P}}{-}O^- + ADP}$$

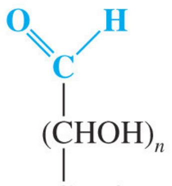
An acyl phosphate

♦ Monosaccharides

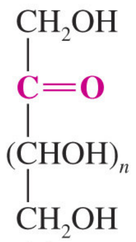
● Classification of Monosaccharides

➔ **Monosaccharides are classified according to:**

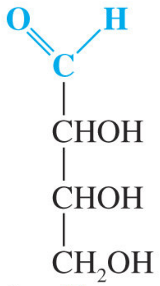
- (1) The number of carbon atoms present in the molecule and
- (2) whether they contain an aldehyde or ketone group



An aldose



A ketose



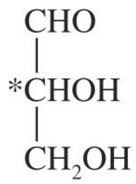
An aldotetrose
C_4

A ketopentose
C_5

● D and L Designations of Monosaccharides

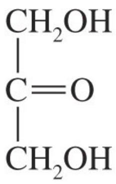
➔ **The simplest carbohydrates are glyceraldehyde, which is chiral, and dihydroxyacetone, which is achiral**

- Glyceraldehyde exists as two enantiomers



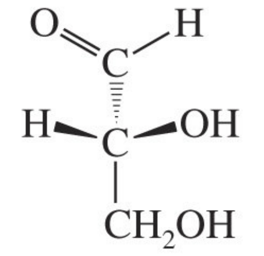
$CHO-{}^*CHOH-CH_2OH$

Glyceraldehyde
(an aldotriose)



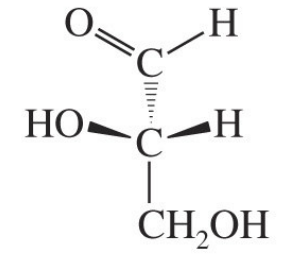
$CH_2OH-C{=}O-CH_2OH$

Dihydroxyacetone
(a ketotriose)



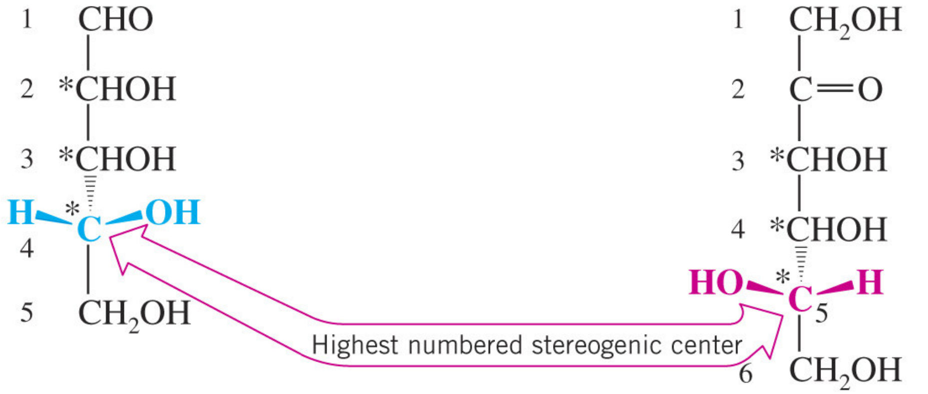
(+)-Glyceraldehyde

and



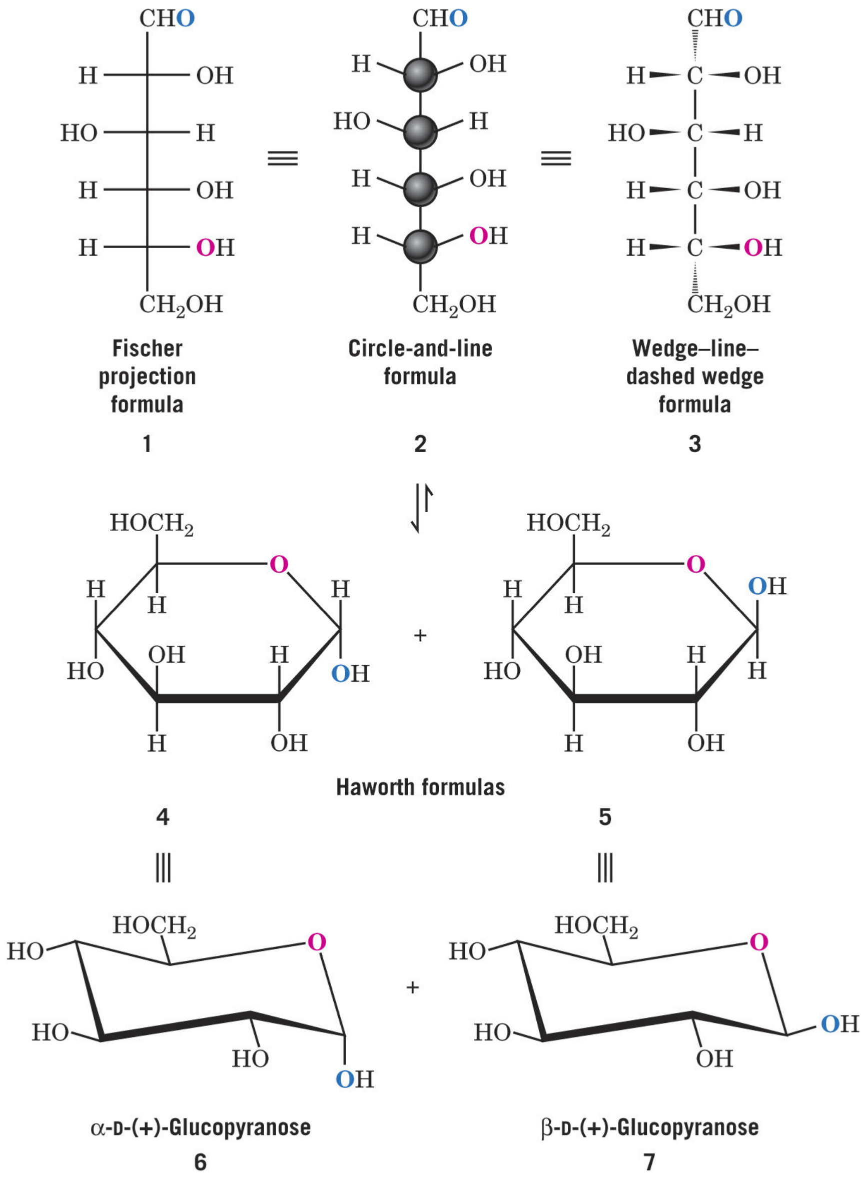
(−)-Glyceraldehyde

- ➔ **In the early 20th century (+)-glyceraldehyde was given the stereochemical designation (D) and (-)-glyceraldehyde was given the designation (L)**
- ➔ **A monosaccharide whose highest numbered stereogenic center has the same configuration as D-(+)-glyceraldehyde is a D sugar**
- ➔ **A monosaccharide whose highest numbered stereogenic center has the same configuration as L-(-)-glyceraldehyde is an L sugar**



A D-aldopentose **An L-ketohexose**

- **Structural Formulas for Monosaccharides**
  - ➔ **Fischer projections are used to represent stereochemistry in carbohydrates**
  - ➔ **In Fischer projections horizontal lines are understood to project out of the plane toward the reader and vertical lines are understood to project behind the plane**
    - **A Fischer projection cannot be removed from the plane of the paper or turned 90° and still represent the molecule accurately**
  - ➔ **Glucose exists primarily in two cyclic hemiacetal forms that are diastereomers of each other**
    - **The cyclic hemiacetal forms interconvert via the open-chain form**
    - **The cyclic hemiacetals differ only in configuration at C1 and are called anomers**
    - **The carbon at which their configurations differ is called the anomeric carbon**
    - **The α-anomer has the C1 hydroxyl trans to the -CH_2OH group**
    - **The β-anomer has the C1 hydroxyl cis to the -CH_2OH group**
  - ➔ **The flat cyclic representation of carbohydrates is called a Haworth formula**
    - **Cyclic glucose actually exists in the chair form**



Fischer projection formula
1

Circle-and-line formula
2

Wedge–line–dashed wedge formula
3

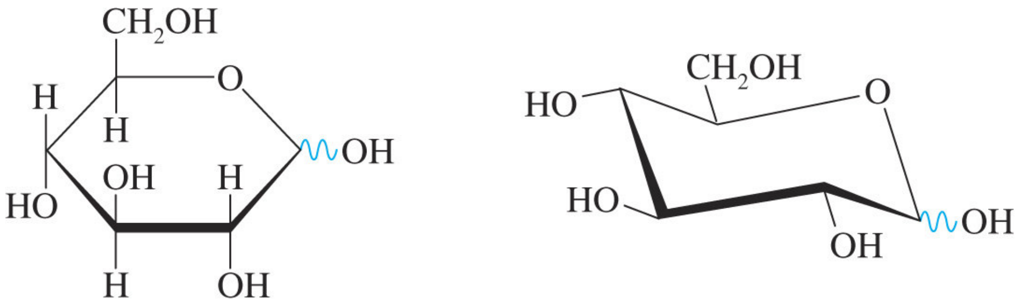
Haworth formulas
4
5

α-D-(+)-Glucopyranose
6

β-D-(+)-Glucopyranose
7

➔ In the β-anomer of glucose all groups around the ring are equatorial

➔ The configuration at the anomeric carbon of a cyclic carbohydrate can be left unspecified using a wavy bond

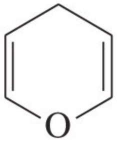


∿ indicates *α* or *β* (three-dimensional view not specified)

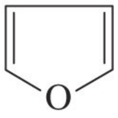
➔ Fischer projections and Haworth formulas can easily be interconverted (next slide)

➔ A six-membered ring monosaccharide is designated a pyranose, *e.g.*, glucose in this form is glucopyranose

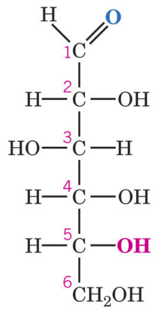
➔ A five-membered ring monosaccharide is designated a furanose,



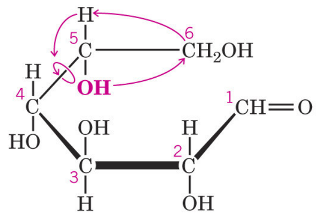
A pyran



Furan

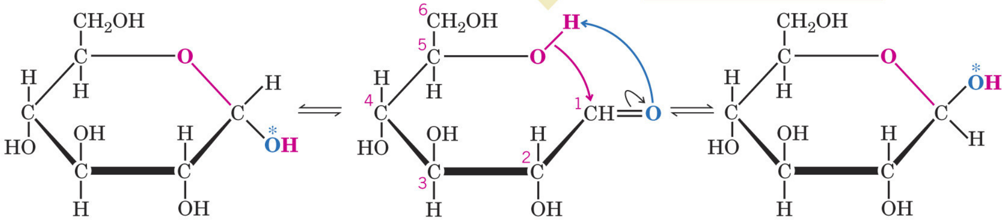


Glucose
(plane projection formula)
When a model of this is made
it will coil as follows:



If the group attached to C4 is
pivoted as the arrows indicate,
we have the structure below.

This —OH group adds
accross the >C=O
to close a ring of
six atoms and make
a cyclic hemiacetal.



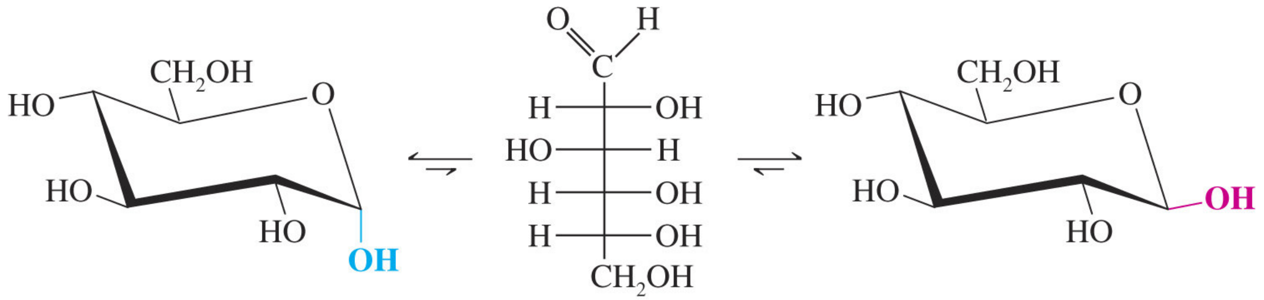
α-D-(+)-Glucopyranose
(Starred –OH is the
hemiacetal –OH,which in α-glucose is on
the *opposite* side of the ring
from the –CH_2OH group at C5.)

Open-chain form of D-Glucose
(The proton transfer step occurs
between separate molecules.
It is not intramolecular
or concerted.)

β-D-(+)-Glucopyranose
(Starred –OH is the
hemiacetal –OH,
which in β-glucose is on
the *same* side of the ring
as the –CH_2OH group at C5.)

♦ Mutarotation

- The α- and β-forms of glucose can be isolated separately
  - Pure α-glucose has a specific rotation of +112°
  - Pure β-glucose has a specific rotation of +18.7°
- When either form of glucose is allowed to stand in aqueous solution, the specific rotation of the solution slowly changes to +52.7°
  - It does not matter whether one starts with pure α- or β-glucose
- Mutarotation is the change in optical rotation as an equilibrium mixture of anomers forms

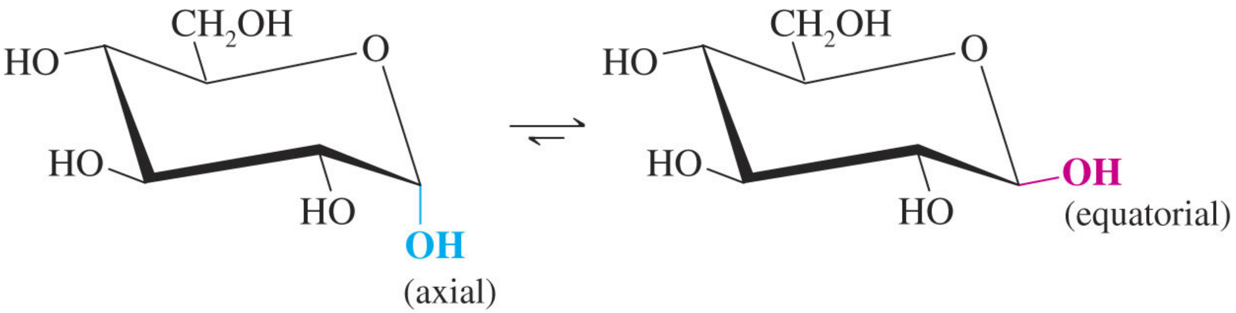


α-D-(+)-Glucopyranose (mp 146°C; $[\alpha]_D^{25} = +112°$)

Open-chain form of D-(+)-glucose

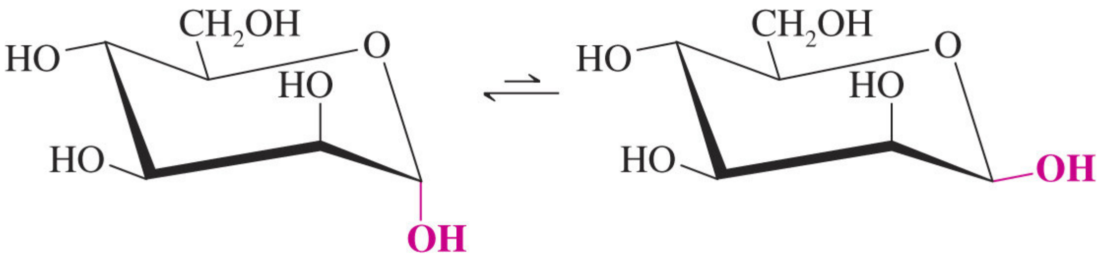
β-D-(+)-Glucopyranose (mp 150°C; $[\alpha]_D^{25} = +18.7°$)

- Mutarotation of glucose results in an equilibrium mixture of 36% α-glucose and 64% β-glucose
  - The more stable β-glucose form predominates
  - A very small amount of the open-chain form exists in this equilibrium



α-D-(+)-Glucopyranose
(36% at equilibrium)

β-D-(+)-Glucopyranose
(64% at equilibrium)



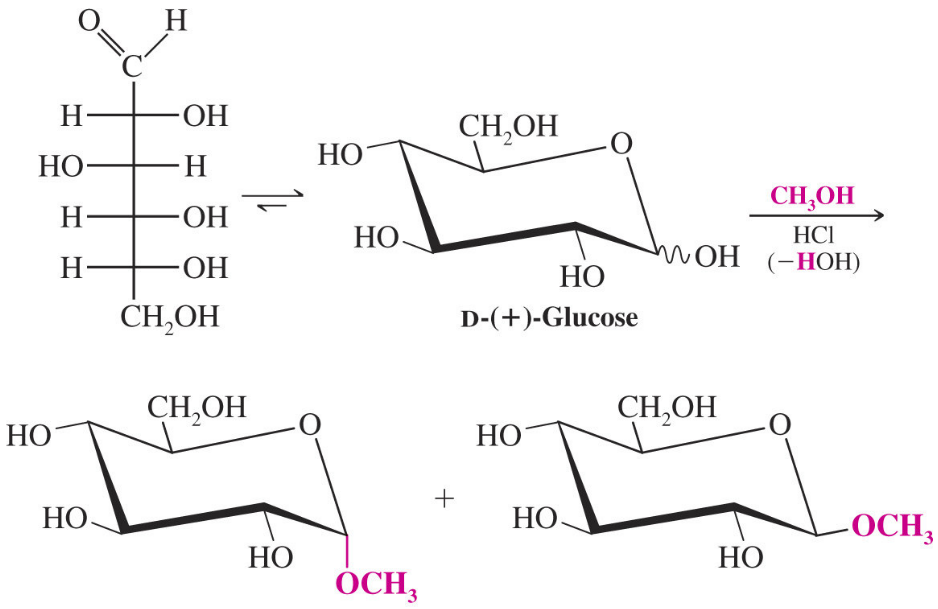
α-D-Mannopyranose
(69% at equilibrium)

β-D-Mannopyranose
(31% at equilibrium)

♦ Glycoside Formation

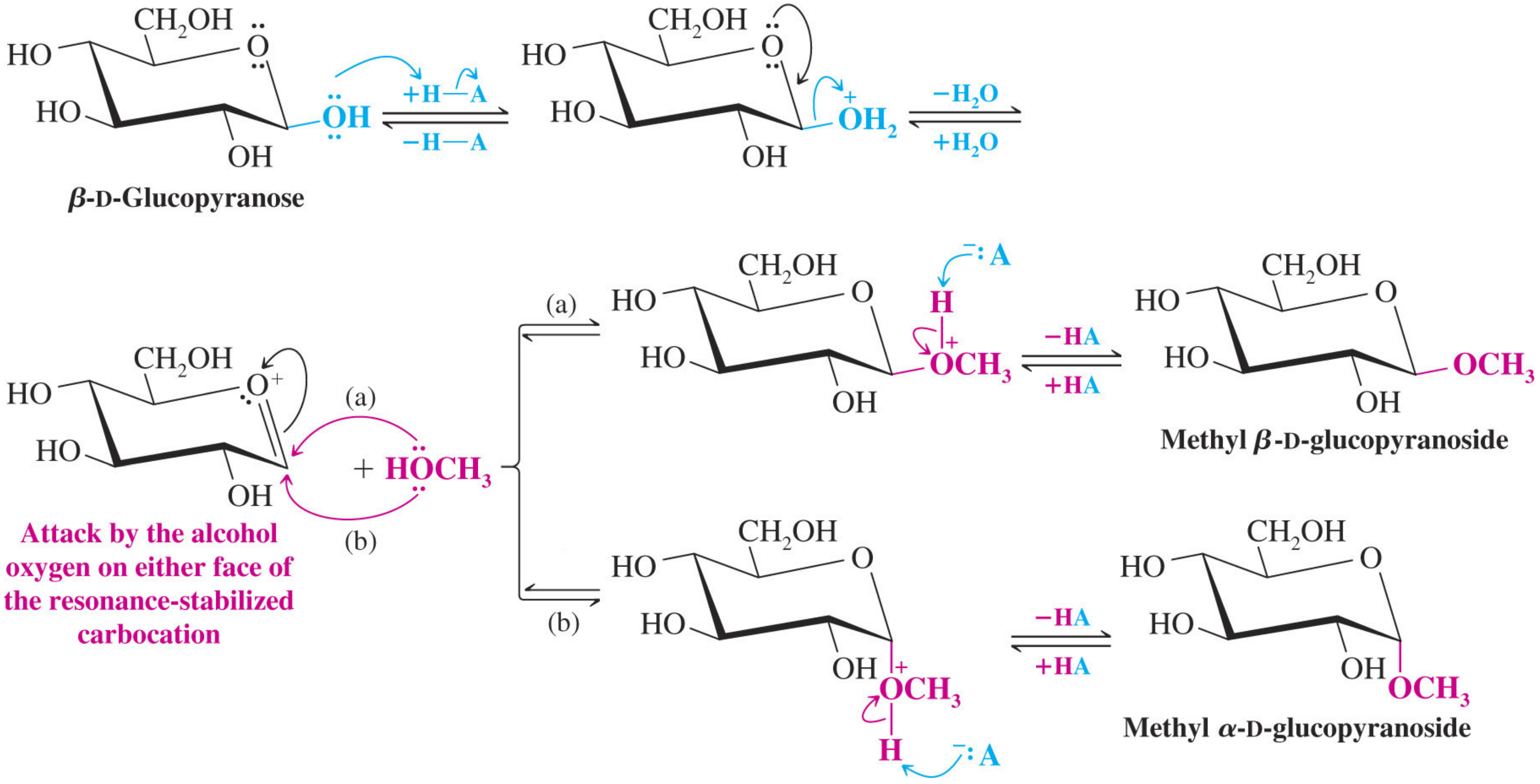
➔ Glycosides are acetals at the anomeric carbon of carbohydrates

- **When glucose reacts with methanol in the presence of catalytic acid, the methyl glycoside is obtained**
- **A glycoside made from glucose is called a glucoside**



Methyl α-D-glucopyranoside
(mp 165°C; $[\alpha]_D^{25} = +158°$)

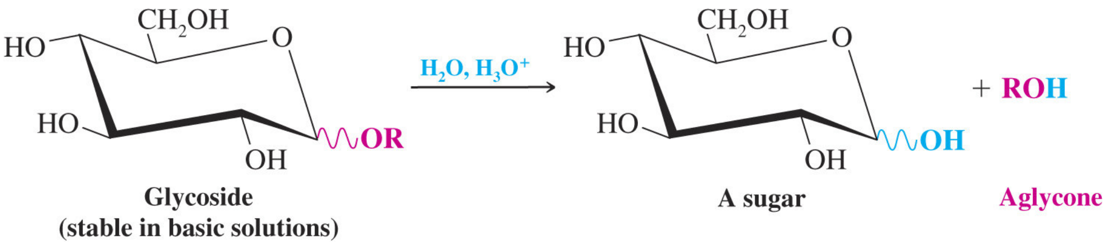
Methyl β-D-glucopyranoside
(mp 107°C; $[\alpha]_D^{25} = -33°$)

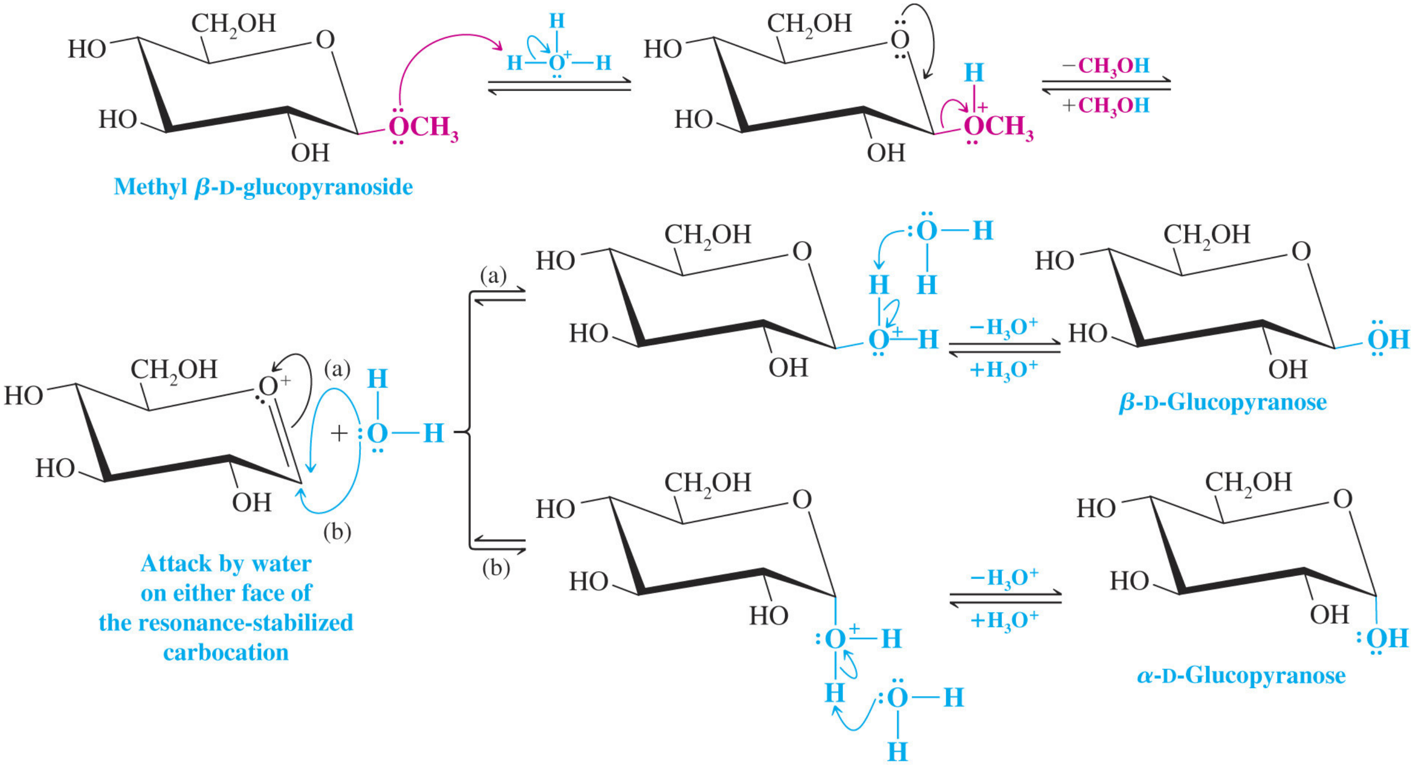


Attack by the alcohol oxygen on either face of the resonance-stabilized carbocation

➔Glycosides can be hydrolyzed in aqueous acid

- The alcohol obtained after hydrolysis of a glycoside is called an aglycone

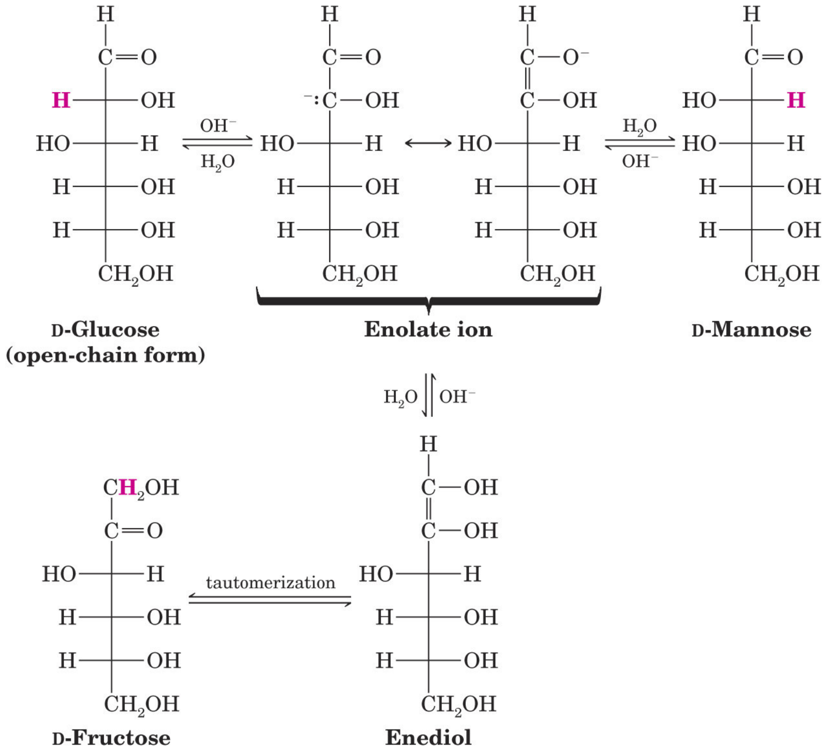




♦ Other Reactions of Monosaccharides

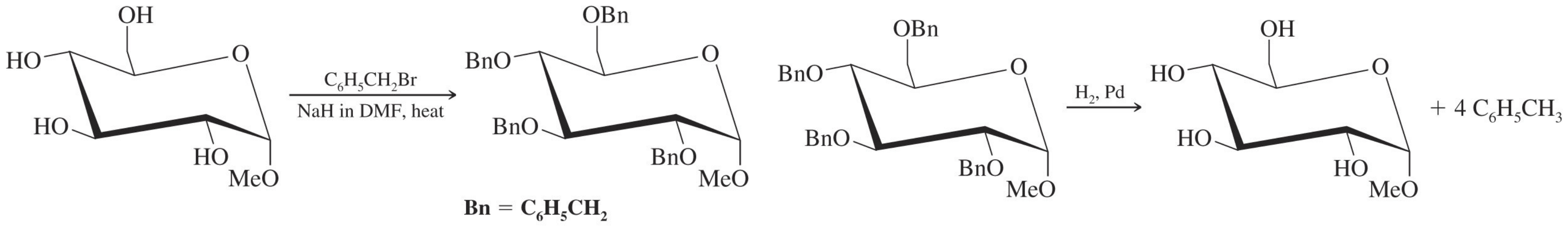
● Enolization, Tautomerization and Isomerization

- ➔Monosaccharides dissolved in aqueous base will isomerize by a series of keto-enol tautomerizations
  - A solution of D-glucose containing calcium hydroxide will form several products, including D-fructose and D-mannose
- ➔A monosaccharide can be protected from keto-enol tautomerization by conversion to a glycoside

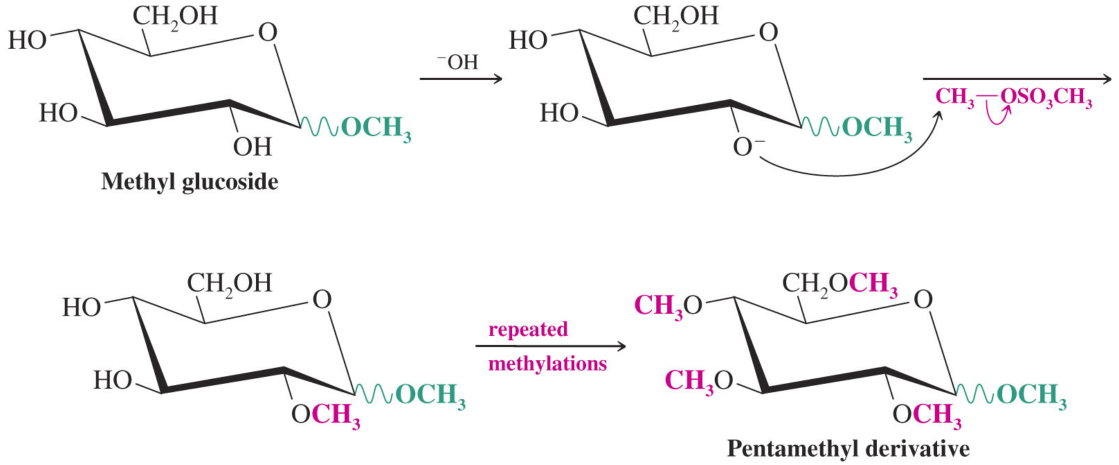


Formation of Ethers

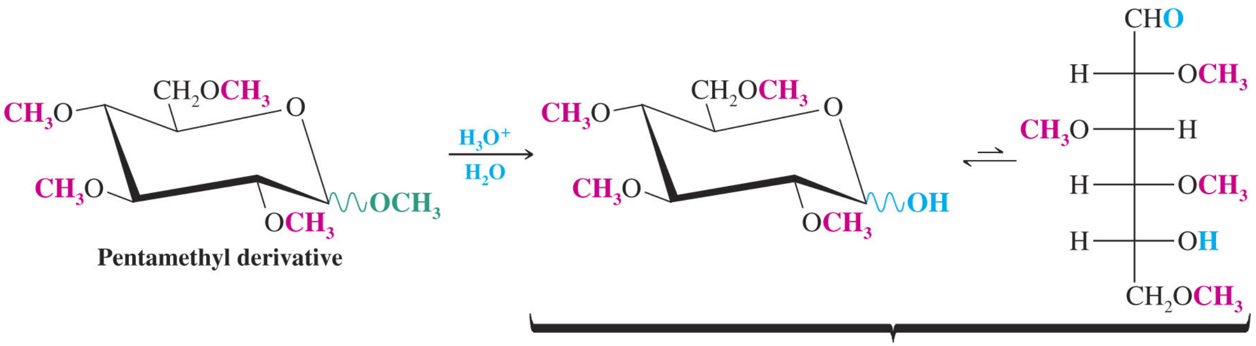
- ➔ The hydroxyl groups of carbohydrates can be converted to ethers by the Williamson ether synthesis
- ➔ Benzyl ethers are commonly used to protect or block carbohydrate hydroxyl groups
  - Benzyl ethers can be easily removed by hydrogenolysis



- ➔ Exhaustive methylation of methyl glucoside can be carried out using dimethylsulfate

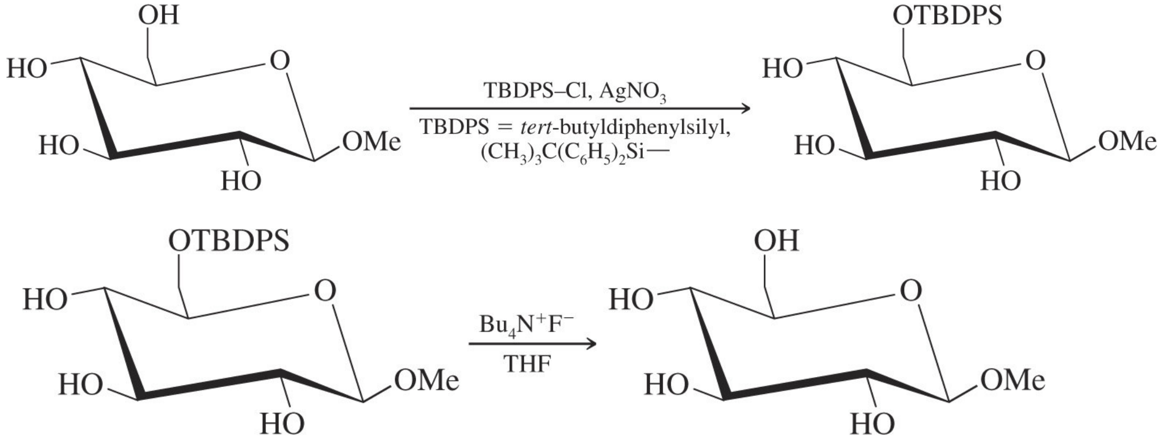


- Exhaustive methylation can be used to prove that glucose exists in the pyranose (6-membered ring) form
  - Hydrolysis of the pentamethyl derivative results in a free C5 hydroxyl

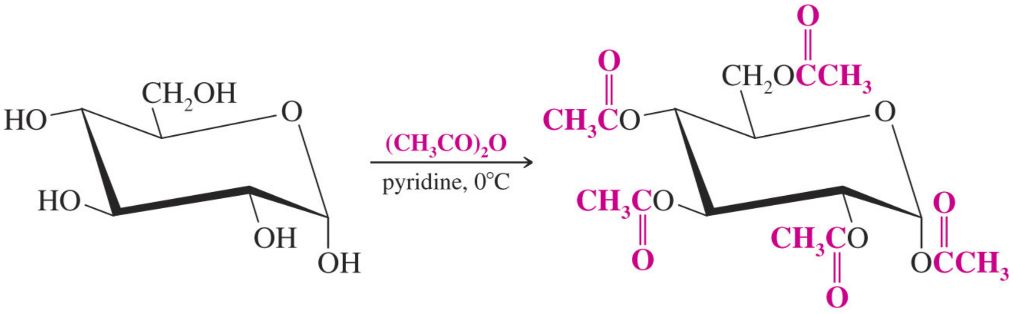


2,3,4,6-Tetra-*O*-methyl-D-glucose

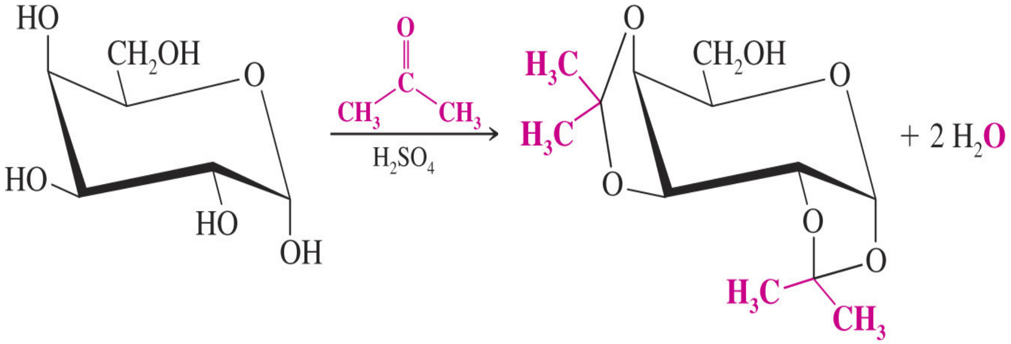
- Silyl ethers are also used as protecting groups for the hydroxyls of carbohydrates
  - Sterically bulky *tert*-butyldiphenylsilyl chloride (TBDPSCl) reacts selectively at the C6 primary hydroxyl of glucose



- **Conversion to Esters**
  - ➔ **Carbohydrates react with acetic anhydride in the presence of weak base to convert all hydroxyl groups to acetate esters**

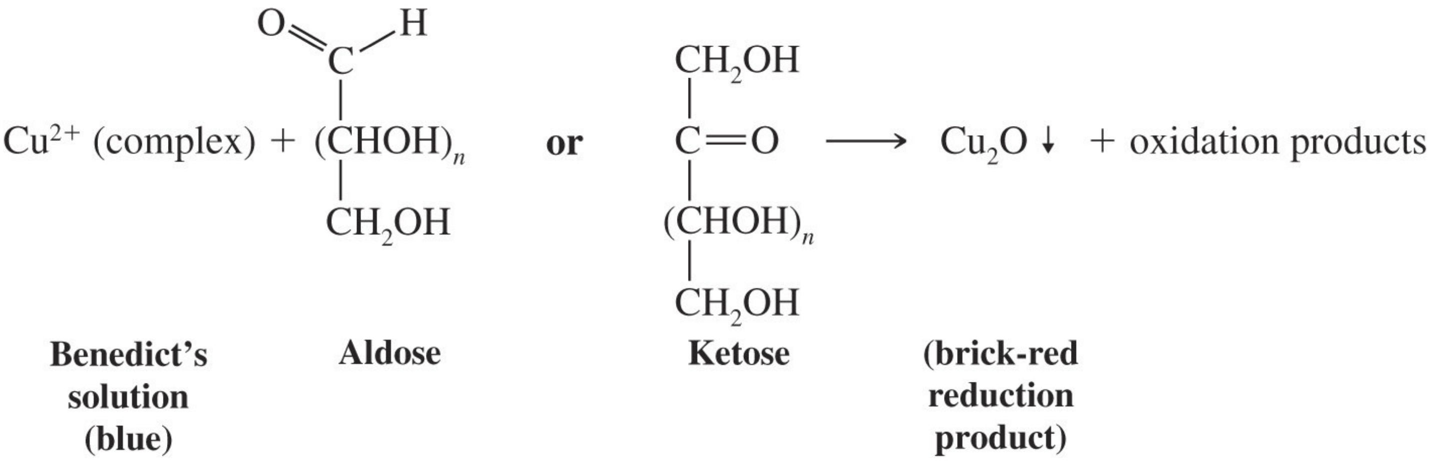


- **Conversion to Cyclic Acetals**
  - ➔ **Carbohydrates form cyclic acetals with acetone selectively between cis-vicinal hydroxyl groups**
    - **Cyclic acetals from reaction with acetone are called acetonides**



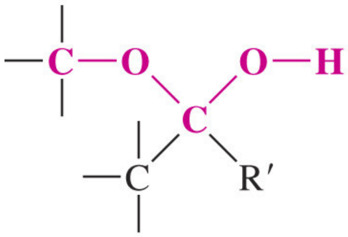
♦ Oxidation Reactions of Monosaccharides

- **Benedict's or Tollens' Reagents: Reducing Sugars**
  - ➔ **Aldoses and ketoses give positive tests when treated with Tollens' solution or Benedict's reagent**
    - **Tollens' reagent [$Ag(NH_3)_2OH$] gives a silver mirror when Ag^+ is reduced to Ag^0**
    - **Benedict's reagent (an alkaline solution of cupric citrate complex) gives a brick red precipitate of Cu_2O**
    - **In basic solution a ketose can be converted to an aldose that can then react with Tollens' or Benedicts's reagent**



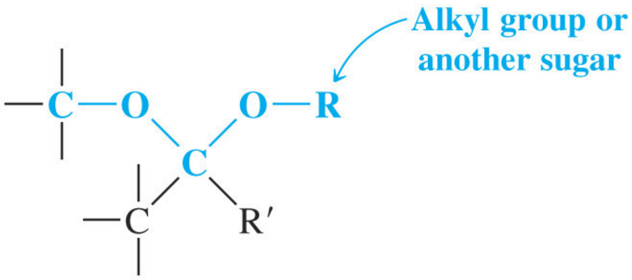
- **Carbohydrates with hemiacetal linkages are *reducing sugars* because they react with Tollens' and Benedict's reagents**
  - **The hemiacetal form is in equilibrium with a small amount of the aldehyde or ketone form, which can react with Tollens' and Benedict's reagents**
- **Carbohydrates with only acetal groups (glycosidic linkages) do not react with these reagents and are called non-reducing sugars**
  - **Acetals are not in equilibrium with the aldehyde or ketone and so cannot react with these reagents**

Reducing Sugar



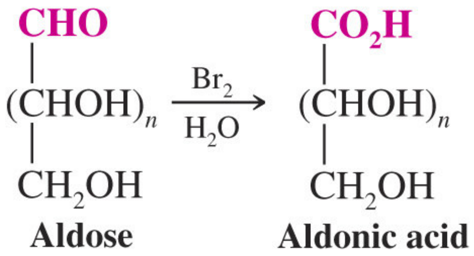
Hemiacetal (R′ = H or = CH_2OH) (gives positive Tollens' or Benedict's test)

Nonreducing Sugar



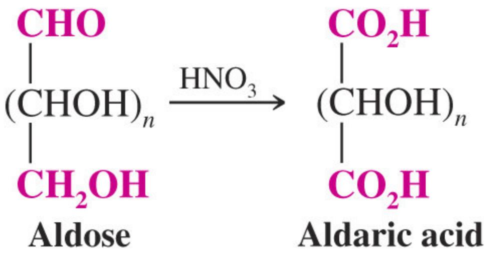
Acetal (R′ = H or = CH_2OH) (does not give a positive Tollens' or Benedict's test)

- **Bromine Water: The Synthesis of Aldonic Acids**
  - ➔ Bromine in water selectively oxidizes the aldehyde group of an aldose to the corresponding carboxylic acid
    - An aldose becomes an aldonic acid

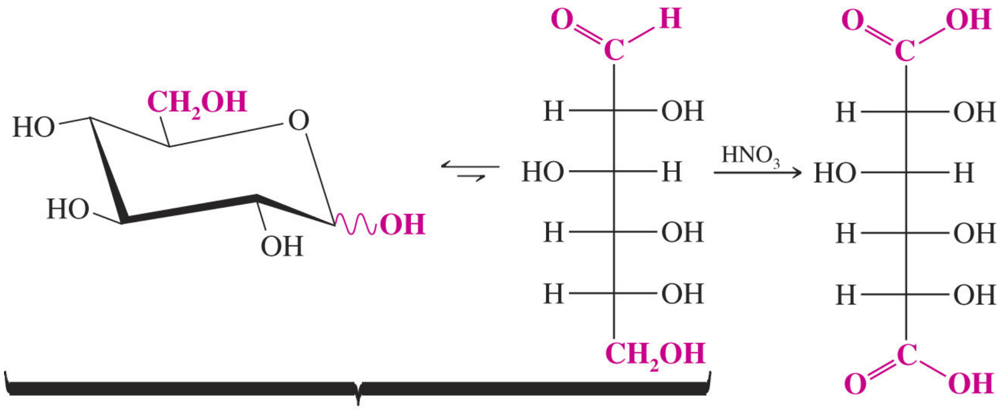


$$\begin{array}{c} CHO \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{array} \xrightarrow[H_2O]{Br_2} \begin{array}{c} CO_2H \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{array}$$

- **Nitric Acid Oxidation: Aldaric Acids**
  - ➔ Dilute nitric acid oxidizes both the aldehyde and primary hydroxyl groups of an aldose to an aldaric acid



$$\begin{array}{c} CHO \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{array} \xrightarrow{HNO_3} \begin{array}{c} CO_2H \\ | \\ (CHOH)_n \\ | \\ CO_2H \end{array}$$

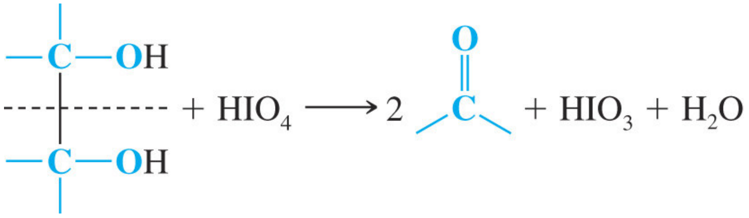


D-Glucose

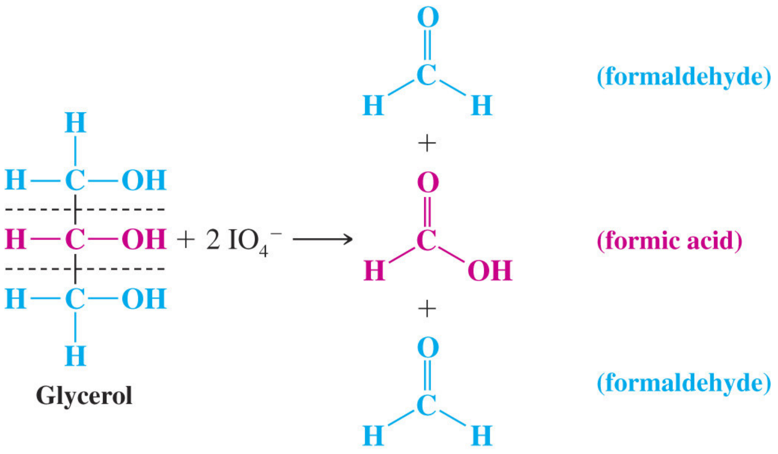
D-Glucaric acid

Periodate Oxidations: Oxidative Cleavage of Polyhydroxy Compounds

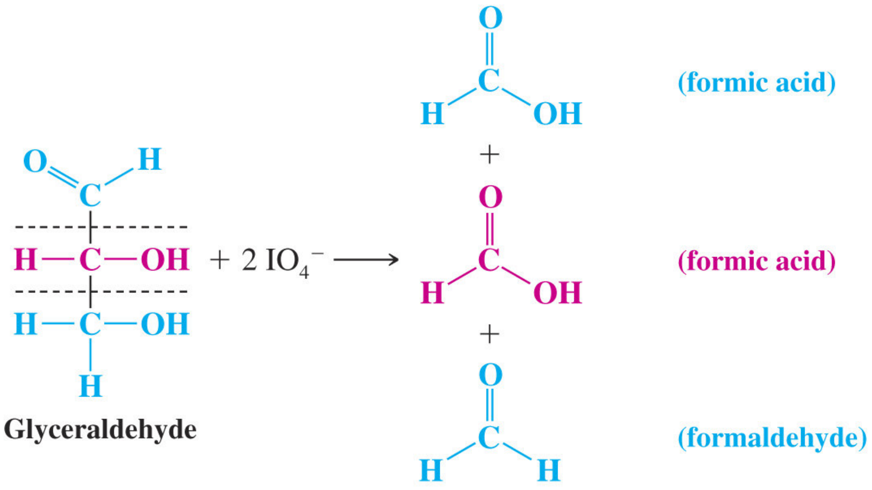
- ➔ Compounds with hydroxyl groups on adjacent carbons undergo cleavage of carbon-carbon bonds between the hydroxyl groups
  - The products are aldehydes, ketones or carboxylic acids

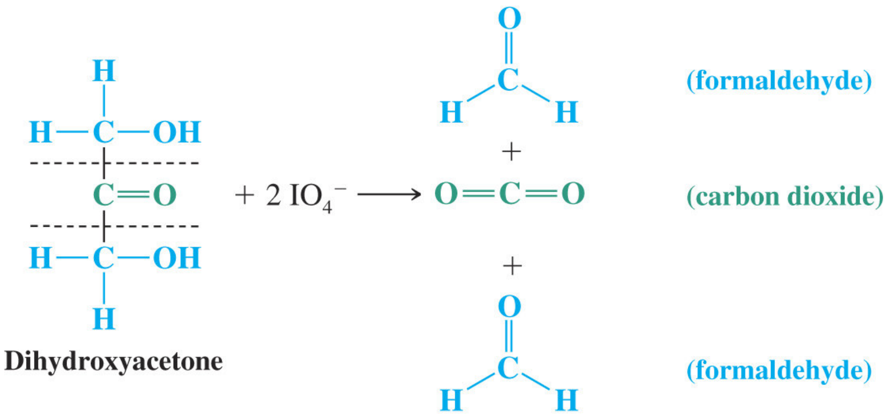


- ➔ With three or more contiguous hydroxyl groups, the internal carbons become formic acid

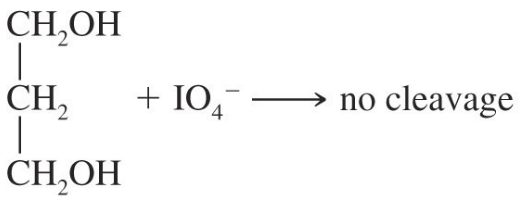


- ➔ Cleavage also takes place when a hydroxyl group is adjacent to an aldehyde or ketone group
  - An aldehyde is oxidized to formic acid; a ketone is oxidized to carbon dioxide

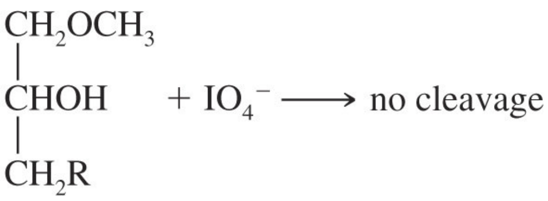




➔ **No cleavage results if there are intervening carbons that do not bear hydroxyl or carbonyl groups**



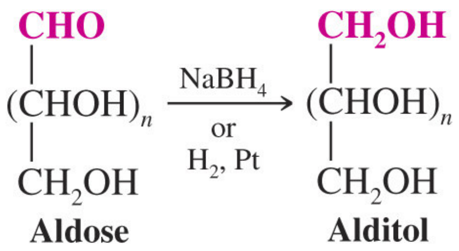
$$\begin{array}{l} CH_2OH \\ | \\ CH_2 \\ | \\ CH_2OH \end{array} + IO_4^- \longrightarrow \text{no cleavage}$$

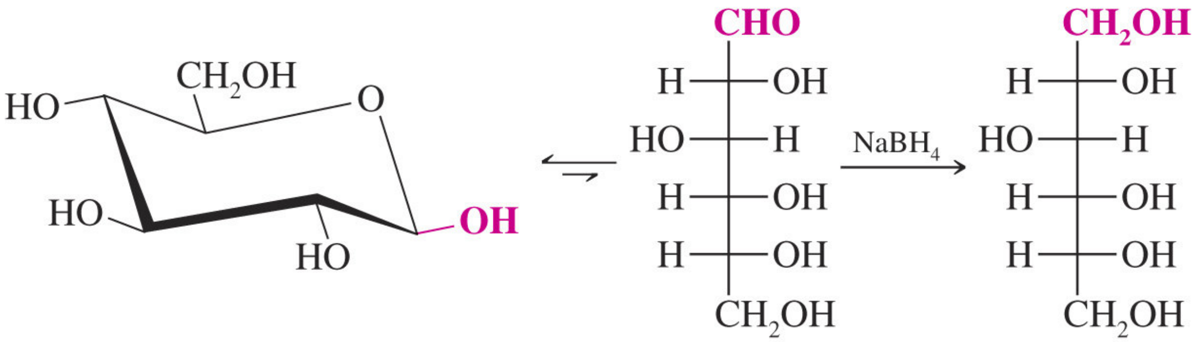


$$\begin{array}{l} CH_2OCH_3 \\ | \\ CHOH \\ | \\ CH_2R \end{array} + IO_4^- \longrightarrow \text{no cleavage}$$

♦ Reduction of Monosaccharides: Alditols

➔ **Aldoses and ketoses can be reduced to alditols**

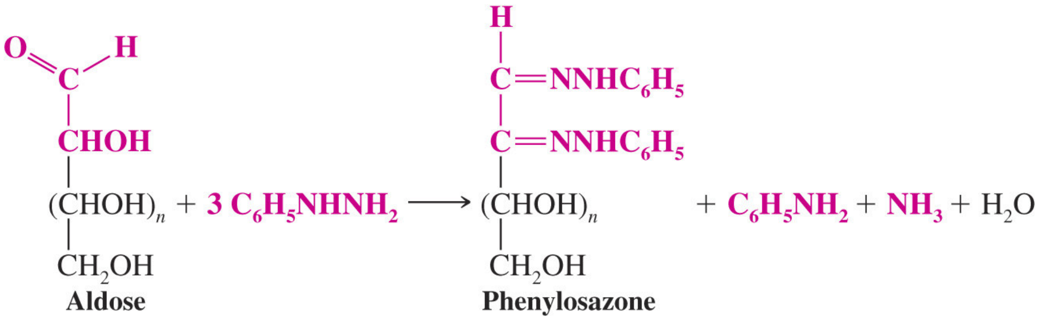




D-Glucitol
(or D-sorbitol)

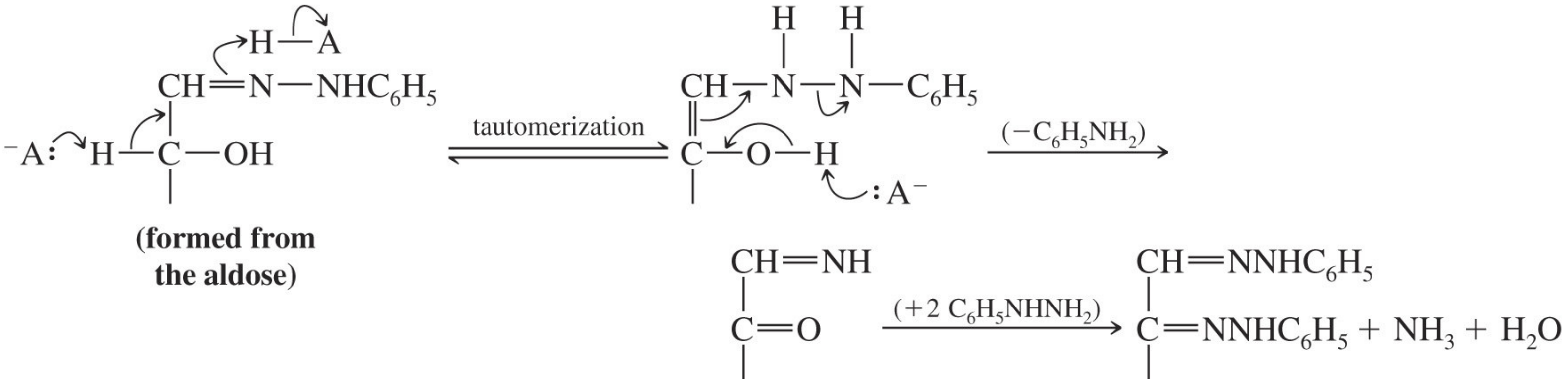
♦ Reactions of Monosaccharides with Phenylhydrazine: Osazones

- ➔ **An aldose or ketose will react with three equivalents of phenylhydrazine to yield a phenylosazone**

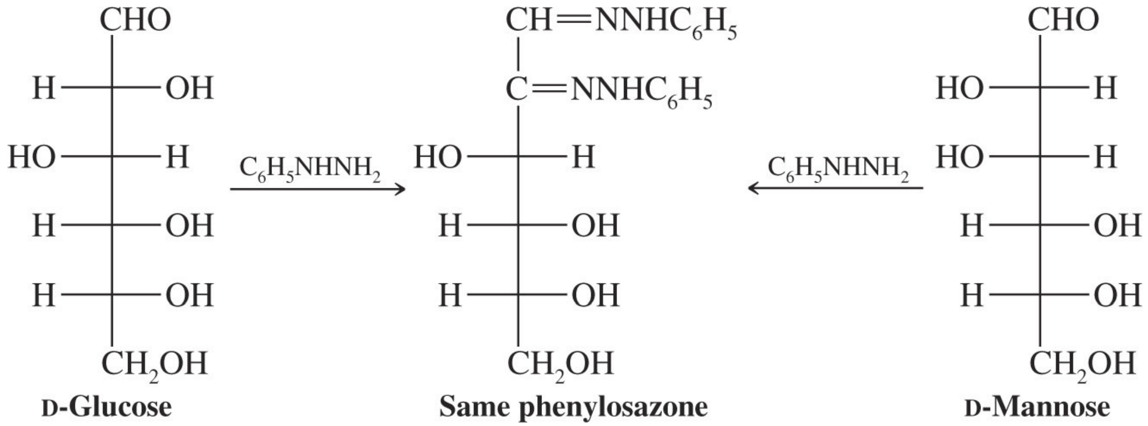


Aldose **Phenylosazone**

- ➔ **The mechanism for phenylosazone formation involves the following steps:**

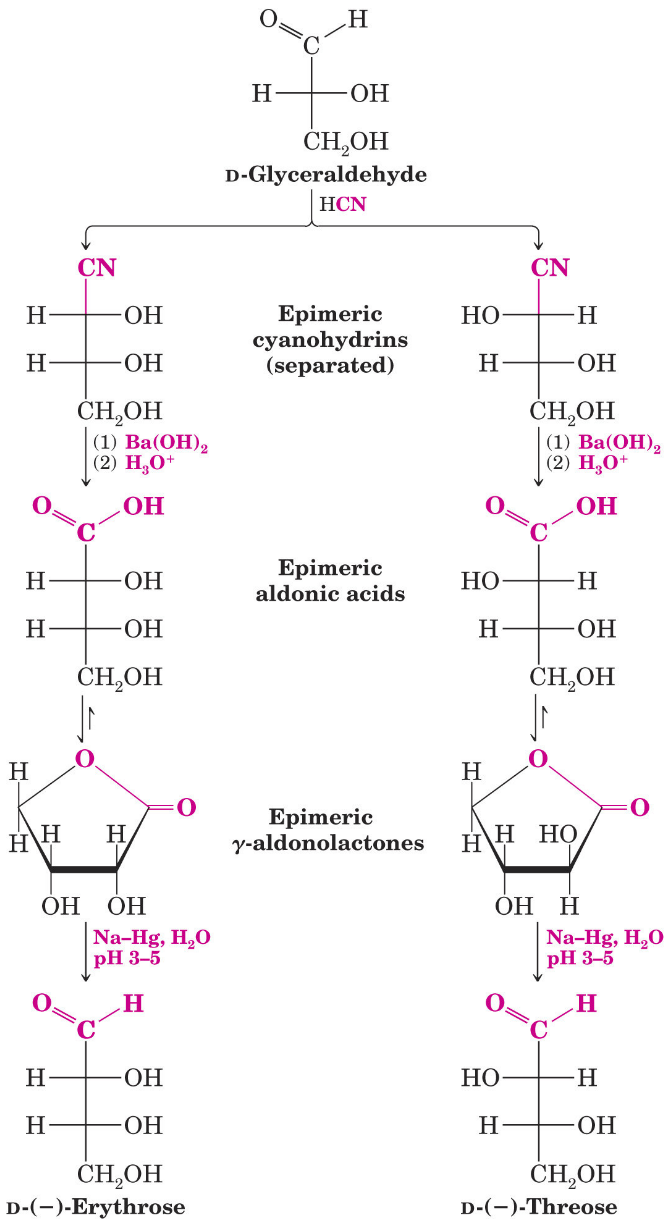


- **Reaction of D-Glucose or D-Mannose with excess phenylhydrazine yields the same phenylosazone**
  - **Therefore, D-glucose and D-mannose differ in configuration only at C2**
  - **Compounds that differ in configuration at only one stereogenic center are called epimers**

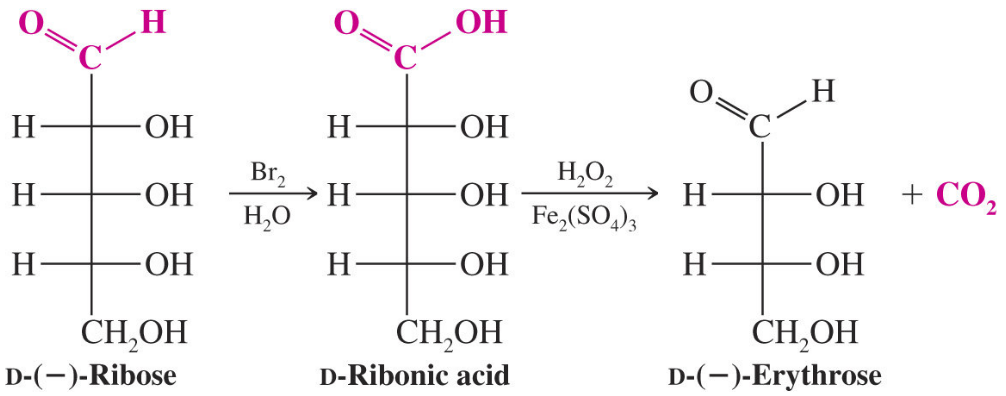


♦ Synthesis and Degradation of Monosaccharides

- **Kiliani-Fischer Synthesis**
  - ➔ **The carbon chain of an aldose can be extended by:**
    - **Addition of cyanide to epimeric cyanohydrins**
    - **Hydrolysis to a mixture of epimeric aldonic acids or aldonolactones**
    - **Reduction of the epimeric aldonic acids or aldonolactones to the corresponding aldoses**
  - ➔ **For example, D-glyceraldehyde can be converted to D-erythrose and D-threose by the Kiliani-Fischer synthesis**

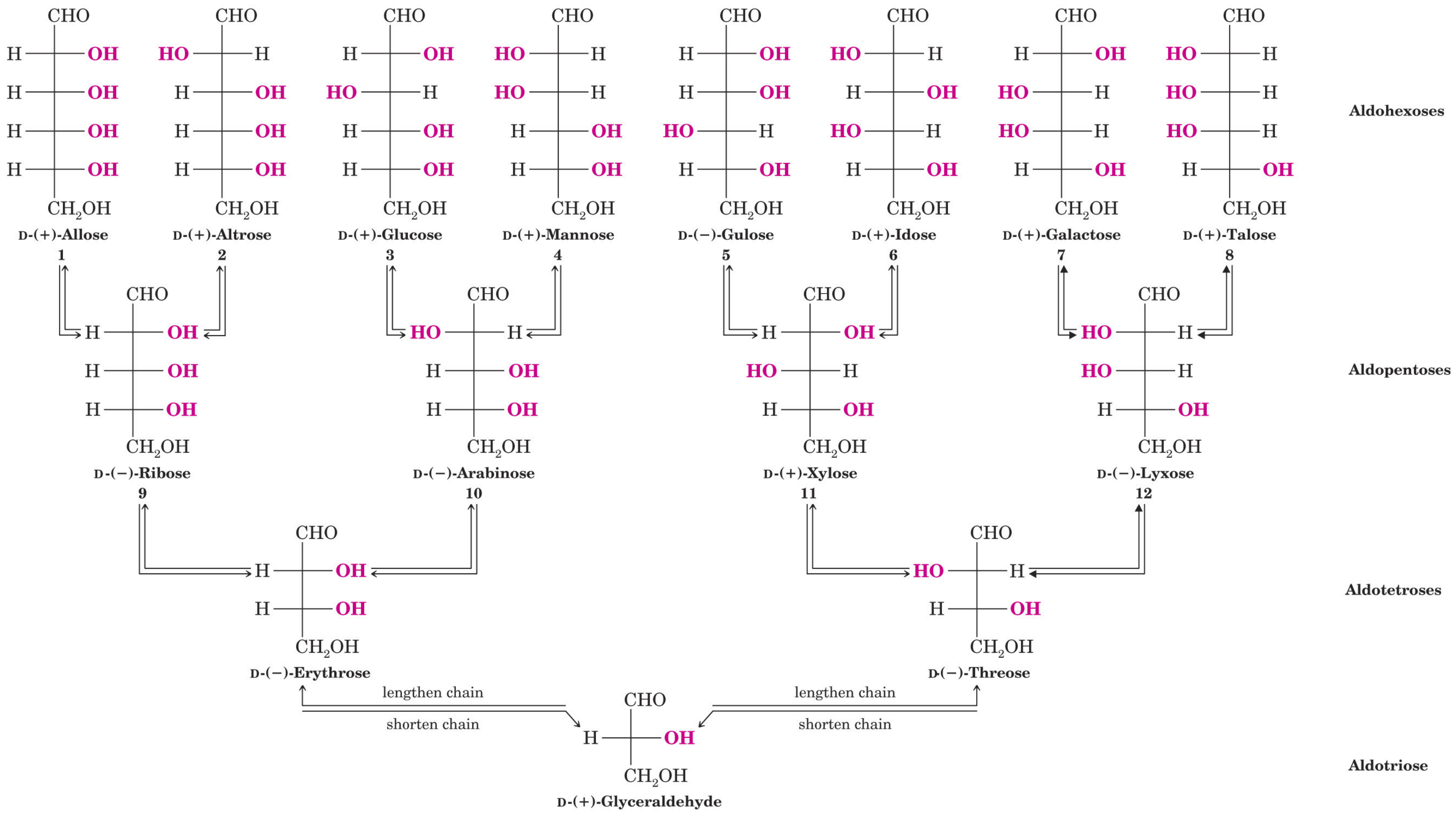

D-Glyceraldehyde
HCN
Epimeric cyanohydrins (separated)
(1) Ba(OH)2
(2) H3O+
Epimeric aldonic acids
Epimeric γ-aldonolactones
Na–Hg, H2O
pH 3–5
D-(−)-Erythrose
D-(−)-Threose

- **The Ruff Degradation**
  - ➔ **An aldose can be shortened by one carbon via:**
    - **Oxidation with bromine water to the aldonic acid**
    - **Oxidative decarboxylation with hydrogen peroxide and ferric sulfate**



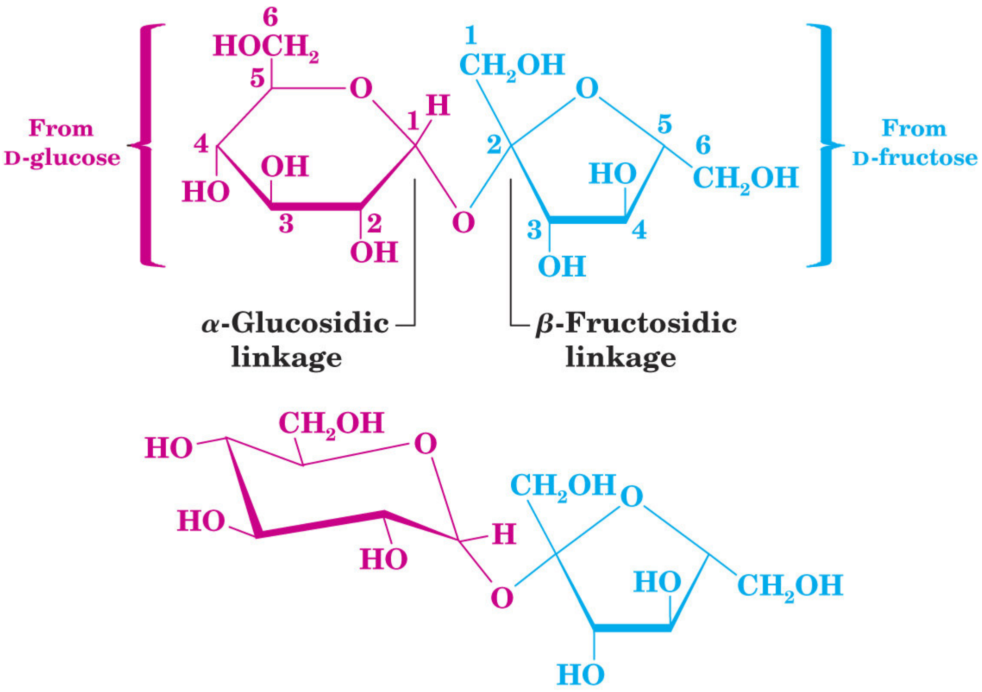
♦ The D Family of Aldoses

➔Most biologically important aldoses are of the D family

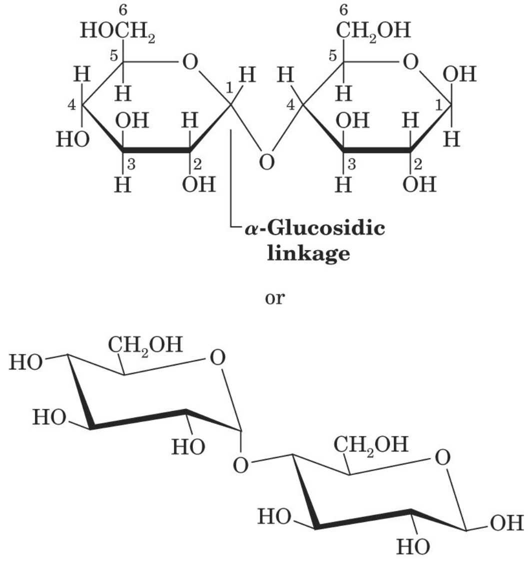


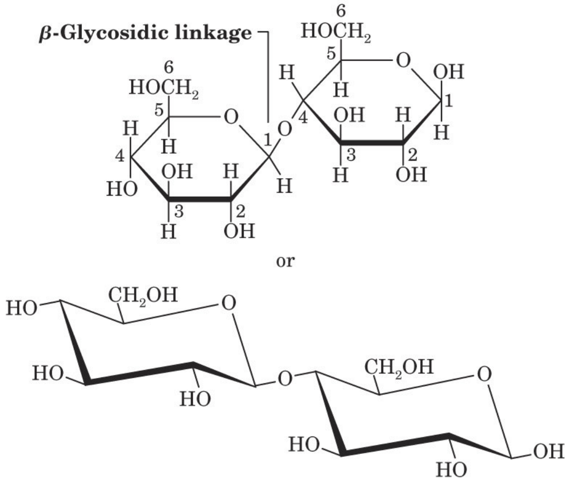
♦ Disaccharides

- Sucrose (Table sugar)
  - ➔ Sucrose is a disaccharide formed from D-glucose and D-fructose
    - The glycosidic linkage is between C1 of glucose and C2 of fructose
    - Sucrose is a nonreducing sugar because of its acetal linkage



- **Maltose**
  - ➔ **Maltose is the disaccharide of D- glucose having an α-linkage**
  - ➔ **Maltose results from hydrolysis of starch by the enzyme diastase**
    - **Maltose has a hemiacetal group in one glucose moiety; it is a reducing sugar**
    - **The two glucose units of maltose are joined by an α-glucosidic linkage**
- **Cellobiose**
  - ➔ **Cellobiose is the disaccharide of D-glucose having a β-linkage**
  - ➔ **Cellobiose results from partial hydrolysis of cellulose**
    - **Cellobiose has a hemiacetal group in one glucose moiety; it is a reducing sugar**
    - **The two glucose units are connected by a β-glucosidic linkage**



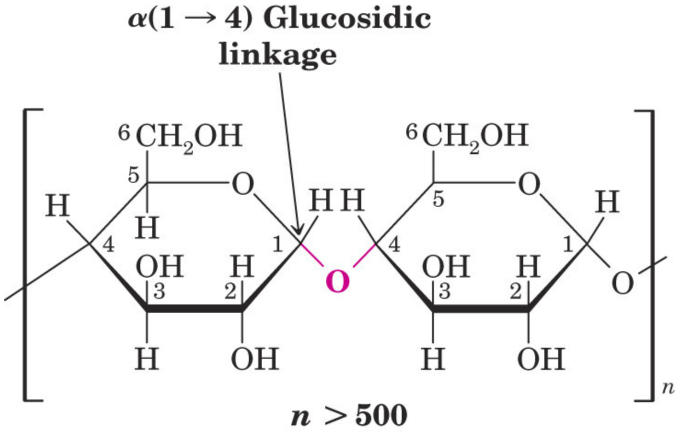


♦ Polysaccharides

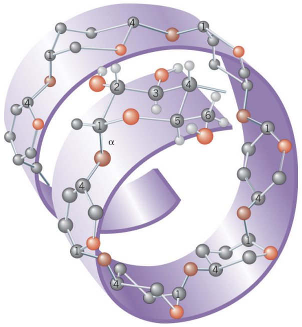
- ➔ Homopolysaccharides are polymers of a single monosaccharide whereas heteropolysaccharides contain more than one type of monosaccharide
  - A polysaccharide made up of only glucose units is called a glucan
  - Three important glucans are starch, glycogen and cellulose

● Starch

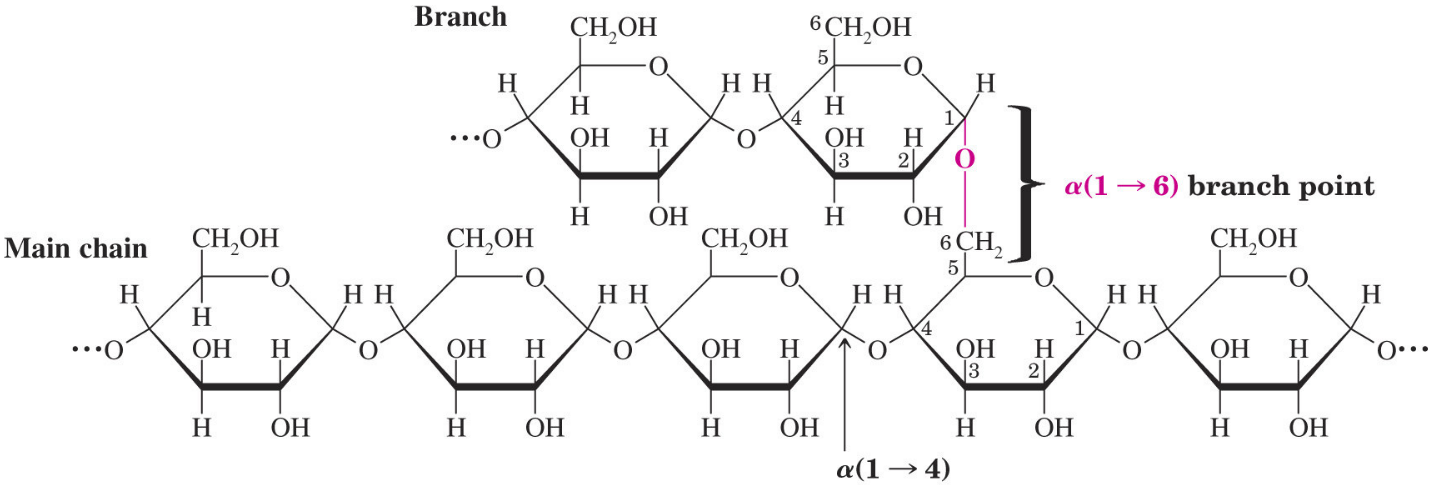
- ➔ The storage form of glucose in plants is called starch
- ➔ The two forms of starch are amylose and amylopectin
- ➔ Amylose consists typically of more than 1000 D-glucopyranoside units connected by α linkages between C1 of one unit and C4 of the next



- ➔ Amylose adopts a very compact helical arrangement

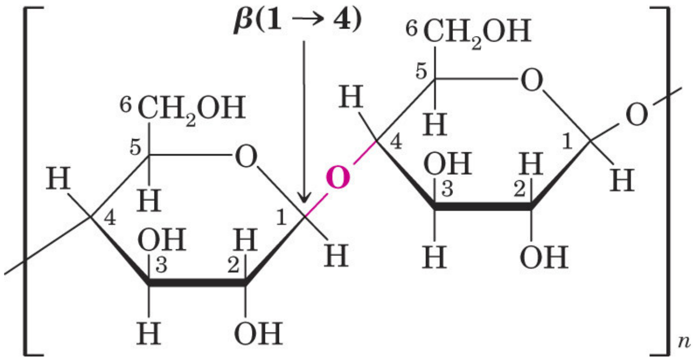


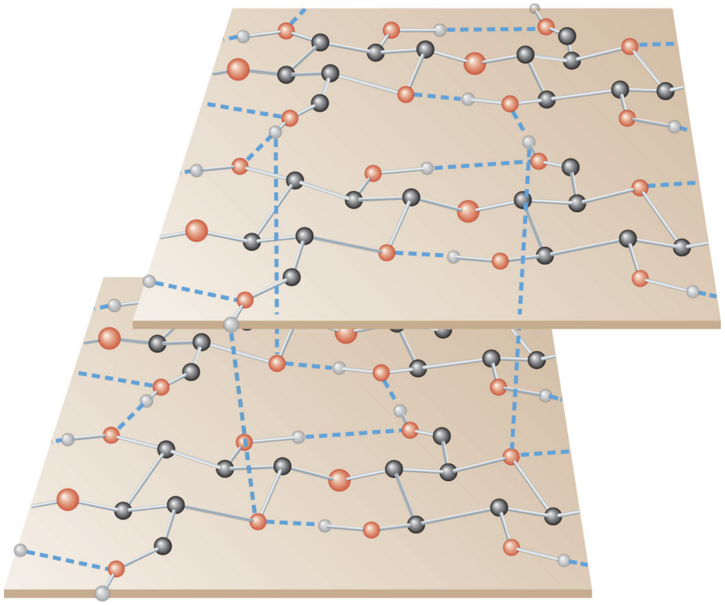
- ➔ Amylopectin is similar to amylose but has branching points every 20-25 glucose units
  - Branches occur between C1 of one glucose unit and C6 of another



- **Glycogen**
  - ➔ **Glycogen is the major carbohydrate storage molecule in animals**
  - ➔ **Glycogen is similar to amylopectin except that glycogen has far more branching**
    - **Branching occurs ever 10-12 glucose units in glycogen**
  - ➔ **Glycogen is a very large polysaccharide**
    - **The large size of glycogen prevents if from leaving the storage cell**
    - **The storage of tens of thousands of glucose molecules into one molecule greatly relieves the osmotic problem for the storage cell (this would be caused by the attempted storage of many individual glucose molecules)**
    - **The highly branched nature of glycogen allows hydrolytic enzymes to have many chain ends from which glucose molecules can be hydrolyzed**
  - ➔ **Glucose is the source of "ready energy" for the body**
    - **Long chain fatty acids of triacylglycerols are used for long term energy storage**

- **Cellulose**
  - ➔ **In cellulose, glucose units are joined by β-glycosidic linkages**
  - ➔ **Cellulose chains are relatively straight**
  - ➔ **The linear chains of cellulose hydrogen bond with each other to give the rigid, insoluble fibers found in plant cell walls**
    - **The resulting sheets then stack on top of each other**
  - ➔ **Humans lack enzymes to cleave the β linkages in cellulose and so cannot use cellulose as a source of glucose**





- **Glycolipids and Glycoproteins of the Cell Surface**
  - ➔**Glycolipids and Glycoproteins are important for cell signaling and recognition**
  - ➔**A, B, and O human blood groups are determined by glycoprotein antigens designated A, B, and H**