CHEM 537
Carbohydrate Biochemistry and Glycobiology
Part I: Monosaccharides & Their Derivatives

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Slide Set 1a

Chapters 11 & 23: *Biochemistry*, Voet/Voet, 4th edition, 2011
Introduction to Glycobiology, Taylor/Drickhamer, 3rd edition, 2011

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Carbohydrate classes according to size

- ❑ monosaccharides - the fundamental “building block” units (monomers)
- ❑ oligosaccharides - comprised of monosaccharides (2-10) linked together via glycosidic bonds
- ❑ polysaccharides - comprised of monosaccharides (10-1000s) linked together via glycosidic bonds

Monosaccharides are “hydrates of carbon” – $(C\cdot H_2O)_n$

poly-hydroxylated aldehydes or ketones

Cellulose is the abundant biopolymer in nature (80% dry weight in plants)

Essential in:

- energy storage and release: glucose and its biopolymers (starch, glycogen)
- biological structure (glycolipids, glycoproteins, cellulose)
- molecular recognition & organization
- genetic information (DNA, RNA)
- cell signaling (GTP, GDP)
- protein stabilization (glycoproteins)
- enzymology (cofactors)
- cell recognition & identity
- membrane organization & other biophysical properties
- strategic solvent perturbation, sol/gel transitions

Oligosaccharides and polysaccharides are structurally diverse.

Carbohydrates have the highest potential for structural diversity among the common biopolymers.

A sample calculation of total possible linear tetramers:

Tetradeoxyribonucleotide: 4 monomers (A,T,G,C)
$(\text{number of different monomers})^{\text{number in polymer}} = 4^4 = 256$ different combinations

Tetrapeptide: 20 monomers (L-amino acids)
$(\text{number of different monomers})^{\text{number in polymer}} = 20^4 = 160{,}000$ different combinations

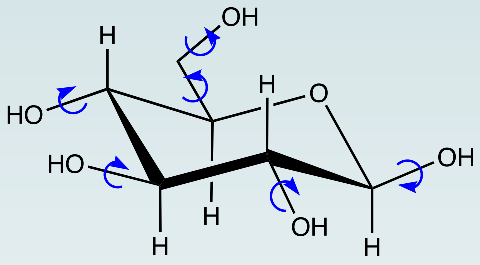
Tetrasaccharide: If the following assumptions are made:

- D-sugars
- biologically common monosaccharides (Glc, Gal, Man, SA, Rib, Fru)
- common derivatizations (NAc,deoxy)
- α or β configuration at C1
- linear linkages (no branched structures) - linkages at O2, O3, O4, O6

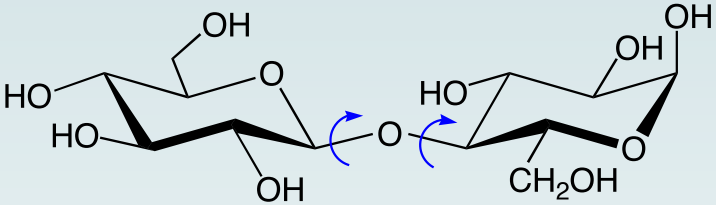
$(6 \times 2 \times 2 \times 4)^4 = 84{,}934{,}656$ possible linear tetrasaccharides

If all naturally occurring monosaccharides with branched linkages are included, the number of possible tetramers becomes astronomical: $\sim 1.4 \times 10^{13}$ possibilities

Monosaccharides and their oligomers and polymers are conformationally dynamic molecules.

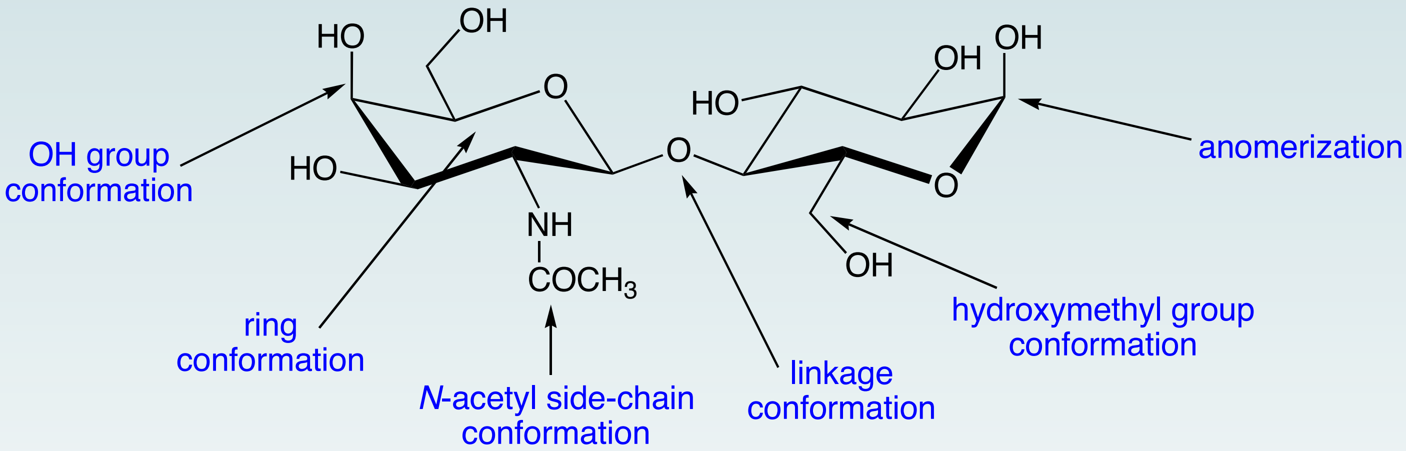


A monosaccharide
β−D-glucopyranose (Glc not Glu)



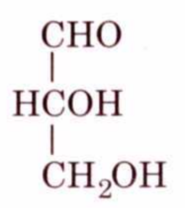
A disaccharide
α−cellobiose

Some structural features of saccharides



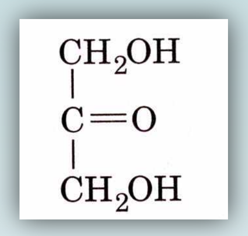
Monosaccharides are polyhydroxylated aldehydes or ketones containing at least three carbons.

