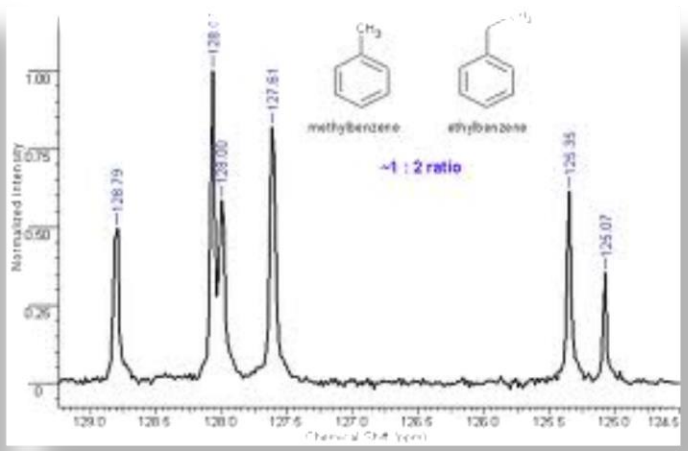
Basics of Natural Products (PHG220)



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PHG 220: Course Description

The following subjects will be covered :

1- Carbohydrates:

Chemical characters of different classes of carbohydrates and their biological significance.

2- Plants containing Glycosides (botanical and chemical characters)

Introduction, Examples of medicinally important Glycosides and their importance as a "Lead Compounds" from the following groups:

Cardiac glycosides, Saponins, Anthracene derivatives, flavonoids and related compounds, Cyanogenic glycosides and thioglycosides.

PHG 220: Course Description

3- Plants containing Alkaloids (botanical and chemical character)

Introduction, Examples of medicinally important Alkaloids and their importance as a "Lead Compounds" from the following groups:

Phenylalkylamine, Tropolone, Imidazole, pyridine, piperidine, tropane, quinoline, isoquinoline, Opium, Indole, Carboline, purine and steroidal alkaloids.

4- Unorganized drugs

Instruction:

- Do not eat or drink inside the classroom.
- Turn off cell phones inside the classroom.
- Be in the classroom on time, No exception.
- Follow the three rules: Respectful, Ready and Responsible.
- Complete home works and assignments neatly and on time.

Marks distribution:

Midterm II (Monday 6-8-1441/30-3-2020)	**20**
4 Quizes	**10**
Final Exam	**20**
Total	**50**

I- Carbohydrates

Definition

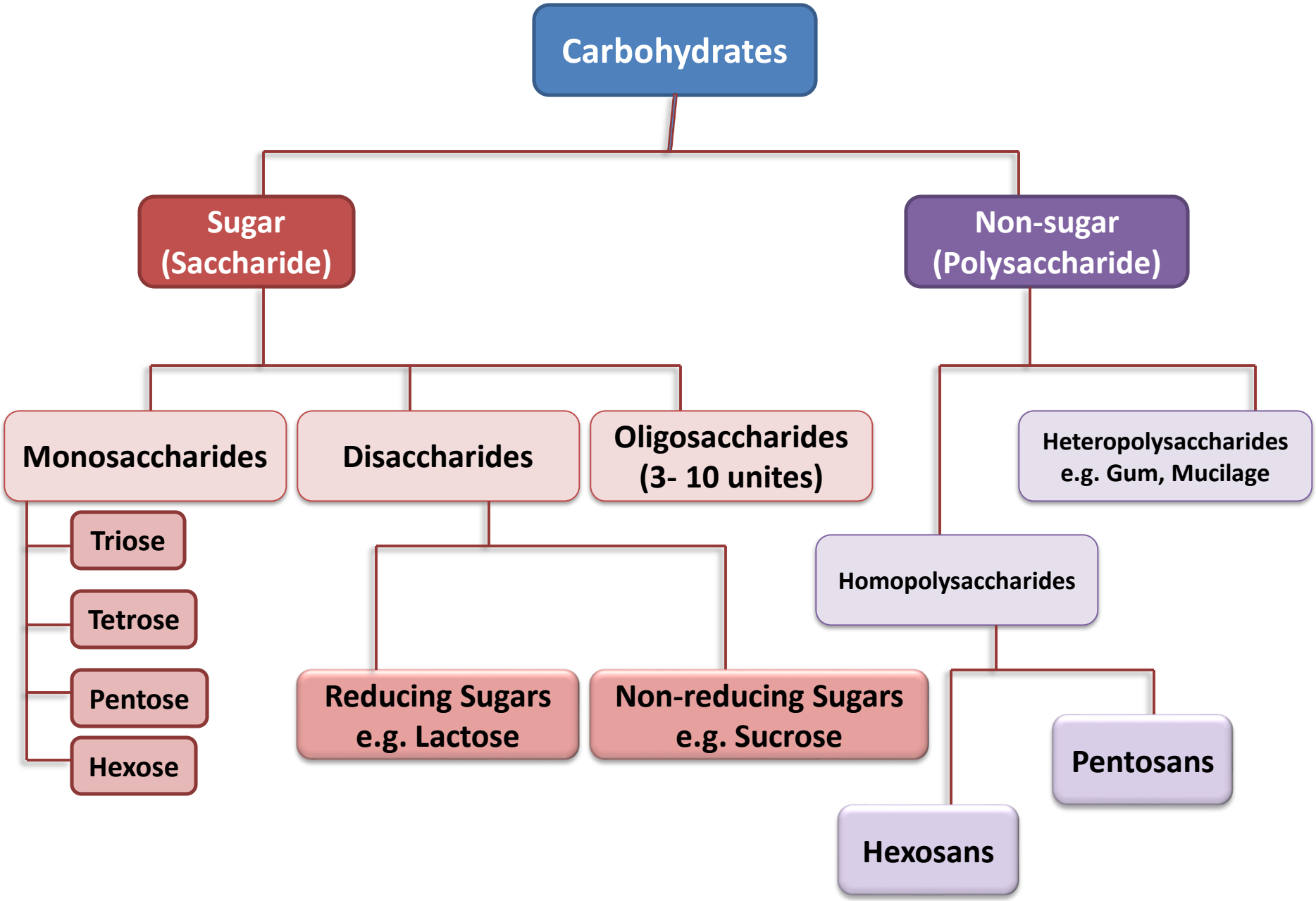
- Organic compounds composed of C, H and O with H and O present in the same ratio as in water. e.g. Glucose $C_6H_{12}O_6$.

Exceptions:

- Deoxy sugars such as Rhamnose $C_6H_{12}O_5$, digitoxose $C_6H_{12}O_4$
- Some non carbohydrates follow the definition:
  - » Acetic acid $C_2H_4O_2$
  - » Formaldehyde HCHO
  - » Lactic acid $C_3H_6O_3$

- **New definition:**

  Optically active Polyhydroxy aldehydes or ketones, or substances that hydrolyze to yield polyhydroxy aldehydes or ketones.


