Bio-organic chemistry

Lecture #8

Classification of carbohydrates. Genetic series of aldoses and ketoses. Stereochemistry of monosaccharides, their mutarotation.

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Carbohydrates

Carbohydrates are the most abundant organic compounds in the plant world. Carbohydrates account for approximately three-fourths of the dry weight of plants. Animals (including humans) get their carbohydrates by eating plants, but they do not store much of what they consume. In fact, **less than 1% of the body weight of animals is made up of carbohydrates.**

The word *carbohydrate means "hydrate of carbon" and derives from the* formula $C_n(H_2O)_m$.

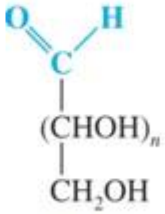
Glucose: $C_6H_{12}O_6$, which can be written as $C_6(H_2O)_6$
Sucrose : $C_{12}H_{22}O_{11}$, which can be written as $C_{12}(H_2O)_{11}$

Most carbohydrates are polyhydroxyaldehydes, polyhydroxyketones, or compounds that yield them after hydrolysis. The simpler members of the carbohydrate family are often referred to as **saccharides because of their sweet taste (Latin: *saccharum, "sugar").***

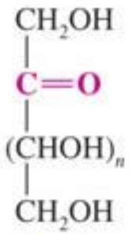
Carbohydrates are classified as **monosaccharides, oligosaccharides, or polysaccharides** depending on the number of simple sugars they contain.

- ✓ **Monosaccharides** – carbohydrates that can not be hydrolyzed to more simple carbohydrates;
- ✓ **Oligosaccharides** – carbohydrates that under the hydrolysis give from 2 to 10 molecules of monosaccharides;
- ✓ **Polysaccharides** – carbohydrates that consists of more then 10 units of monosaccharides

- **Monosaccharides**
  - Classification of monosaccharides
    - They are classified according to:
      - **(1)** **number of C atoms in the molecule**
      - **(2)** **the presence of aldehyde or ketone group**

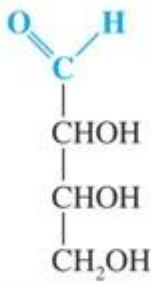


Aldose



$CH_2OH-C(=O)-(CHOH)_n-CH_2OH$

Ketose

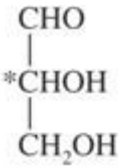


Aldotetrose
4C atoms and
aldehyde group

$CH_2OH-C(=O)-CHOH-CHOH-CH_2OH$

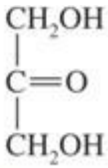
Ketopentose
5C atoms and
ketone group

- There are only two trioses:



$CHO-{}^{*}CHOH-CH_2OH$

Glyceraldehyde



$CH_2OH-C(=O)-CH_2OH$

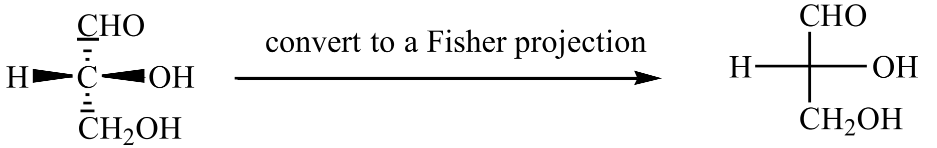
Dihydroxyacetone

Representation of saccharide molecules

Fischer Projection Formulas

Two-dimensional representations called **Fischer projections to show the configuration of carbohydrates** are commonly used.

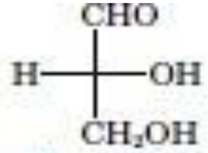
To draw a Fischer projection, draw a three-dimensional representation of the molecule oriented so that the vertical bonds from the stereocenter (atom bonded with 4 different groups) are directed away from you and the horizontal bonds from it are directed toward you (none of the bonds to stereocenter are in the plane of the paper). Then write the molecule as a cross, with the stereocenter indicated by the point at which the bonds cross.



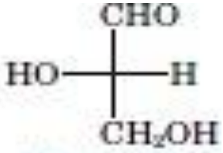
3D representation

Fischer representation

Molecules, having a stereocenter can exist in the form of stereoisomers, called **enantiomers. Enantiomers are nonsuperimposable mirror images** . Their chemical and physical properties are the same with the exception that one enantiomer rotates plane of polarized light to the right, another – to the left by the same angle.



D-Glyceraldehyde
$[\alpha]_D^{25} = +13.5°$



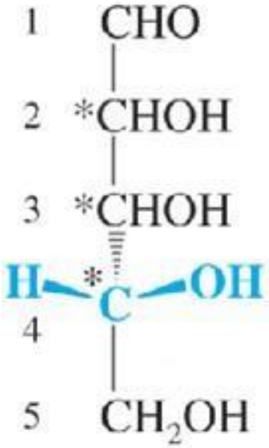
L-Glyceraldehyde
$[\alpha]_D^{25} = -13.5°$

Emil Fischer (*German chemist*) proposed that these enantiomers be designated **D and L**, but he had no experimental way to determine which enantiomer has which specific rotation. Only In 1952 it was proved that his assignment of the D,L-configuration to the enantiomers of glyceraldehyde is correct.

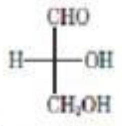
D-glyceraldehyde and L-glyceraldehyde serve as reference points for the assignment of relative configurations to all other aldoses and ketoses. The reference point is the **penultimate** carbon—that is, the **next-to-the-last** carbon on the chain.

D-monosaccharide has the same configuration at its penultimate carbon as D-glyceraldehyde (its -OH group is on the right) in a Fischer projection;

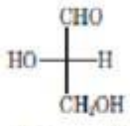
L-monosaccharide has the same configuration at its penultimate carbon as L-glyceraldehyde (its -OH group is on the left).



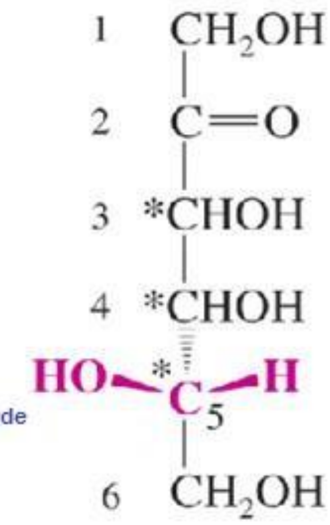
D-Aldopentose



D-Glyceraldehyde

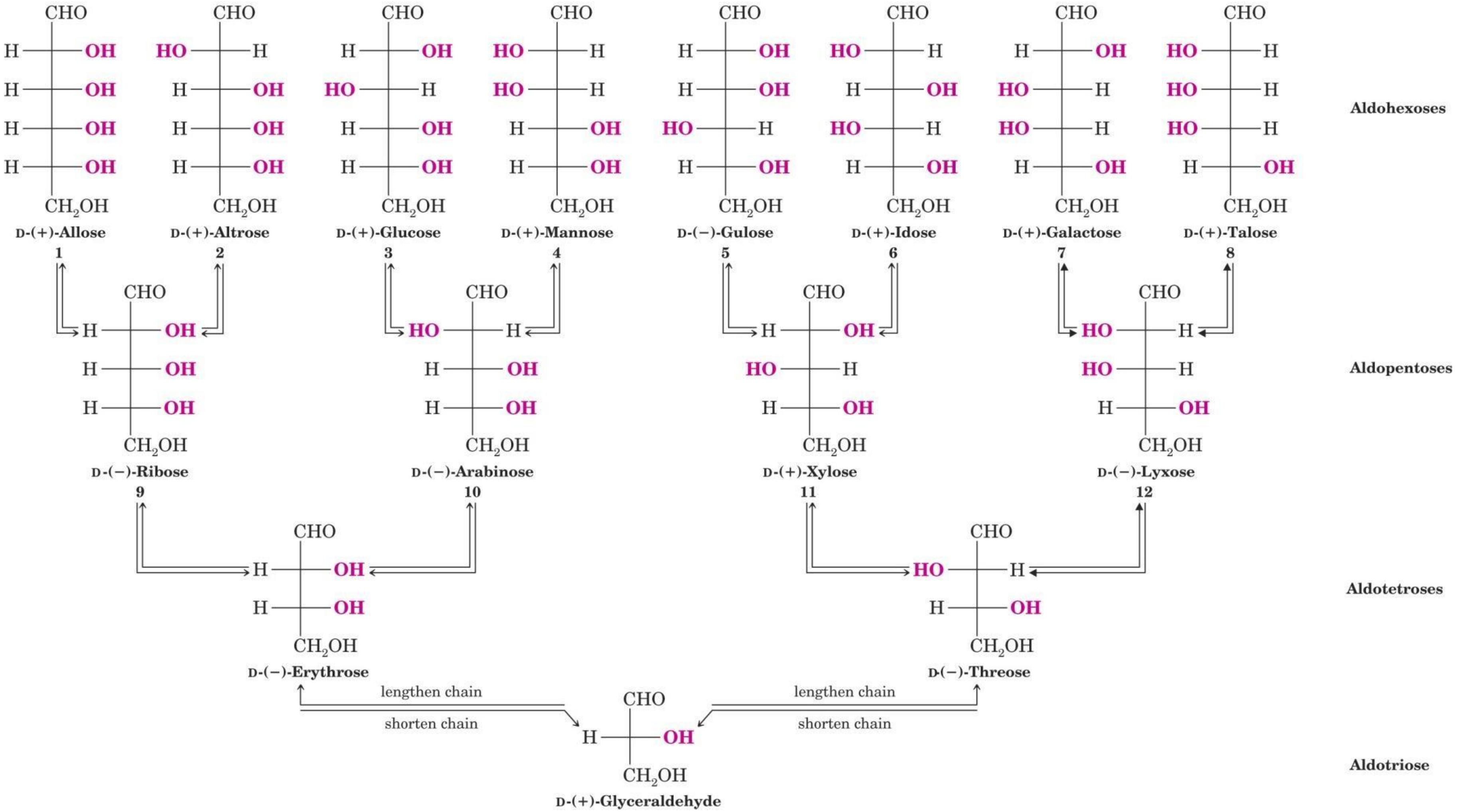


L-Glyceraldehyde

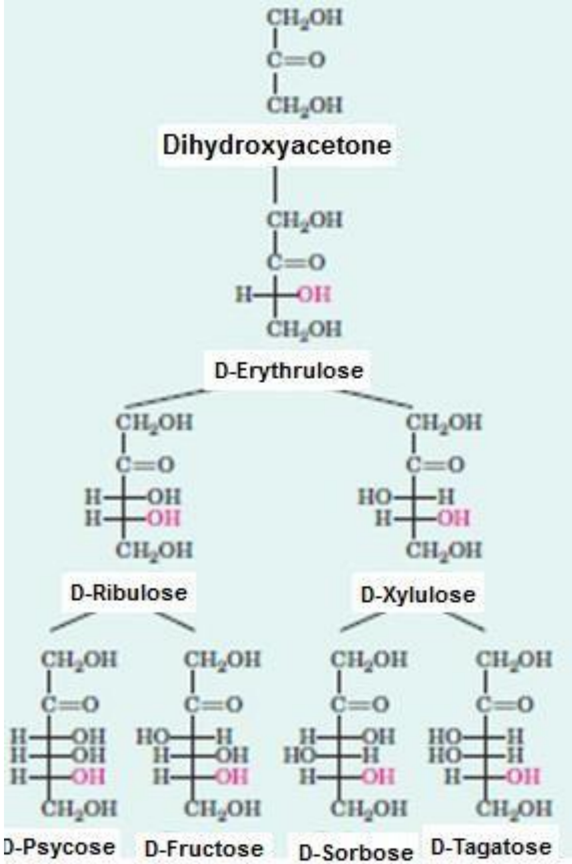


L-ketohexose

Configurational Relationships among the Isomeric D-Aldotetroses, D-Aldopentoses, and D-Aldohexoses