Emil Fischer
1852-1919



$$\begin{array}{c} CHO \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

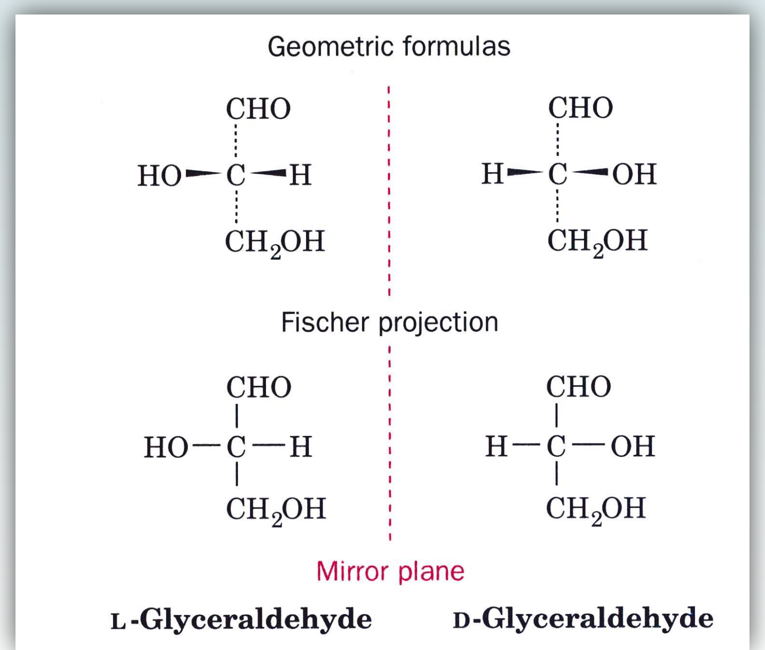
D-glyceraldehyde
(chiral)



$$\begin{array}{c} CH_2OH \\ | \\ C{=}O \\ | \\ CH_2OH \end{array}$$

dihydroxyacetone
(achiral)

Fischer projection:
- horizontal bonds: toward viewer
- vertical bonds: away from viewer



Monosaccharide families

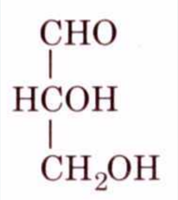
Classified according to the type of carbonyl group
and the number of carbon atoms they contain.

aldehyde: aldoses
ketone: ketoses

Number of carbons: triose = 3; tetrose = 4; pentose = 5; hexose = 6; heptose = 7, etc.

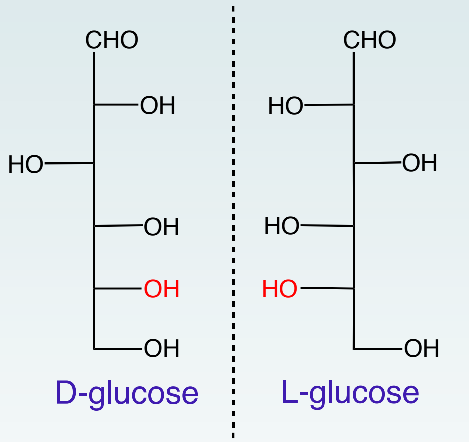
Convention: D-Sugars have the same configuration at their asymmetric penultimate carbon as does D-glyceraldehyde. L-Sugars are mirror images of D-sugars.

These are Fischer projections and imply specific stereochemistry at each chiral carbon.



