❖ Carbohydrates

- Carbohydrates are **polyhydroxy** (poly-alcohol) **aldehydes** or **ketones** **(carbonyl group C=O)**
- They are also called saccharides (sugars)
- The basic chemical formula of a single sugar ➔ **{$C_n(H_2O)_n$, $(CH_2O)_n$}** → each carbon has H_2O around it

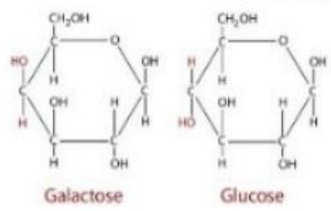
- **Carbohydrates have many functions:**
  1) **Source of energy** (energy stored in the bonds)
  2) **Structural** (cellulose and chitin)
  3) **Building blocks** forming larger molecules
  4) Cellular and immune **recognition** ➔ they are found on the surface of the cell & they are very hydrophilic

- **Carbohydrates can be classified according to:**

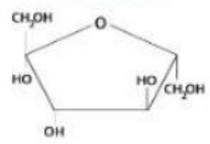
1) The number of sugars that constitute the molecule

- **Monosaccharides:** consist of **1 sugar** (a single saccharide has 2 or more hydroxyl groups)

  Examples on some common monosaccharides:



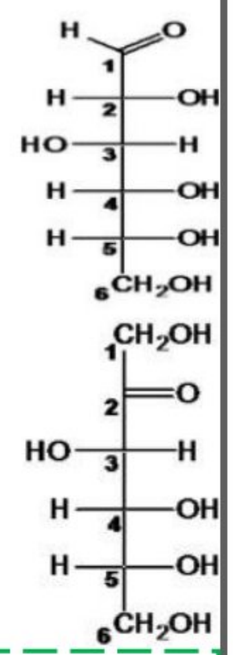
Fructose



- ➢ **Glucose:** It is the essential energy source found in **every disaccharide & polysaccharide** → it has a **mild sweet** flavour ➔ it is known as **blood sugar**
- ➢ **Galactose:** **Hardly tastes sweet**, and rarely found as a single sugar naturally
- ➢ **Fructose:** It is the sweetest sugar (found in fruits & honey and added to soft drinks, cereal & desserts)

- **Disaccharides:** consist of 2 sugars
- **Oligosaccharides:** consist of a few sugars
- **Polysaccharides:** consist of many sugars

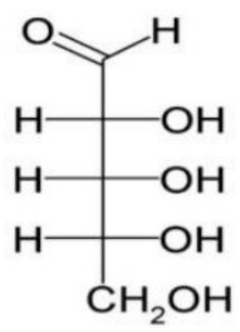
- Most carbohydrates are found naturally in **bound form** rather than as simple sugars:
  - **Polysaccharides** (starch, cellulose, inulin, gums)
  - **Glycoproteins** and **proteoglycans** (hormones, blood group substances, antibodies)
  - **Glycolipids** (cerebrosides, gangliosides) & **Glycosides**
  - **Mucopolysaccharides** (hyaluronic acid)
  - **Nucleic acids** (DNA, RNA)

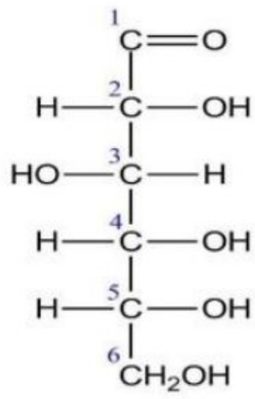


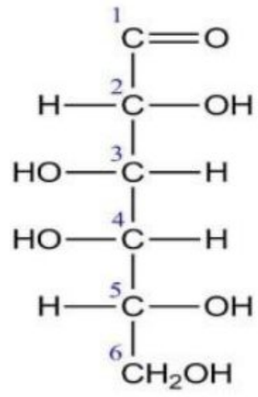
- Sugars end with **-ose** (glucose, fructose…)
  - ➢ If a sugar is an aldehyde (has a peripheral carbonyl group) → it is called **aldose**
    - ✓ Such as **Ribose, Glucose, Mannose & Galactose**
  - ➢ If a sugar is a ketone (has a carbonyl group in the middle) → it is called **ketose**
    - ✓ Such as **Fructose**

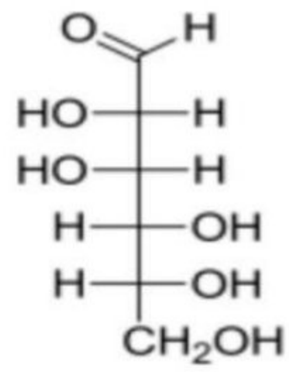
2) The number of carbons a sugar contains:

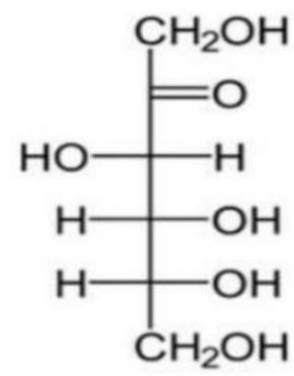
- **Triose** (3-Carbons / Dihydroxyacetone (ketose), Glyceraldehyde (aldose))
- **Tetrose** (4-C)
- **Pentose** (5-C / such as ribose)
- **Hexose** (6-C / such as glucose, galactose, mannose and fructose)
- **Heptose** (7-C)