Carbohydrates
Sugar (Saccharide)
Non-sugar (Polysaccharide)
Monosaccharides
Disaccharides
Oligosaccharides (3- 10 unites)
Heteropolysaccharides e.g. Gum, Mucilage
Triose
Tetrose
Pentose
Hexose
Reducing Sugars e.g. Lactose
Non-reducing Sugars e.g. Sucrose
Homopolysaccharides
Pentosans
Hexosans

Physical Characters

Condition:

Sugars are white, crystalline in shape and with sharp melting points, while polysaccharides are white amorphous solids.

Taste:

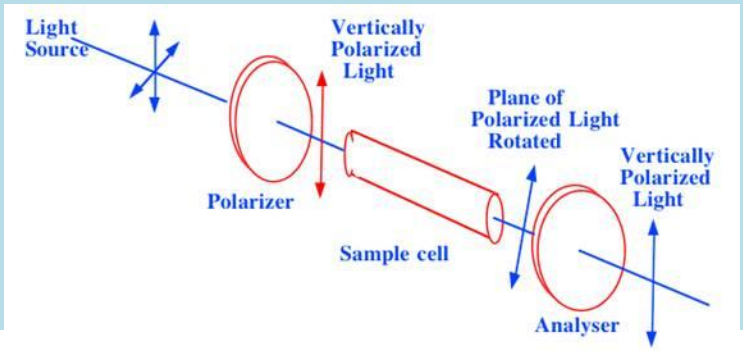
Sugars have a sweet taste. Polysaccharides are tasteless.

Solubility:

Monosaccharides are soluble in cold water and hot alcohol. Polysaccharides are partially soluble in hot water.

Optical activity:

A compound is optically active when, in solution, it is capable to rotate the plane of polarized light either to right (**dextrorotatory, *+*** or ***d***) or to the left (**levorotatory, -** or ***l***).

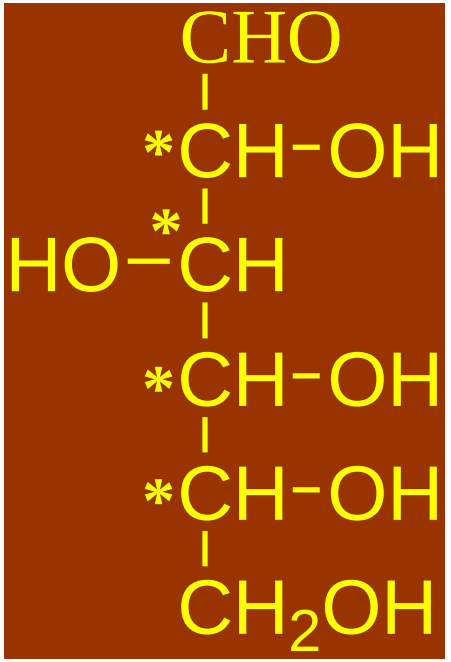


Sugar isomers

- Hexoses like glucose have 4 asymmetric (chiral) carbons.
- Number of isomers can be calculated from the formula:

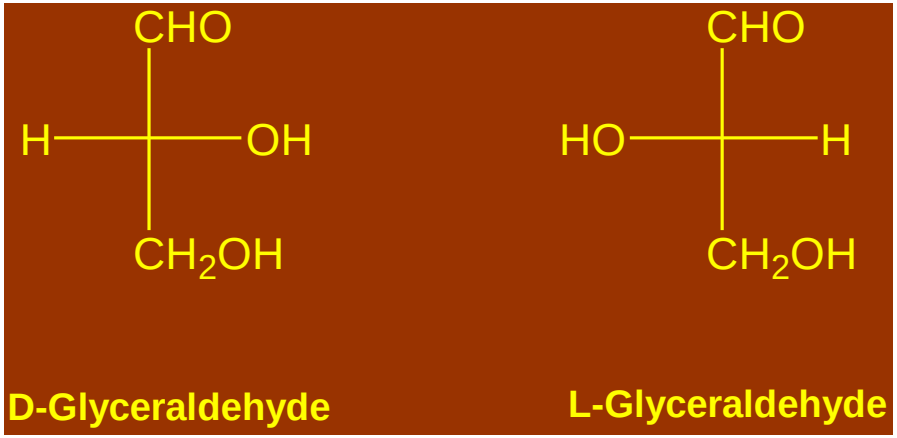
  Number of isomers = 2^n

  $= 2^4 = 16$



D and L in Sugars

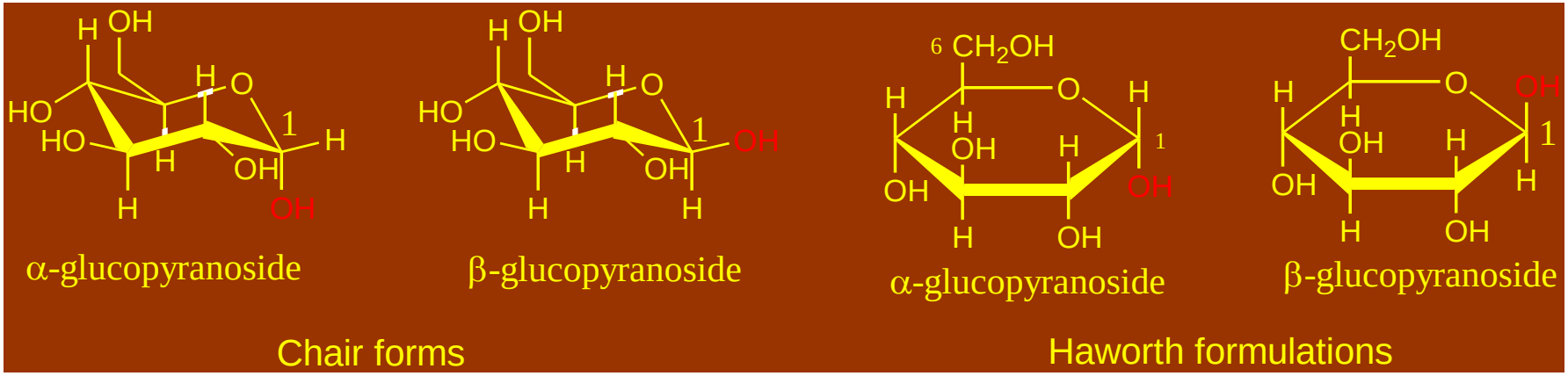
A monosaccharide in which the OH group attached to the carbon atom next to the CH_2OH (farthest asymmetric carbon atom from the carbonyl group) is always to the right is designated as a "D-sugar" and that with the same OH to the left as "L -sugar".



α- and β- anomers of Glucose

When sugars undergo cyclization C-1 became a new chairal carbon and two isomers exist. They are called " Anomers".

