Nafith Abu Tarboush
DDS, MSc, PhD
natarboush@ju.edu.jo
www.facebook.com/natarboush

Carbohydrates

Topic goals

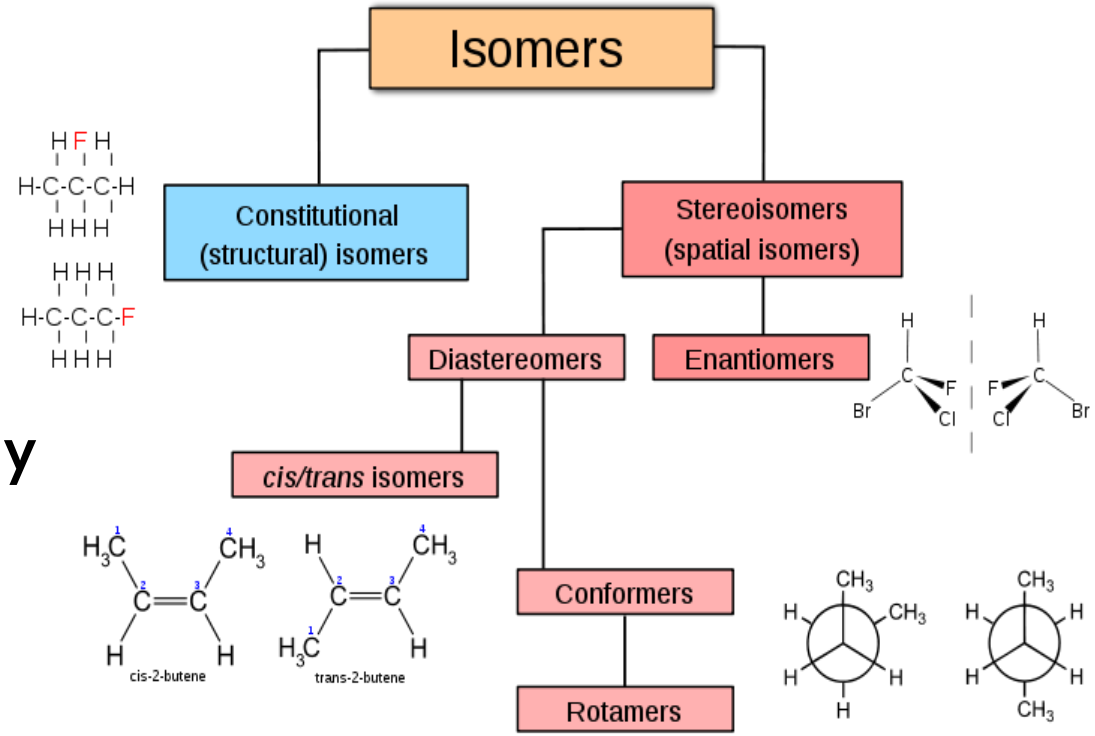
- Two major goals:
- 1. Monosaccharides: to recognize their structure, properties, & their stereochemistry
- 2. The nature of di-, oligo-, & polysaccharides

LECTURES OUTLINE

- 1. Monosaccharide structures
  - ✓ Aldoses and ketoses
  - ✓ Optical isomers
    - Fischer projections
    - Enantiomers, Diastereomers, & Epimers
  - ✓ Cyclic structures
    - Hemiacetals and hemiketals
    - Anomers & Haworth projections
    - Furanoses and pyranoses
- 2. Monosaccharide reactions
  - ✓ Oxidation-reductions, Esterification, glycosides, & Sugar derivatives
- 3. Oligosaccharides
  - ✓ Sucrose & Lactose
- 4. Polysaccharides
  - ✓ Cellulose & starch (Forms of starch: Amylose & Amylopectin)
  - ✓ Glycogen
  - ✓ Chitin
  - ✓ Cell walls
  - ✓ Glycosaminoglycans
- 5. Glycoproteins

Isomers

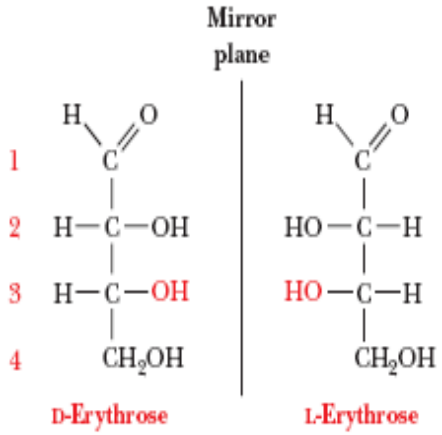
- Greek: isos = "equal", méros = "part"
- Compounds with similar molecular formula but different structural formulas
- Isomers do not necessarily share similar properties
- Two main forms:
  - Structural isomerism
  - Stereoisomerism (spatial isomerism)

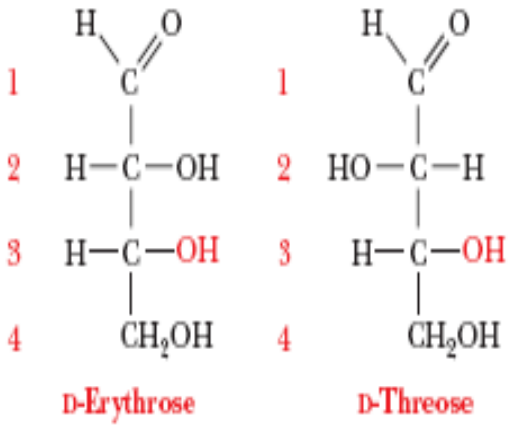


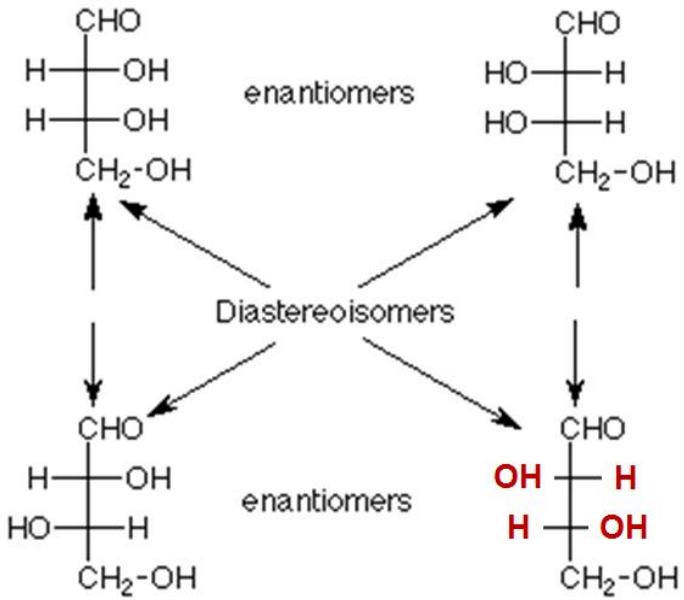
Isomers

- 1. Structural (constitutional) isomers: atoms & functional groups are joined together in different ways (2° vs. 3° alcohol)

- 2. Stereoisomers: bond structure is the same, but geometrical positioning of atoms & functional groups in space differs
  - ✓ Enantiomers: non-superimposable mirror-images
  - ✓ Diastereomers: NOT mirror-images
  - ✓ Epimers –differ only at one chiral center

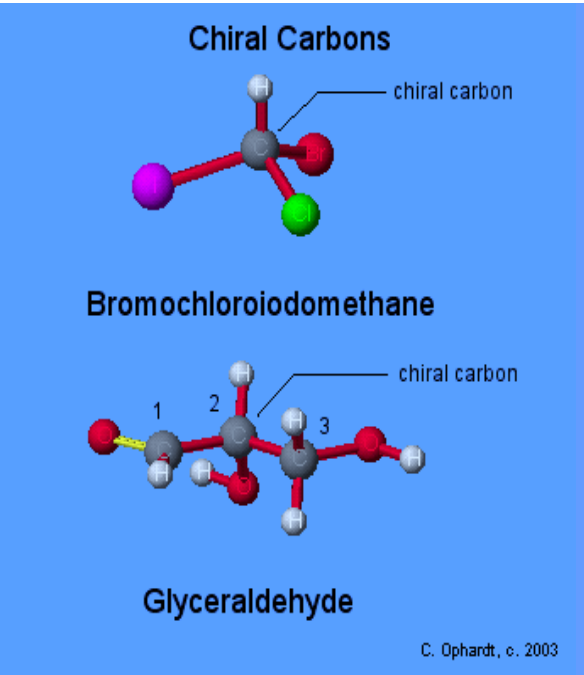


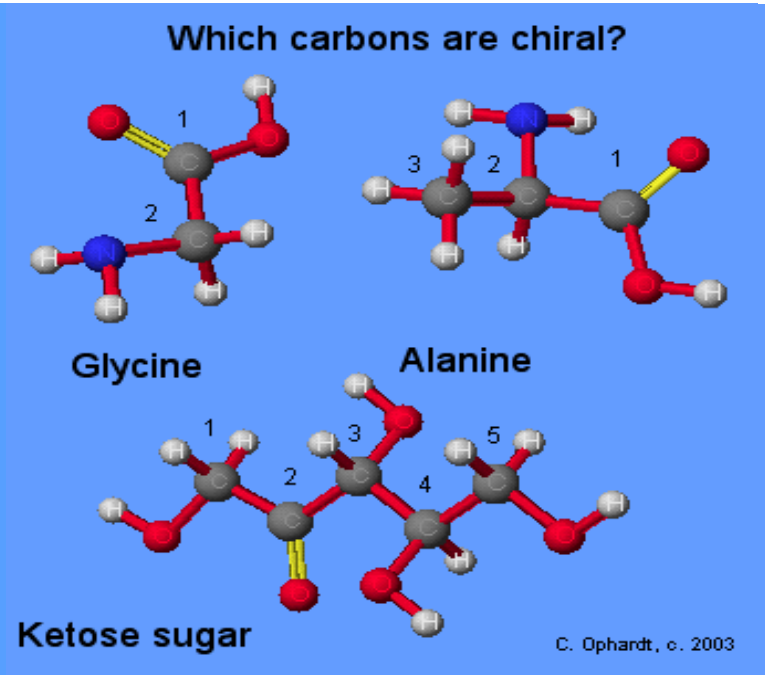


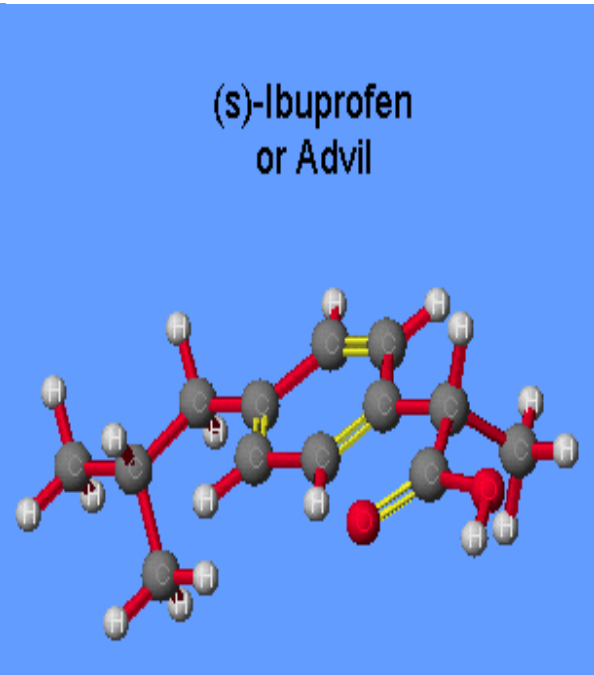


Chirality

- Chiral carbon: four different "groups"
- Chiral carbon in stereoisomers: "stereocenter"
- Achiral means NOT chiral
- The possible number of stereoisomers that we can have is 2^n(where n is the number of chiral carbons)



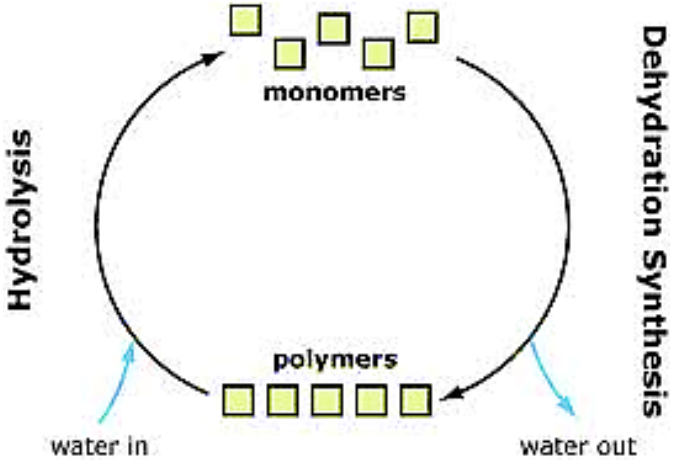




Biomacromolecules

- Subunits: the small building blocks (precursors) used to make macromolecules
- Macromolecules: large molecules made of subunits
  - ✓ Carbohydrates (monosaccharides)
  - ✓ Proteins (amino acids)
  - ✓ Nucleic acids (nucleotides)
  - ✓ Lipids (fatty acids)
- Relationship (monomers and polymers)
- How water is removed?
  1) "H" & "OH"
  2) 2 "H" & "O"

- Except for lipids, these macromolecules are also considered polymers

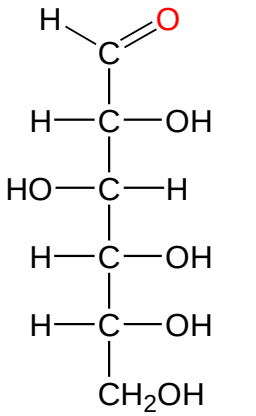


Carbohydrates "Saccharides"

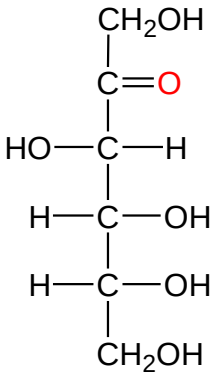
- Carbohydrates: glycans that have the following basic formula (n varies from 3-8)

$(CH_2O)_n$ or $H-\overset{\overset{|}{}}{\underset{\underset{|}{}}{C}}-OH$

- It is a polyhydroxy (aldehyde) or (ketone), or a substance that gives these compounds on hydrolysis



D-glucose



D-fructose

- Monosaccharide: a carbohydrate that cannot be hydrolyzed to a simpler one
- Aldose: a monosaccharide containing an aldehyde group (glyceraldehyde is the simplest)
- Ketose: a monosaccharide containing a ketone group (dihydroxyacetone is the simplest)

Carbohydrates - Functions

1) Major energy source
2) Intermediates in biosynthesis of other basic biochemical structures (fats and proteins)
3) Associated with other structures (vitamins & antibiotics)
4) On cells surfaces: cell–cell interactions & immune recognition, activation of growth factors
5) Structural tissues: polysaccharides (cellulose & bacterial cell walls)

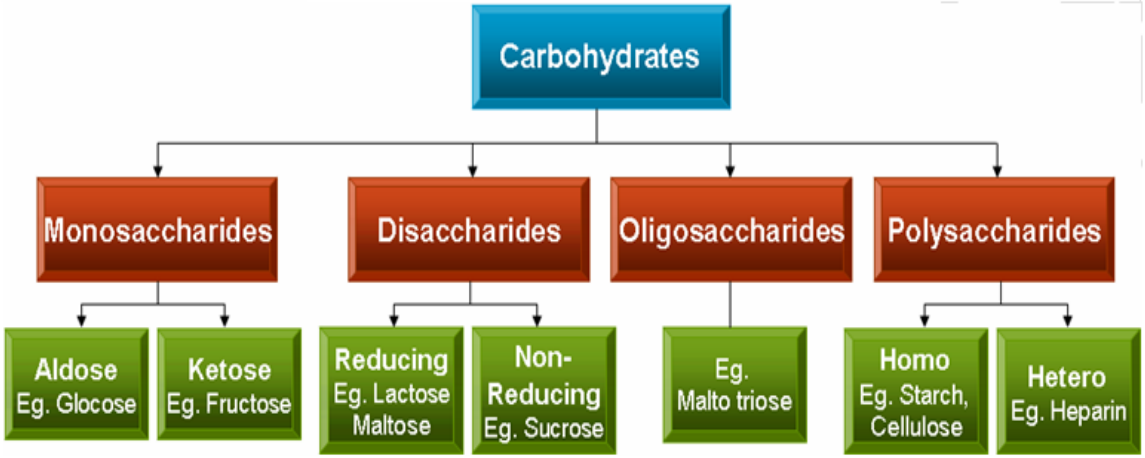
Carbohydrates - Forms

- Monosaccharides – carbohydrates that cannot be hydrolyzed to simpler carbohydrates (glucose & fructose)
- Disaccharides – carbohydrates that can be hydrolyzed into two monosaccharide units (sucrose $\rightarrow$ glucose + fructose)
- Oligosaccharides – carbohydrates that can be hydrolyzed into a few monosaccharide units (fructo-oligosaccharides (FOS), found in many vegetables)
- Polysaccharides – carbohydrates that are polymeric sugars (starch or cellulose)