D-Ribose

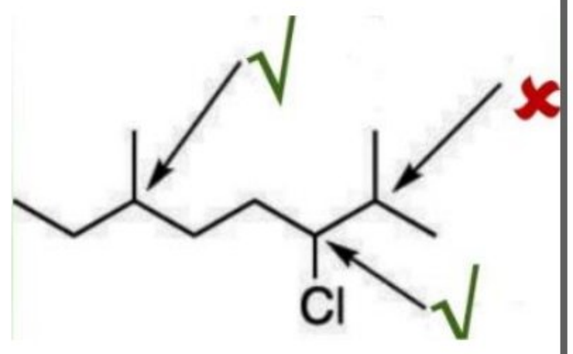

D-glucose


D-galactose


D-mannose


Fructose

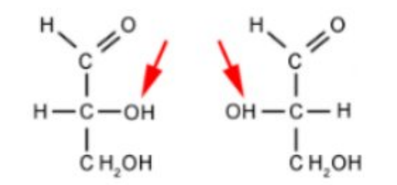
- **Chirality:** The ability of a molecule to rotate clockwise or counterclockwise
- **Chiral center (chiral carbon):** It is a carbon bound to **4 different groups**
  - In sugars → the **first & last carbons** are **Achiral** (not chiral)
  - The **carbon of the carbonyl group** is also **Achiral** (double & triple bonds makes the carbon achiral)



❖ Isomerism

- Isomers are molecules with **same molecular formula** but differ in their **chemical structure and atoms arrangement** ➔ isomers can also differ in their properties

- We have 2 types of isomers:
  1) **Stereoisomers:** Isomers with the same molecular formula & sequence of atoms (constitution) **but** differ in the 3D orientation of their atoms in the space. They have 2 types:
     - **Enantiomers:** Two stereoisomers that are **mirror images** of each other & non-superimposable (not identical) ➔ forming **L, D-isomers**
       - ✓ If the OH on the last chiral carbon is on the **right** → **D**-isomer
       - ✓ If the OH on the last chiral carbon is on the **left** → **L**-isomer


D-Glyceraldehyde L-Glyceraldehyde

     - **Diastereomers:** Two or more stereoisomers of a compound having different configurations at one or more (**but not all**) of the chiral carbons and are **not mirror images** of each other
       - ✓ **Epimers:** A type of diastereomers, in which they differ in **only one** chiral carbon (Every epimer is a diastereomer, but not every diastereomer)

  2) **Constitutional isomers:** Molecules with the same molecular formula but have different bonding patterns and atomic organization

- We can know the number of isomers of a molecule by:

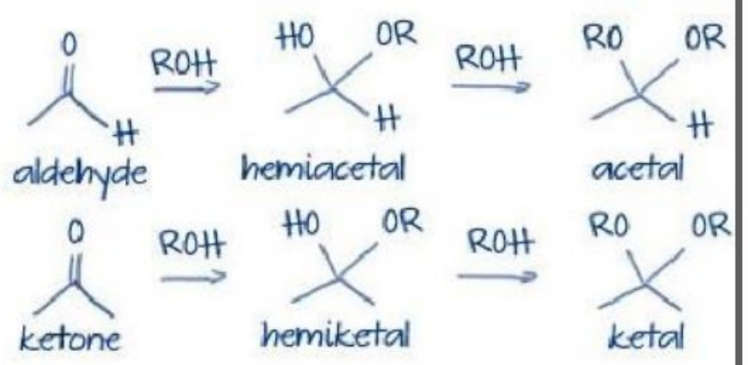
  isomers = 2^n (n is the number of chiral carbons)
  - ✓ Glucose, mannose and galactose have $2^4 = 16$ isomers
  - ✓ Fructose has $2^3 = 8$ isomers

- **Notes:**
  1) D-glucose, L-glucose are **enantiomers**
  2) Glucose, Mannose, Galactose are **epimers**
  3) Glucose and fructose are **constitutional isomers**
  4) Sugars in our bodies are **only D-isomers** (enantiomers)
  5) Enantiomers are 2 forms of the same sugar, diastereomers are 2 different sugars

❖ Fisher Projections

- It is 2-D representation of the 3-D structure of organic molecules
- In the representation:
  - ➢ The atom on the top is carbon 1 → because it is the closest to the functional (carbonyl) group
  - ➢ If the molecule has one chiral center and its OH is on the **right → D**- isomer, **left → L**-isomer
  - ➢ If the molecule has many chiral centers → we use the last chiral center (penultimate carbon)
  - ➢ Sugars have open and ring structures (**most** of sugars are in the ring structure, having **equilibrium** between the amount of ring and open structures)
    - ✓ OH going to the **left** in the open chain, is actually going **upward** the ring
    - ✓ OH going to the **right** in the open chain, is actually going **downward** the ring

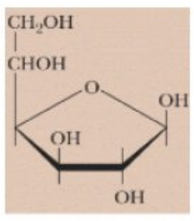
❖ Acetal, Ketal, Hemiacetal, Hemiketal

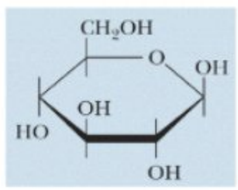


- Acetal & Ketal are molecules having **2 ether (R-O-R) groups** on the same carbon
- Hemiacetal & Hemiketal are molecules having **alcohol (R-OH) and ether (R-O-R)** on the same carbon
  - ➢ Hemiacetal formed by the reaction of Aldehyde + Alcohol
  - ➢ Hemiketal formed by the reaction of ketone + Alcohol
  - ➢ The difference between is in H atom bonded to Hemiacetal and R bonded to Hemiketal