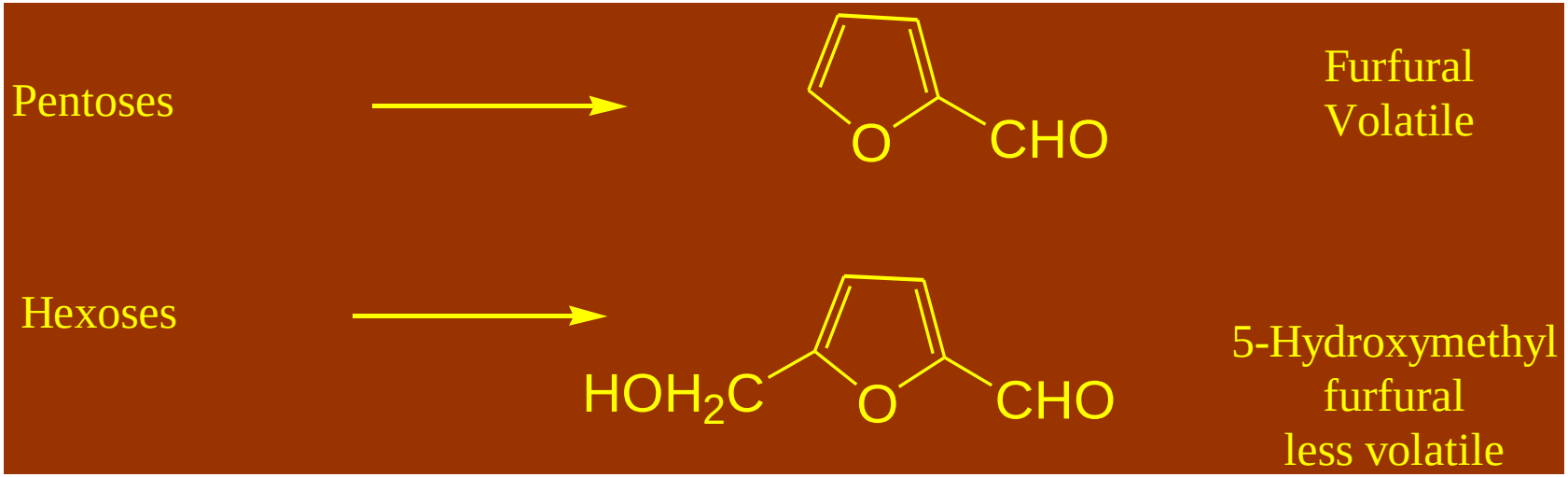
- **In the α-anomer the OH group is directed downside and in the β-anomer is directed to the upper side.**
- **These two forms have different specific rotation, in solution an equilibrium exists between the two forms (mutarotation phenomenon).**



Chemical Reaction for Carbohydrates

1- Effect of conc. acids:

Treatment with **conc. mineral acid** (HCl or H_2SO_4) leads to **dehydration of sugars** and formation of the corresponding **furfural**.



Reaction of furfural with amines resulted in Shiff's bases with different colours used as colour tests such as:

1- Molisch's test:

- **Any carbohydrate + Alcoholic α-naphthol then add conc. H_2SO_4 on the wall of the test tube ⟶ Violet ring between the two layers.**

2- Resorcinol test (for keto-hexoses):

- **Sugar solution + few crystals of Resorcinol + Equall volume of conc. HCl and warm on water bath ⟶ Rose Red Colour.**

3- Furfural test (Differentiate between Pentoses and Hexoses):

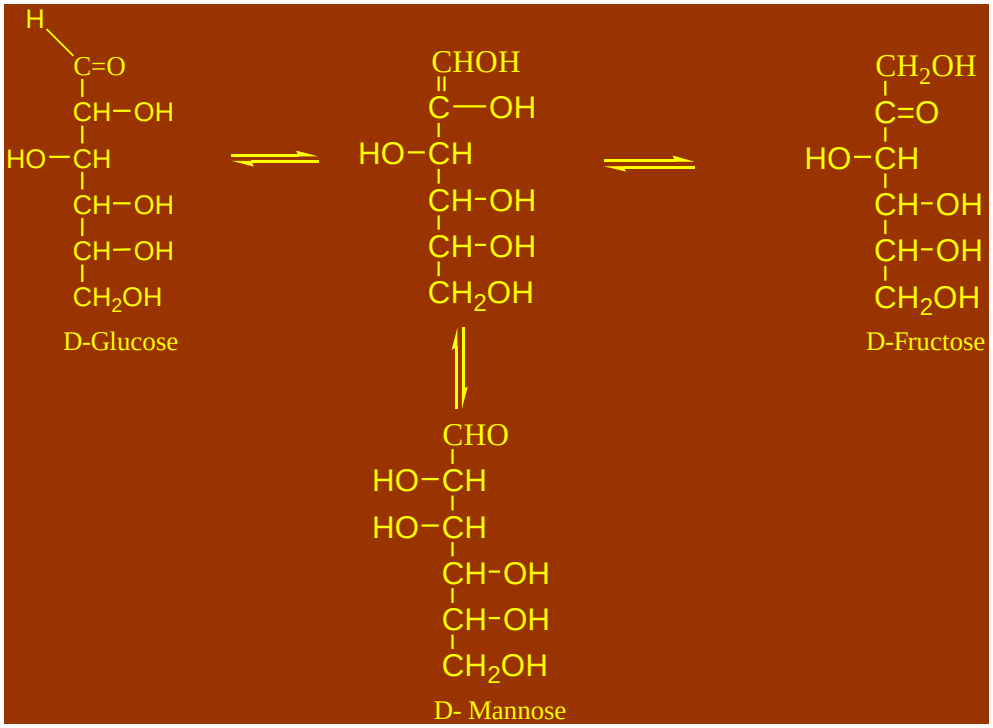
- **Pentose + Conc. Acid and heat, expose the vapours to Aniline acetate paper ⟶ Red colour**
- **Hexoses give negative result.**

Chemical Reaction for Carbohydrates (Cont.)

2- Effect of alkali:

a- Strong alkalis: Polymerization.

b- Weak alkalis: Isomerization.