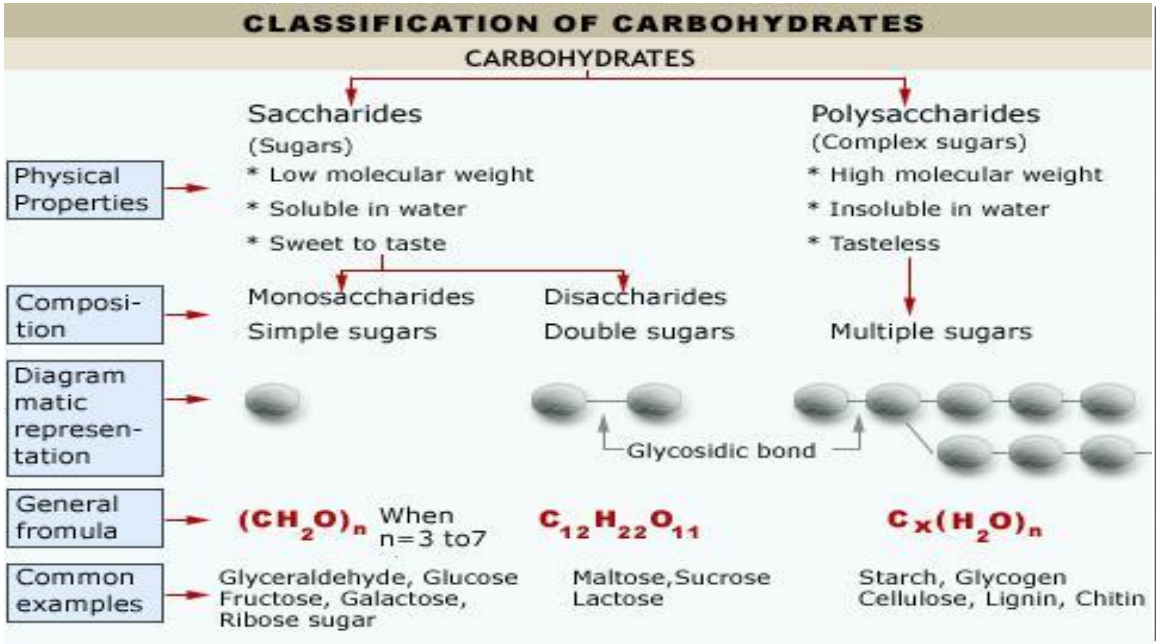
Carbohydrates – natural forms

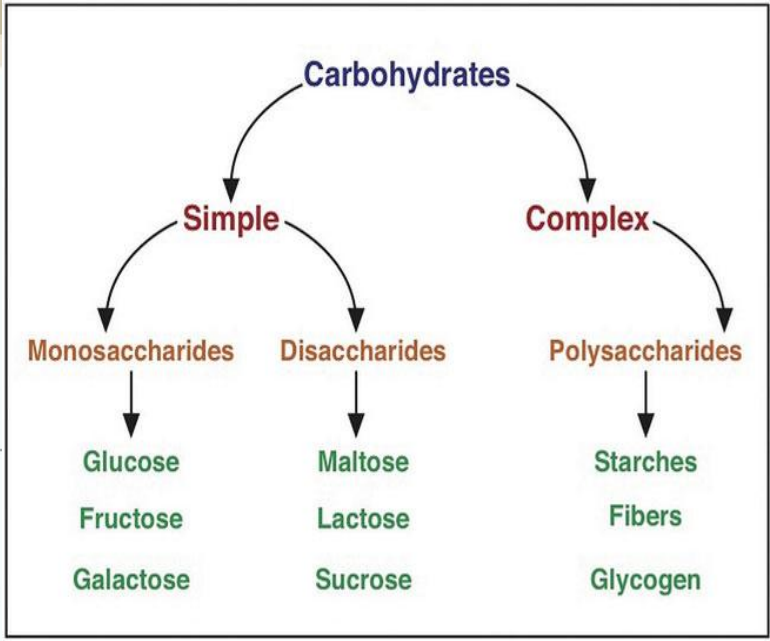
- Most carbohydrates are found naturally in bound form rather than as simple sugars
  - ✓ Polysaccharides (starch, cellulose, inulin, gums)
  - ✓ Glycoproteins and proteoglycans (hormones, blood group substances, antibodies)
  - ✓ Glycolipids (cerebrosides, gangliosides)
  - ✓ Glycosides
  - ✓ Mucopolysaccharides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

Carbohydrates - Classification



Carbon Atoms	General terms	Aldehydes	Ketones
3	Triose	Aldotriose	Keto triose
4	Tetrose	Aldotetrose	Ketotetrose
5	Pentose	Aldopentose	Ketopentose
6	Hexose	Aldohexose	Ketohexose
7	Heptose	Aldoheptose	Ketoheptose

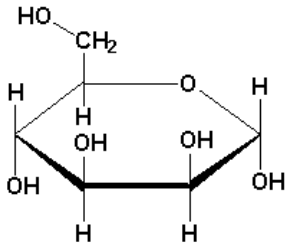




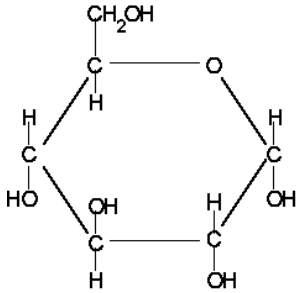
Common Monosaccharides

- Glucose, fructose, galactose, mannose: All are 6 carbon hexoses:
  - 6 Cs, 12 Hs, 6 Os
- Arrangement of groups & atoms differs: varying sweetness

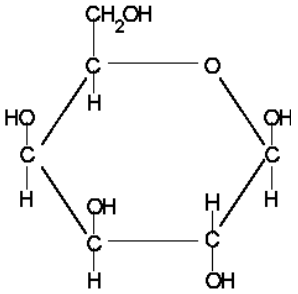
- Glucose:
  - ✓ Mild sweet flavor
  - ✓ Known as blood sugar
  - ✓ Essential energy source
  - ✓ Found in every disaccharide & polysaccharide



Mannose

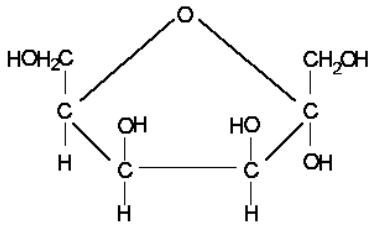


Glucose



Galactose

- Fructose:
  - ✓ Sweetest sugar, found in fruits & honey
  - ✓ Added to soft drinks, cereals, deserts



Fructose

- Galactose:
  - ✓ Hardly tastes sweet & rarely found naturally as a single sugar

Monosaccharides

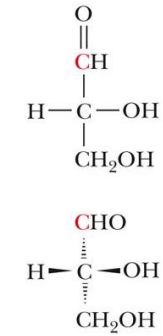
- Monosaccharides are classified by their number of carbon atoms
- Trioses are simplest carbohydrate monosaccharides
- Glyceraldehyde contains a stereocenter & exists as a pair of enantiomers (mirror-images)

1 A comparison of glyceraldehyde (an aldotriose) and dihydroxyacetone (a ketotriose).

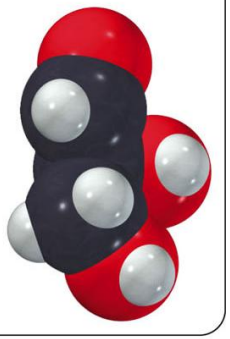
Glyceraldehyde

Dihydroxyacetone

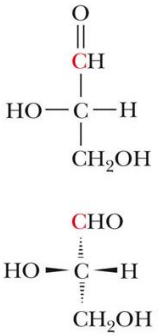
2 The structure of D-glyceraldehyde and a space-filling model of D-glyceraldehyde.



D-Glyceraldehyde



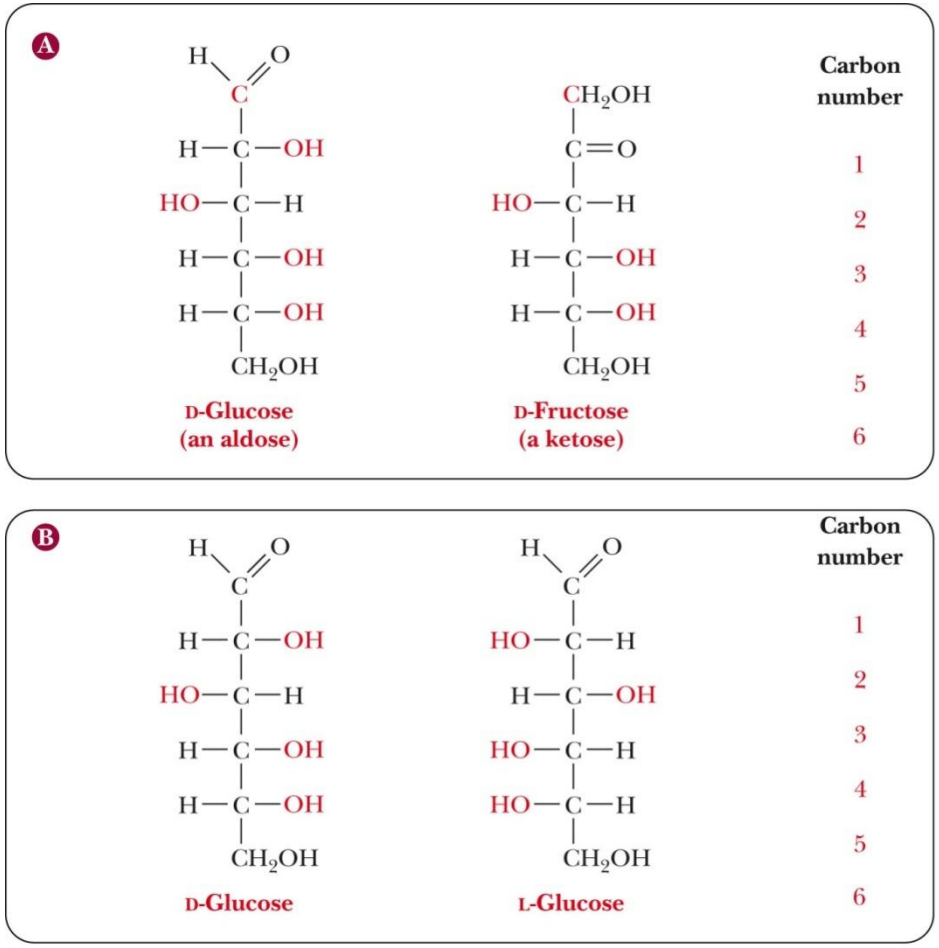
3 The structure of L-glyceraldehyde and a space-filling model of L-glyceraldehyde.



L-Glyceraldehyde

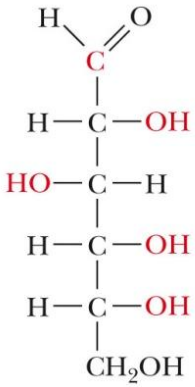
The two dimentional representation Fischer Projections

- **Fischer projection:**
  - ✓ **Bonds are written in a two dimensional representation showing the configuration of tetrahedral stereocenters**
  - ✓ **Horizontal lines represent bonds projecting forward**
  - ✓ **Vertical lines represent bonds projecting to the rear**

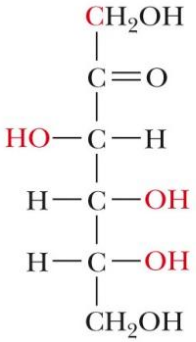


D,L Monosaccharides

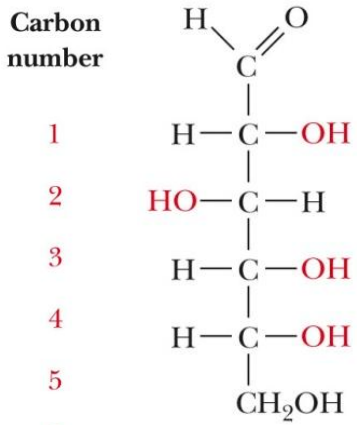
- According to the conventions proposed by Fischer
  - ✓ D-monosaccharide: a monosaccharide that, when written as a Fischer projection, has the -OH on its penultimate carbon on the right
  - ✓ L-monosaccharide: a monosaccharide that, when written as a Fischer projection, has the -OH on its penultimate carbon on the left



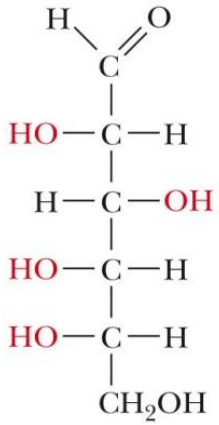
D-Glucose
(an aldose)



D-Fructose
(a ketose)



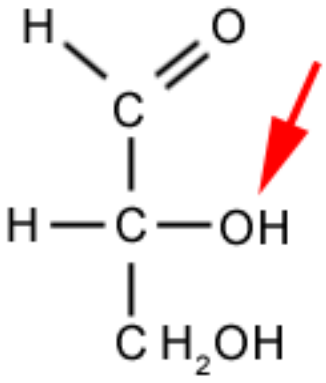
D-Glucose



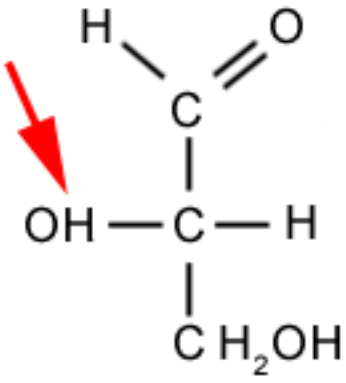
L-Glucose

Trioses

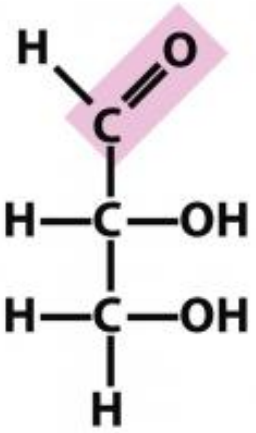
- The simplest aldose & ketose
- Three carbon units
- D & L isomers