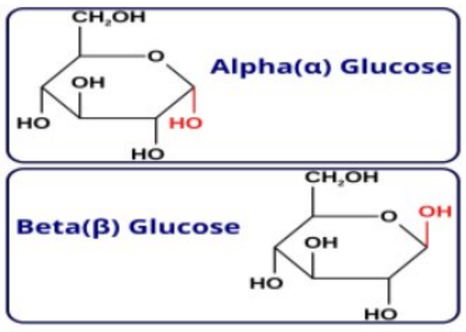
- To form a ring we **bend the open chain** to allow **OH** to react with the **carbonyl group** forming hemiacetal or hemiketal
  - ➢ We determines which OH reacts with the carbonyl by → the **stability of the molecule**
    - ✓ Most of glucose rings are 6 membered rings (carbonyl with OH on carbon 5 because it is the most stable with the least steric repulsion)
    - ✓ Glucose can also form a 5 membered ring but it is minor (rare)
    - ✓ Most of fructose rings are 5 membered but can also form 6 membered rings (rare)

- If the ring is **5 membered** (consists of 4 C & 1 O atom) → it is called **Furanose**
- If the ring is **6 membered** (consists of 5 C & 1 O atom) → it is called **Pyranose**


Furanose form


Pyranose form

- Rings form **more isomers** than open chains, because of the removal of the double bond between C and O in the carbonyl group
  - ➢ **Anomers:** Isomers that differ only in their anomeric carbon (Carbon 1 in aldose and 2 in ketose)
    - ✓ If the OH of the anomeric carbon is **up to the ring** (the same orientation as the last carbon) it is called **Beta (β)**
    - ✓ If the OH of the anomeric carbon is **down to the ring** (opposite to the last carbon orientation) it is called **alpha (α)**

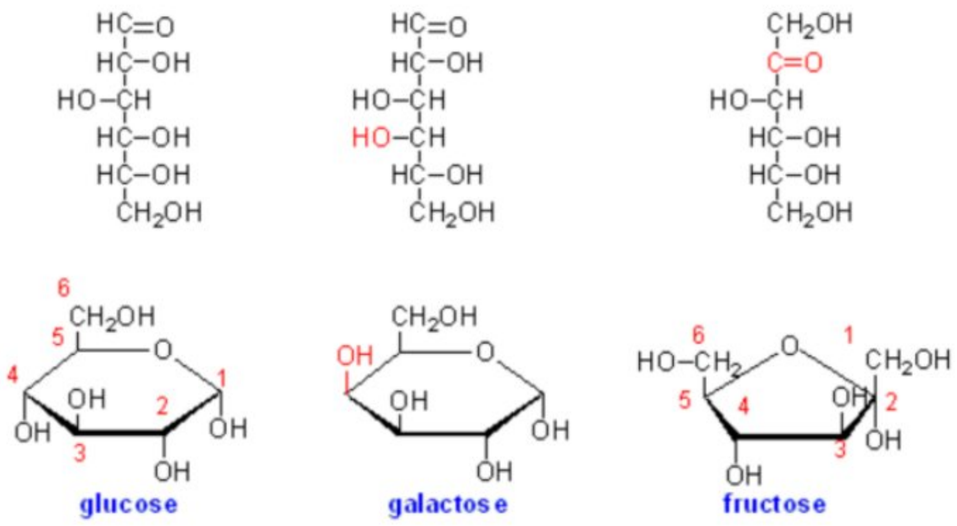


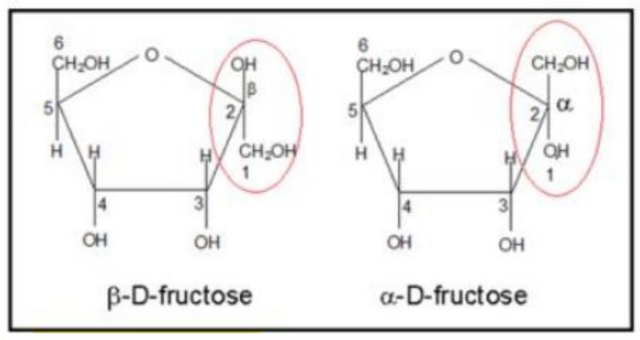
- **Beta configuration** is found in **structural** molecules (such as cellulose and chitin) because the bond between them is diagonal → making it <u>stronger and restrict the movement</u> of the macromolecule

- **Alpha configuration** form bonds easier to be formed and much <u>weaker</u> than beta so it is found in molecules responsible for **energy storage** (starch and glucose)

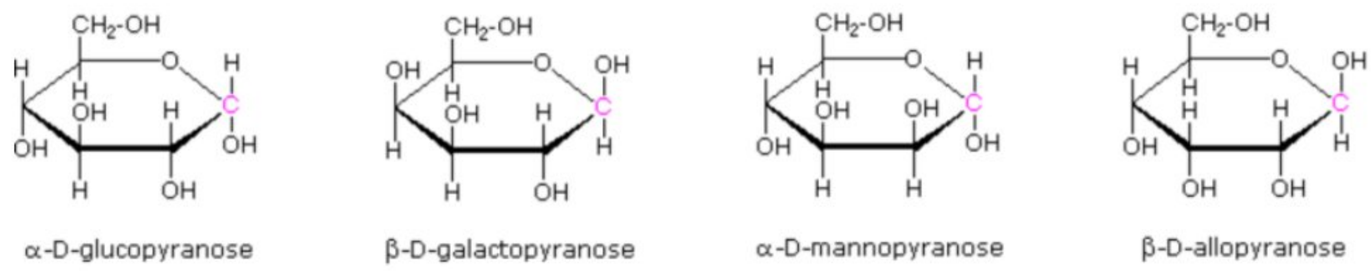
- Our bodies **don't have enzymes** to digest sugars with **beta** configuration so we cant use energy in them

- **Remember:** We look to the:
  - Anomeric carbon to determine alpha (down) and beta (up) configurations
  - Last chiral center to determine D (down the ring, right in the open chain) & L- isomers (up to the ring, left in the open chain)





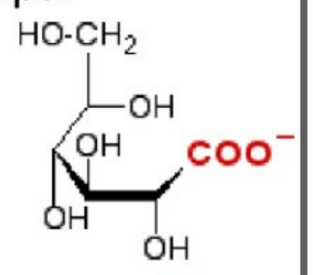
Examples of Some Pyranose Forms of Hexoses