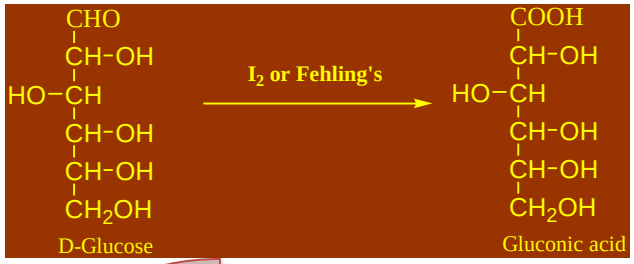


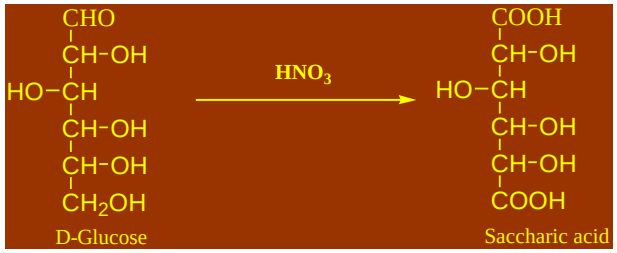
3- Oxidation

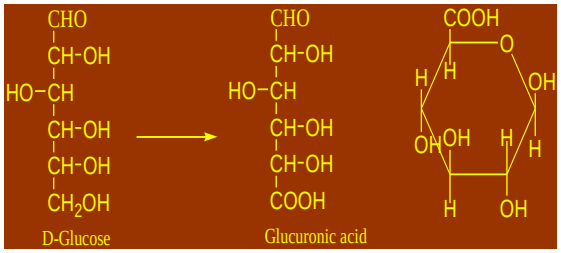
Mild These are oxidizing agents like **Bromine water** that convert the CHO group to COOH to produce **"onic acids".**

Strong These are oxidizing agents like **HNO_3** that convert the CHO and CH_2OH group to COOH to produce **"aric acids"**.

Enzymatic Takes place in plants and resulted in the oxidation of the primary alcohol group only producing **"uronic acids".**







Colour test based on this reaction: Fehling's reduction test:

Sugar solutions + Fehling's A ($CuSO_4$) + Fehling's B (NaOH, NaK tartarate rochell salt), heat on water bath ⟶ Red Precipitate of Cu_2O

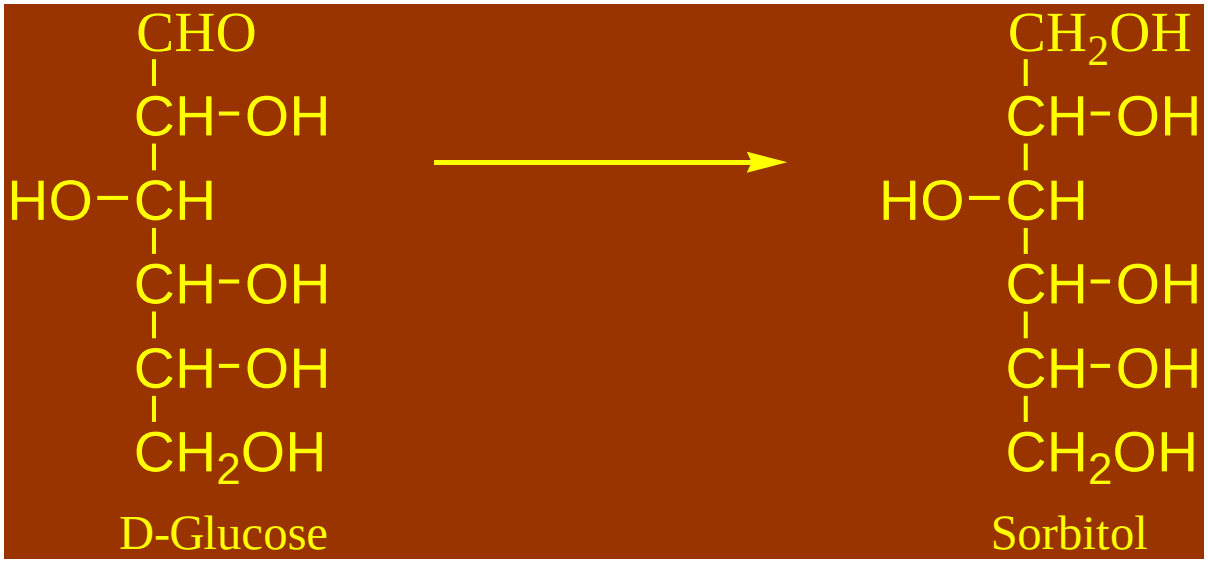
4- Reduction

This resulted in the reduction of the CHO to CH_2OH producing "Sugar Alcohols". Sodium borohydride or H2/Pt are examples of reducing agents.

Glucose → Sorbitol

Galactose → Dulcitol

Mannose → Mannitol

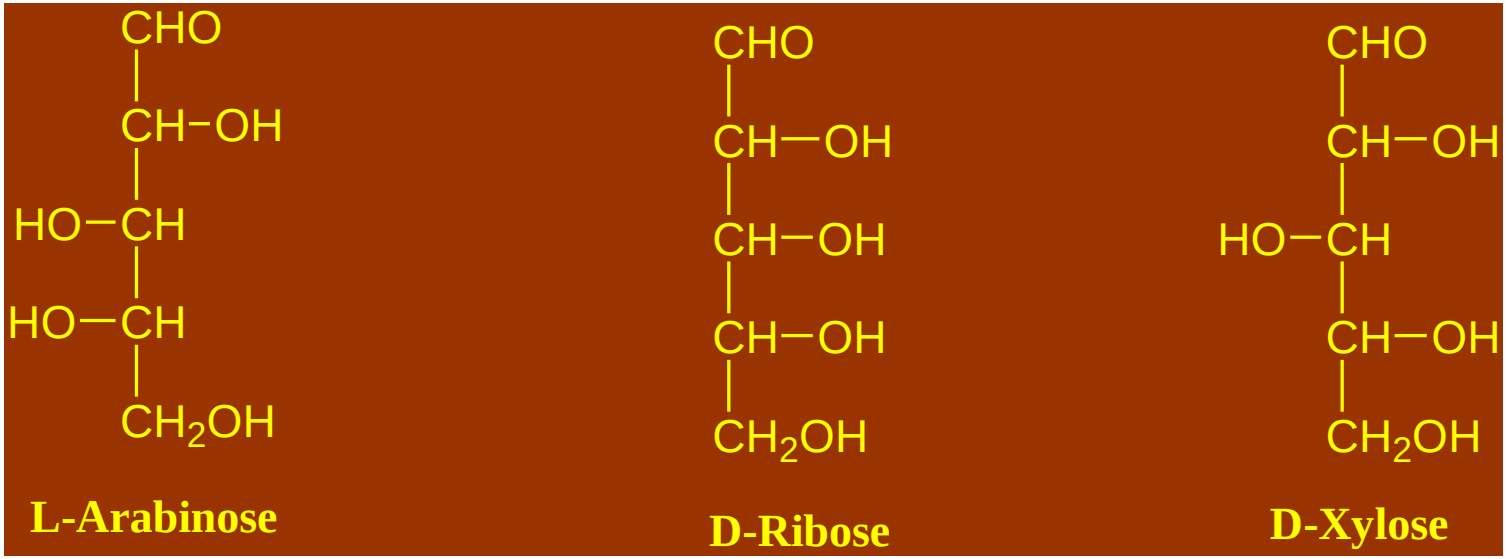


Monosaccharaides

1- Pentoses

Examples:

- **α-D-Ribose:** found in all plant and animal cells as the carbohydrate part of nucleic acids e.g. ribonucleic acid (RNA).
- **α-D-Xylose** (or wood sugar)**:** prepared from corncobs, bran, straw (or any woody material)
- **α-L-Arabinose** (or pectin sugar)**:** found in gums, pectic substances, accompanying hemicelluloses and forms the sugar part of several glycosides.