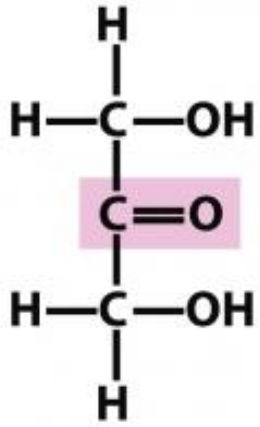
D-Glyceraldehyde



L-Glyceraldehyde



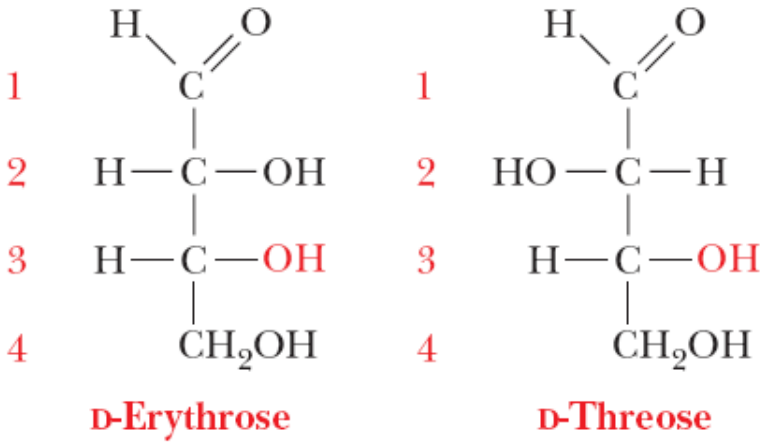
Glyceraldehyde, an aldotriose

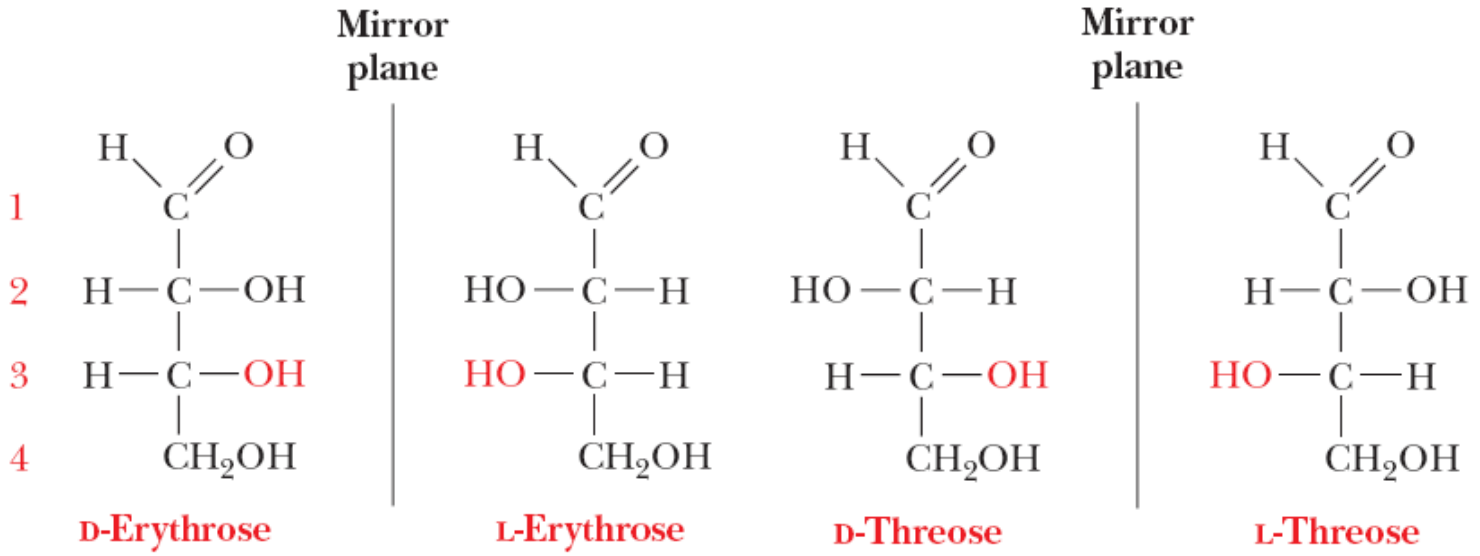


Dihydroxyacetone, a ketotriose

Aldotetroses

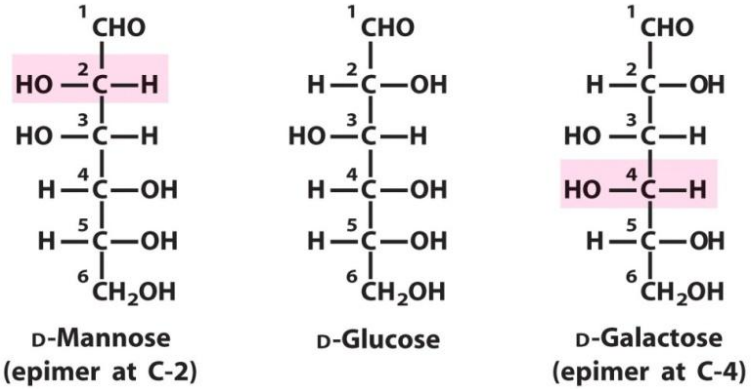
- D-erythrose & L-erythrose (enantiomers)
- D-erythrose & D-threose (diastereomers)



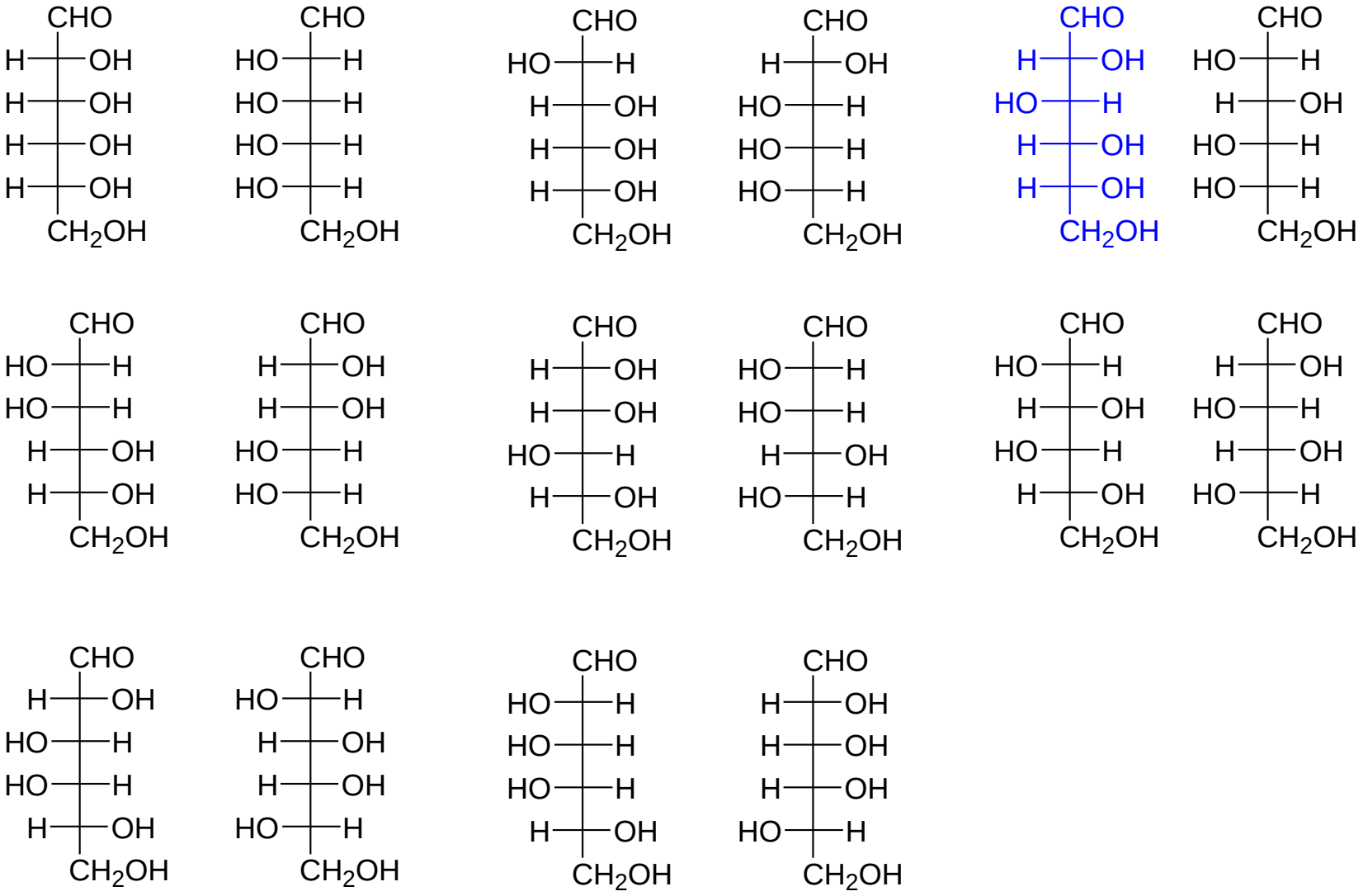


Pentoses & Hexoses

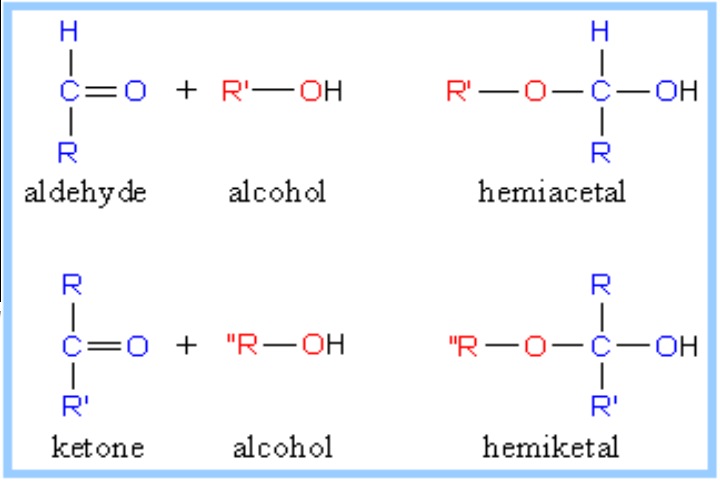
- Most of the sugars we encounter in nature, especially in foods, contain either five or six carbon atoms (glucose, mannose, galactose). Epimers
- Aldopentoses & Aldohexoses (how many chiral carbons? How many stereoisomers?)
- Some stereoisomers are much more common in nature
  - D sugars predominate in nature: e.g. in living organisms, only D-ribose & D-deoxyribose are found in RNA and DNA, respectively



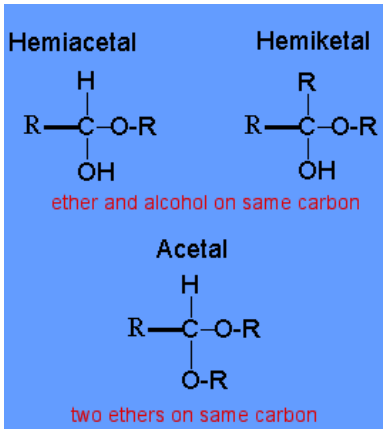
Glucose Isomers

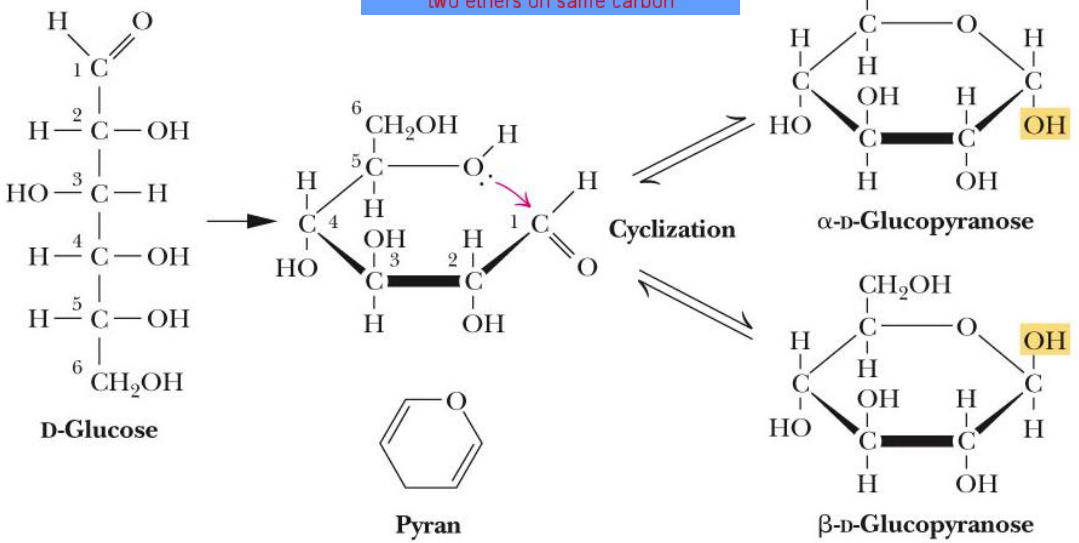


Cyclization of sugars



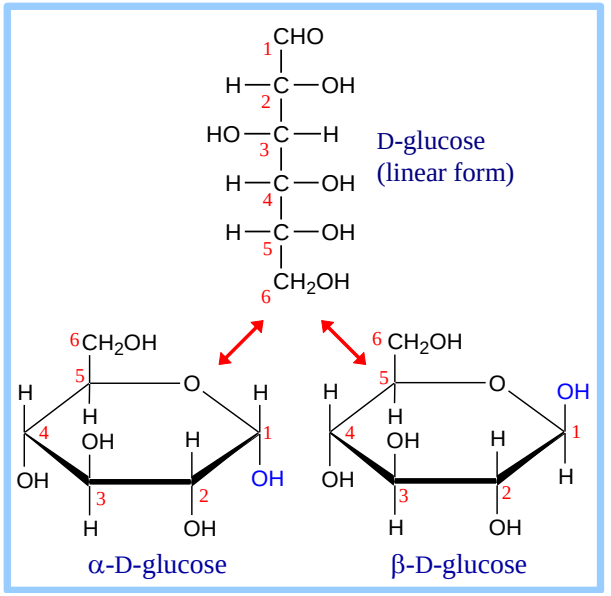
- Cyclization of sugars takes place due to interaction between functional groups on distant carbons, C1 to C5, to make a cyclic hemiacetal
- Cyclization using C2 to C5 results in hemiketal formation
- In both cases, the carbonyl carbon is new chiral center and becomes an anomeric carbon
- Anomers: differ only at their anomeric carbon, either α or β

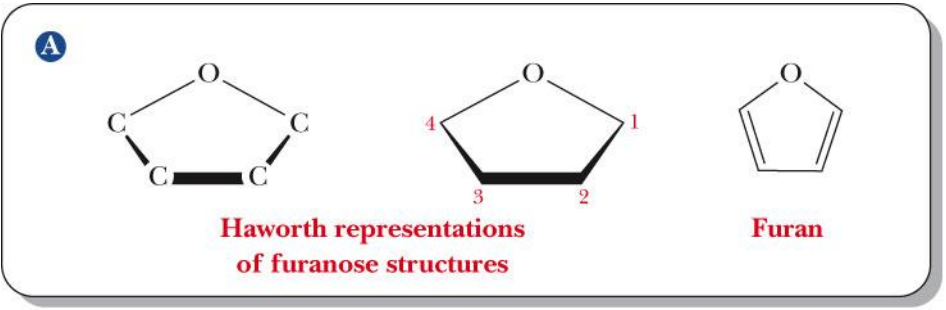


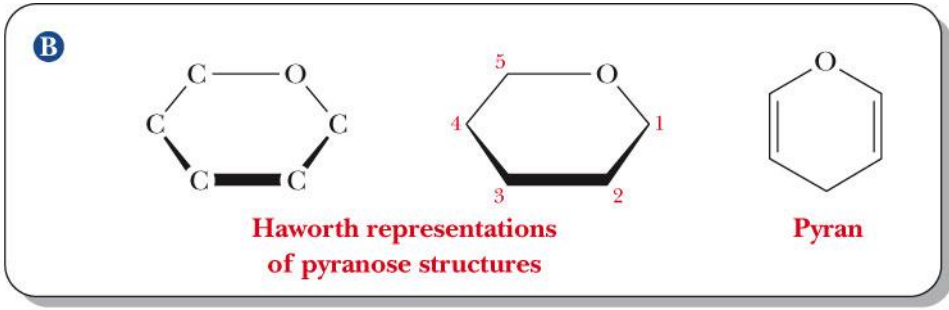


Haworth Projections

- Haworth projections
  - ✓ Five- & six-membered hemiacetals/ketals are represented as planar pentagons or hexagons
  - ✓ Most commonly written with the anomeric carbon on right & hemiacetal/ketal oxygen to the back right
  - ✓ The designation β- means that anomeric carbon -OH is cis to the terminal -CH_2OH; α- means that it is trans