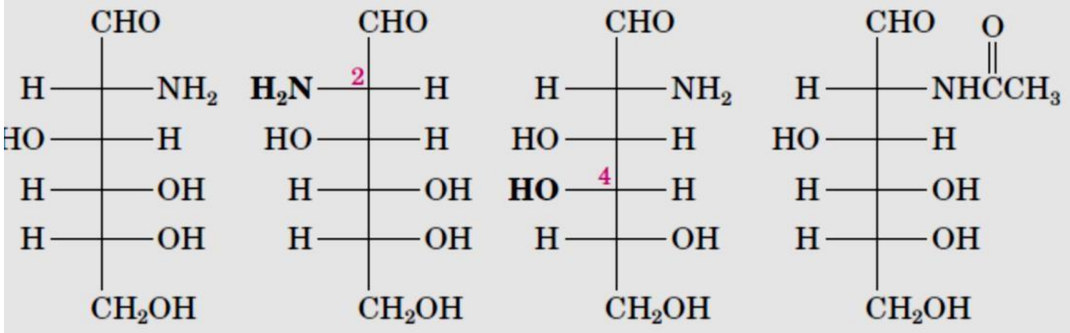


Configurational Relationships among the D-2-Ketoses



Amino Sugars

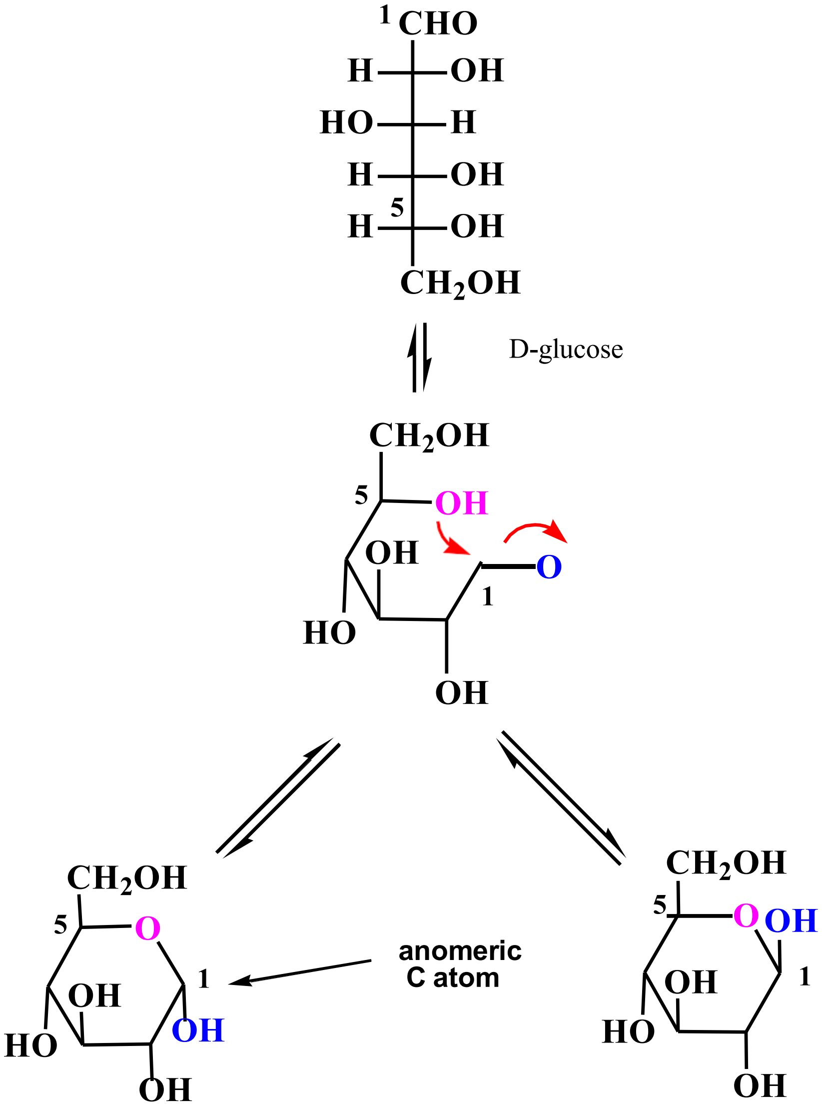
Amino sugars contain an -NH_2 group in place of an -OH group. **Only three amino sugars are common in nature: D-glucosamine, D-mannosamine, and D-galactosamine.**



D-glucosamine D-Mannosamine D-Galactosamine N-Acetyl-D-glucosamine

N- Acetyl-D-glucosamine, a derivative of D-glucosamine, is a component of many polysaccharides, including connective tissue such as cartilage. It is also a component of chitin, the hard, shell-like exoskeleton of lobsters, crabs, shrimp, and other shellfish.

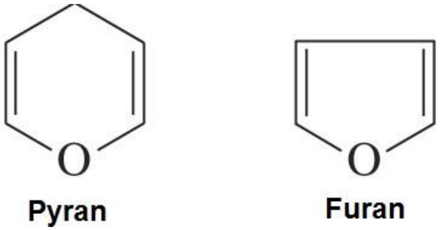
Cyclic form of monosaccharides



D-α-glucopyranose

D-β-glucopyranose

The names of cyclic form of saccharides come from the names of heterocycles

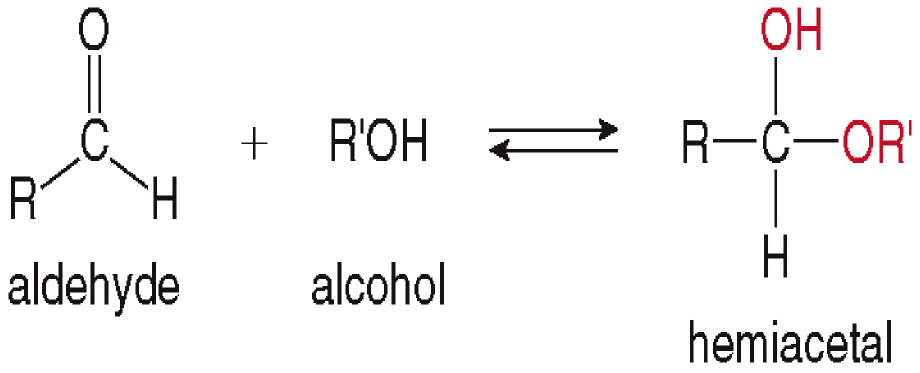


The new carbon stereocenter created in forming the cyclic structure is called an **anomeric carbon**.

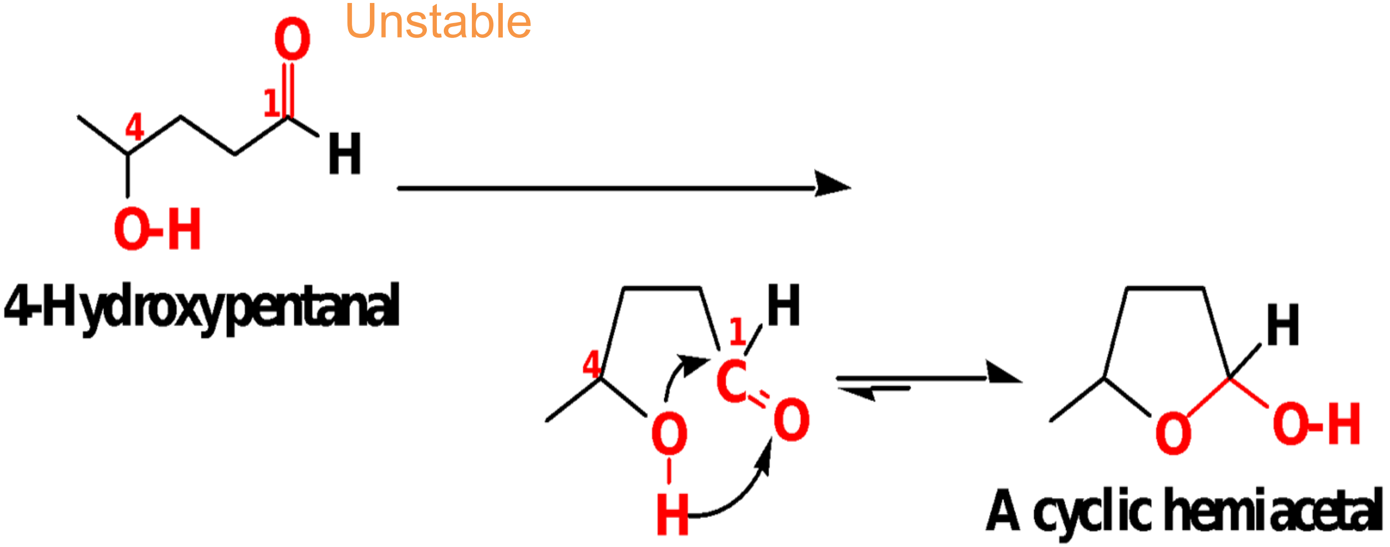
Stereoisomers that differ in configuration only at the anomeric carbon are called **anomers.**

Cyclic Structure – Haworth Structure

Aldehydes and ketones react with alcohols
to form hemiacetals



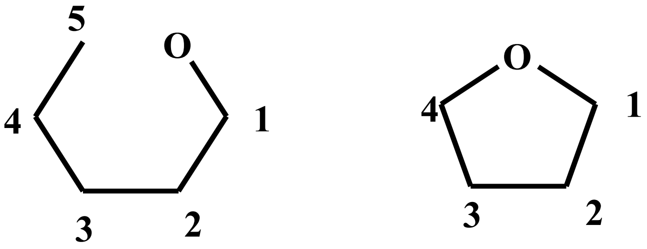
Unstable



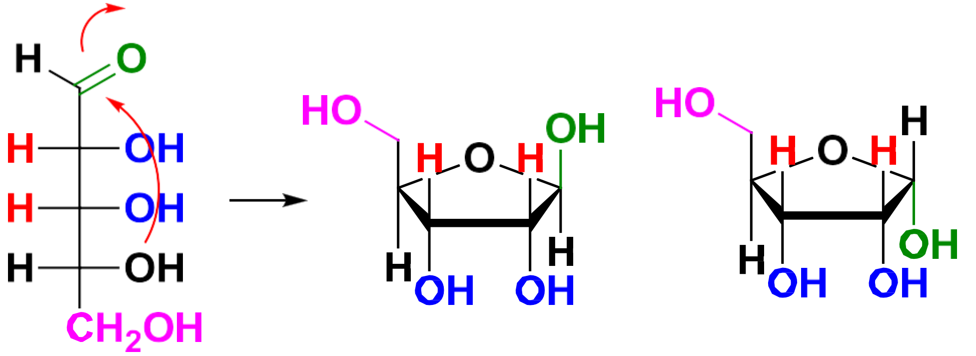
Stable

Rules for drawing Haworth projections

- ✓ Draw either a 6- or 5-membered ring including oxygen as one atom and number the ring clockwise starting next to oxygen.