2- Hexoses

A- α-D-Glucose
(dextrose, grape sugar, blood sugar or cornmon sugar)

Occurrence:

Widely distributed in nature. Present in Grape and blood.

Preparation:

D-Glucose is **commercially** prepared from **starch** by:

- **Autoclaving** (at **150 ^{0}C**) an aqueous starch suspension (15-20%) with **dilute acid** (0.03 N hydrochloric acid) for **30 minutes** (complete hydrolysis).

Uses:

- **As source of energy either by mouth or IV injection.**
- **IV solutions to restore blood volume.**
- **Shocks following insulin administration.**
- **As osmotic diuretic.**
- **Sweetening agent for Pharmaceutical preparations, ice-cream and candy.**

Liquid glucose

Preparation:

It is prepared by **partial acid hydrolysis of starch** using **dilute hydrochloric acid** and **heating** for **20 minutes** at about **30 pounds pressure**.

Composition:

It consists of a mixture of **glucose, dextrin, maltose and water**.

Uses:

Used as sweetening agent, as substitute for sucrose and as an excipient in massing pills.

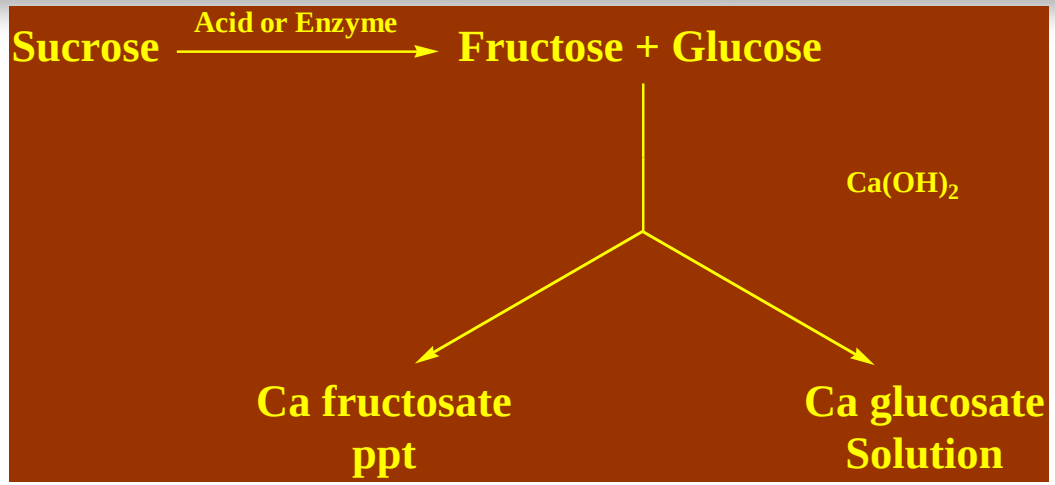
B- Fructose (Levulose, Fruit Sugar)

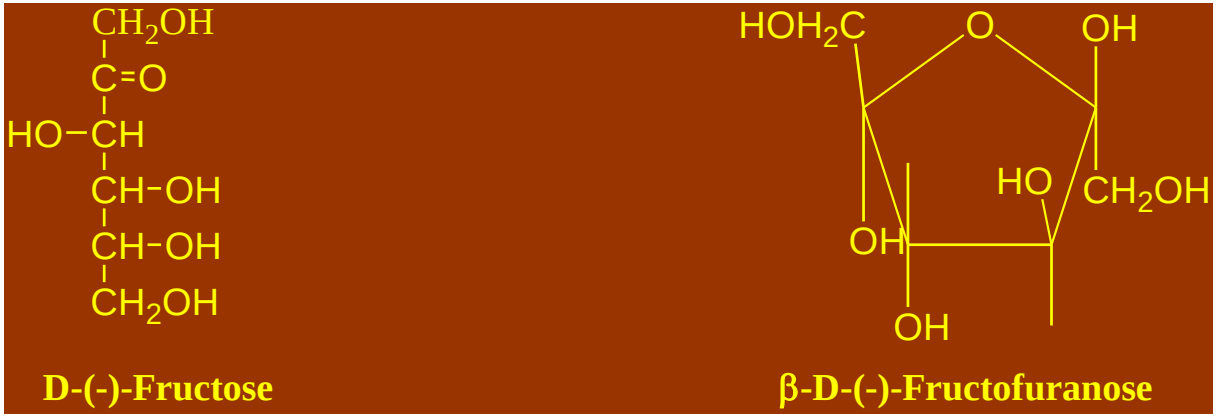
Preparation:

- Acid hydrolysis of Inulin.
- Hydrolysis of Sucrose.

Uses:

- Infant food.
- Diabetic food.
- Diet control.





Some Monosaccharide Derivatives in Pharmacy and Medicine

1- Gluconic acid and its salts:

Preparation:

Gluconic acid is prepared from glucose by **mild oxidation** using either dilute HNO_3 or Br_2/Na_2CO_3 or Electrically or by **fermentation** using *Acetobacter aceti*.

Uses:

- **Ca gluconate** is used (by i.v. or orally) for treatment **calcium deficiency**.
- **Ferrous gluconate,** (orally or by i.v.) is used in **iron deficiency**.

- These salts are characterized by being more easily absorbed than other Ca or Fe salts.

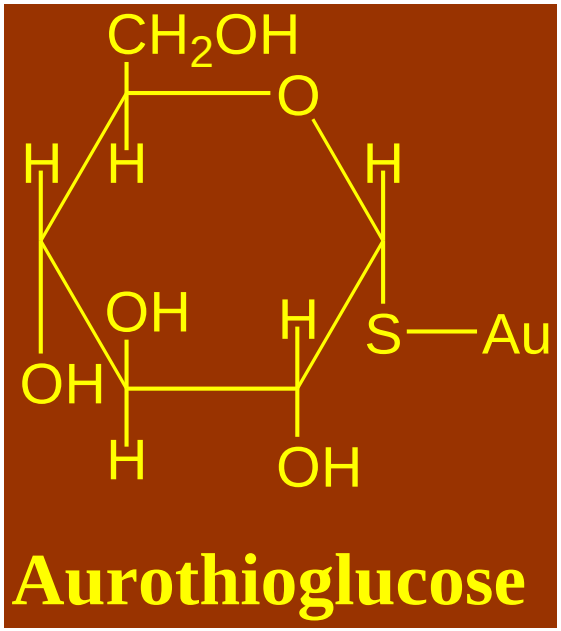
2- Glucuronic Acid:

- Naturally present in Gums and Mucilage's. It can be prepared by Enzymatic oxidation of glucose.
- Uses:

  Treatment of certain arthritic condition as it is a component of cartilages, joint capsules and fluids, nerve sheath and tendons.