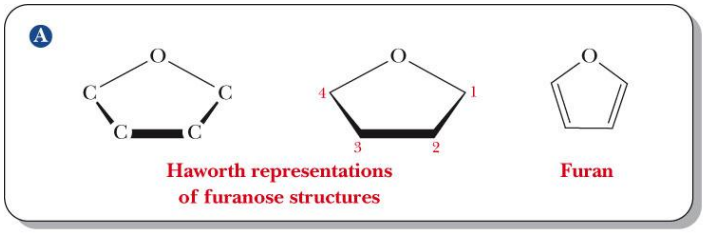


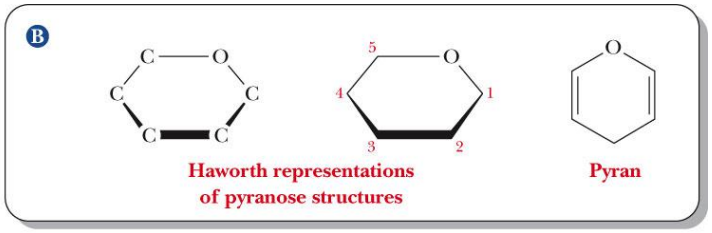


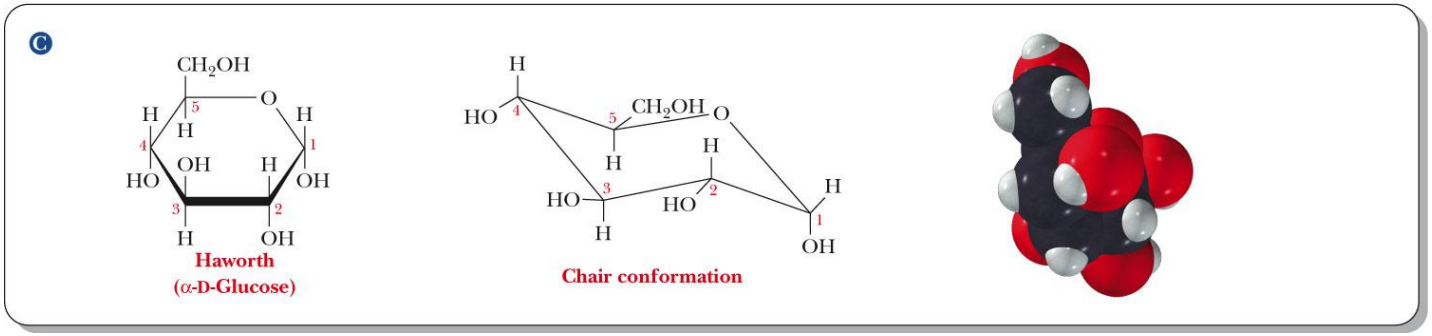


Haworth Projections (Cont'd)

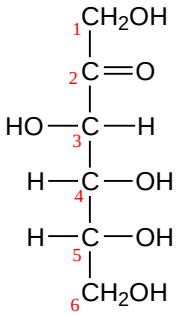
- ✓ A six-membered hemiacetal ring is called pyranose
- ✓ A five-membered hemiacetal ring is called furanose
- ✓ Five-membered rings are so close to being planar that Haworth projections are adequate to represent furanoses
- ✓ For pyranoses, the six-membered ring is more accurately represented as a strain-free chair conformation



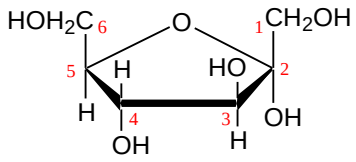




Haworth Projections (Cont'd)

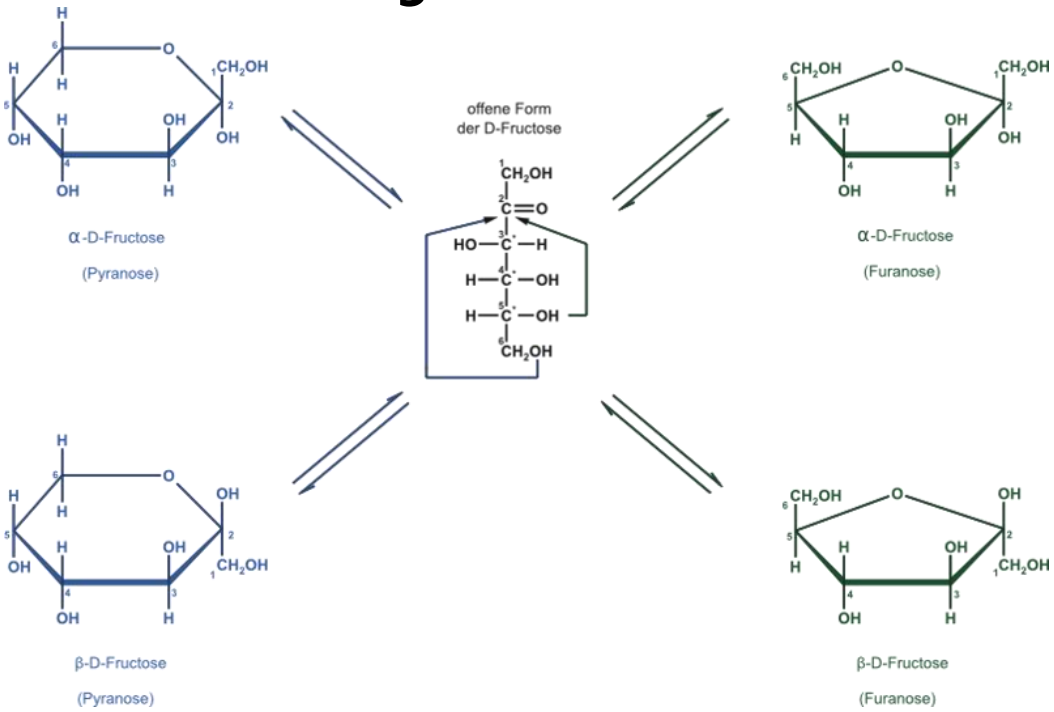


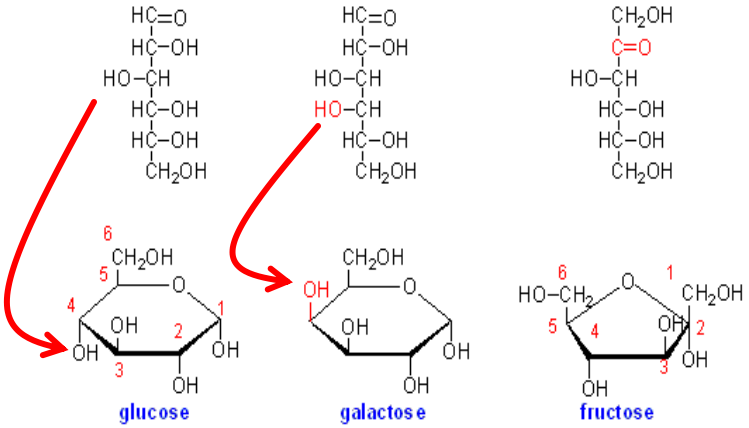
D-fructose (linear)



α-D-fructofuranose

- Fructose forms either
  - ✓ a 6-member pyranose ring, by reaction of the C2 keto group with the OH on C6, or
  - ✓ a 5-member furanose ring, by reaction of the C2 keto group with the OH on C5

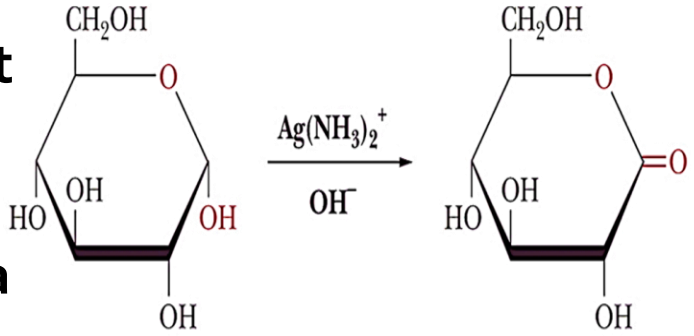




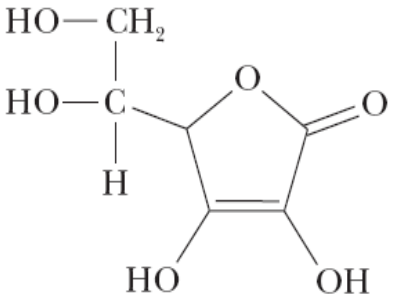
Modified Sugars

Reaction of Monosaccharides Reducing Sugars - Oxidation

- Oxidation-reduction reactions: energy metabolism vs. photosynthesis
- Reducing sugar (oxidation process): one that reduces an oxidizing agent (aldoses)
- Oxidation of a cyclic hemiacetal form gives a lactone



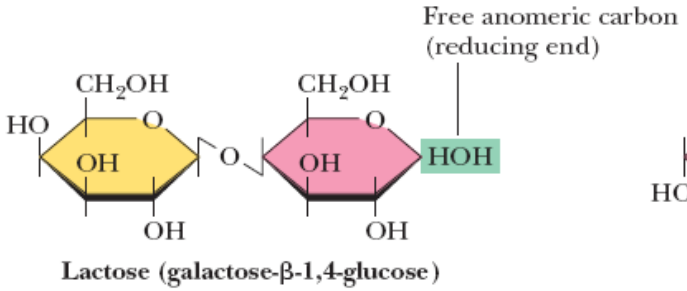
- Vitamin C (ascorbic acid) is an unsaturated lactone
- Air oxidation followed by hydrolysis of the ester bond, leads to loss of activity
- A lack of fresh food can cause vitamin C deficiencies, which, in turn, can lead to the disease scurvy



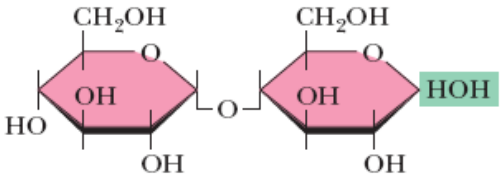
Ascorbic acid
(Vitamin C)

Reducing Sugars – monosaccharides & Disaccharides

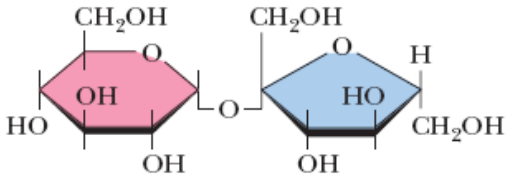
- The presence of free anomeric carbon
- Reducing vs. non-reducing sugars (all monosaccharides, aldoses & ketoses). Also, most disaccharides (sucrose?)
- Oxidation of ketoses to carboxylic acids does not occur



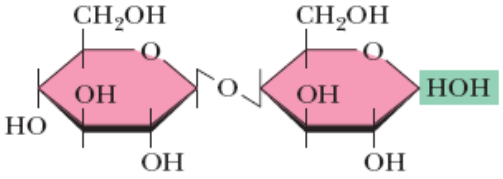
Lactose (galactose-β-1,4-glucose)



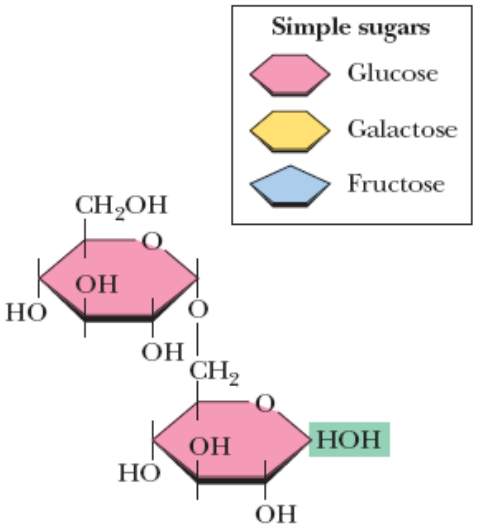
Maltose (glucose-α-1,4-glucose)



Sucrose (glucose-α-1,2-fructose)



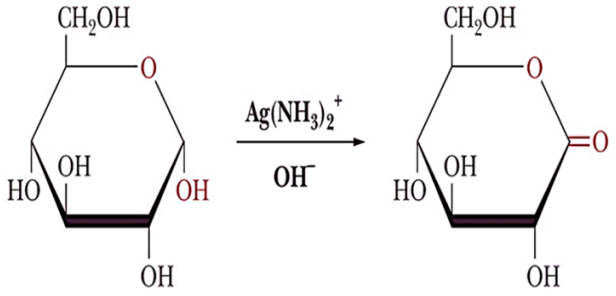
Cellobiose (glucose-β-1,4-glucose)



Isomaltose (glucose-α-1,6-glucose)

Tests for reducing sugars

1) Tollen's solution (oxidizing agent); silver ammonia complex ion, $Ag(NH_3)^{2+}$:



- ✓ Silver precipitates as a silver mirror

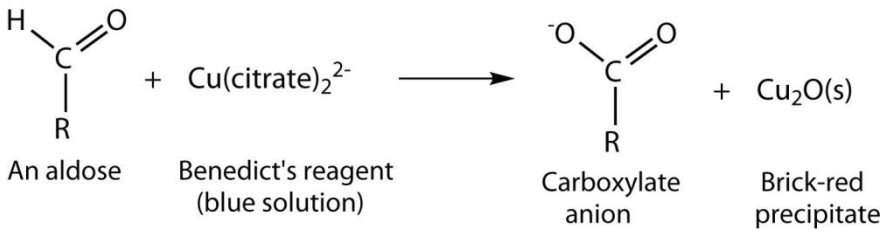
- ✓ If anomeric carbons are involved in glycosidic linkage, there will be a negative Tollen's reagent test

2) Glucose oxidase: <u>specific for glucose</u>, but not other reducing sugars

- Based on the use of the enzyme glucose oxidase

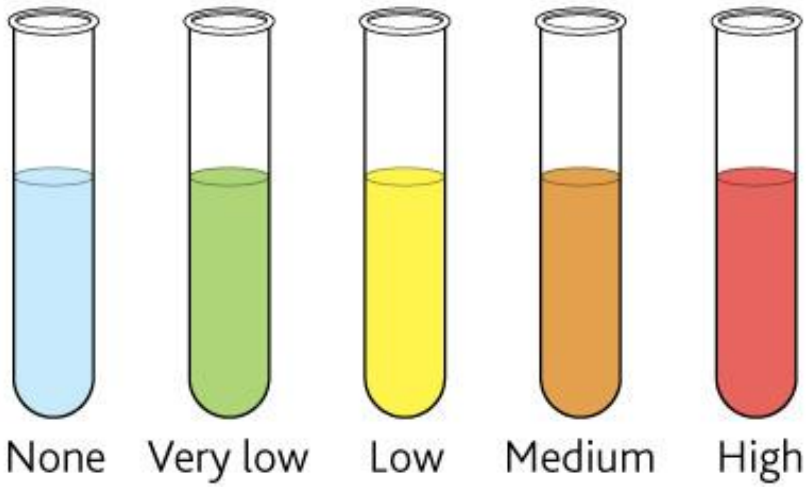
Tests for reducing sugars

3) **Benedict's reagent:**



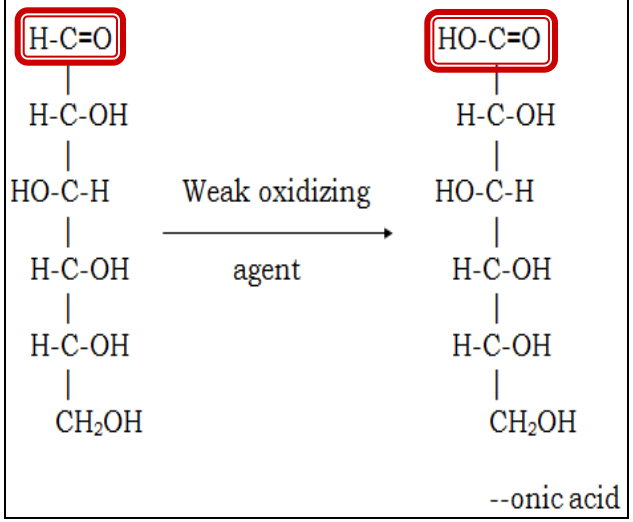
- **A positive test is shown by a color change:**
  - **Clear blue ⟶ brick-red (precipitate)**

- **Greenish: 0.5%**
- **Yellowish: 1%**
- **Orange: 1.5%**
- **Red: 2% or higher concentration**