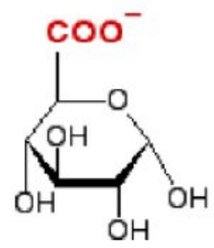
Modified Sugars

❖ Sugar acids (Oxidized)

- **Oxidation ➔ The Increase in the oxygen or decrease in the hydrogen**
- **All monosaccharides** can be oxidized → because they have free carbons with reactive groups:
  - Carbonyl (Aldehyde, Ketone) on the **anomeric carbon** → It is **more reactive**
  - Alcohol (OH, hydroxyl) on the **last carbon** → **less reactive**
    - ✓ Oxidation forms a **carboxyl group** (COOH)



- So, monosaccharides can be oxidized on 2 positions (the anomeric & the last carbons)
- The position of oxidation depends on the **oxidizing agent ➔** If the oxidizing agent is:
  - **Weak** → It oxidizes the **anomeric** carbon (because it is more reactive)
  - **Strong** → It oxidizes **both** anomeric & the last carbon
  - The only way to oxidize the **last carbon** without the anomeric one → we **must** use an **enzyme** (because it is specific and selective)

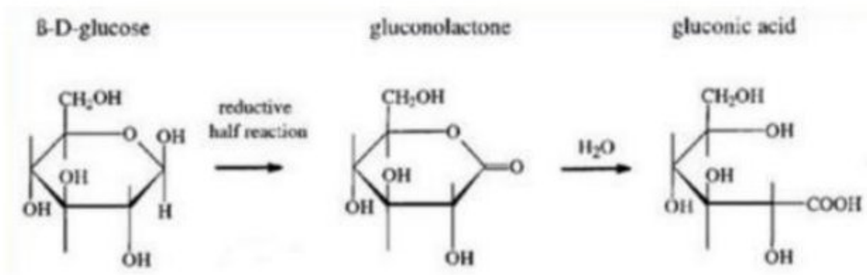


- We can know the position of oxidation by the **suffix** at the end of the molecule's name, If the suffix is:
  - **–onic ➔** the **anomeric** carbon is oxidized
  - **–uronic ➔** the **last carbon** is oxidized
  - **–aric ➔** the **both carbons** are oxidized (it has 2 carboxyl groups)

- **Note:**
  - Aldehydes are oxidized **directly**, but ketones are oxidized **indirectly** (it is **converted into aldehyde then oxidized**)

- **Ketone** is converted to the intermediate "**enediol**" which has a double bond between 2 carbons with 2 OH groups → then converted into **Aldehyde**
- As we said before **All monosaccharides can be oxidized** by a weak oxidizing agent → so they are **reducing sugars** (the anomeric carbon is free)

- Both forms of monosaccharides can be oxidized (rings and open chains)
- Oxidation of **rings involves the formation of lactone**
  - The ring is oxidized forming **lactone** (by releasing the H of OH and then forming a double bond with O forming a ketone) → Then water converts lactone into a carboxylic acid (oxidation is done)

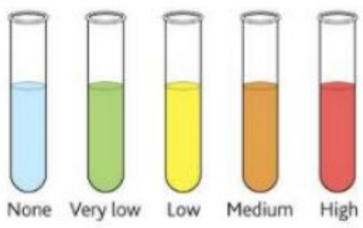


- **Note:**
  - **Vitamin C (ascorbic acid)** is an unsaturated lactone → Air **oxidation** of ascorbic acid, followed by hydrolysis of the ester bond, leads to **loss of activity** as a vitamin
  - Vitamin C is imoportant for **making collagen**
  - A lack of fresh food can cause vitamin C deficiencies → can lead to **scurvy** → making weak collagen leading to spontaneous bleeding, pain in the limbs, fractures and loss of teeth

- ## Oxidation Tests:

1) Benedict's test:

- It is used to know if a reducing sugar presents in the solution and its amount (concentration)
- It is done by adding the Benedict's reagent to the solution (which contains Cupper as an oxidizing agent) and then heated
- If the oxidation occurred → **Cu2O will precipitate** (which is red) → so **changing the color** of the solution according to the amount of the reducing sugar ➔ the color varies from green to dark red (brick) or rusty-brown



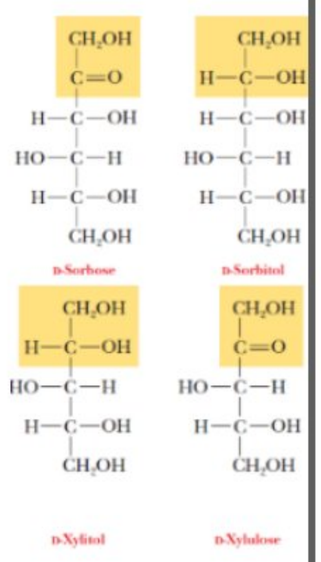
2) Tollen's test:

- A more recent method for the **detection of glucose**, but not other reducing sugars, is based on the use of the enzyme **glucose oxidase**
- If there is glucose → **silver will precipitate** on the walls of the tube forming a mirror

- The **diabetic test** depends on the oxidation of glucose (only) by the enzyme **glucose oxidase**
  - Glucose is oxidized into peroxide and then peroxidase is transformed into a colored substance
  - The depth of the color depends on → the concentration of glucose in the blood

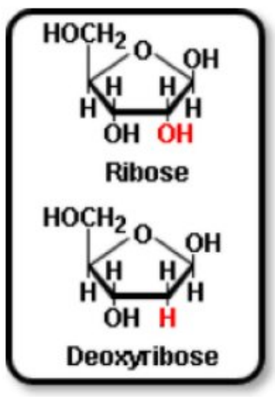
❖ Sugar alcohol (reduction)