3- Aurothioglucose:

- Treatment of rheumatic arthritis by IM injection.

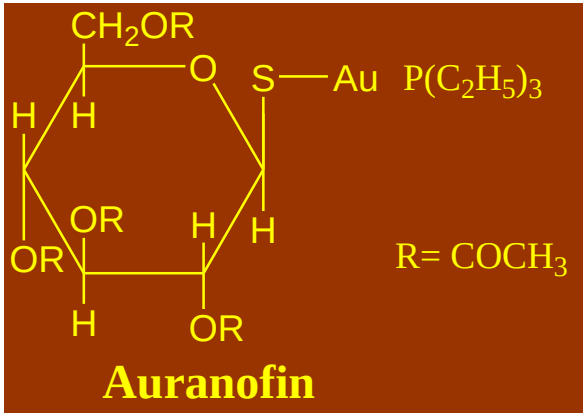


Aurothioglucose

4-Auranofin:

It is the alkyl Phosphine Gold complex with Acetylated thioglucose.

Treatment of rheumatic arthritis



Auranofin

5- Sorbitol and Mannitol:

Preparation: Sorbitol is prepared by reduction of glucose and mannitol by reduction of mannose.

Uses of sorbitol:

- Mild laxative, osmotic diuretic
- Sweetening agent
- in some food and cosmetics industries.

Uses of mannitol:

- osmotic diuretic, laxative
- Vasodilator
- in laboratory diagnosis of kidney function.

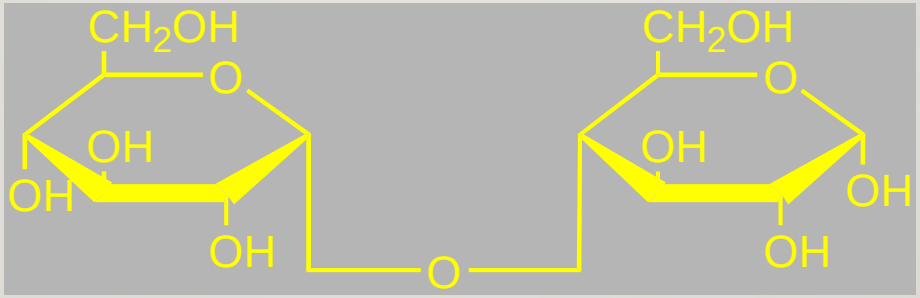
DISACCHARIDES

According to the position of the linkage between the sugar units, disaccharides are classified into reducing such as maltose and lactose and non-reducing such as sucrose .

REDUCING DISACCHARIDES

1- MALTOSE

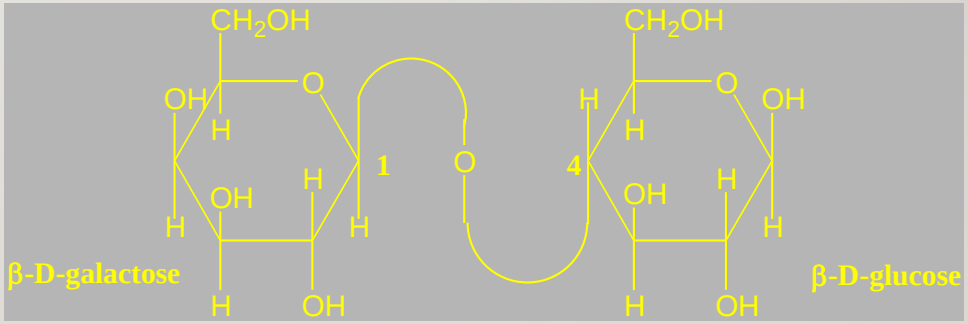
- **Sources:**
  - It is the main constituent of malt and germinating cereals.
- **Structure:**
  - It consists of two glucose units, linked by α1-4. It is hydrolyzed by maltase enzyme (α-glucosidase).



- **Uses:**
  - Nutrient.

2- LACTOSE

- **Sources:**
  - Lactose is the principal sugar of mammalian milk. It is not present in higher plants.
- **Structure:**
  - It consists of **galactose** and **glucose**, linked by a β **1— 4** linkage. It is hydrolysed by Emulsin enzyme.

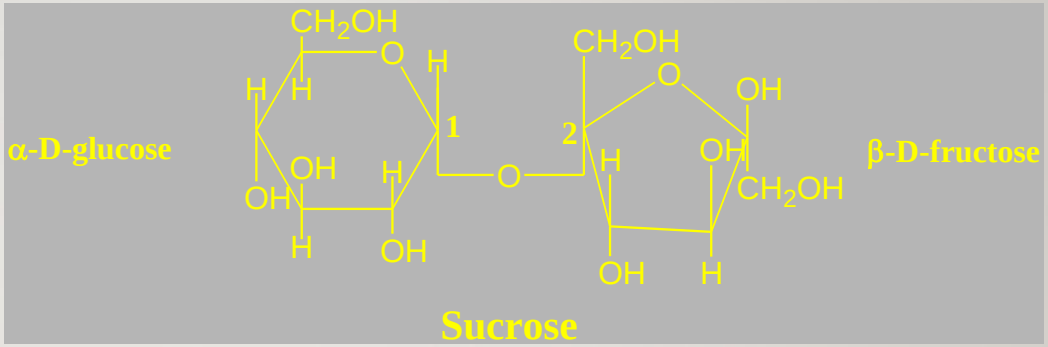


- **Uses:**
  - Nutrient.
  - Diluents in tablets.

NON-REDUCING DISACCHARIDES

1- SUCROSE

- Sources:
  - Sugar cane.
  - Sugar beet.