$$\begin{array}{c} CHO \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

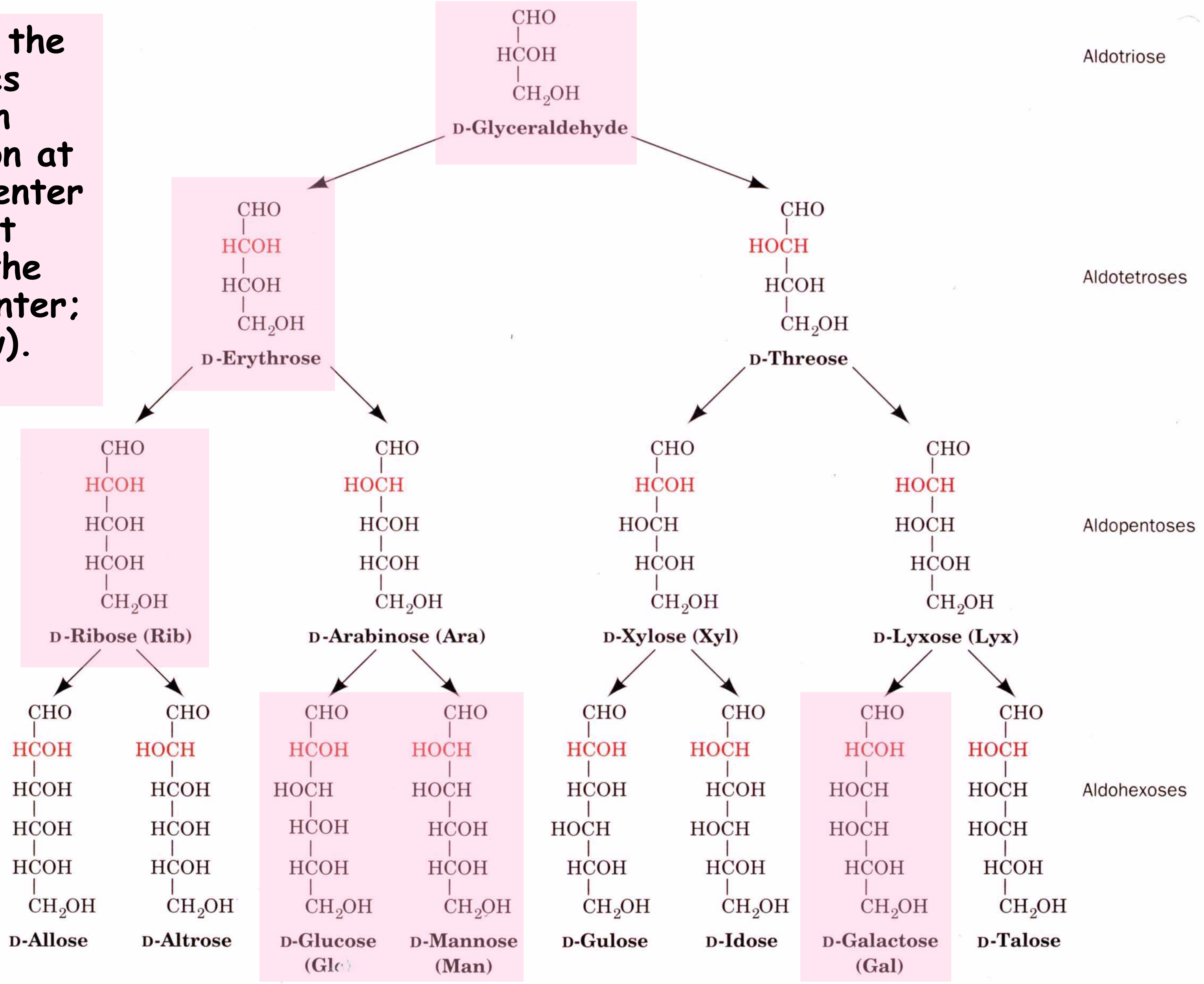
D-glyceraldehyde as reference



mirror images (enantiomers)

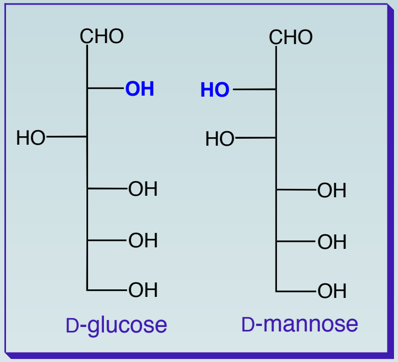
D-Sugars are more biologically abundant than L-sugars.

Epimers of the D-aldoses differ in configuration at one chiral center (does not apply to the anomeric center; see below).

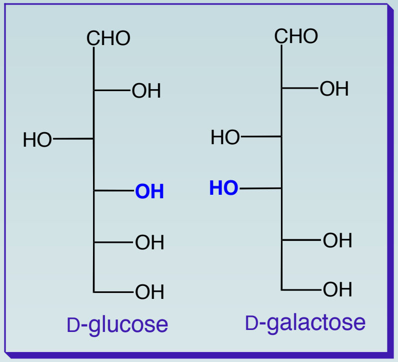


Example: an aldohexose has 4 chiral centers and 2^4 or 16 stereoisomers (8 D (shown above) and 8 L)

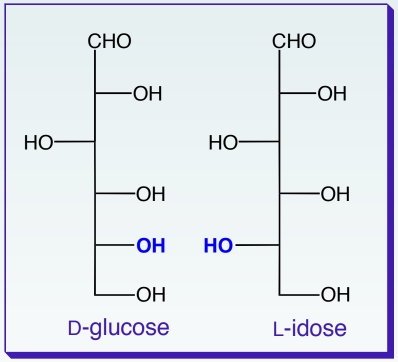
Some structural relationships in aldohexoses



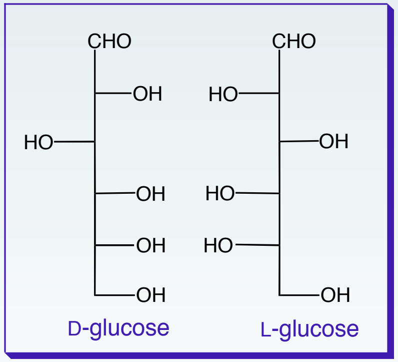
D-Glucose and D-mannose are C2-epimers.