- ✓ If the substituent is to **the right** in the Fisher projection, it **will be drawn down** in the Haworth projection (Down-Right Rule)

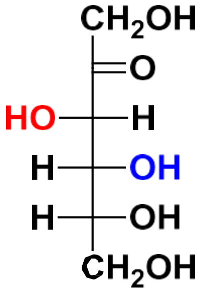


D-Ribose β-D-ribofuranose α-D-ribofuranose

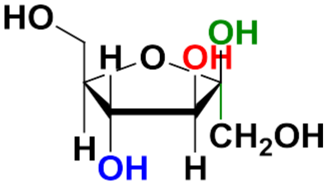
- ✓ For D-sugars the **highest numbered carbon** (furthest from the carbonyl) **is drawn up**. For L-sugars, it is drawn down
- ✓ for D-sugars, **the OH group at the anomeric** position is drawn **down for** α and **up for** β. For L-sugars α is up and β is down

Conformation Representations

A five-membered furanose ring is so close to being planar that Haworth projections provide adequate representations of furanoses.

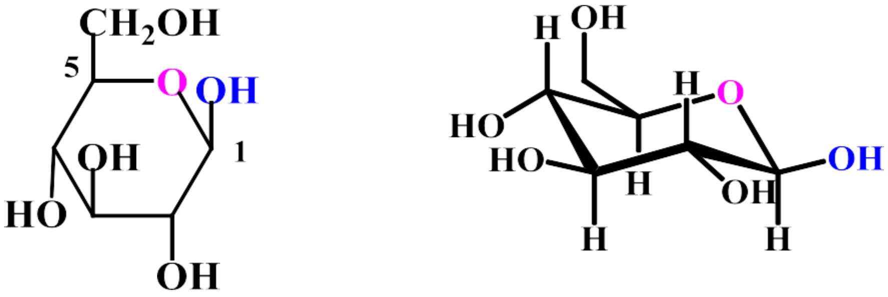


D-Fructose



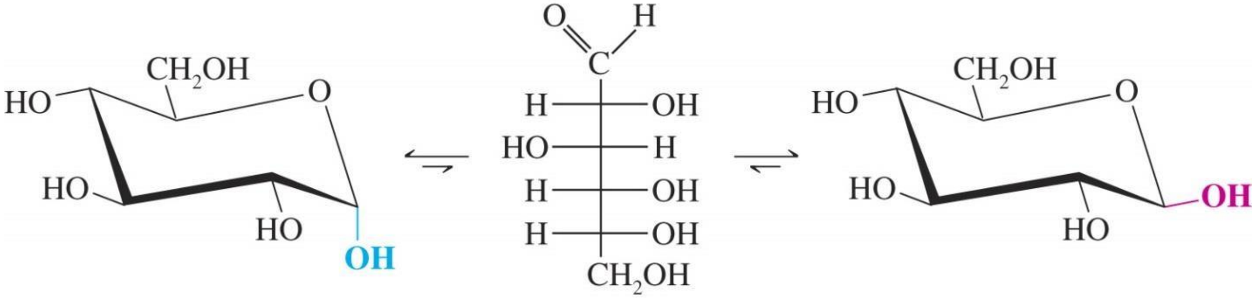
β-D-fructofuranose

For pyranoses, the six-membered ring is more accurately represented as a **chair conformation.**



D-β-glucopyranose

- 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

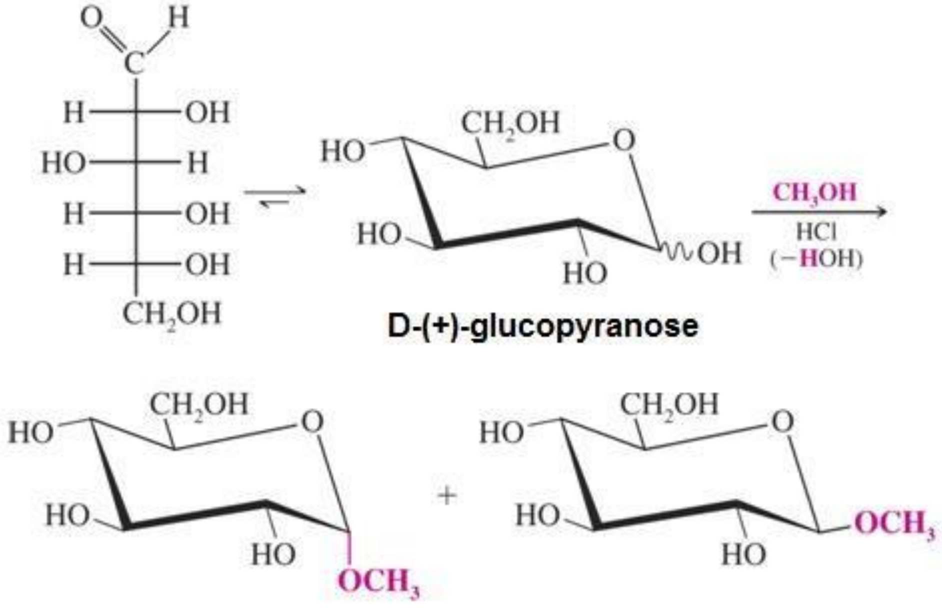
β-D-(+)-Glucopyranose
(mp 150°C; $[\alpha]_D^{25}$ = +18.7°)

- 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 (0.003%) of the open-chain form exists in this equilibrium

Characteristic Reactions of Monosaccharides

Formation of Glycosides (Acetals)

Treatment of a monosaccharide with an alcohol yields an acetal, as illustrated by the reaction of β-D-glucopyranose with methanol.



D-(+)-glucopyranose

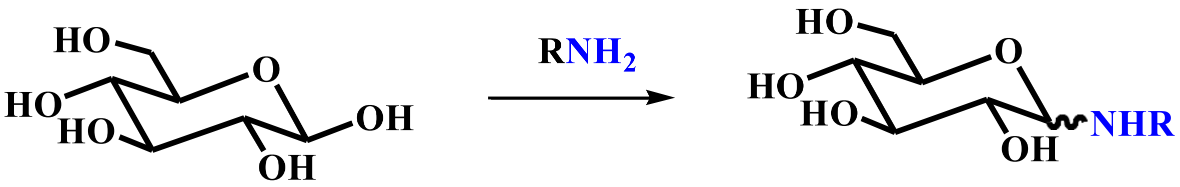
Methyl α-D-glucopyranoside
(mp 165°C; $[\alpha]_D^{25} = +158°$)

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

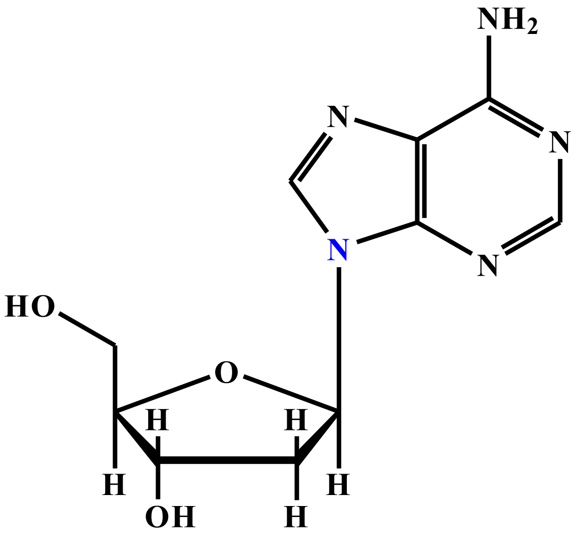
A cyclic acetal derived from a monosaccharide is called a **glycoside**, and the bond from the anomeric carbon to the -OR group is called a **glycosidic bond**. **Mutarotation is not possible in a glycoside** because an acetal—unlike a hemiacetal—is no longer in equilibrium with the open-chain carbonyl containing compound. **Glycosides are stable in water and aqueous base**; like other acetals. However, **they are hydrolyzed in aqueous acid** to an alcohol and a monosaccharide.

N-Glycosides

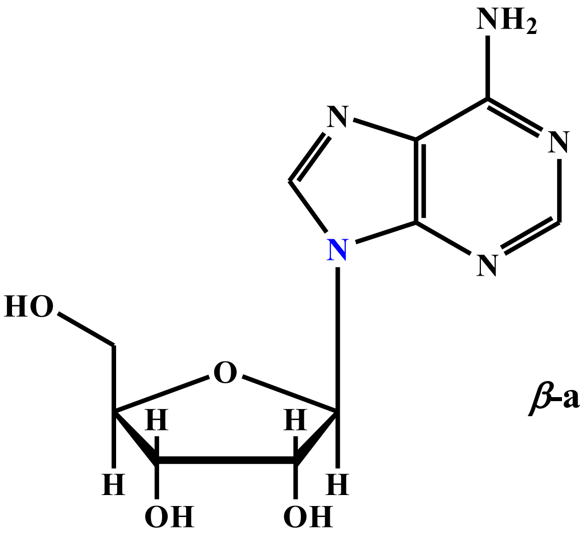
N-Glycosides – glycosides in which anomeric carbon atom is connected with nitrogen atom.



Among natural N-glycosides the most important are nucleosides (found in DNR and RNR). For example:



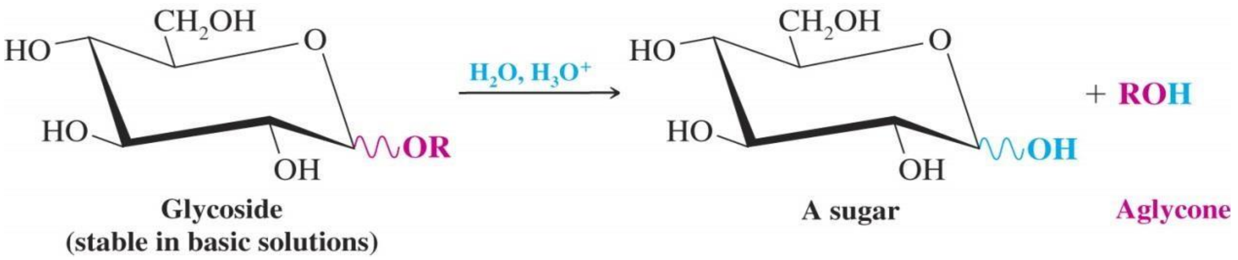
2’-Deoxyadenosine

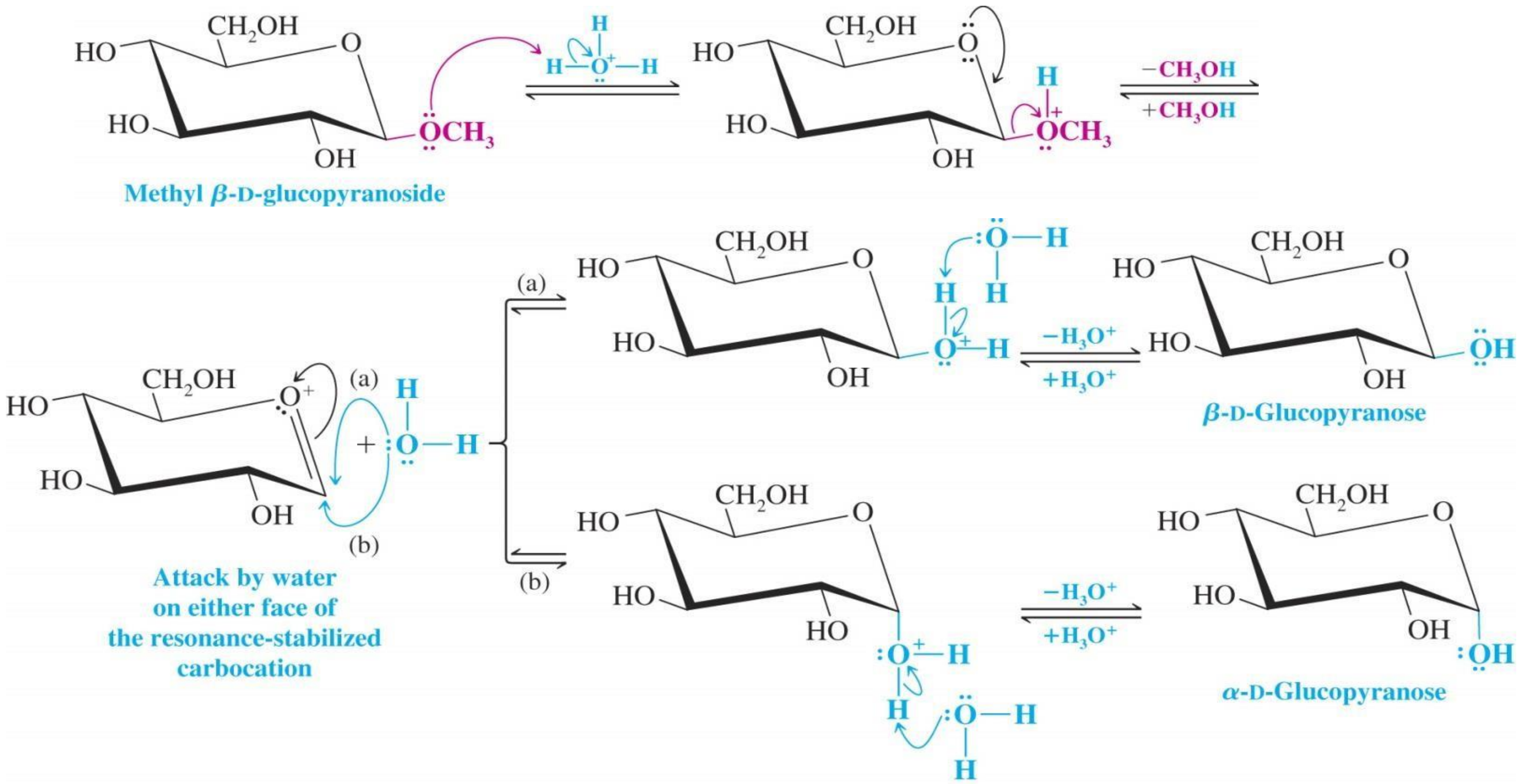


Adenosine

β-anomers

- Glycosides can be hydrolyzed in aqueous acid
  - The alcohol obtained after hydrolysis of a glycoside is called an aglycone

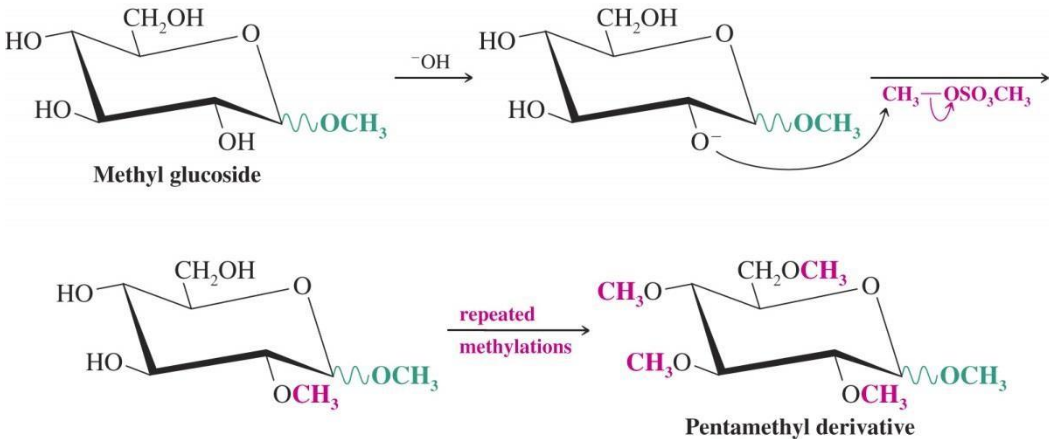




Formation of Ethers

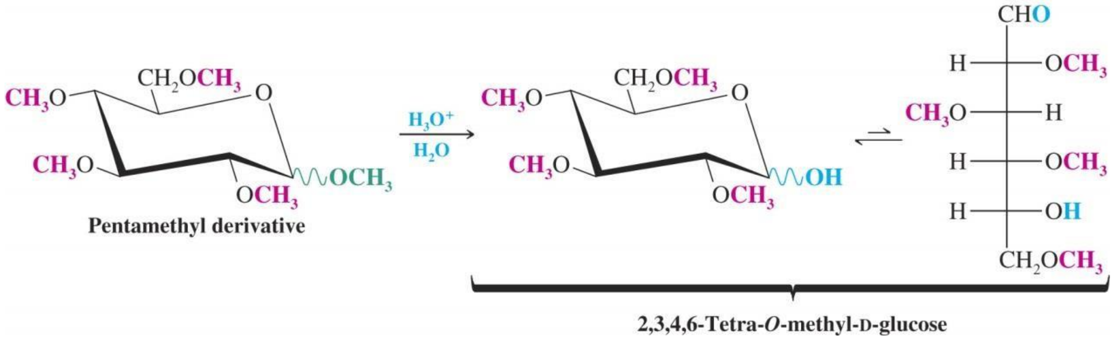
The hydroxyl groups of carbohydrates can be converted to ethers by the Williamson ether synthesis

Exhaustive methylation of methyl glucoside can be carried out using dimethylsulfate



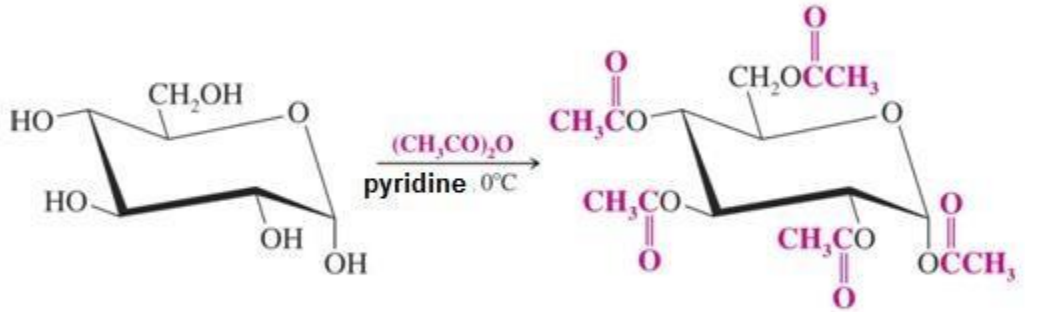
Exhaustive methylation can be used to prove that glucose exists in the pyranose (6-membered ring) form

- **Hydrolysis of the pentamethyl derivative results in a free C5 hydroxyl**



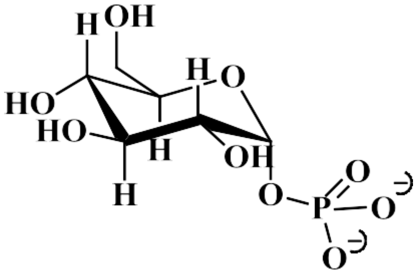
Formation of Esters

Carbohydrates as polyhydroxylic alcohols react easily with acids (organic and inorganic) or their anhydrides to give the corresponding esters.

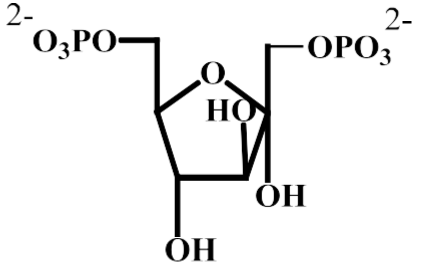


1,2,3,4,5,6-hexaacetyl-α-D-glucopyranose

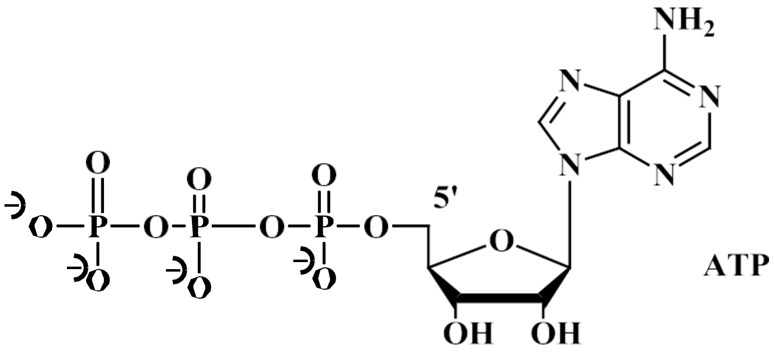
Mono- and diphosphoric esters are important intermediates in the metabolism of monosaccharides. Note, that phosphoric acid is a strong enough acid so that at the pH of cellular and intercellular fluids, both acidic protons of a phosphoric ester are ionized, giving the ester a charge of -2.



α-D-glucopyranose 1-phosphate

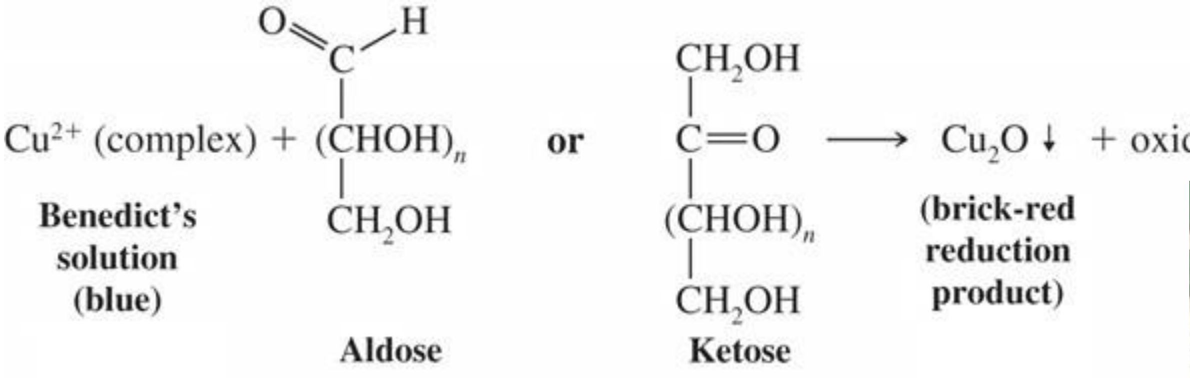


α-D-fructofuranose 1,6-diphosphate

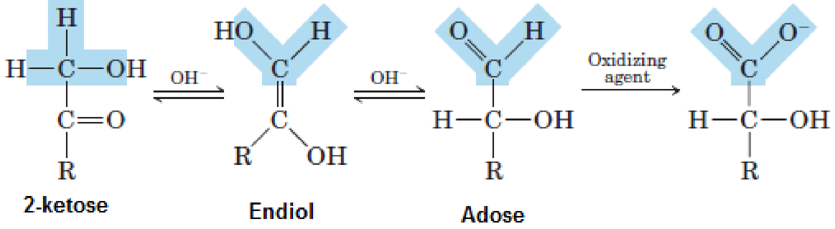


Adenosine 5'-triphosphate

- 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



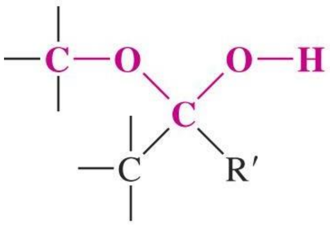
2-Ketoses are also reducing sugars. Carbon 1 of a ketose is not oxidized directly. Instead, under the basic conditions of this oxidation, a 2-ketose exists in equilibrium with an aldose by way of an enediol intermediate. The aldose is then oxidized by the mild oxidizing agent.