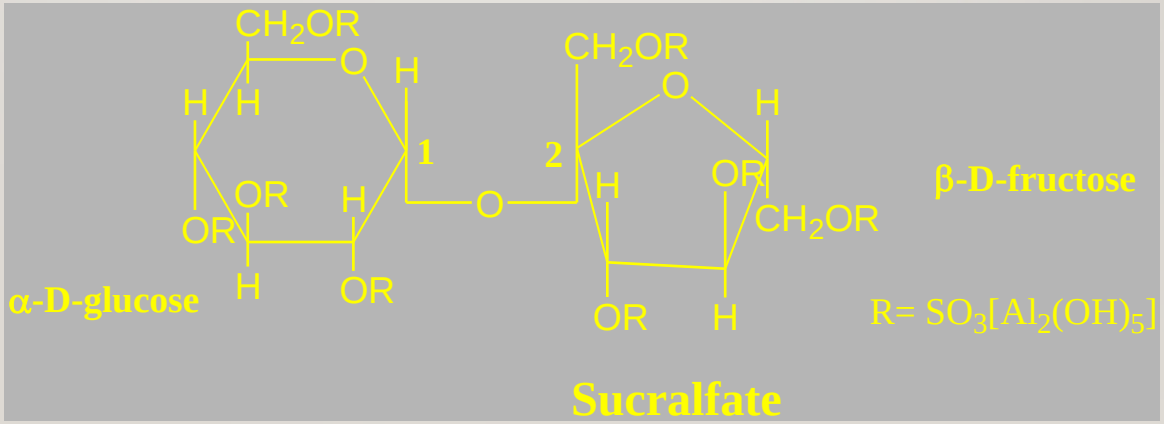


- Properties:
  - It is readily soluble in water.
  - It has a sweetening power more than glucose and less than fructose.
  - It does not reduce Fehling's solution.
- Uses:
  - Used in **syrup preparation**, **tablet manufacture**, **nutrien**t and **demulcent** .
  - Sucrose is also used in **preparation of dextran** (a polysaccharide used as plasma substitute)

SOME SYNTHETIC SUCROSE DERIVATIVES

1- Sucralfate:

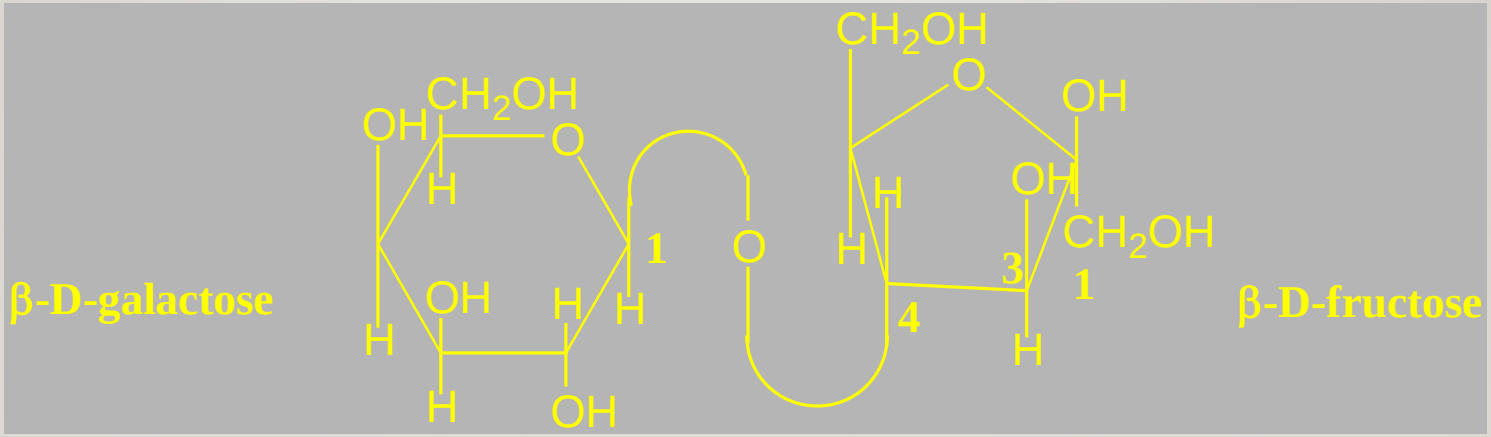
- It is basic aluminium salt of the fully sulfated derivative of sucrose.
- **Uses:** Treatment of peptic and duodenal ulcers.
- Mechanism: Form protective complexes with proteins.



2- Lactulose:

- Prepared by alkaline rearrangement of lactose.
- Uses: Laxative in chronic constipation.

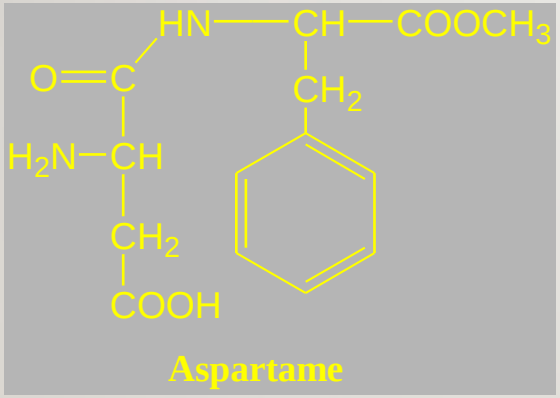
  Treatment of systemic encephalopathy.
- Mechanism of action: It is not digestible. Bacterial flora convert it to lactic and acetic acids that irritate the intestinal wall. Increase acidity of intestine moves ammonia from blood to the intestine for neutralization.



NATURAL SWEETNERS

1- Aspartame:

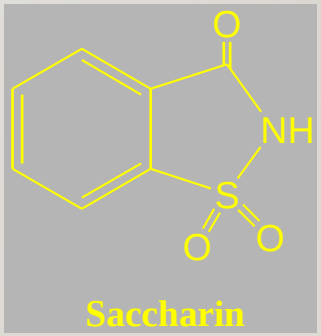
- It is a dipeptide 1500 times more sweet than sucrose.
- *N*-(L-α-Aspartyl)-L-phenylalanin-methylester
- It is not stable in alkaline medium or at high temperature.



Aspartame

2- Saccharin:

- 3500 times more sweet than sucrose.
- Doubtful carcinogenic effect.



Saccharin

3- Sorbitol:

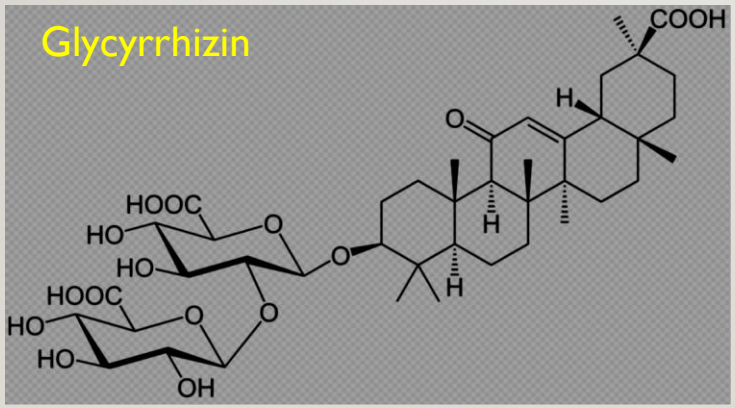
- Reduction product of glucose.
- Half sweetening power of sucrose.