- **Reduction ➔ The decrease of O, increase in H or the gain of electrons**
- By reducing a sugar we are converting the **carbonyl group** (**Ketone & Aldehyde**) → into **hydroxyl** (**alcohol**) → the resulting molecules have the suffix **–itol**
- **Examples:** Sorbitol (from sorbose), xylitol (from xylulose) and mannitol which are used to **sweeten food** products
- The resulted molecules still have a sweet taste but they are not sugars → so they won't enter sugar metabolism pathways



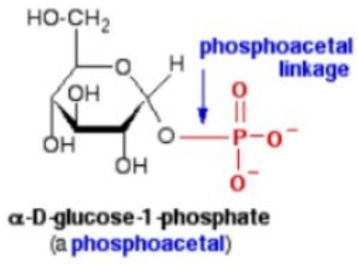
❖ Deoxy-sugars (reduction)

- One or more hydroxyl groups are replaced by hydrogens (so **reduction** occurs to the **Hydroxyl** (alcohol))
- Example: **2-deoxyribose** in DNA
  - ➢ In DNA ribose is deoxy (lost O) on C number 2 → making DNA **more stable and less reactive** (because O is a reactive atom) → preventing mutations
  - ➢ RNA has ribose → less stable and more reactive → work momentarily and the degraded



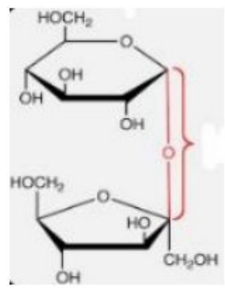
❖ Sugar esters (esterification)

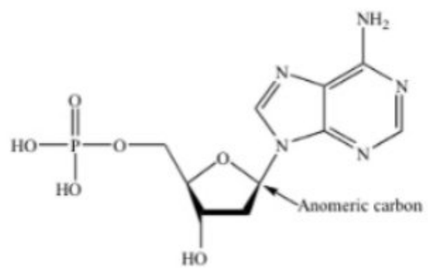
- **Esterification: The formation of ester bond by adding molecules such as phosphate**
- Sugar esters are produced by the **phosphorylation** (adding phosphate) of **hydroxyl groups**



❖ Glycosides

- Sugars forms a **glycosidic bond** with other molecules on its **anomeric carbon**
- If this bond links the **anomeric carbon** with **oxygen**, it is called O-glycoside
- If this bond links the **anomeric carbon** with **nitrogen**, it is called N-glycoside (such as the glycosidic bonds between the ribose and the nitrogenous base in the **nucleotides**)
- If this bond links the **anomeric carbon** with **carbon**, it is called C-glycoside
- If this bond links the **anomeric carbon** with **sulfur**, it is called thioglycoside

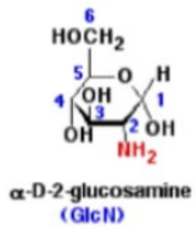




- Glycosides derived from furanoses are called **furanosides**, and those derived from pyranoses are called **pyranosides**, regardless if they are N- or O- linked

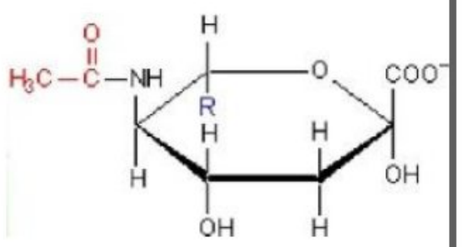
❖ Amino sugars

- The **OH group** in a sugar (on any C other than the anomeric) is replaced by an **amino group** (NH_2) → adding –amine to the end of the sugar
- Amino sugars can form amides by binding to an **acyl group** ($C{=}OCH_3$)



❖ Sialic acid

- It has a carboxyl group on carbon 1 & an amino group on carbon 4
- It is the **terminal residue of the oligosaccharides of glycoproteins and glycolipids**
- It is also called N-**Acetylneuraminate**
- The precursor (synthesized from) → **amino sugar & neuraminic acid**



❖ Disaccharids

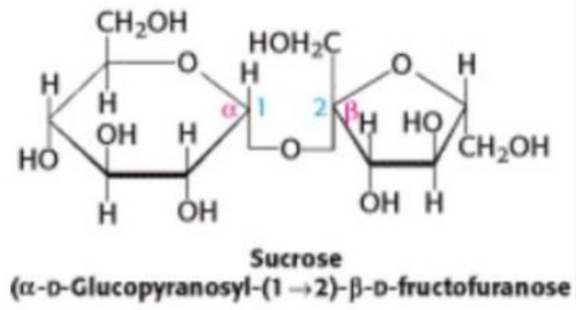
- Sugars made of 2 monosaccharides joined by **a glycosidic bond**
  - ➢ If those monosaccharides are **similar** it is called **homo-disaccharide** and if they are **different** it is called a **hetero-disaccharide**
- Disaccharides are synthesized using the enzyme **glycosyltransferase**

- There are a variety of disaccharides, they differ in:
  - ➢ The type of monosaccharides involved and their stereoisomerism (D,L)
  - ➢ The carbon involved in the linkage (Carbon number 1, 2, 3, 4 or 5…)
  - ➢ The order of the 2 sugar units (monosaccharides)
  - ➢ Anomeric configuration of OH on carbon 1 (Alpha and Beta)

- Abundant disaccharides:

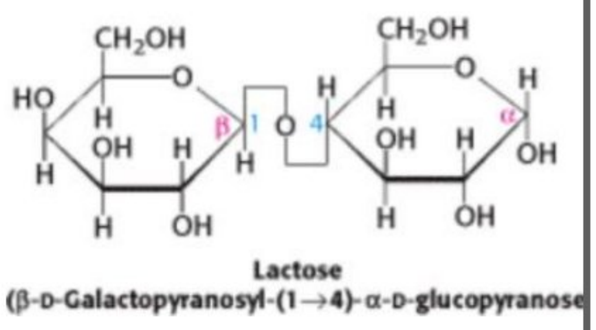
1) Sucrose:

- ➢ Consists of **α-Glucose + β-Fructose** → when react together they form sucrose and H_2O (dehydration is the reaction of building)
- ➢ Molecular formula → **$C_{12}O_{11}H_{22}$**
- ➢ The bond is formed between carbon 1 in glucose and carbon 2 in fructose (**both carbons are anomeric**) → it is a <u>non-reducing sugar</u>



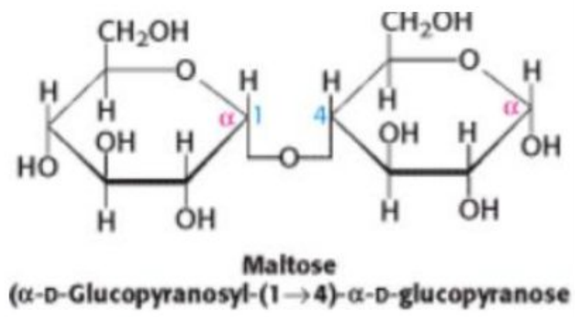
2) Lactose:

- ➢ Consists of **β-Galactose + α-Glucose**
- ➢ Molecular formula → **$C_{12}O_{11}H_{22}$**
- ➢ The bond is formed between carbon 1 in galactose and carbon 4 in glucose → it is a <u>reducing sugar</u>
- ➢ It is **milk sugar**

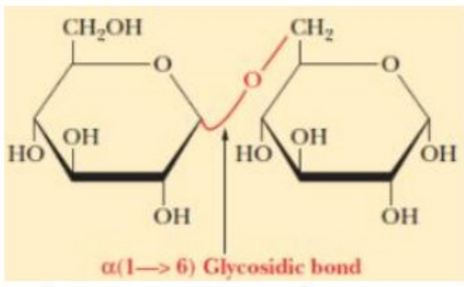


3) Maltose

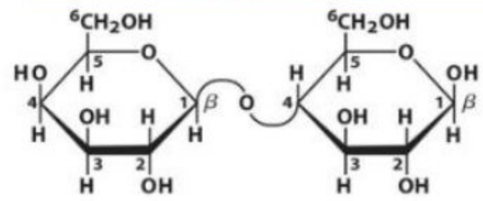
- ➢ Consists of **α-Glucose + α-Glucose**
- ➢ Molecular formula → **$C_{12}O_{11}H_{22}$**
- ➢ The bond is formed between carbon 1 and carbon 4 in glucose → it is a <u>reducing sugar</u>



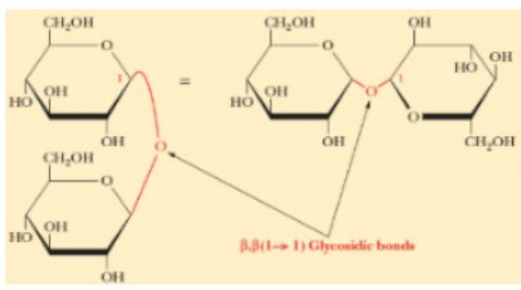
- Disaccharides can have different forms, for example:
  - ➢ 2 Glucose monomers can be linked via a 1 → 6 glycosidic bond rather than 1 → 4



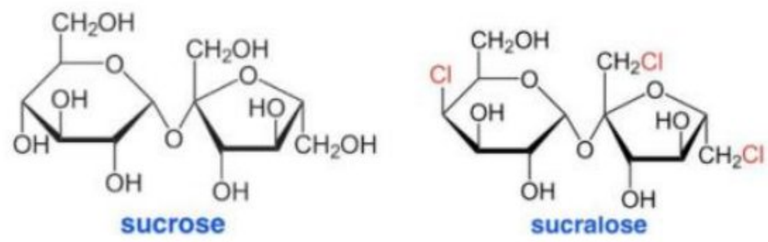
  - ➢ Lactose has a β form → in which both Galactose and Glucose are in the β configuration



  - ➢ We can also find a disaccharide of 2 β-glucose with a 1 → 1 glycosidic bond links them



- **Sucralose** is an **artificial sweetener** (not natural)
  - Synthesized by replacing OH groups in sucrose by Cl
  - Splenda is a brand of this artificial sweetener



Milk problems:

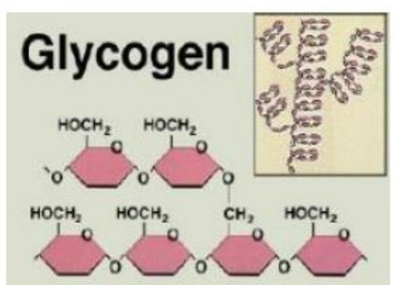
- **Lactose degraded** in our intestines by the enzyme **lactase**
  - Babies have a high activity of lactase (the highest activity at 1 month) and then it is reduced until reaching 6 year (here the activity will remain constant and equals the activity in adults)
  - A deficiency of this enzyme in the intestinal villi allows lactase of intestinal bacteria to digest it producing **hydrogen gas, carbon dioxide, and organic acids** and leading to digestive problems (bloating and diarrhea) ➔ that is called **Lactose intolerance**
- **Galactosemia: Missing a galactose-metabolizing enzyme** → non-metabolized galactose accumulates within cells and is converted to the hydroxy sugar **galactitol**, which cannot escape cells. Water is drawn into cells and the swelling causes cell damage, **particularly in the brain**, resulting in severe and **irreversible retardation** and also causes **cataract**