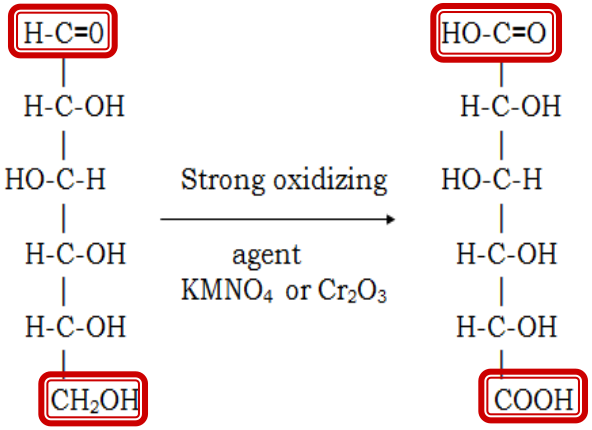
Reaction of Monosaccharides Oxidation

a. Weak oxidizing agent

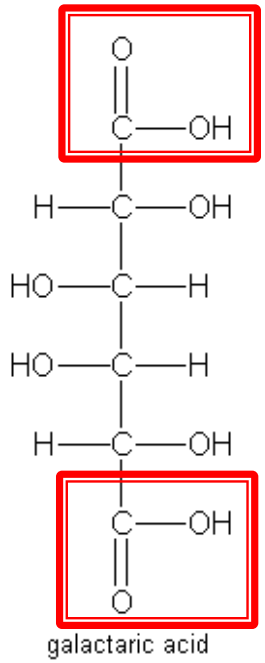


--onic acid

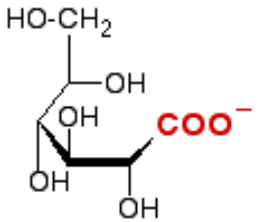
b. Strong oxidizing agents



-aric acid
A dicarboxylic acid

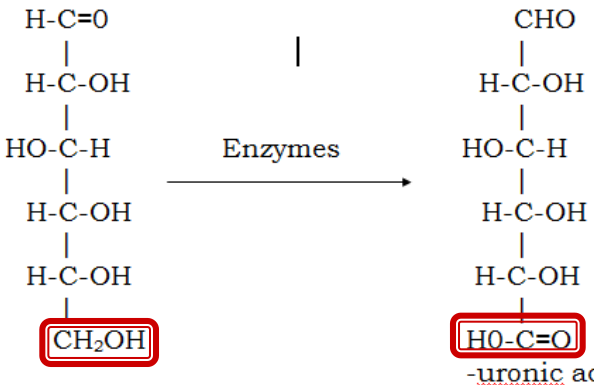


galactaric acid

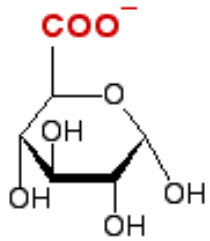


D-gluconate
(D-gluconic acid, **GlcA**)
from **oxidation of glucose C1 aldehyde)**

c. Oxidation of primary alcohol end in biological systems



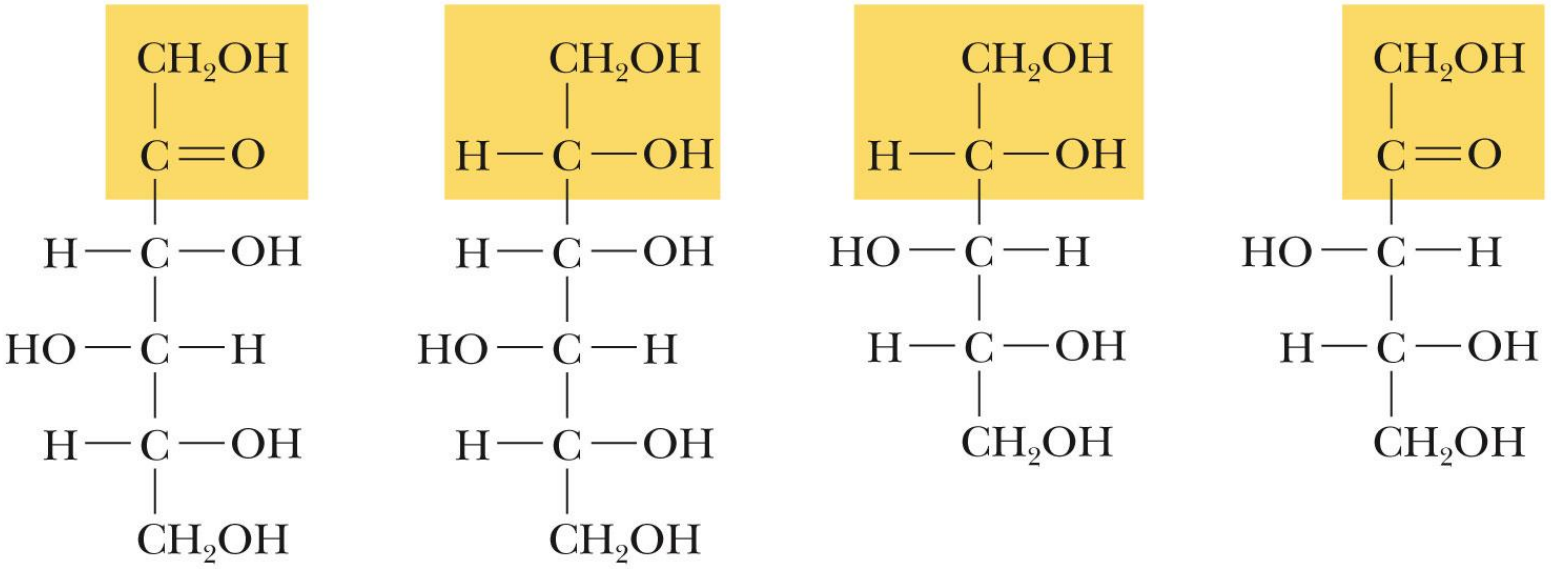
-uronic acids



α-D-glucuronate
(D-glucuronic acid, **GlcUA**)
from **oxidation of glucose C6 OH**

Reaction of Monosaccharides Reduction

1) **Reduction of the carbonyl group to a hydroxyl group by a variety of reducing agents (eg. $NaBH_4$)**
   - **The product is a polyhydroxy compound called an <u>alditol</u>**
   - **<u>Xylitol & sorbitol</u>: derivatives of xylulose & sorbose, have commercial importance (sweeteners in sugarless chewing gum & candy)**

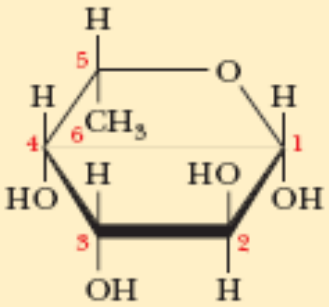


Reaction of Monosaccharides Reduction

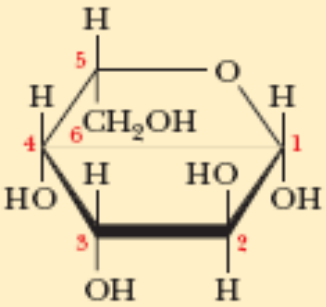
2) Deoxy sugars, a hydrogen atom is substituted for one of the hydroxyl groups of the sugar

- L-fucose (L-6-deoxygalactose): some glycoproteins including the ABO blood-group antigens

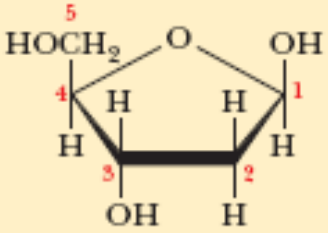
- D-2-deoxyribose: in DNA



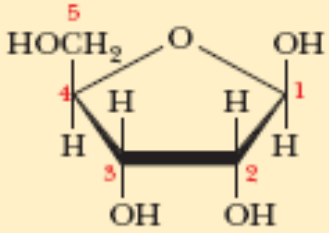
β-L-Fucose
(6-Deoxy-β-L-galactose)



β-L-Galactose

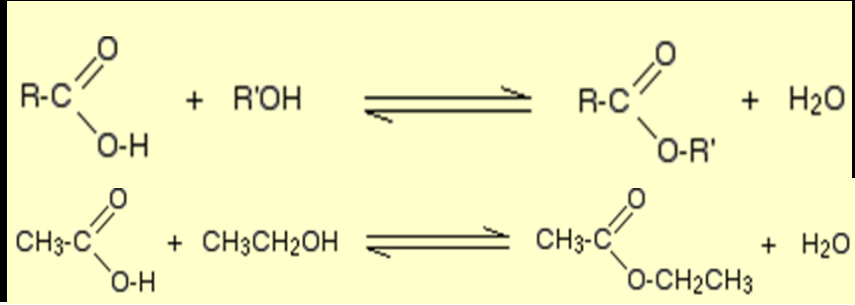


β-D-Deoxyribose
(2-Deoxy-β-D-ribose)

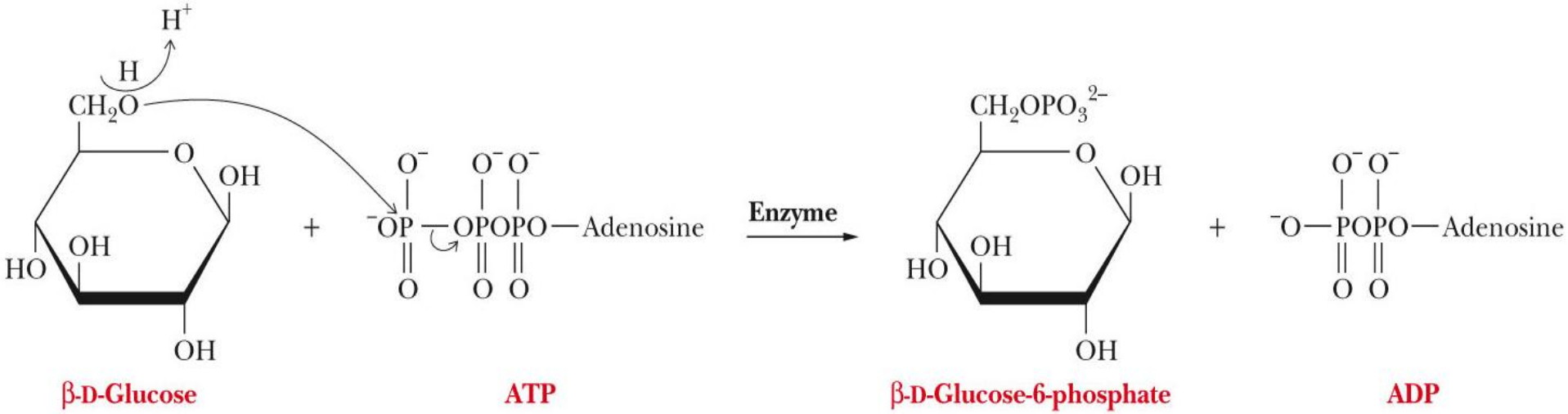


β-D-Ribose

Esterification - Phosphoric Esters



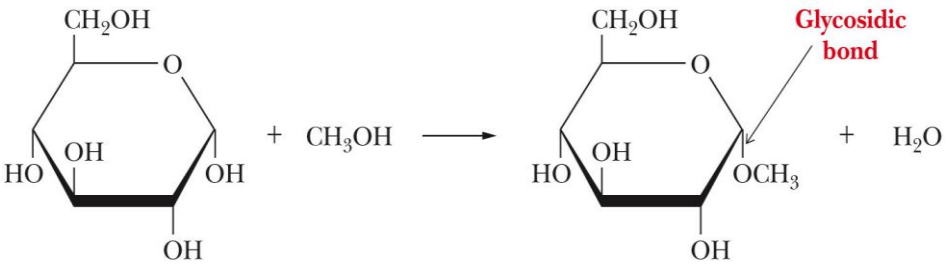
- Hydroxyl groups behave exactly like alcohols;
  - React with acids & acid derivatives to form esters
- Phosphate esters: particularly important (the usual intermediates in breakdown of carbohydrates to provide energy)
- ATP: the most common donor

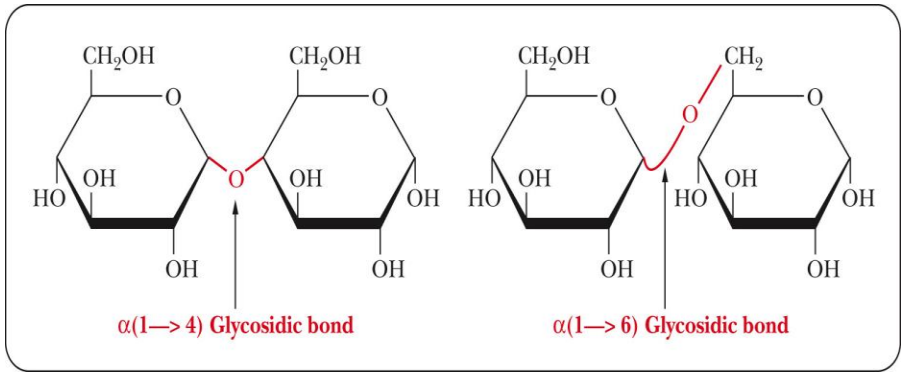


Glycosidic Bond Formation
Formation of full acetal

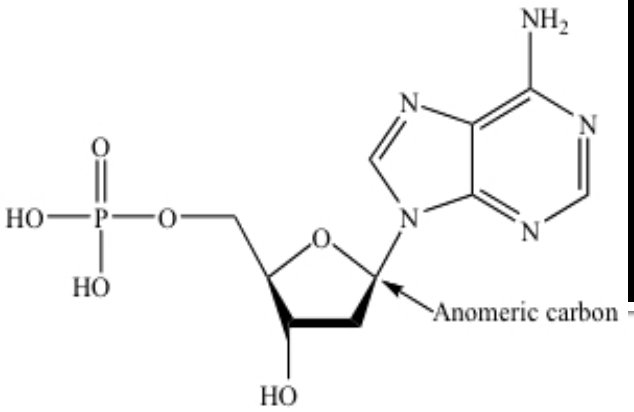
- Glycoside: the -OH of the anomeric carbon is replaced by –OR
- Glycosidic bond: bond from the anomeric carbon to the -OR group

- Involves the anomeric carbon of the sugar in its cyclic form
  - ✓ Derived from furanoses: furanosides
  - ✓ Derived from pyranoses: pyranosides
- The basis for the formation of (di/oligo/poly)saccharides
- Nature of them depends on types & linkages (Two Different Disaccharides of α-D-Glucose)



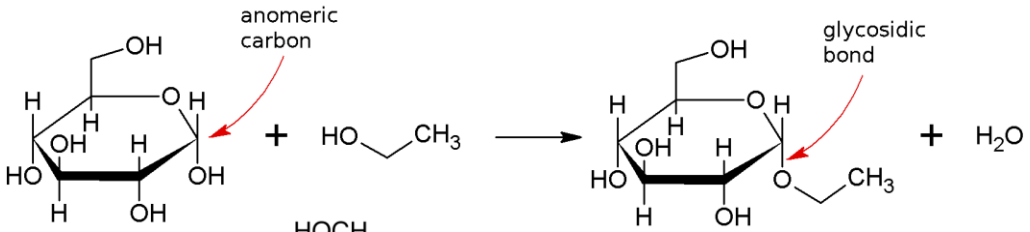


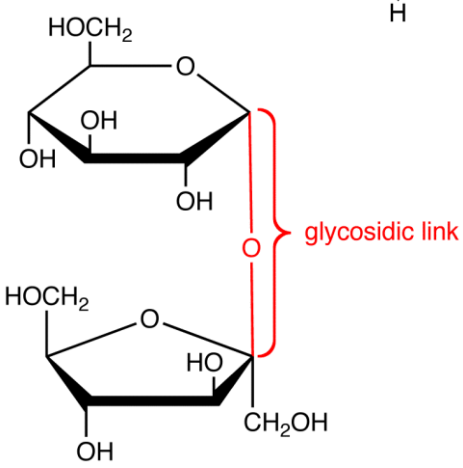
Glycosidic Bond Formation



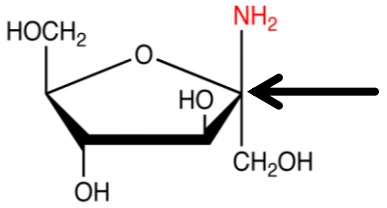
- Glycosides can be linked by:

1) O- (an O-glycoside)





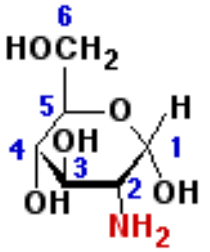
2) N- (a glycosylamine)



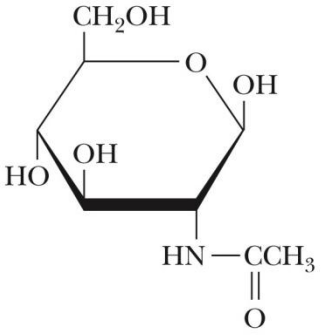
Anomeric carbon

N-glycoside

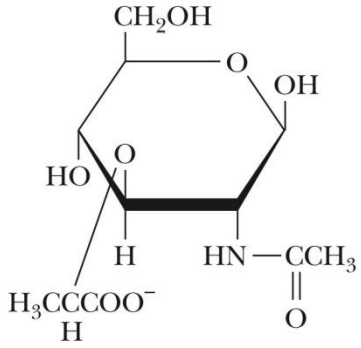
5) Amino sugars



α-D-2-glucosamine (GlcN)