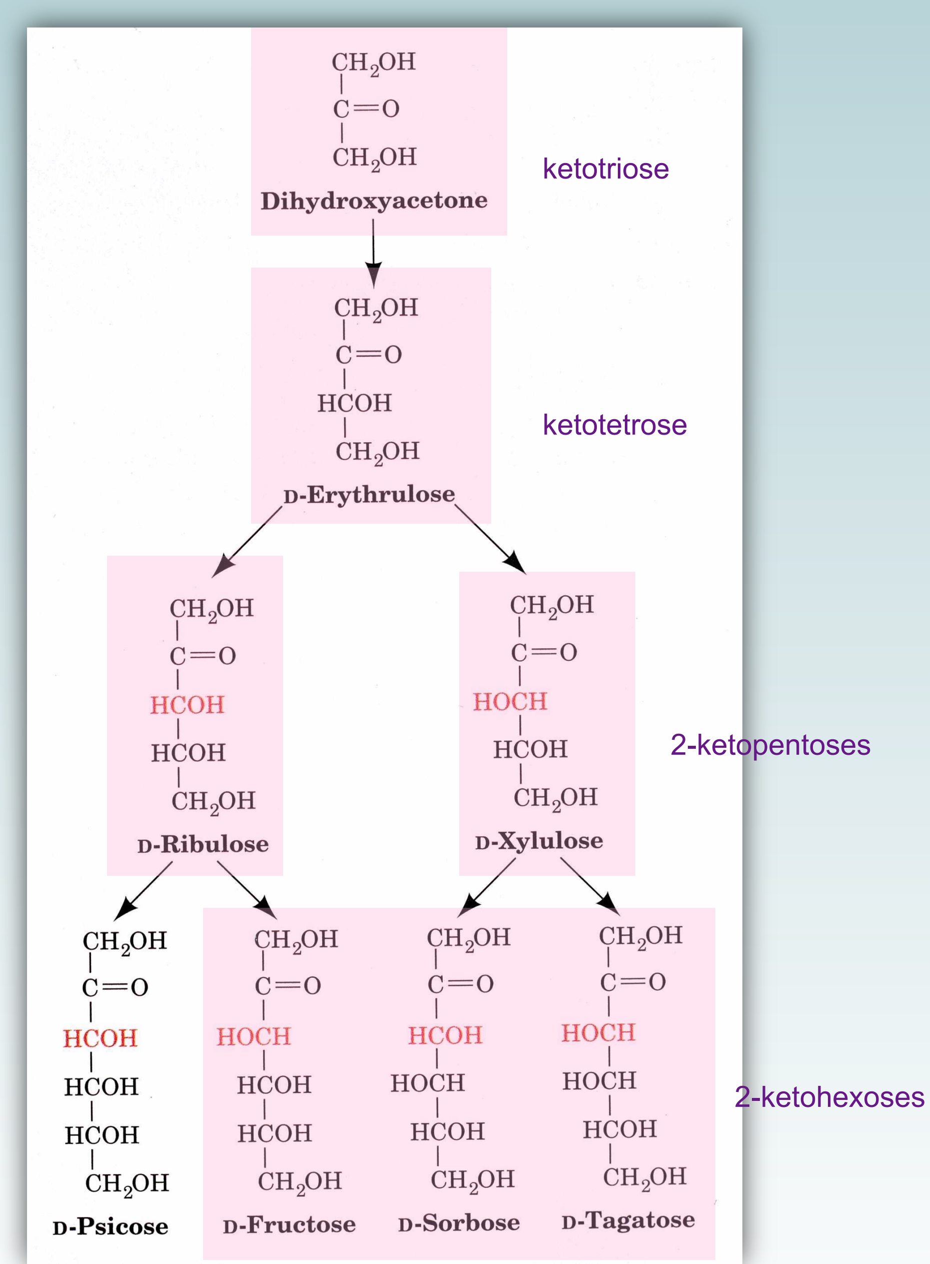
D-Glucose and D-galactose are C4-epimers.



D-Glucose and L-idose are C5-epimers. Note that inverting configuration only at C5 of D-glucose does not produce L-glucose. To generate the latter, inversion of all chiral centers is required (relative configuration is conserved).

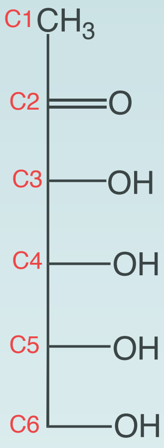


Epimers of D-2-ketoses having 3 to 6 carbons

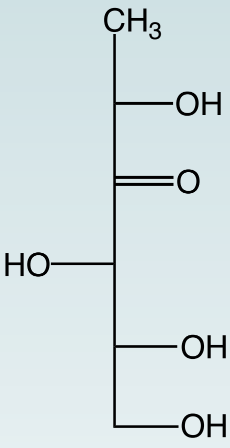


Example: a 2-ketohexose has 3 chiral centers and 2^3 or 8 stereoisomers (4 D and 4 L)

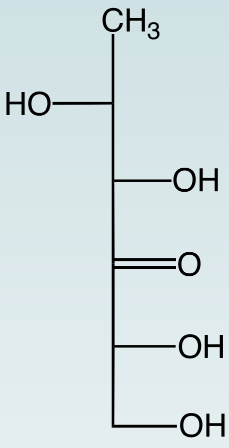
Other types of ketoses



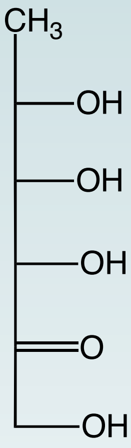
2-ketohexose
(cyclizable: furanoses
and pyranoses)



3-ketohexose
(cyclizable: furanoses
only)



4-ketohexose
(non-cyclizable)



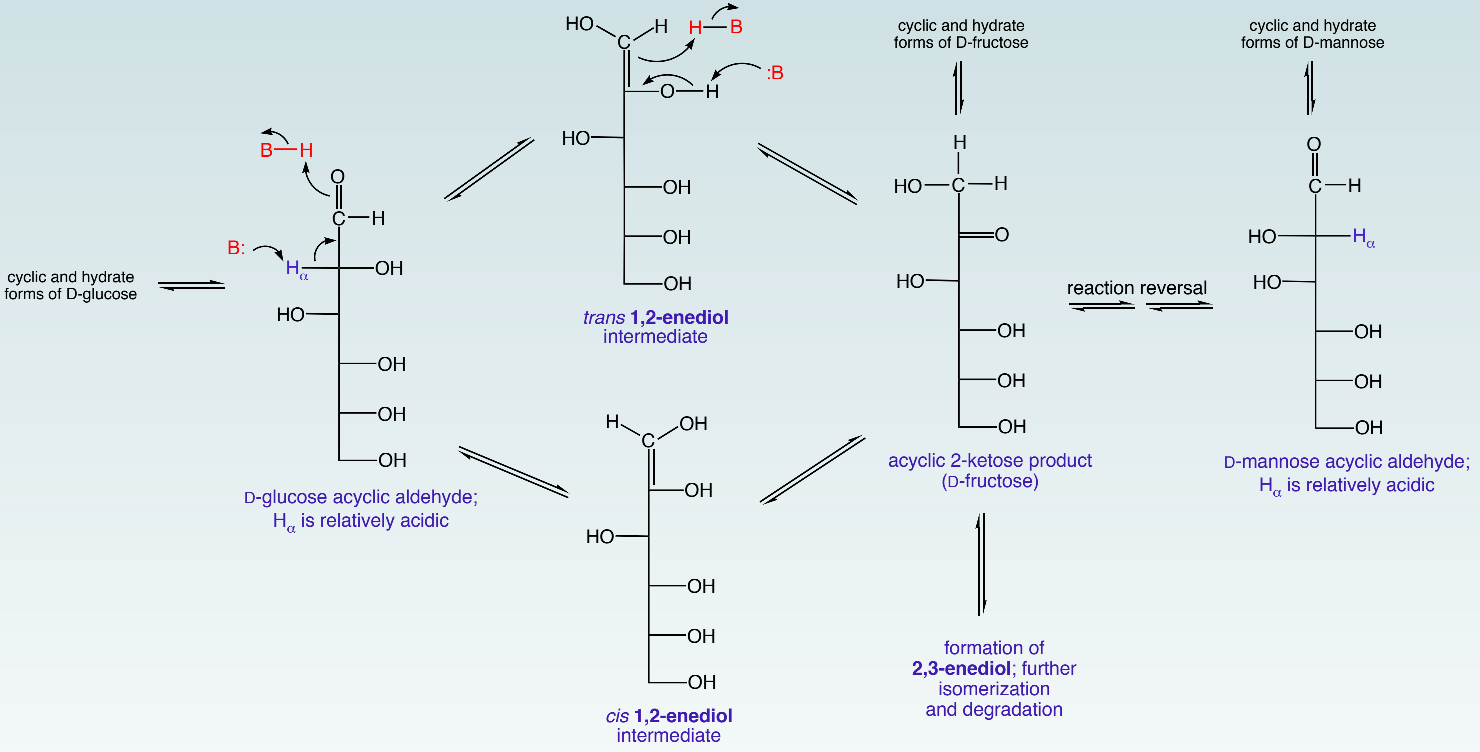
5-ketohexose
(cyclizable: furanoses
only)

Illustrated for a deoxyketose

Aldose - 2-ketose isomerization in solution: A base-catalyzed reaction

(Lobry deBruyn- Alberta van Ekenstein reaction)

A chemical pathway for the interconversion of an aldose with its 2-ketose



Since chirality at C2 is lost in transit through the enediol intermediates, both C2-epimeric D-aldoses are observed at equilibrium. The formation of both *cis* and *trans* enediols is possible during non-enzyme catalyzed aldose-ketose isomerization.

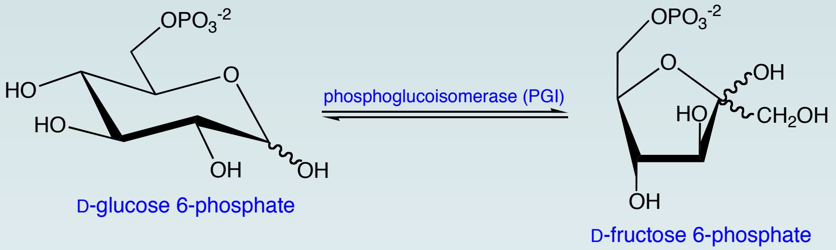
overall reaction: D-glucose $\rightleftharpoons$ D-fructose $\rightleftharpoons$ D-mannose

Aldose - 2-ketose isomerization *in vivo*

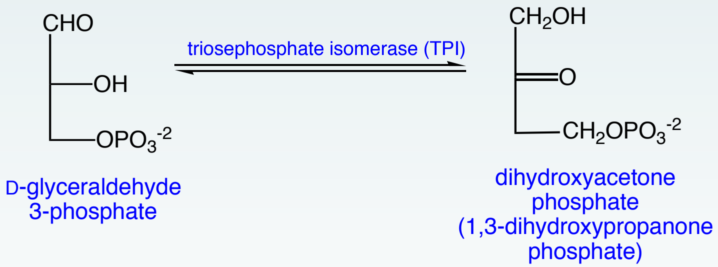
Catalyzed by aldose/ketose isomerases

Examples:

- phosphoglucoisomerase (PGI)



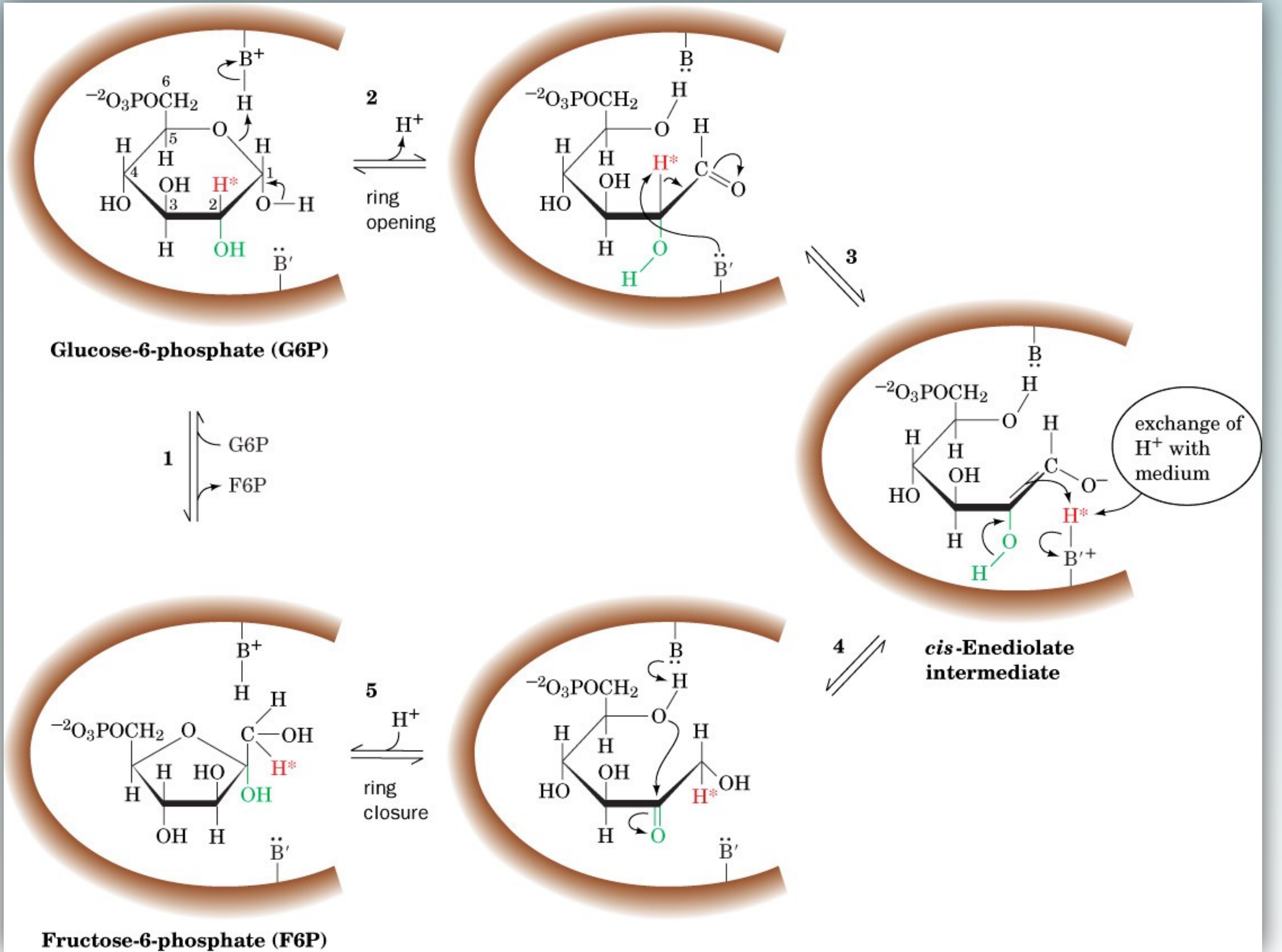
- triosephosphate isomerase (TPI)



In enzyme-catalyzed aldose-ketose isomerization, a 2-ketose is equilibrated with only one aldose due to the involvement of only one configuration of ene-diol intermediate (*cis* only). The chirality of the enzyme active site allows only one type of enediol to form.

Reaction mechanism of phosphoglucoisomerase (PGI)

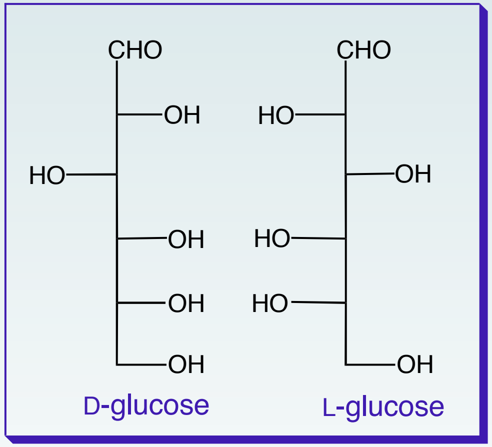
PGI has isomerase and anomerase catalytic properties



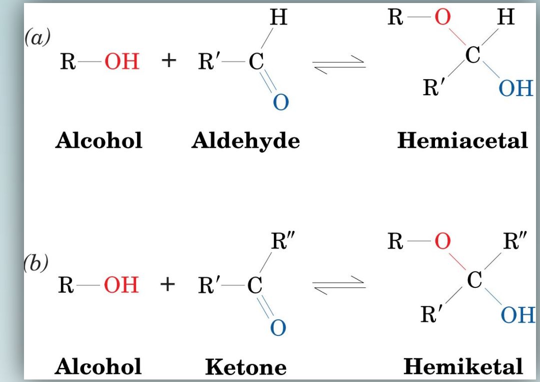
Proof of the relative configuration of glucose by Fischer

Berichte der deutschen chemischen Gesellschaft **1891**, *24*, 1836.
(original paper)

F. Lichtenthaler, *Angew. Chem. Intl. Ed. Engl*. **1992**, *31*, 1541-1556.
(contemporary review)



Monosaccharide anomerization/mutarotation

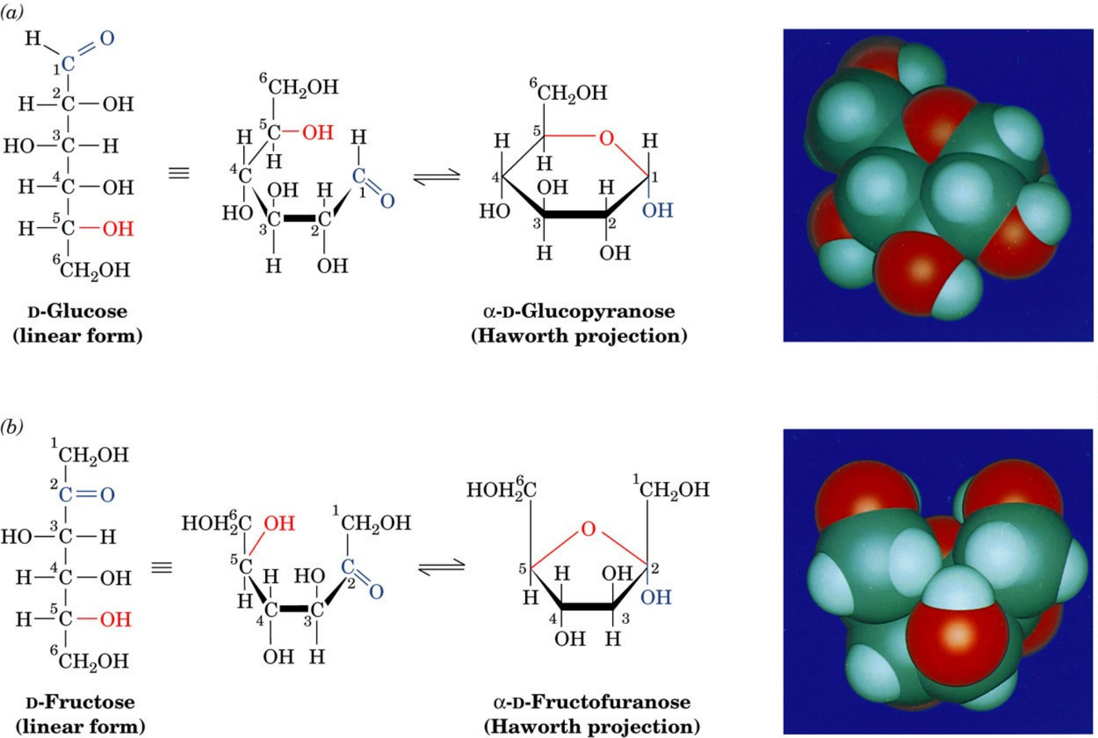


Alcohols react spontaneously and reversibly with aldehydes and ketones to form *hemiacetals* and *hemiketals*, respectively.

Monosaccharides undergo the same reaction intramolecularly to form cyclic structures. This cyclization reaction (anomerization) is spontaneous and reversible in aqueous solution. It is acid-, base- and water catalyzed.

6-Membered rings are known as pyranoses; 5-membered rings are known as furanoses.

Cyclic forms predominate in aqueous solutions of all monosaccharides capable of cyclization.



Space-filling models courtesy of Robert Stodola, Fox Chase Cancer Center

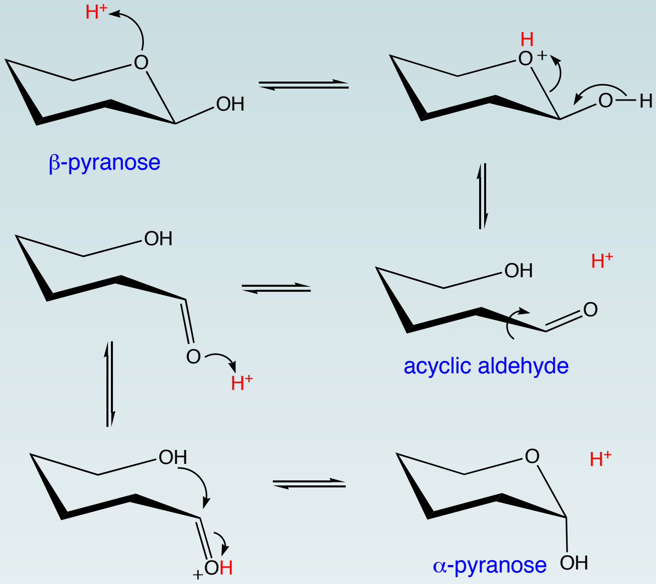
Distinction between anomerization and mutarotation

Anomerization: refers to the spontaneous interconversion of cyclic (anomeric) forms of sugars in solution (*e.g.,* aldoses and ketoses); can be applied generally to describe any process or condition under which anomers interconvert (*e.g.,* anomerization of glycosides)

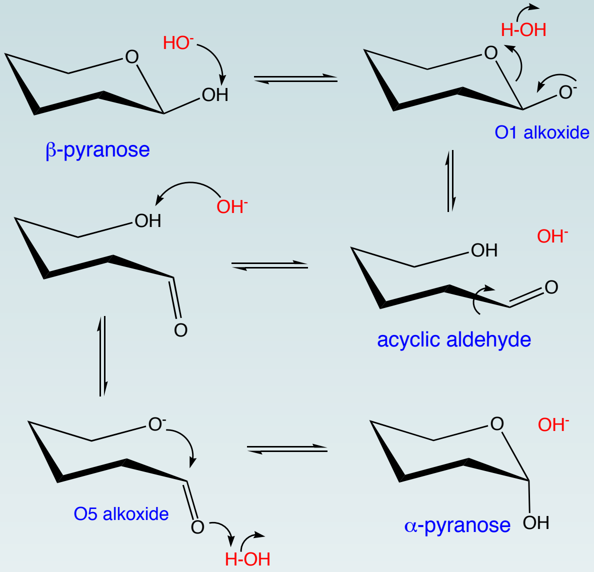
Mutarotation: refers to the change in the rotation of plane-polarized light that occurs when an aqueous solution containing a specific anomeric form of a reducing sugar (*e.g.,* α-D-glucopyranose) is allowed to equilibrate; after extended incubation, an equilibrium mixture of anomers is produced characterized by an averaged optical rotation (specific rotation). When an aqueous solution of a reducing sugar no longer rotates plane-polarized light, an equilibrium mixture of anomers has been achieved.

Catalysis of monosaccharide anomerization in solution

H^+-, OH^- and water-catalyzed mechanisms



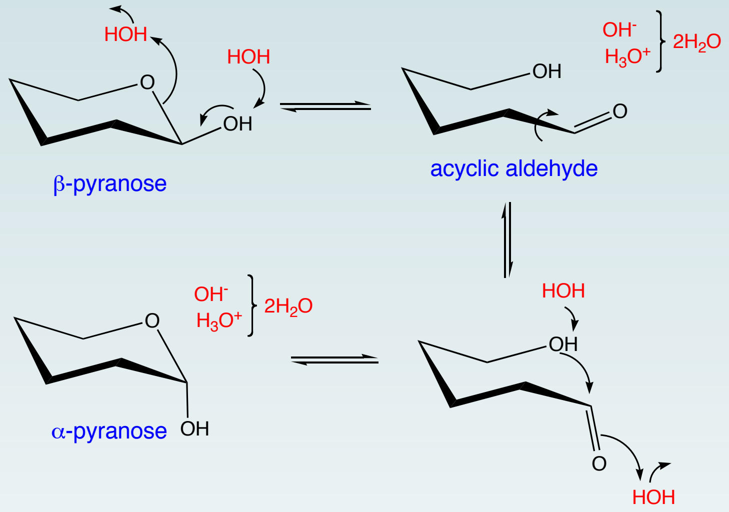
H^+-catalyzed



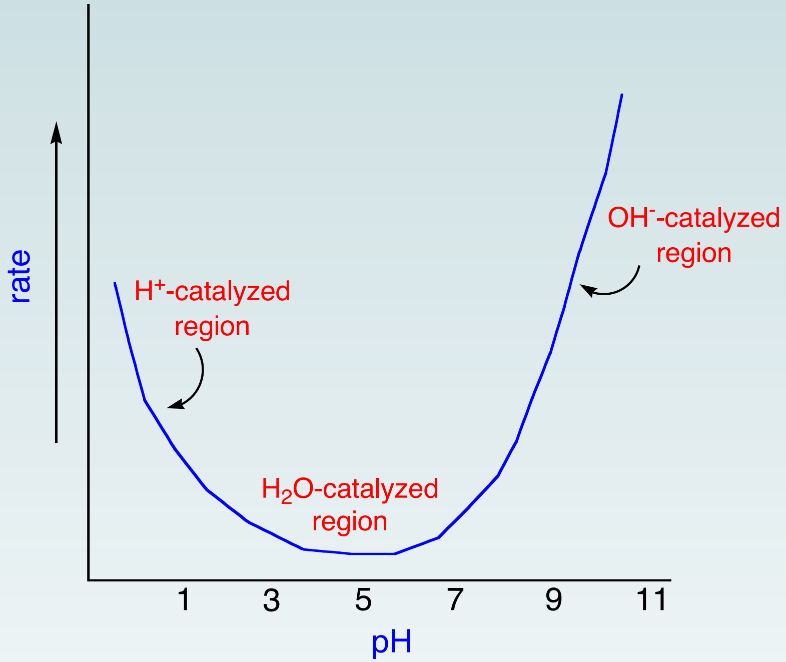
OH^--catalyzed

Ring-closure of the acyclic aldehyde can occur in a 1,4-fashion when possible to give furanoses.

Catalysis of monosaccharide anomerization in solution



water-catalyzed



Typical pH-rate profile for anomerization of an aldose