- 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

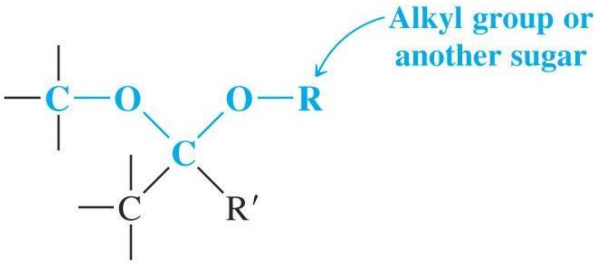
- Carbohydrates with only acetal groups (glycosidic linkages) do not react with these reagents and are called non-reducing sugars
  - Acetals are not in equilibrium with the aldehyde or ketone and so cannot react with these reagents

Reducing Sugar



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

Nonreducing Sugar

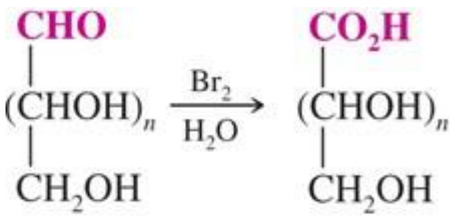


Alkyl group or another sugar

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

● Oxidation to Aldonic Acids

Bromine in water selectively oxidizes the aldehyde group of an aldose to the corresponding carboxylic acid. **An aldose becomes an aldonic acid:**

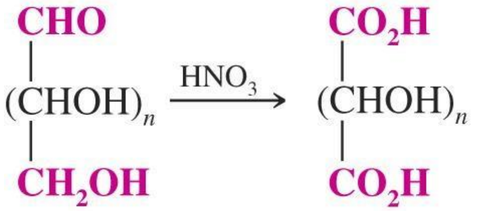


$$\begin{matrix} CHO \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{matrix} \xrightarrow[H_2O]{Br_2} \begin{matrix} CO_2H \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{matrix}$$

Aldose　　Aldonic Acid

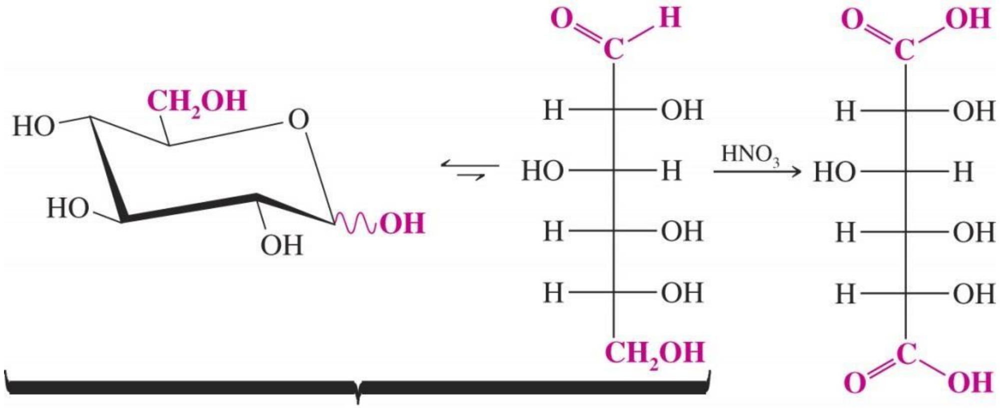
– Nitric Acid Oxidation: Aldaric Acids

Dilute nitric acid oxidizes both the aldehyde and primary hydroxyl groups of an aldose to an aldaric acid:



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

Aldose　　Aldaric acid

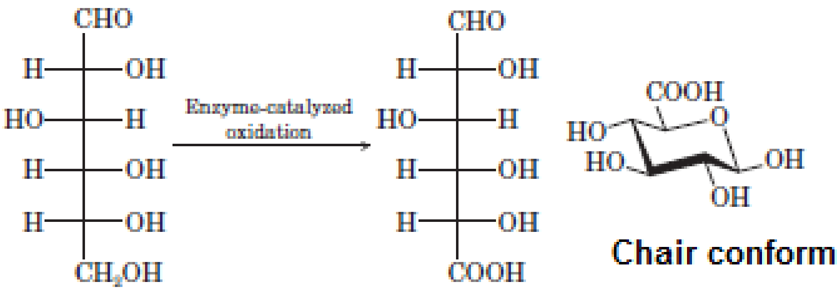


D-Glucose

D-Glucaric acid

- **Oxidation to Uronic Acids**

Enzyme-catalyzed oxidation of the primary alcohol at carbon 6 of a hexose yields a uronic acid.



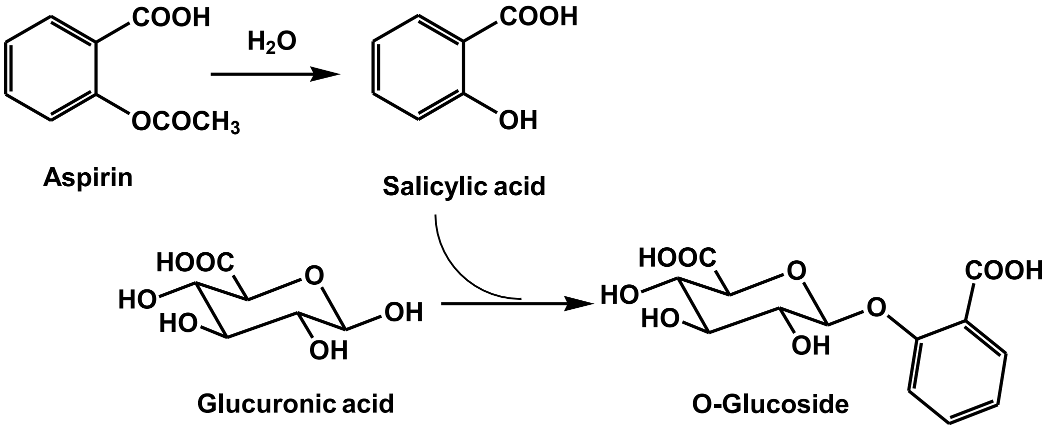
D-Glucose

Fischer projection

Chair conformation

D-Glucuronic acid

The body also uses D-glucuronic acid to detoxify foreign phenols and alcohols. In the liver, these compounds are converted to glycosides of glucuronic acid (glucuronides), usually more soluble in water, and excreted in the urine.



Aspirin

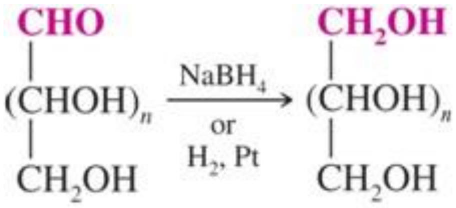
Salicylic acid

Glucuronic acid

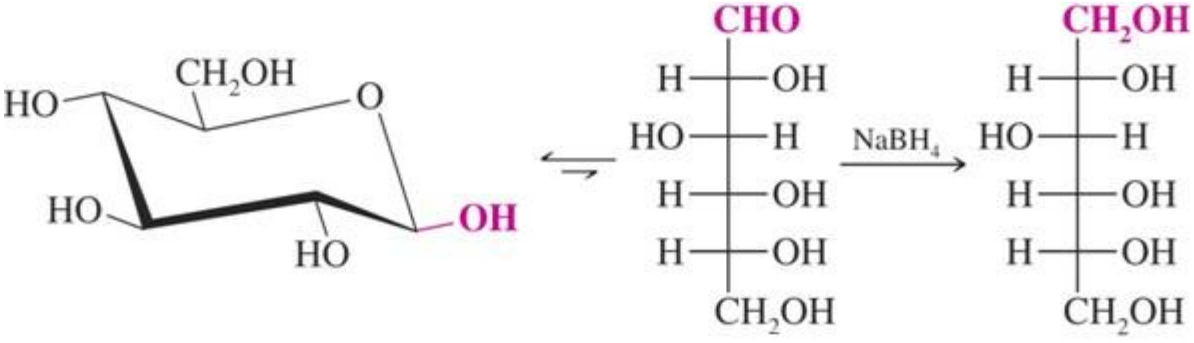
O-Glucoside

Reduction to Alditols

The carbonyl group of a monosaccharide can be reduced to a hydroxyl group by a variety of reducing agents, including H_2/Pt and sodium borohydride. The reduction products are known as **alditols**. The names of alditols are made by dropping the -**ose** from the name of the monosaccharide and adding -**itol**.



Aldose **Alditol**



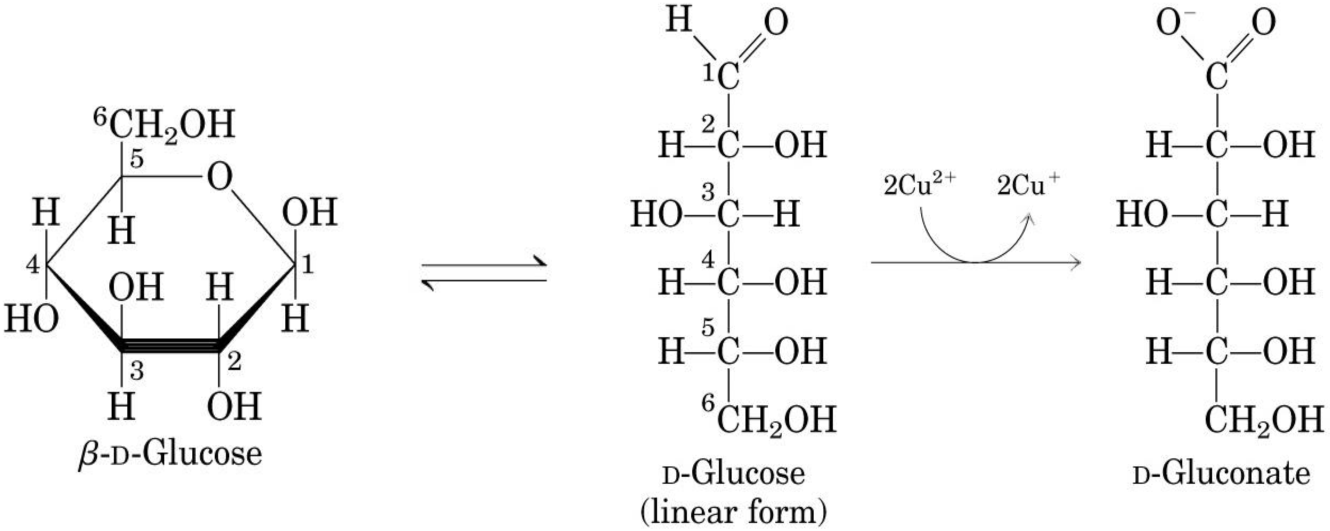
D-glucose

D-glucitol (D-sorbitol)

In the reaction the open-chain form takes part. Only a small amount of this form is present in solution but, as it is reduced, the equilibrium between cyclic hemiacetal forms (only the β form is shown here) and the open-chain form shifts to replace it.

MONOSACCHARIDES: REDUCING SUGARS

- Sugars with free anomeric carbon atoms that are reasonably good reducing agents and will reduce hydrogen peroxide, ferricyanide or certain metals such as Cu^{2+}.