N-Acetyl-β-D-glucosamine



N-Acetylmuramic acid

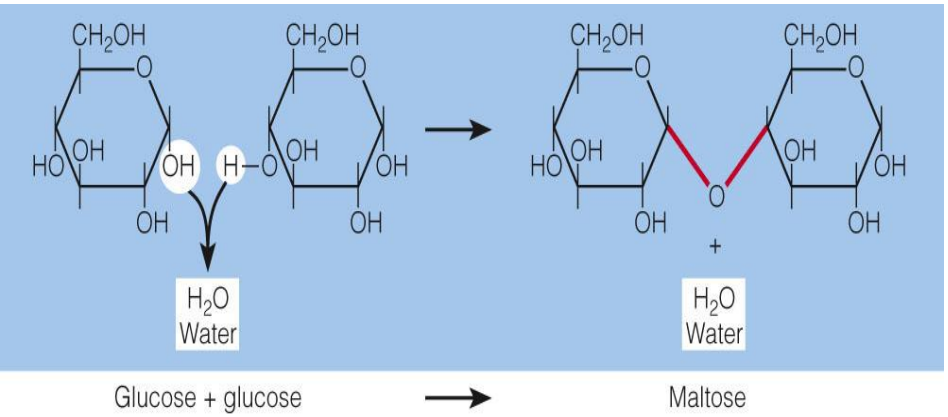
3) S-(a thioglycoside)

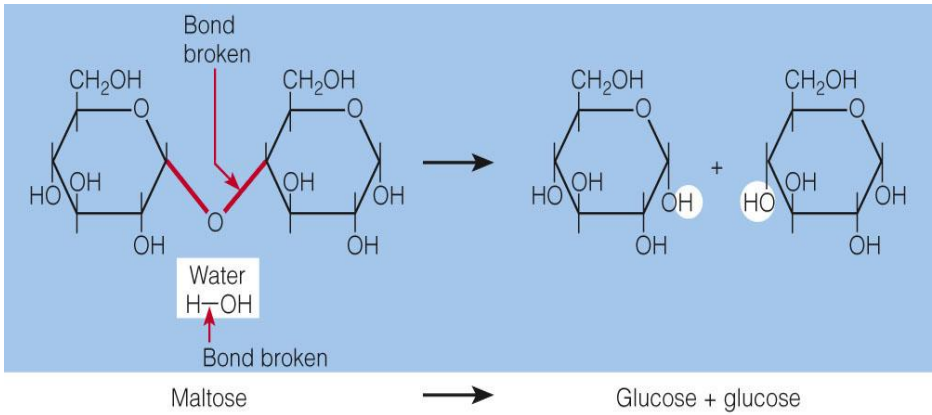
4) C- (a C-glycoside)

Disaccharides

Disaccharides

- Pairs of monosaccharides (always glucose)
- Condensation reactions & Hydrolysis reactions
- Maltose is produced during fermentation
- Sucrose is refined from sugarcane, tastes sweet, and is readily available
- Lactose is found in milk & milk products





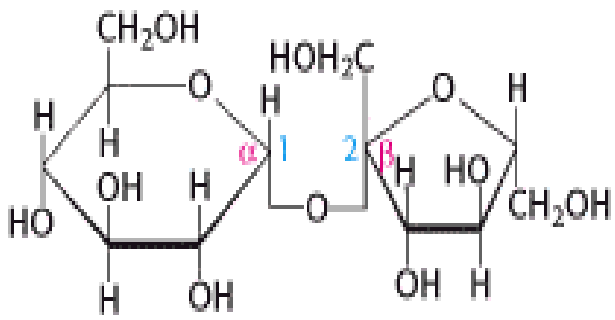
Disaccharides

- Naming (common vs. systematic)
- Reducing vs. non-reducing

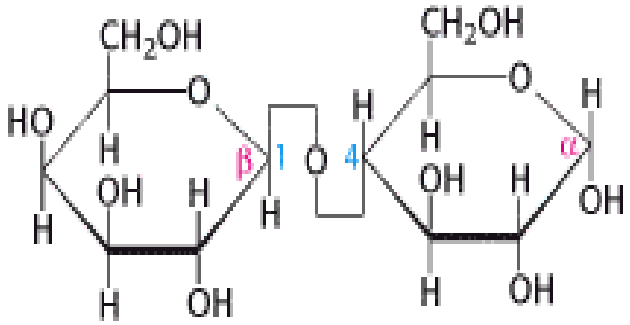
- Sucrose
  - ✓ Table sugar: D-glucose & D-fructose (α-1,2-glycosidic bond)

- Lactose
  - ✓ D-galactose & D-glucose (β-1,4-glycosidic bond). Galactose is a C-4 epimer of glucose

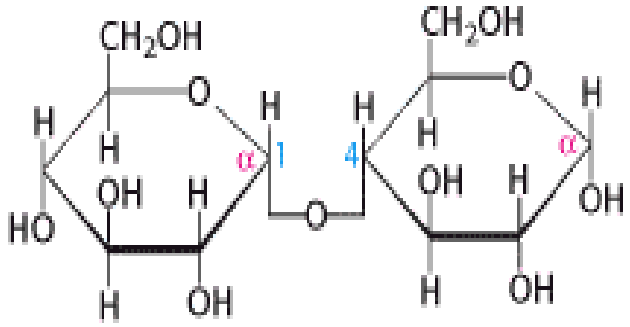
- Maltose
  - ✓ Two units of D-glucose (α-1,4-glycosidic bond)
  - ✓ Formed from the hydrolysis of starch



Sucrose
(α-D-Glucopyranosyl-(1→2)-β-D-fructofuranose



Lactose
(β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose

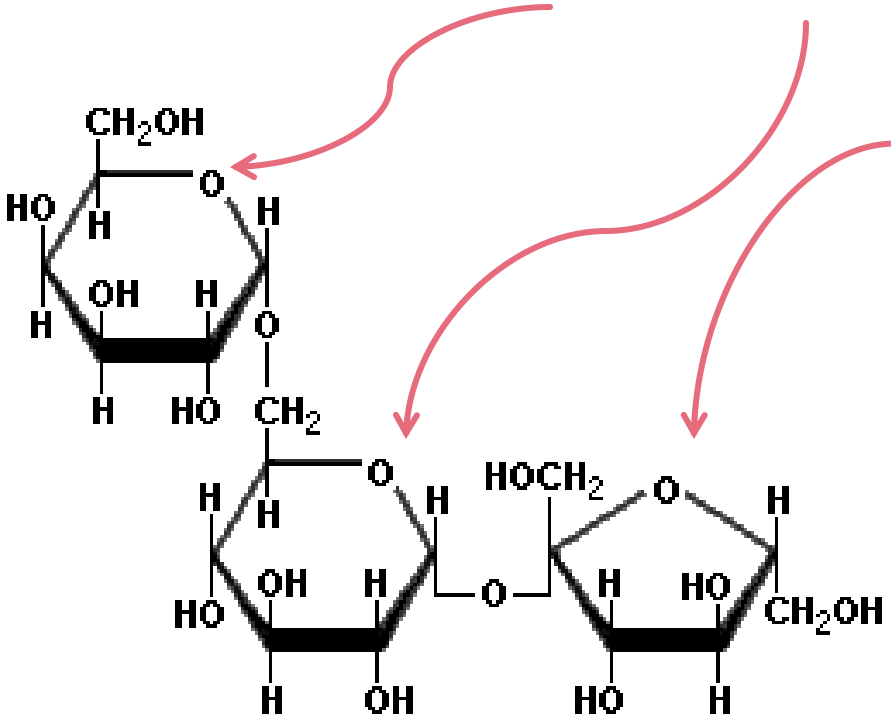


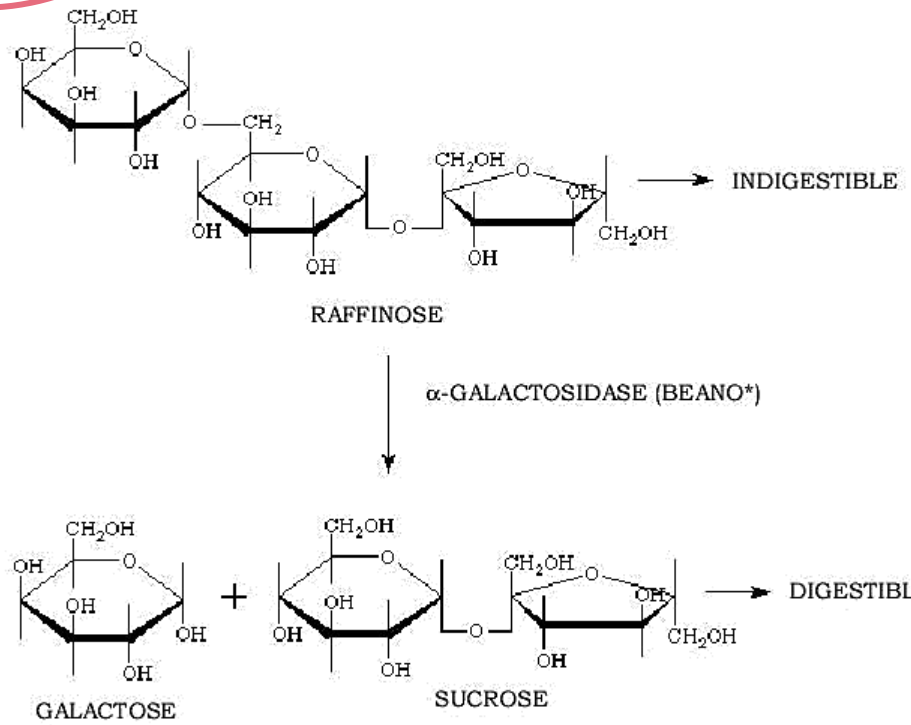
Maltose
(α-D-Glucopyranosyl-(1→4)-α-D-glucopyranose

Oligosaccharides

Oligosaccharides

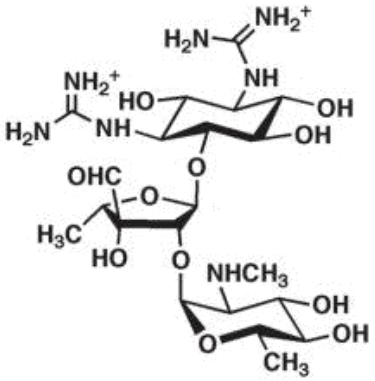
- Raffinose; plenty in peas and beans
- Composed of galactose, glucose & fructose



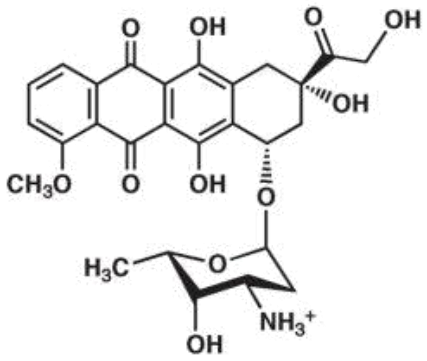


Oligosaccharides

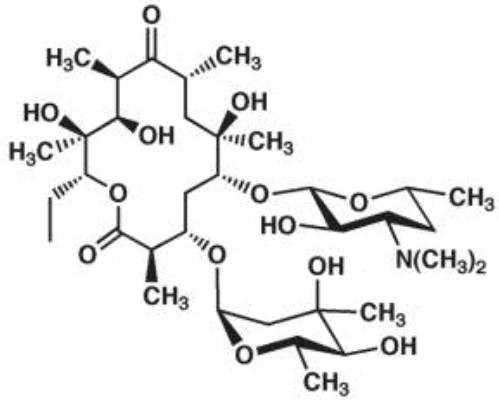
- **Oligosaccharides as drugs:**
  - **Streptomycin and erythromycin (antibiotics)**
  - **Doxorubicin (cancer chemotherapy)**
  - **Digoxin (cardiovascular disease)**



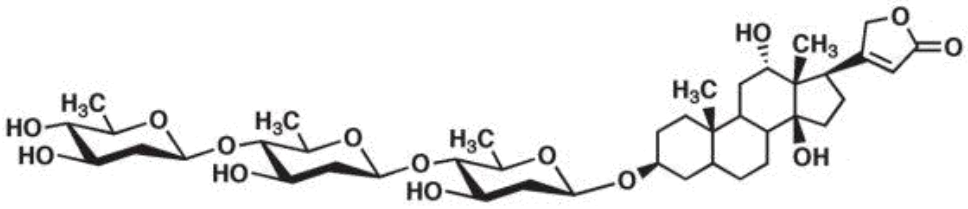
Streptomycin



Doxorubicin



Erythromycin A



Digoxin

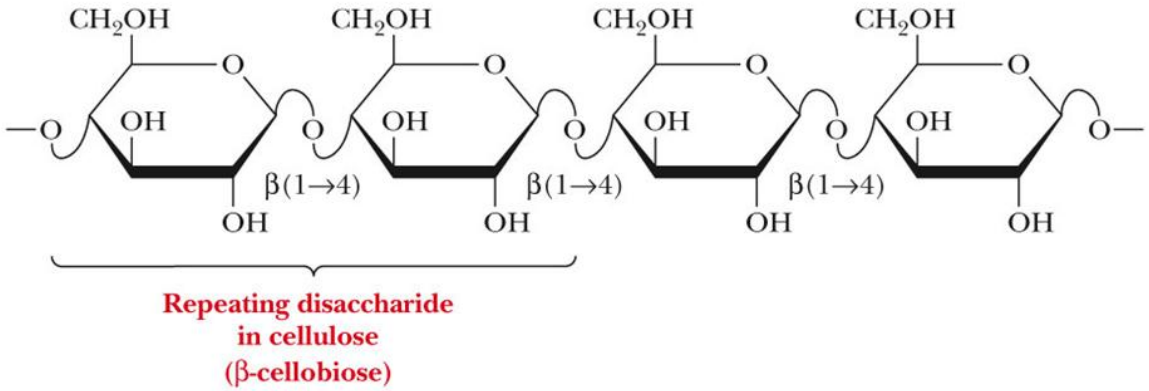
Polysaccharides

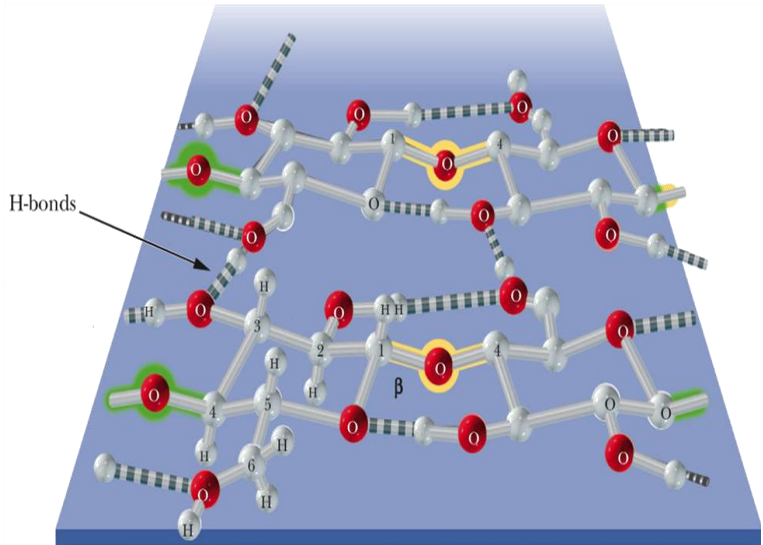
Structures and Function of Polysaccharides

- Polysaccharides:
  - ✓ Homopolysaccharide (most common)
  - ✓ Heteropolysaccharide (di- in a repeating sequence)
- Glucose is the most common monomer
- Complete characterization of a polysaccharide: monomers, sequence & type of glycosidic linkage
- Cellulose & chitin: β-glycosidic linkages; structural materials
- Starch & glycogen: α-glycosidic linkages; storage polymers in plants & animals, respectively

Cellulose

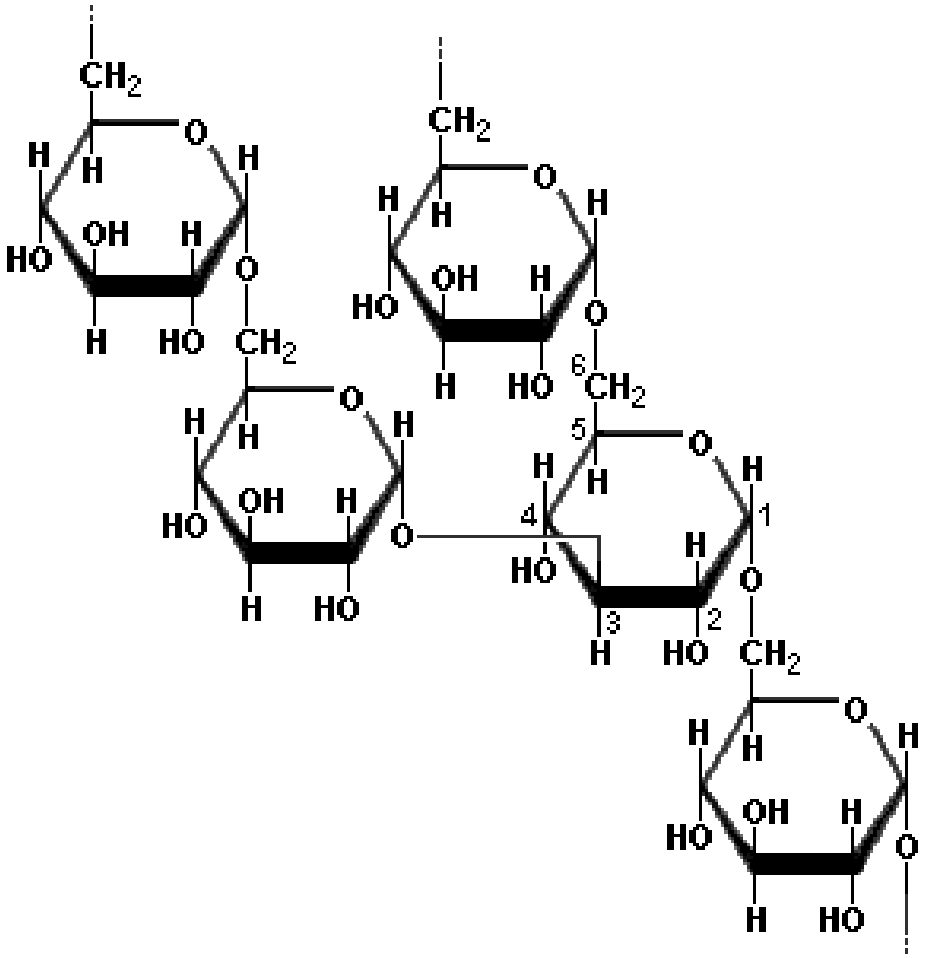
- Major structural component of plants, especially wood and plant fibers
- A linear polymer (≈ 2800 D-glucose units per molecule)
- β-1,4-glycosidic bonds
- Extensive intra- & inter-molecular hydrogen bonding between chains
- Cellulases, animals?