❖ Oligosaccharids

- Consists of a few monosaccharides, such as **Raffinose** it is:
  - It is found in Found in **beans and vegetables like cabbage, brussel, sprouts, broccoli, asparagus**
  - A Tri-saccharide made of **α-Galactose + α-Glucose + β-Fructose (Galactose + Sucrose)**
  - We (as humans) **lack the alpha-galactosidase enzyme** that is needed to break down raffinose, but intestinal bacteria can ferment it into hydrogen, methane, and other gases
- Some Oligosaccharides are involved in **drugs**, such as:
  - **Streptomycin & Erythromycin** (antibiotics)
  - **Doxorubicin** (cancer chemotherapy)
  - **Digoxin** (a drug for cardiovascular diseases)

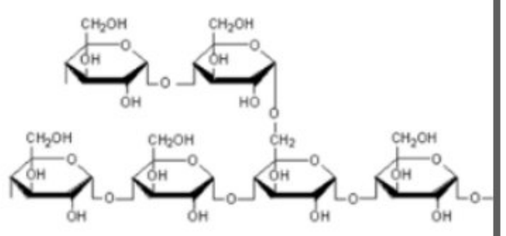
❖ Polysaccharides

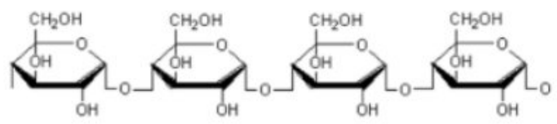
- Consists of many monosaccharides → they can be similar (Homo-polysaccharide) or different (Hetero)
- **What determine the features of a polysaccharide:**
  - The type of monosaccharides and their number (length)
  - Branching
  - Purpose (Storage [Glycogen, starch, dextran], Structural [Cellulose, Pectin, Chitin])
- **Glycogen:**
  - Branched polysaccharide with **α-Glucose** monomers linked by **α (1 → 4)** linkage with **α (1 → 6)** linkage at the branching points
  - It is a **storage polysaccharide** found in **animal** cells is granules (in humans it presents mainly in liver and muscle cells)
  - When we have excessive glucose in our body → it is stored as Glycogen



- It is a **non-reducing sugar**

- **Starch:**
  - It is a **storage polysaccharide** found in **plant** cells is granule in the cytosol
  - Polysaccharide with **α-Glucose** monomers, and it has 2 forms:
    - ✓ 80-90% Branched → **Amylopectin**
    - ✓ 10-20% Unbranched → **Amylose**





- **Notes:**
  - **Glycogen is more (highly) branched than amylopectin** (Glycogen has a branch every 10 residues but amylopectin has a branch every 25 residue)
  - Branching is important in making the molecule **water soluble preventing crystallizing** & branching make it easy to **access glucose**

- **Dextran:**
  - It is a **storage polysaccharide** found in **Yeast & Bacteria**
  - Branched polysaccharide with **α-Glucose** monomers, linked by **α (1 → 6) linkage**
  - In the branches the linkage is **→ 1-2, 1-3, 1-4**

- **Cellulose:**
  - It is a **structural polysaccharide** found in **plant** cells
  - Unbranched polysaccharide with **β-Glucose** monomers, linked by **β (1 → 4) linkage**
  - Many polysaccharide chains of cellulose present parallel to each other as fibers and these fiber are hydrogen-bonded to each other
  - We can't degrade (digest) cellulose → because we **don't have** a **β-Galactosidase**

- **Chitin:**
  - It is a **structural polysaccharide** found in **the exoskeleton of animals**
  - Unbranched polysaccharide with **N-Acetyl-β-Glucose** monomers, linked by **β (1 → 4) linkage**

- **Pectin:**
  - It is a **structural Hetero-polysaccharide**, used as a gelling agent

- **Note:**

A sample that contains only a few molecules of a large polysaccharide, each molecule with a single reducing end, might well produce a negative test because there are **not enough reducing** ends to detect

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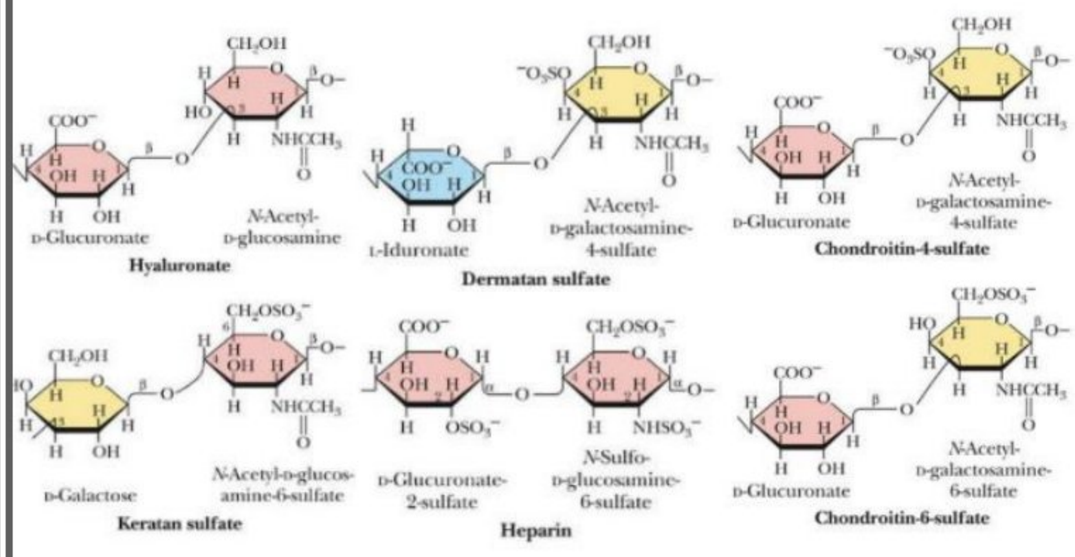
❖ GAGs (Glycosaminoglycans)