β-D-Glucose

D-Glucose (linear form)

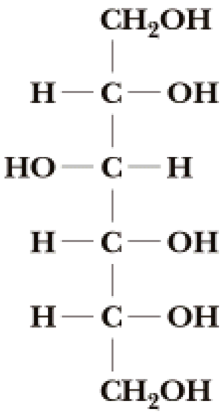
D-Gluconate

MONOSACCHARIDES: SUGAR DERIVATIVES

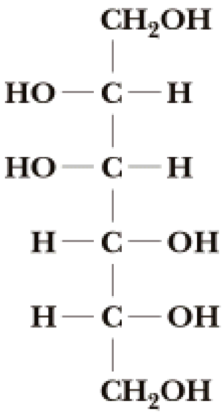
A variety of chemical and enzymatic reactions produce derivatives of the simple sugars:

1) **Reductions**: alditols and deoxy sugars:

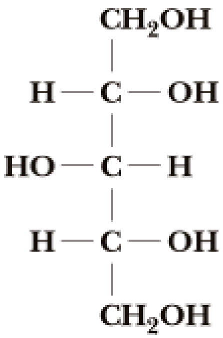
Alditols: carbonyl group is reduced to alcohol (-itol).



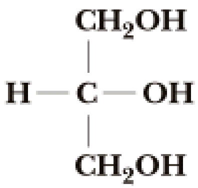
D-Glucitol (sorbitol)



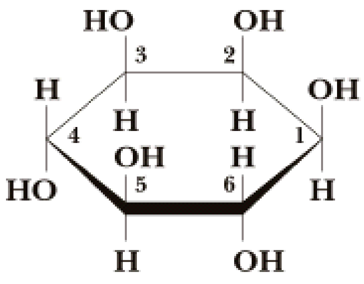
D-Mannitol



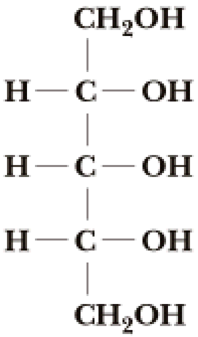
D-Xylitol



D-Glycerol



myo-Inositol

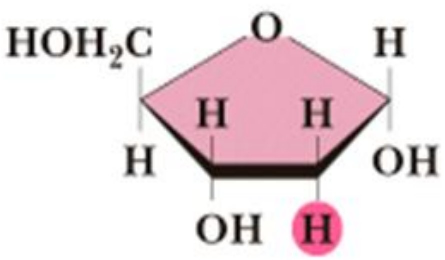


D-Ribitol

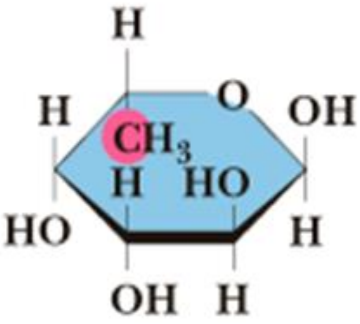
MONOSACCHARIDES: SUGAR DERIVATIVES

1) **Reductions**: alditols and deoxy sugars:

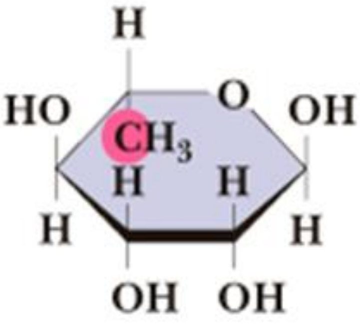
Deoxy sugars: one or more hydroxyl groups are replaced by hydrogens.



2-Deoxy-α-D-Ribose



α-L-Fucose (Fuc)

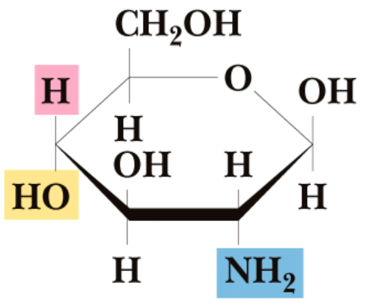


α-L-Rhamnose (Rha)

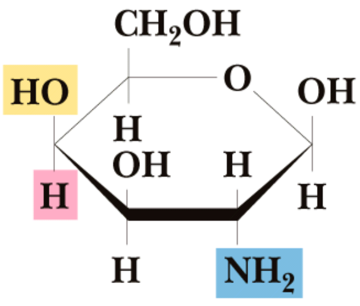
(they are part of glycoproteins and glycolipids)

MONOSACCHARIDES: SUGAR DERIVATIVES

2) **Amino sugars**: amino group at the C-2 position.

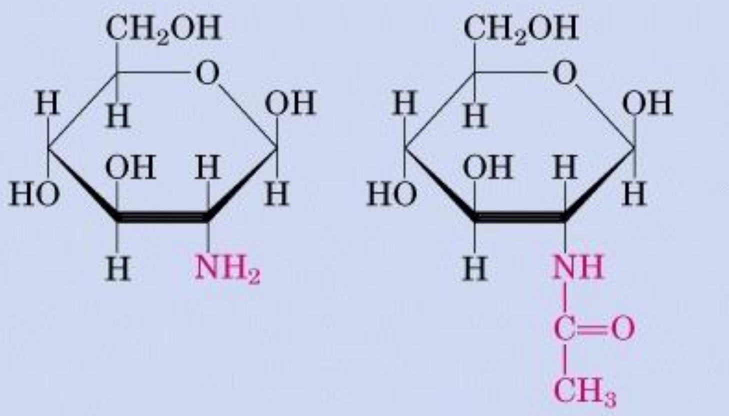


β-D-Glucosamine

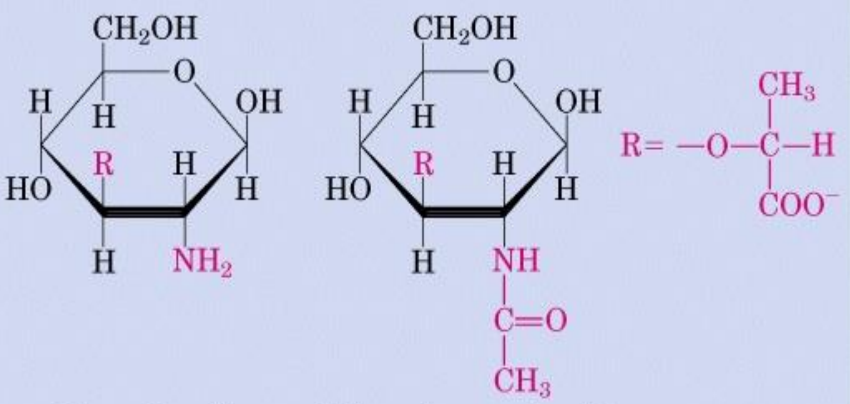


β-D-Galactosamine

- The amino groups can accept an acetyl group. The final products are sugars derivatives with important biological roles:



β-D-Glucosamine N-Acetyl-β-D-glucosamine

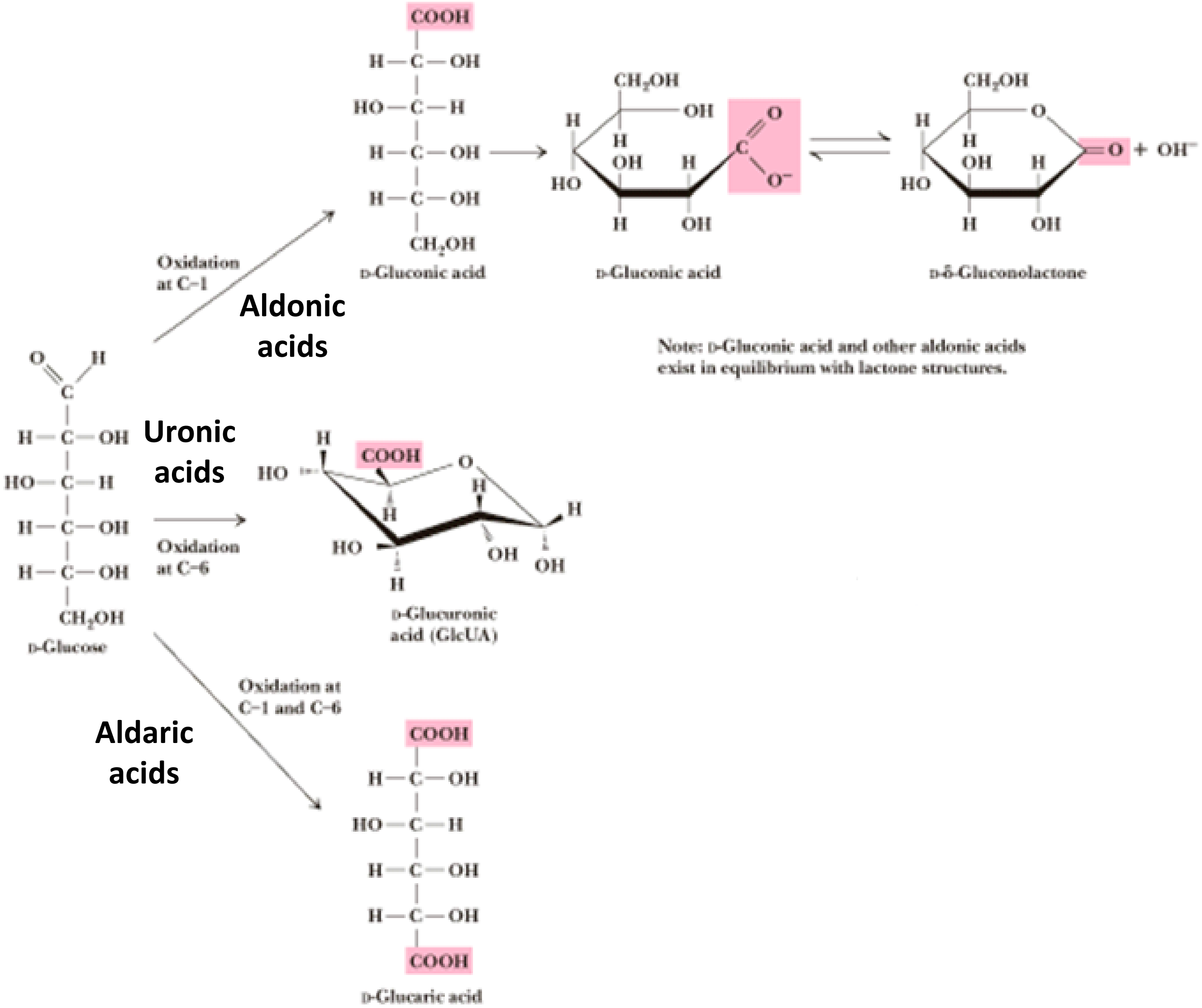


Muramic acid N-Acetylmuramic acid

(They are part of the bacterial wall)

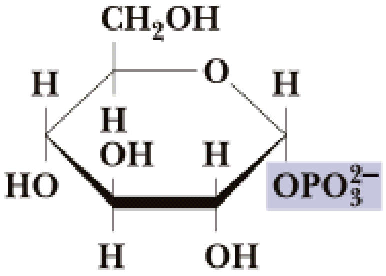
MONOSACCHARIDES: SUGAR DERIVATIVES

3) **Oxidations**: Oxidation at the aldoses C-end.