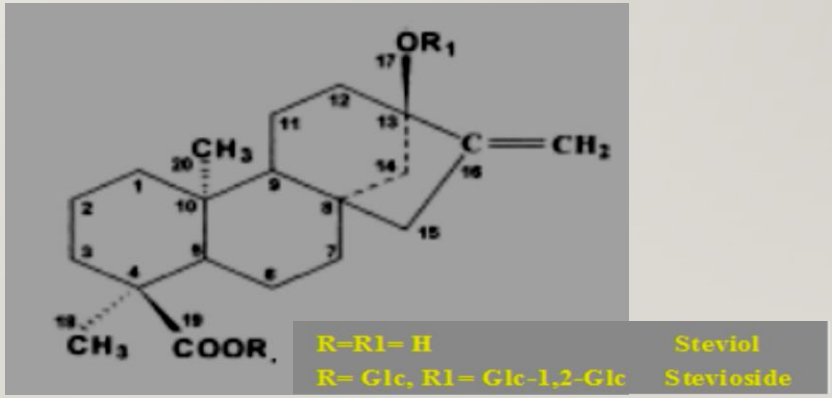
4- Glycyrrhizin:

- **Triterpenoidal saponin obtained from Liquorice.**
- **50 more sweet than sucrose but develop unpleasant taste by time.**

5- Steviol & Stevioside:

- Diterpene and its glycoside obtained from *Stevia rebaudiana*.
- 300 times more sweet than sucrose.
- Stable and non calorigenic.





POLYSACCHARIDES
A- HOMOPOLYSACCHARIDES
1- STARCH

Widely distributed in plants. The most common commercial sources are rice, wheat, maize and potato.

Structure:

It is a glucose polymer

Uses:

- Dusting powder
- Antidote for iodine poisoning.
- Diluents in powders and tablets manufacture.
- Nutrient, demulcent, protective and adsorbent.
- Starting material in the manufacture of glucose, liquid glucose, maltose, and dextrins.

2- DEXTRINS

- Prepared by **partial starch hydrolysis** enzymatically or acid hydrolysis.

- **Uses:** A source of readily digestible carbohydrates for infants
  Substitutes for natural gums as adhesives.

3- Dextran

- Dextran is obtained from sucrose by the action of a bacterial enzyme obtained from ***Leuconostic mesenteroides***.
- **Uses:** - As plasma expander for emergency treatment in cases of shock due to hemorrhage, trauma or severe burns.

- Dextran sulphates can be used as anticoagulants, in treatment of ulcer and in preparation of sephadex.

4- Inulin

- Reserve polysaccharide in some members of the family Compositae. It is a polymer of fructose (β-1, 2-fructofuranose).
- **Uses:** Culture Media. Test for kidney function.

5- CELLULOSE

Cellulose is the main constituent of **cell walls** of plants.

Cellulose is β-1,4 linked glucose.

Cellulose can not be digested by mammals.

Powdered cellulose: In chromatographic separations, suspending agent and tablet excipient.

Cellulose derivatives

Methyl cellulose:

Prepared by methylation of cellulose with methyl chloride under pressure. It swells in water to produce a viscous, colloidal solution.

It is used to increase the viscosity and to stabilize lotions, suspensions, pastes, and ointments.

In ophthalmic preparations as protectant.

It is also used **bulk laxative** in chronic constipation and in **treatment of obesity** as it gives feeling of fullness.

Cellulose acetate phthalate:

For tablet coating.

B- HETEROPOLYSACCHARIDES

I- PLANT GUMS

A- Gum Acacia

Structure:

It consists mainly of **arabin**, the calcium salt of **arabic acid.** Gum acacia contains oxidase enzyme.

Acid hydrolysis of arabic acid yields **L-rhamnose**, **D-galactose, L-arabinose and glucuronic acid**

Uses:

stabilizer in emulsions and suspending agent.

D**emulcent**

B- Gum Tragacanth

Structure:

Composed of D-galactose, L-arabinose, D-xylose, L-fucose, and galacturonic acid.

Uses:

As gum Acacia but better for oxidizable drugs and in cosmetics.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GUM
TRAGACANTH
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NATURAL GUM
FREE

2- AGAR-AGAR

Agar is obtained from red algae.

Agar is formed of two main components, agarose and agaropectin.

Agarose is a neutral galactose polymer, free from sulfate.

Agaropectin is formed of galactose and galacturonic acid units partially esterified with sulfuric acid.

Uses:

Preparation of bacteriological culture media.

Emulsifier, thickener for ice cream.

Treatment of ulcers and chronic constipation.

3- ALGINIC ACID

Obtained from Brown algae.

Alginic acid is mainly composed of D-mannuronic acid units, in addition to a small number of L-guluronic acid.

Uses:

Stabilizer, thickener, emulsifier, deflocculating, jelling and slimming agent.

It is used in dentistry, food and cosmetic industries.

It has important pharmaceutical applications in formulation of creams, ointments, pastes, jellies and tablets.

4- PECTIN

Obtained from apple pomace and inner portion of citrus rind.

Form viscous solutions in water.

Composed of arabinose, galactose and galactouronic acid.

Average molecular weight 100,000- 250,000.

Uses:

1- Pectin is topically applied as a paste in cases of burns and ulcers.

2- It is of great importance in treatment of diarrhea and dysentery. It acts as a detoxifying agent by conjugation with toxins.

3- It is used as a gel and emulsion stabilizer and in manufacture of jellies and jams.

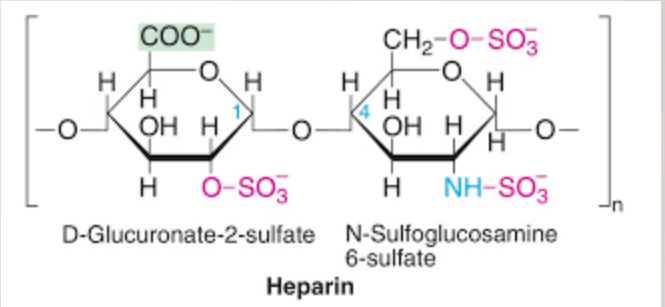
5- HEPARIN

UNFRACTIONATED HEPARIN (UH)

Obtained from lung and liver tissues of animals.

Heparin is a **highly sulfated, linear polysaccharide formed of repeated 1→ 4 linked glucuronic acids and glucosamine residues.**

Average molecular weight 3,000- 30,000.



Uses:

Anticoagulant. It is recommended in cases of pregnancy as it is not terratogenic and does not cross the placenta.

Side effects:

Osteoporosis.

Laboratory monitoring is essential.

6- LOW MOLECULAR WEIGHT HEPARIN (LMWH)

Average molecular weight 5,000 Dalton.

Obtained by hydrolysis of Heparin by Heparinase enzyme at 37 ^{0}C for 4- 8 hr followed by chromatographic purification.

Uses:

Anticoagulant.

Advantage:

Self administration is possible in most cases.

Laboratory monitoring is not required.