- **Hetero**-polysaccharides composed of **repeated units of disaccharides**
  - The first monomer is an **amino sugar** (glucosamine, galactosamine) **→** positively charged due to the amino group
  - At least one of the 2 monomers must have a **negatively charged carboxylate or sulfate group**

- These modifications are important → **increasing the polarity & solubility** → increasing the **viscosity** so they can act in shock absorbance
- **<u>Examples on these repeating units (disaccharides):</u>**
  - **Hyaluronate** → present in the synovial fluid, vitreous humor & ECM of loose connective tissue → it contributes in shock absorbance (lubricant fluid, preventing friction between bones)
  - **Chondrotin sulfate** → Cartilage, bones, heart valves → the most abundant GAG
  - **Heparin** → in the mast cells → natural anticoagulant
  - **Dermatan sulfate** → in the skin
  - **Keratan sulfate**
  - **Heparan sulfate**

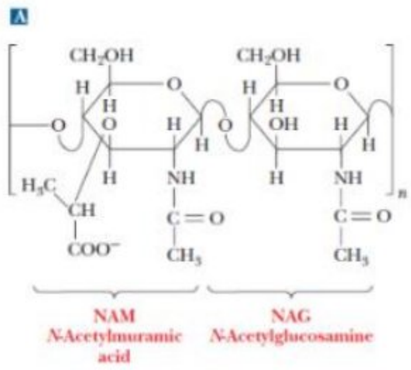


GAG	Localization	Comments
Hyaluronate	synovial fluid, **vitreous humor, ECM of loose connective tissue**	**the lubricant fluid , shock absorbing** As many as 25,000 disaccharide units
Chondroitin sulfate	**cartilage**, bone, heart valves	**most abundant GAG**
Heparan sulfate	basement membranes, components of cell surfaces	contains higher acetylated glucosamine than heparin
Heparin	component of intracellular granules of mast cells lining the arteries of the lungs, liver and skin	**A natural anticoagulant**
Dermatan sulfate	skin, blood vessels, heart valves	
Keratan sulfate	cornea, bone, cartilage aggregated with chondroitin sulfates	Only one not having uronic acid

❖ Proteoglycans

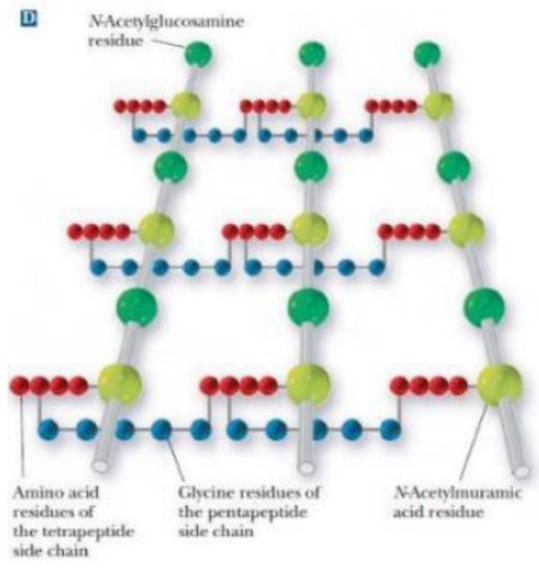
- Consist of sugars (major) with proteins (minor)
- Has many functions and features:
  - **Lubricant**
  - **Structural component of the connective tissue**
  - **Mediate adhesion of cells to the extracellular matrix**
  - **Bind factors that stimulate cell proliferation**

- **Bacterial cell wall consists of proteoglycans**, containing a repeating unit of a disaccharide of **NAM & NAG** as monomers → linked together via **β (1 → 4) linkage**
  - <u>NAM = N-Acetylmuramic acid</u> → it is a modified glucose (has <u>lactic acid</u> on its <u>carbon number 3</u>)
  - <u>NAG = N-Acetylglucoseamine</u>



❖ Proteoglycans

- Similar to proteoglycans → consist of chains of repeated units of **NAM + NAG** → these chains are cross linked by peptides (not proteins) containing a few number of amino acids:
  - NAM is linked to 4 amino acids (Ala,Gln,**Lys,Ala**)
  - A short chain consist of **5 Gln residues** links the sugar chains
  - Gln chain attach to the **3rd amino acid of NAM (lys) and the 4th one (Ala)**



- So Ala and Lys link the chain of repeated disaccharides indirectly by attaching to the Gln chain
- **Proteoglycans**

❖ Glycoprotiens

- Proteins (Major) modified by adding sugar (minor) → linked by:
  - **O-Glycosidic bond ➔ with the hydroxyl of Serine (Ser), Threonine (Thr), Hydroxylysine (HLys)**
  - **N-Glycosidic bond ➔ with the amide group of asparagine (Asn,N)**

- Glycoproteins act **receptors** on the surface of the cell to bind ligands (sugar is needed for this binding)

- ***Significance of protein-linked sugars:***
  1) **Protein folding**
  2) **Protein targeting**
  3) **Prolonging protein half life:** More sugar linked to the protein makes it → **harder** to be broken → and extends its half life (such as collagen which has a long half life)
  4) **Cell-Cell recognition** (such as blood types)
  5) **Signaling:** binding of ligands (mainly hormones)

- Blood types:

According to the ABO system there are 4 types (A,B,AB,O) differ in the type of the terminal sugar of the oligosaccharide on the surface of RBCs, If this terminal residue is:

- **N-Acetylgalactoseamine (GalNAc) ➔ A**
- **Galactose (Gal) ➔ B**
- **None ➔ O**
- **Gal and GalNAc as separate chains on the same RBC ➔ AB**