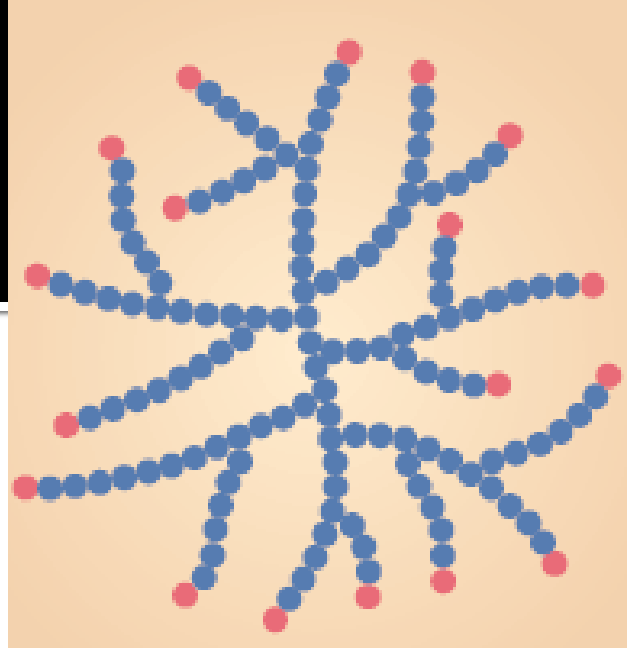


Dextran

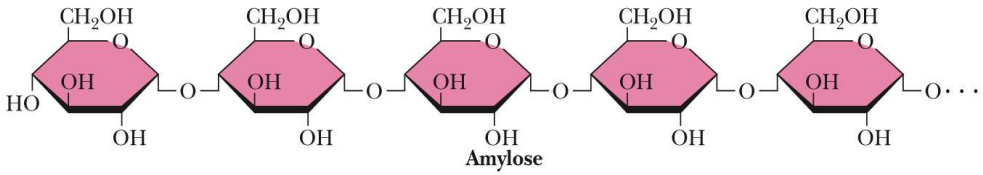
- Yeast & bacteria
- A storage polysaccharide
- α-(1-6)-D-glucose with branched chains
- Branches: 1-2, 1-3, or 1-4



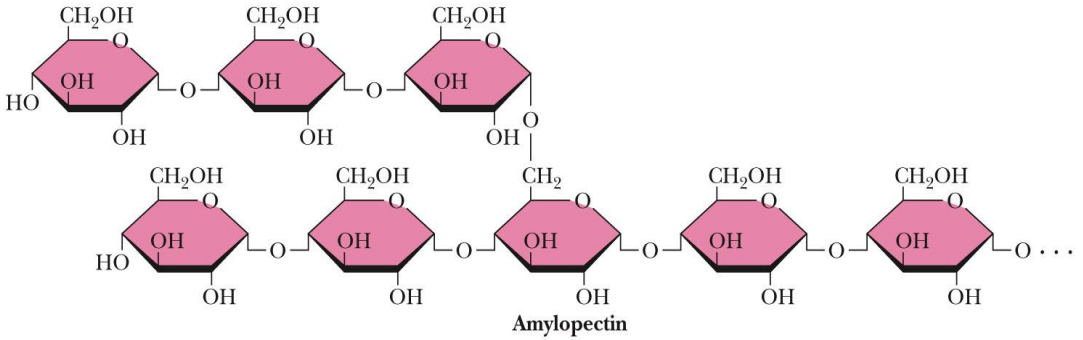
Starch



- Energy storage in plants
- A polymers of α-D-glucose units
- A mylose:
  - Continuous, unbranched chains
  - Up to 4000 α-D-glucose units
  - α-1,4-glycosidic bonds



- Amylopectin:
  - Highly branched polymer
  - 24-30 units of D-glucose
  - α-1,4-glycosidic bonds & branches created by α-1,6-glycosidic bonds

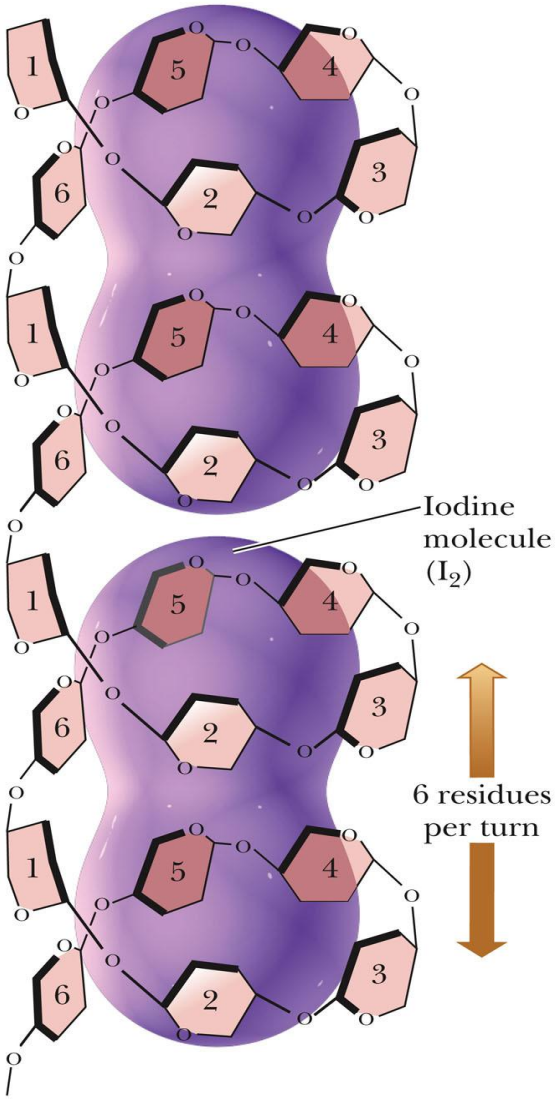


Starch

- Amylases catalyze hydrolysis of α-1,4-glycosidic bonds
- β-amylase is an exoglycosidase and cleaves from the non-reducing end of the polymer
- α-amylase is an endoglycosidase and hydrolyzes glycosidic linkages anywhere along the chain to produce glucose and maltose
- Can amylose & amylopectin be completely degraded to glucose and maltose by the two amylases?
- Debranching enzymes catalyze the hydrolysis of α-1,6-glycosidic bonds

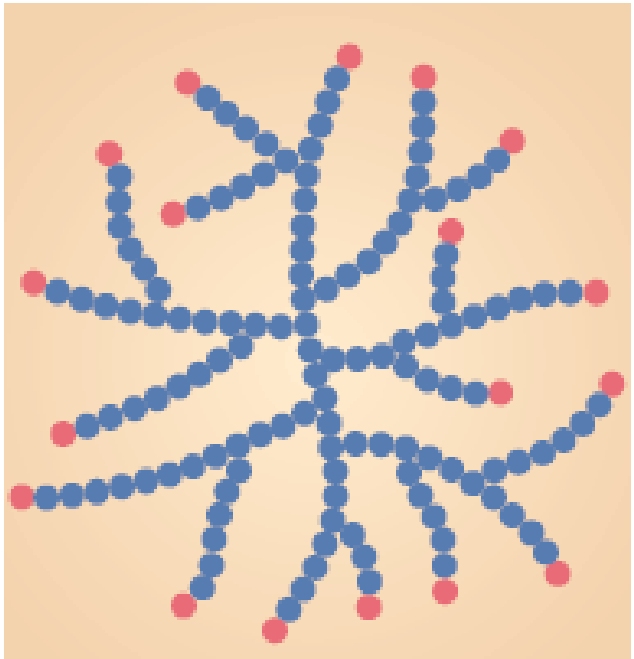
Iodine can Fit Inside Amylose to Form Starch-Iodine Complex

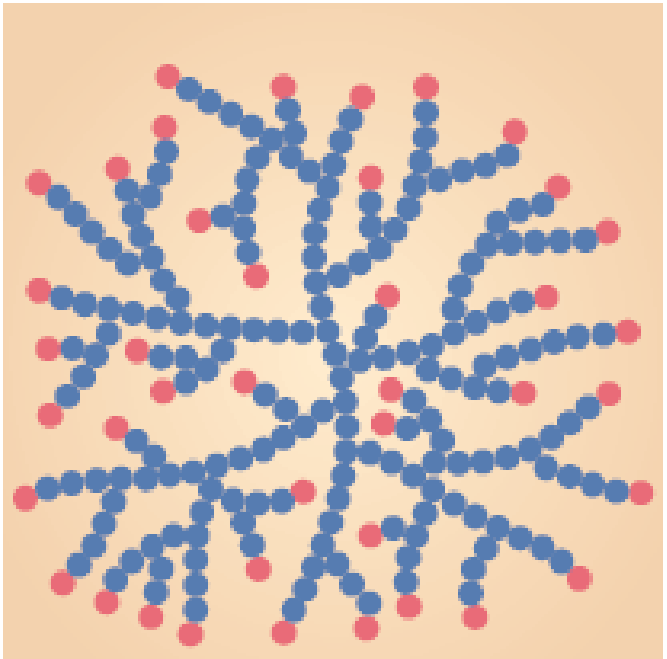
- Amylose occurs as a helix with six residues per turn
- Iodine molecules can fit parallel to the long axis of the helix
- Six turns of the helix, containing 36 glycosyl residues:
  - Required to produce the characteristic blue color of the complex



Glycogen

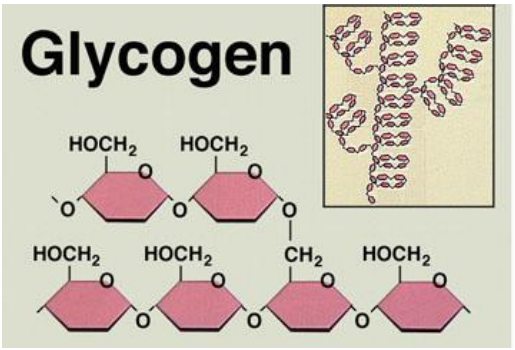
- A branched-chain polymer of α-D-glucose (amylopectin)
- A chain of α(1 → 4) linkages with α(1 → 6) linkages
- Glycogen is more highly branched (≈ 10 residues)
- The average chain length is 13 glucose residues
- At the heart of every glycogen molecule is a protein called Glycogenin

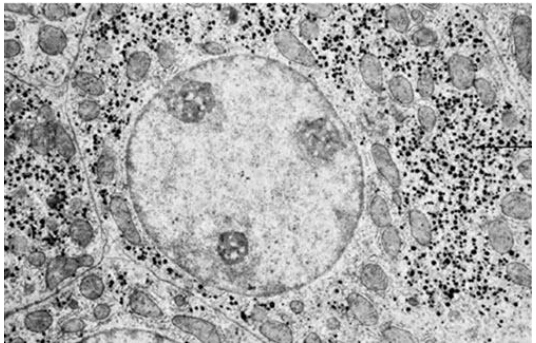




Glycogen

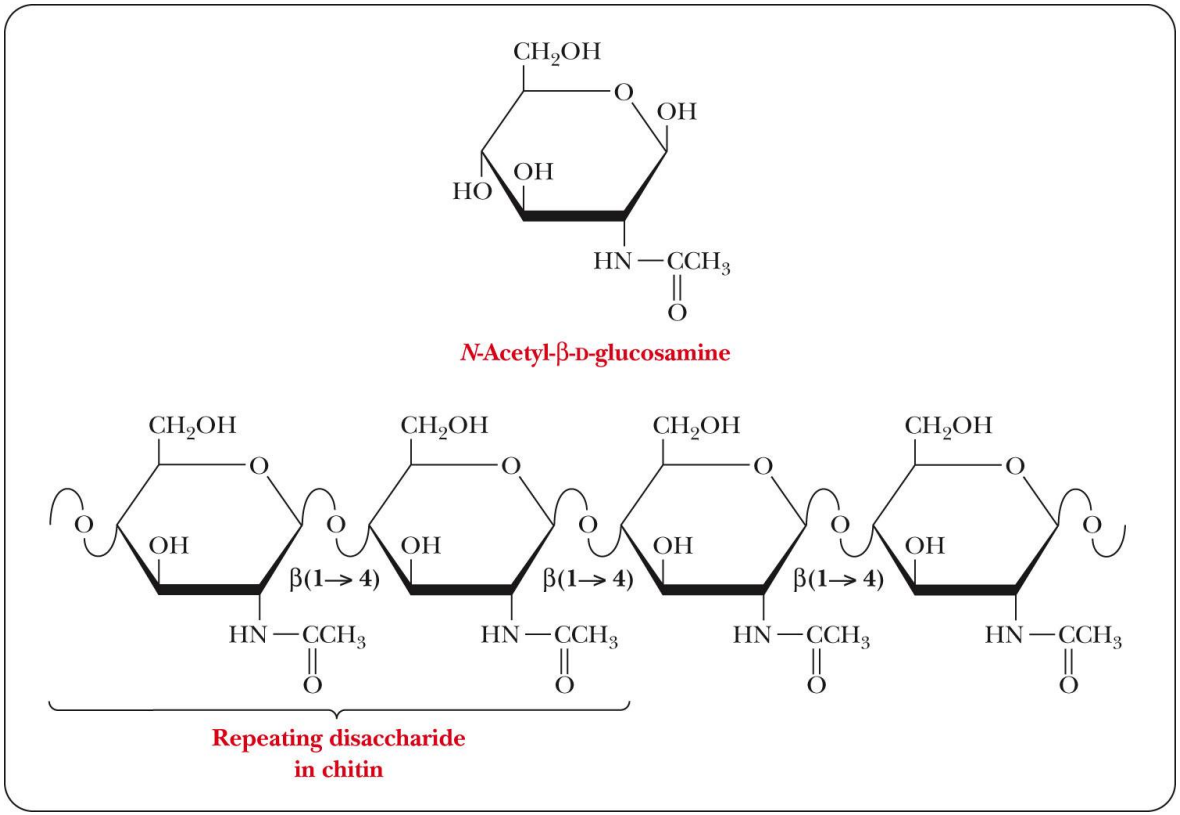
- Found in animal cells in granules (similar to starch in plants)
- Granules: liver & muscle cells, but hardly in other cell types
- Various degradative enzymes:
  - ✓ Glycogen phosphorylase: cleaves one glucose at a time from the non-reducing end of a branch to produce glucose-1-P
  - ✓ Debranching enzymes
- Is the number of branch points significant?
  - ✓ The higher, the higher the water solublility (plant vs. animals)
  - ✓ The higher, the higher potential targets for enzymes (plant vs. animals)





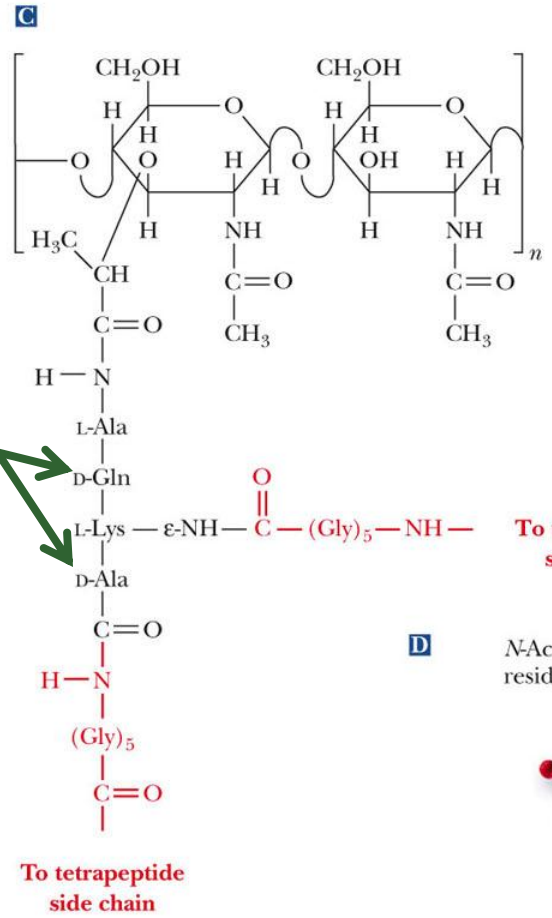
Chitin

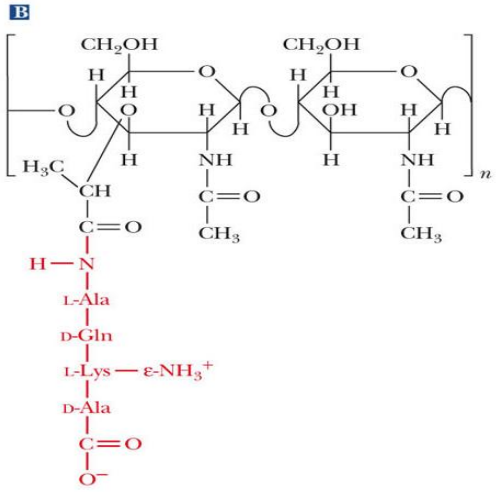
- The major structural component of the exoskeletons of invertebrates, such as insects; also occurs in cell walls of algae, fungi, & yeasts
- Composed of units of N-acetyl-β-D-glucosamine joined by β-1,4-glycosidic bonds



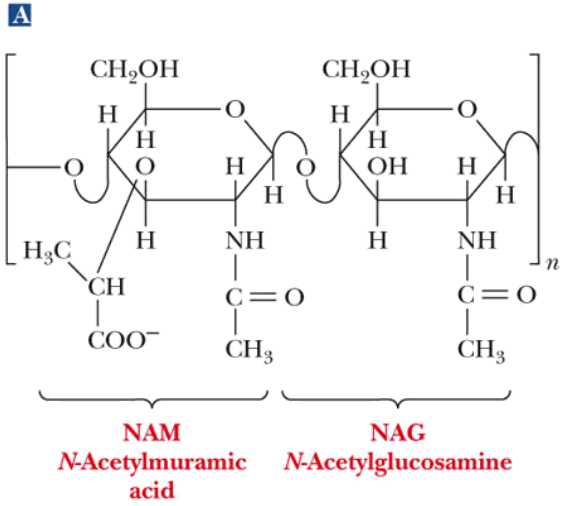
Bacterial cell walls

- Prokaryotic cell walls are constructed on the framework of the repeating unit NAM-NAG joined by β-1,4-glycosidic bonds
- Ala-Gln-Lys-Ala

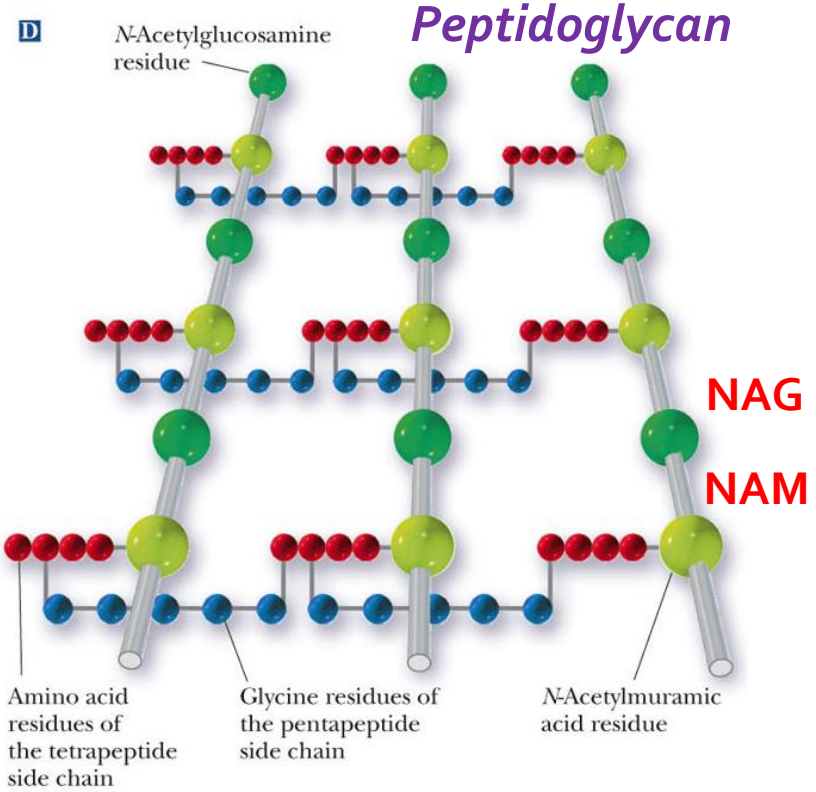




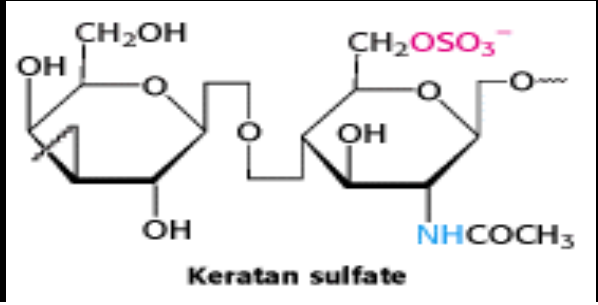
The cross-;inked material is named Peptidoglycan



N-Acetylmuramic acid does not occur in eukaryotic cell walls

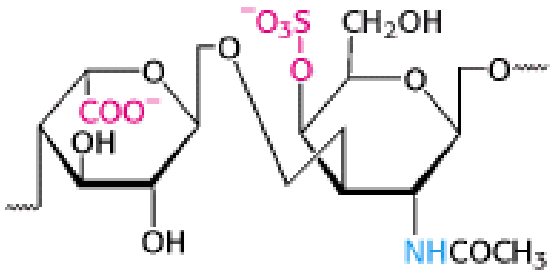


Glycosaminoglycans

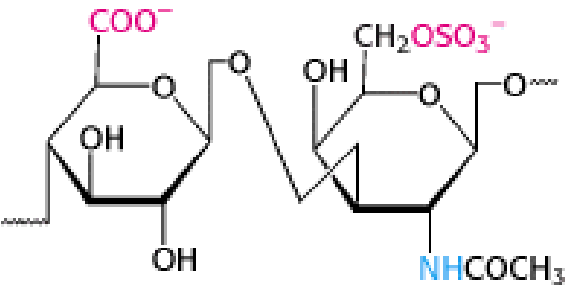


Keratan sulfate

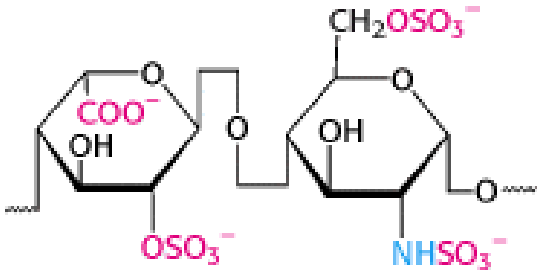
- Polysaccharides based on a repeating disaccharide:
  - Amino sugar + negatively charged (SO_4^{-2} or COO^-)
  - Heparin: natural anticoagulant
  - Hyaluronic acid: a component of the vitreous humor of the eye & the lubricating fluid of joints
  - Chondroitin sulfate and keratan sulfate: components of connective tissue



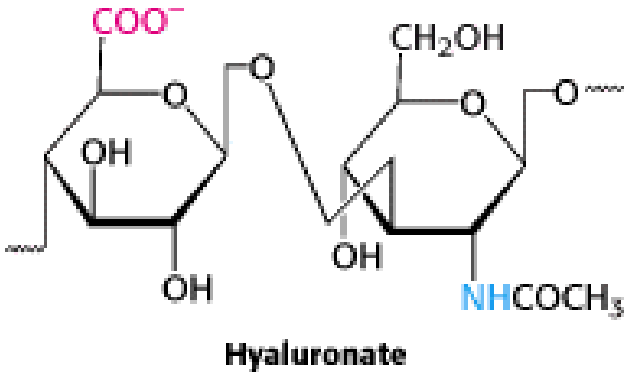
Dermatan sulfate



Chondroitin 6-sulfate



Heparin



Hyaluronate

Localization and function of GAG

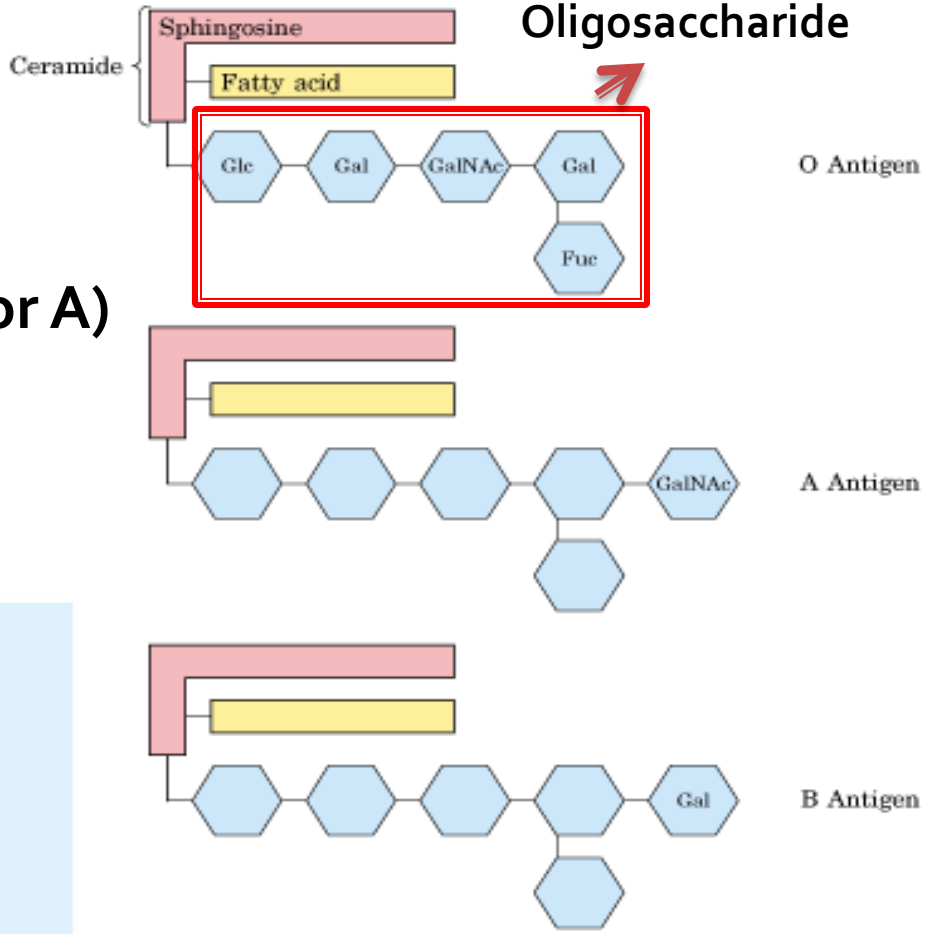
GAG	Localization	Comments
Hyaluronate	*synovial fluid, vitreous humor,* ECM of loose connective tissue	*the lubricant fluid , shock absorbing* As many as 25,000 disaccharide units
Chondroitin sulfate	*cartilage, bone*, heart valves	*most abundant GAG*
Heparan sulfate	*basement membranes*, components 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*	

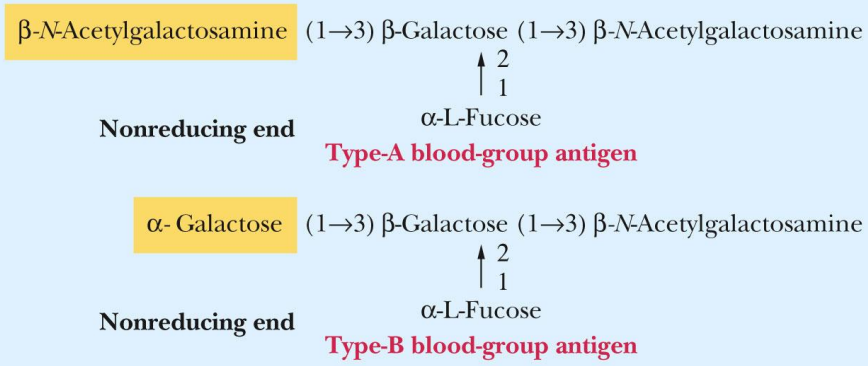
Glycoproteins

- Carbohydrate units covalently bonded to a polypeptide chain
  - ✓ Antibodies are glycoproteins
  - ✓ Oligosaccharide portion act as antigenic determinants
  - ✓ Among the first antigenic determinants discovered were the blood group substances
  - ✓ In the ABO system, individuals are classified according to four blood types: A, B, AB, and O
  - ✓ At the cellular level, the biochemical basis for this classification is a group of relatively small membrane-bound carbohydrates

Structures of Blood-Group Antigenic Determinants

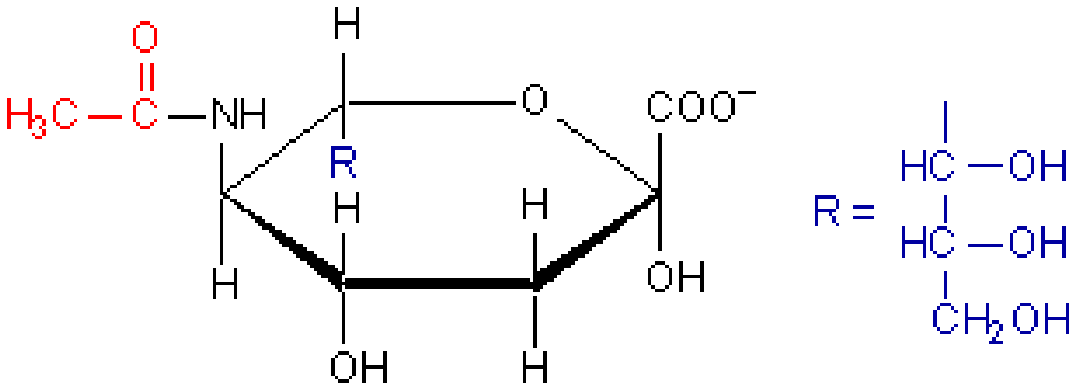
- Three different structures:
  - ✓ A, B, and O
- The difference:
  - ✓ *N*-acetylgalactosamine (for A)
  - ✓ Galactose (for B)
  - ✓ None (for O)





Sialic acid

- ***N*-acetylneuraminate**, (***N*-acetylneuraminic acid, also called sialic acid) is derived from the amino sugar, neuraminic acid and is often found as a terminal residue of oligosaccharide chains of glycoproteins giving glycoproteins negative charge



N-acetylneuraminate (sialic acid)

Proteoglycans

- Lubricants
- Structural components in connective tissue
- Mediate adhesion of cells to the extracellular matrix
- Bind factors that stimulate cell proliferation