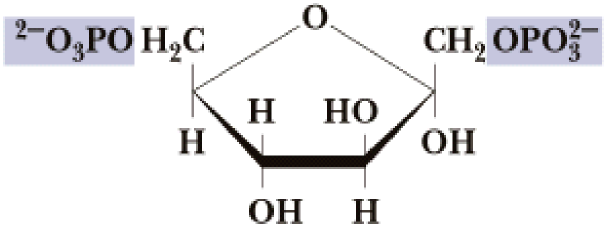


MONOSACCHARIDES: SUGAR DERIVATIVES

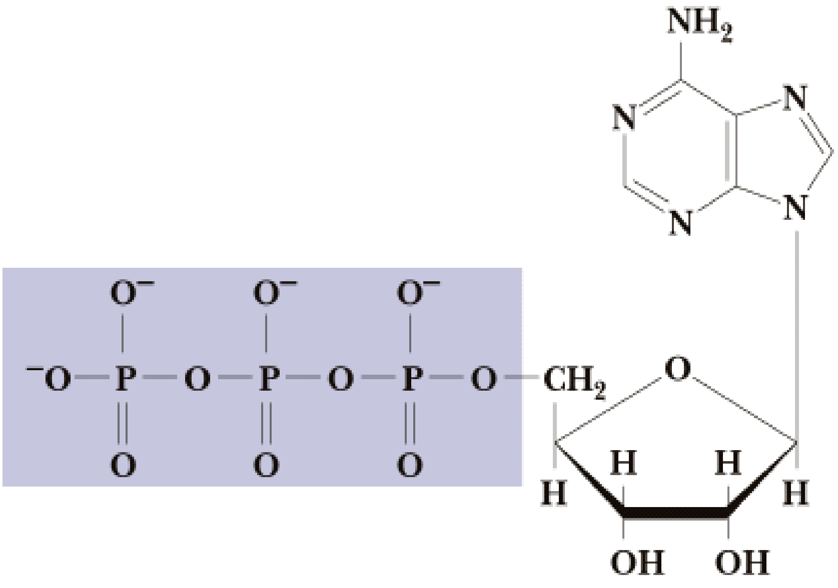
4) **Sugar esters**: Phosphate and sulphate ester of monosaccharides.



α-D-Glucose-1-phosphate



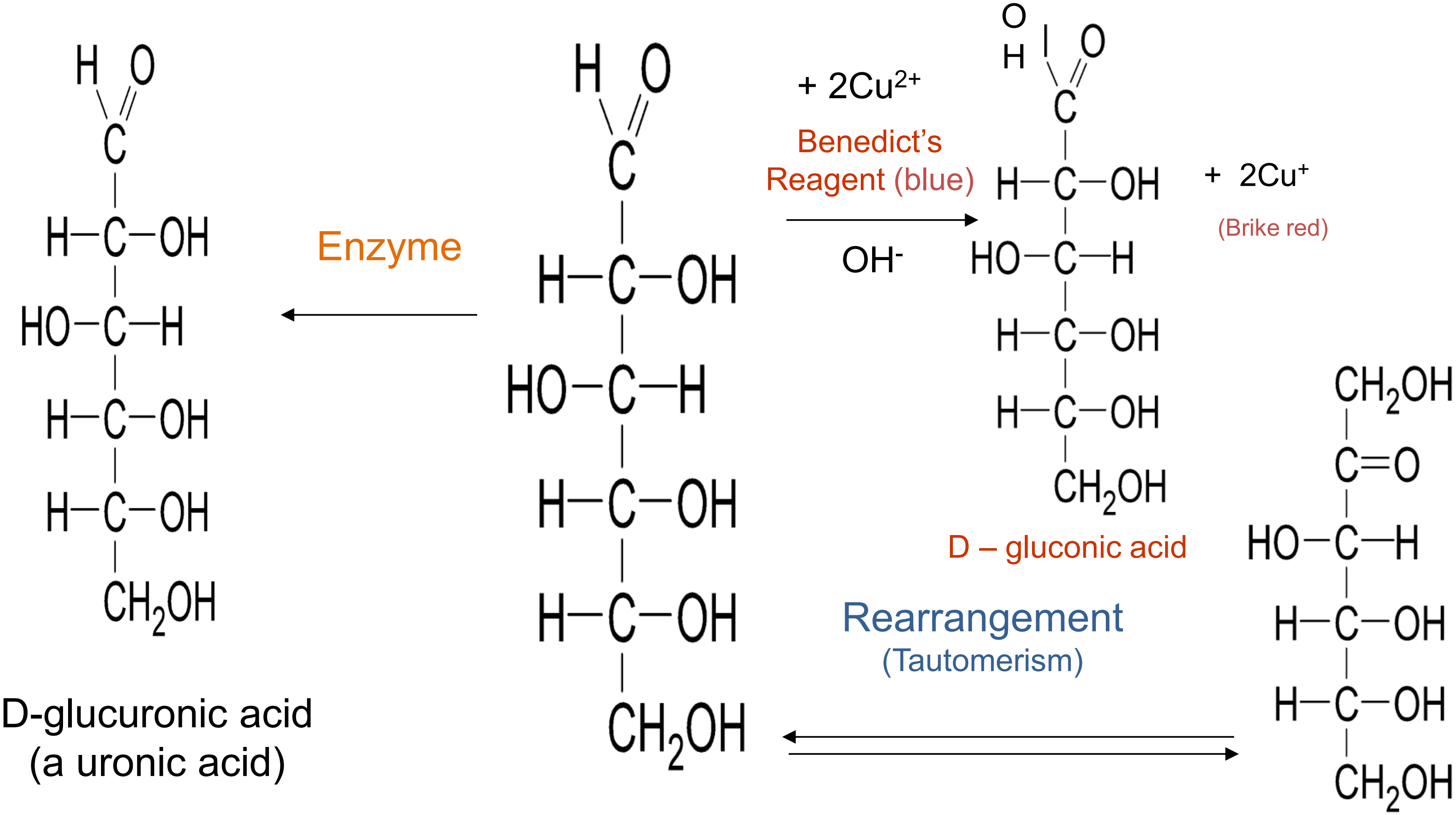
α-D-Fructose-1,6-bisphosphate



Adenosine-5'-triphosphate

Chemical properties of Monosaccharides

Oxidation of Monosaccharides



Enzyme

+ $2Cu^{2+}$

Benedict's Reagent (blue)

OH^-

+ $2Cu^{+}$

(Brike red)

Rearrangement (Tautomerism)

D-glucuronic acid
(a uronic acid)

D - glucose

D – gluconic acid

D-fructose (ketose)

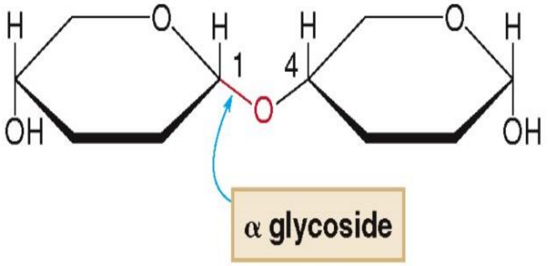
Disaccharides

- Consists of two monosaccharides linked by a *glycosidic bond* (when one –OH group reacts with another –OH group).

Glucose + Glucose → Maltose + H_2O

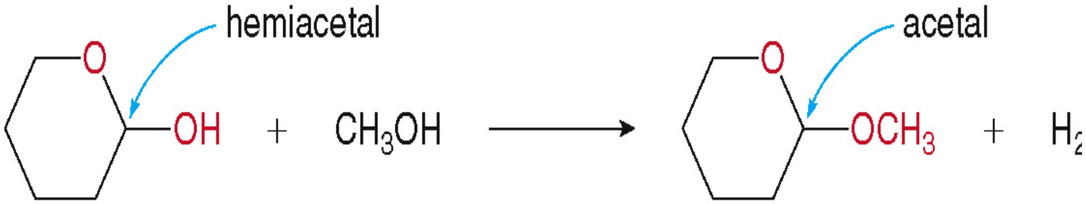
Glucose + Galactose → Lactose + H_2O

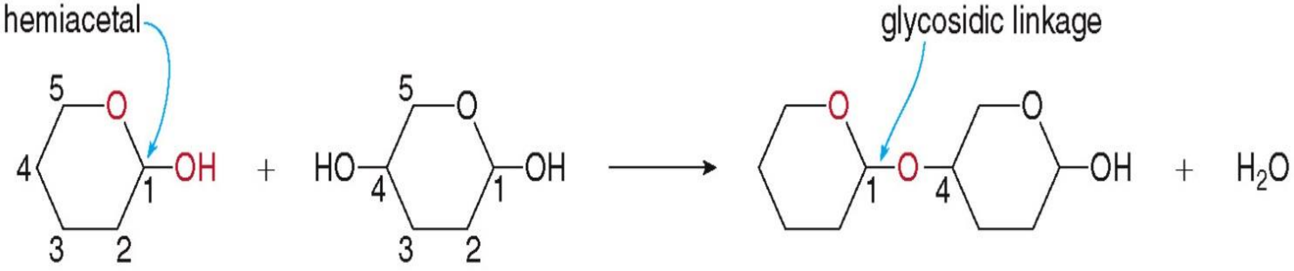
Glucose + Fructose → Sucrose + H_2O



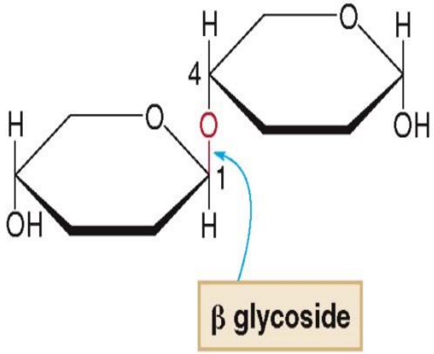
The glycoside bond is **down.**

1→4-α-glycosidic linkage





general structure of a disaccharide

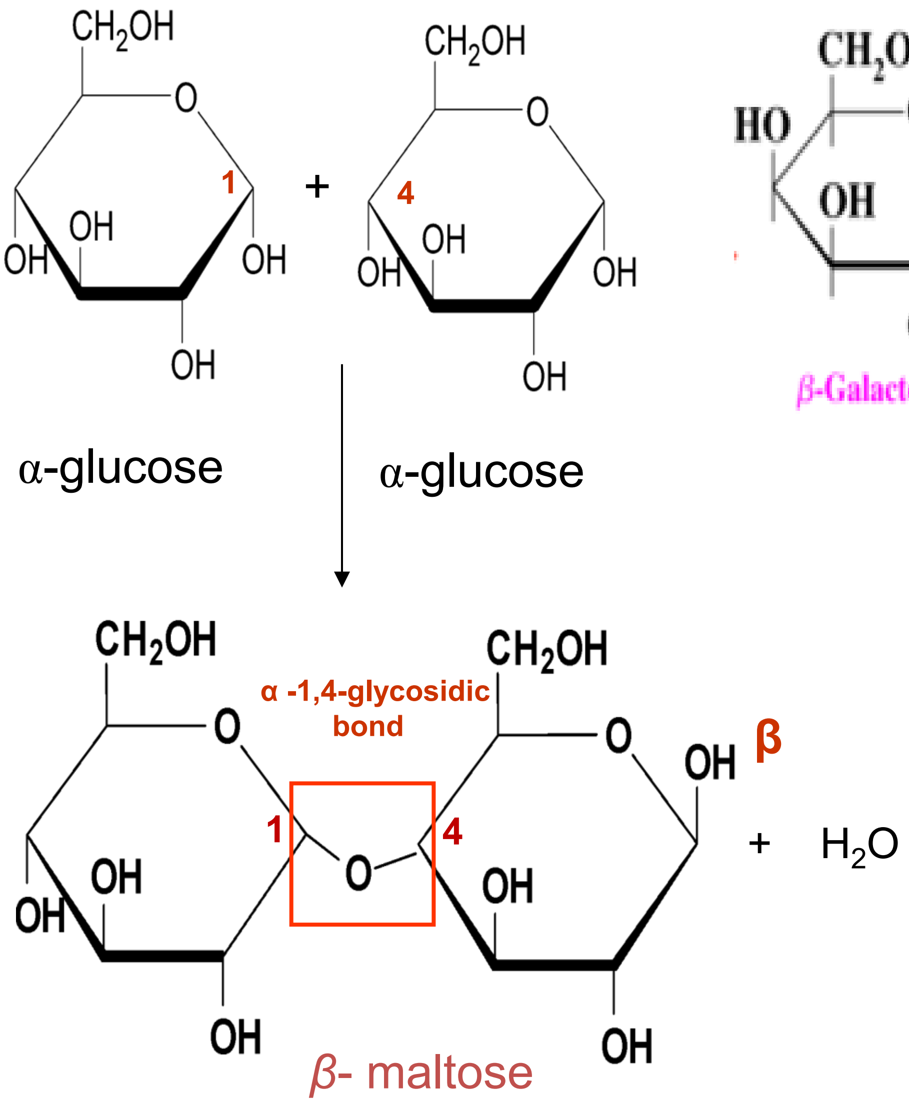


The glycoside bond is **up.**

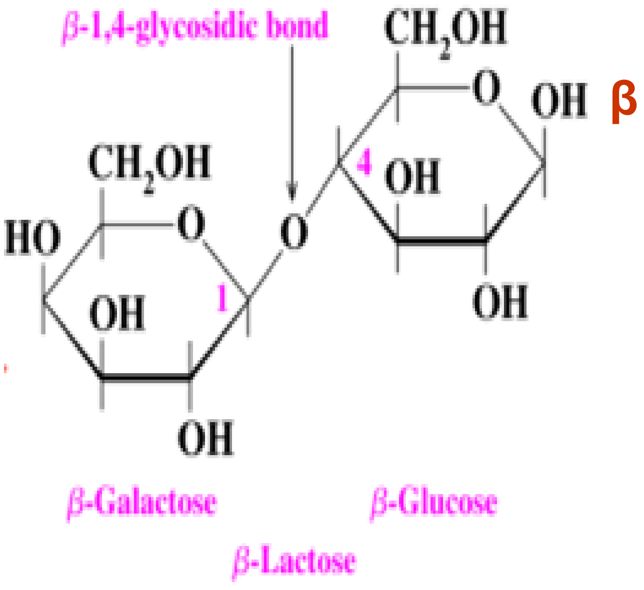
1→4-β-glycosidic linkage

Disaccharides

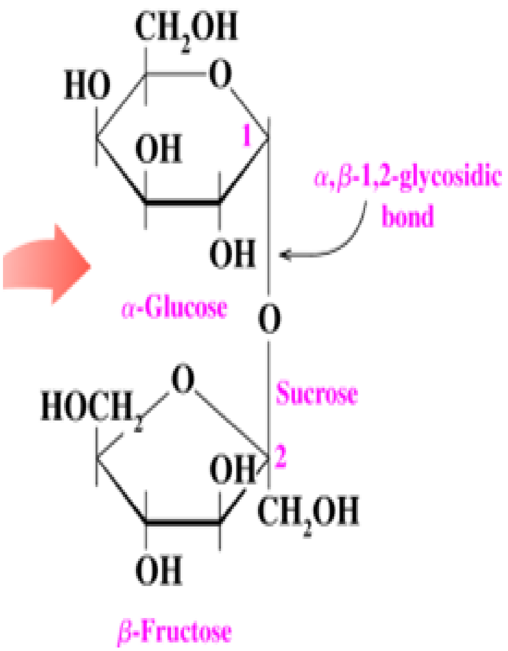
Maltose:



Lactose:



Sucrose:



Artificial sweeteners

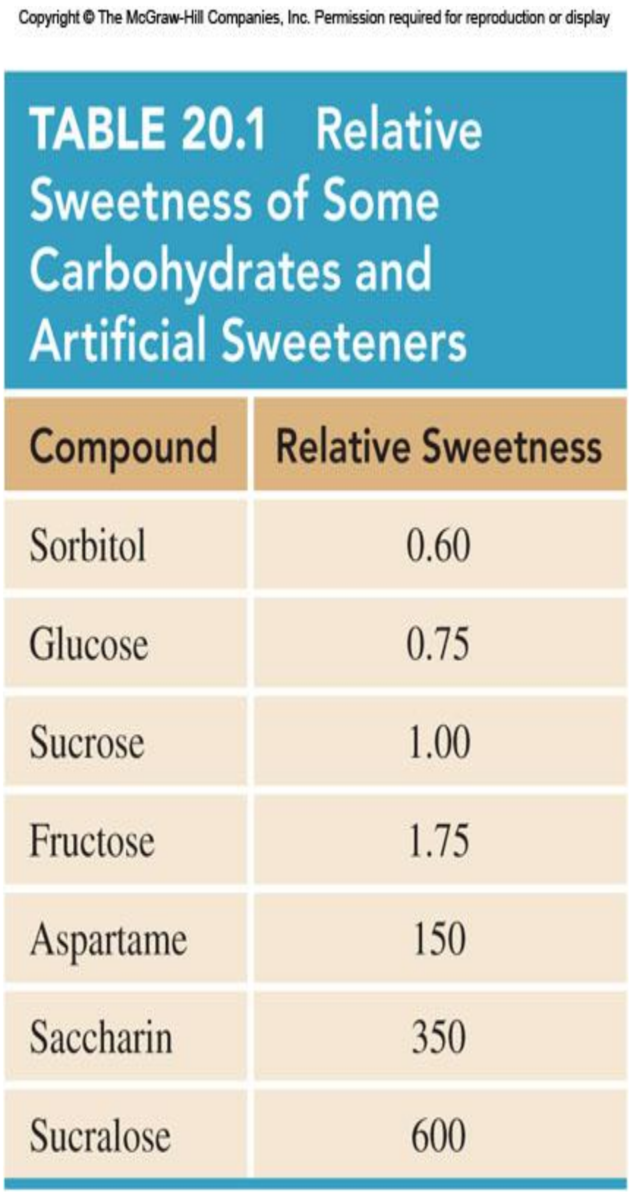
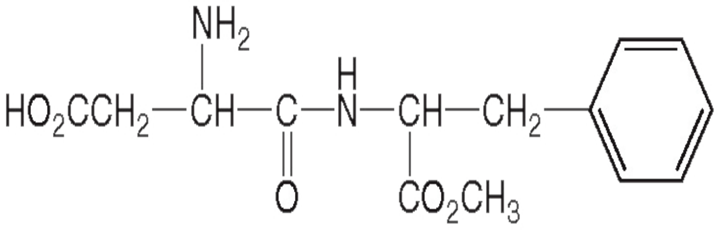


TABLE 20.1 Relative Sweetness of Some Carbohydrates and Artificial Sweeteners

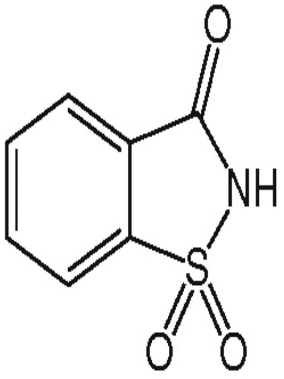
Compound	Relative Sweetness
Sorbitol	0.60
Glucose	0.75
Sucrose	1.00
Fructose	1.75
Aspartame	150
Saccharin	350
Sucralose	600

Aspartame:



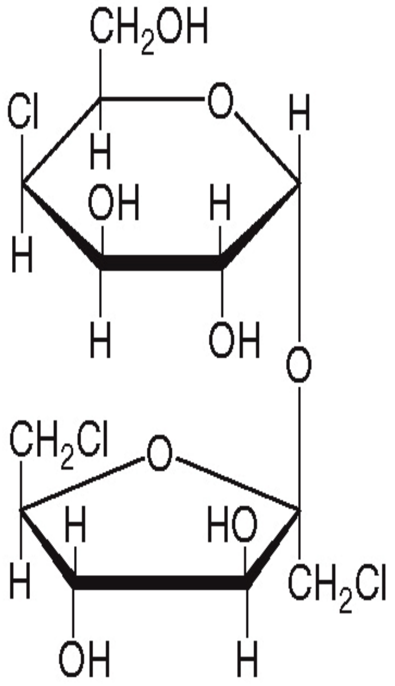
aspartame
(Trade name: Equal)

Saccharine:



saccharin
(Trade name: Sweet'n Low)

Sucralose:

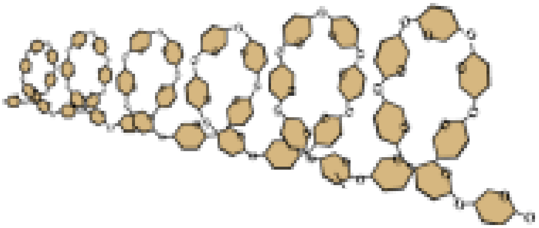


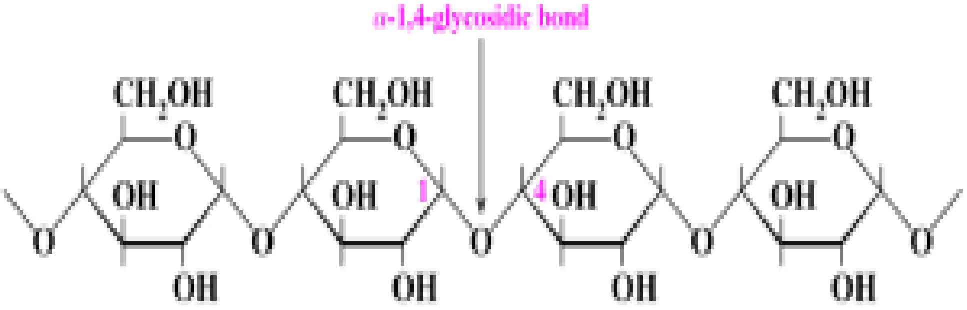
sucralose
(Trade name: Splenda)

Polysaccharides

Polymers of many monosaccharides units

Amylose:





Glycogen:

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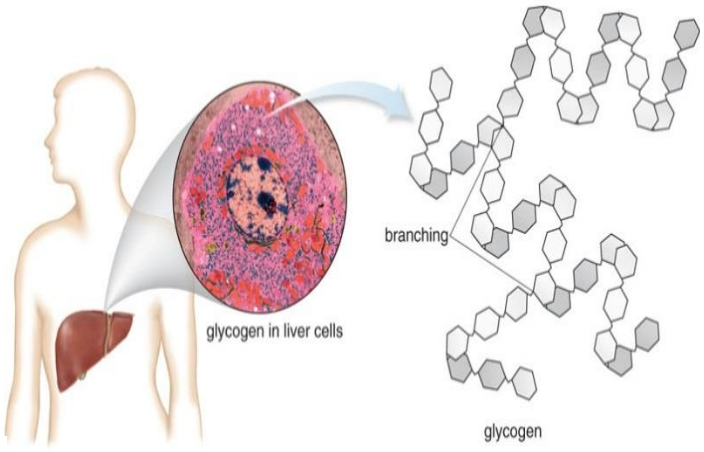

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Amylopectin: