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

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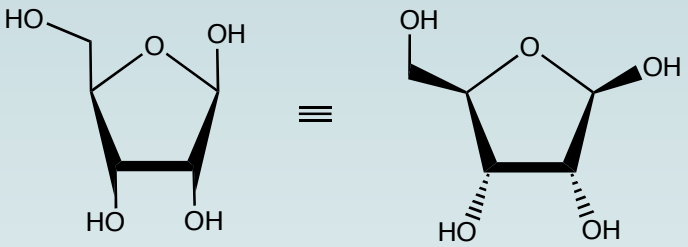
Slide Set 1b

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

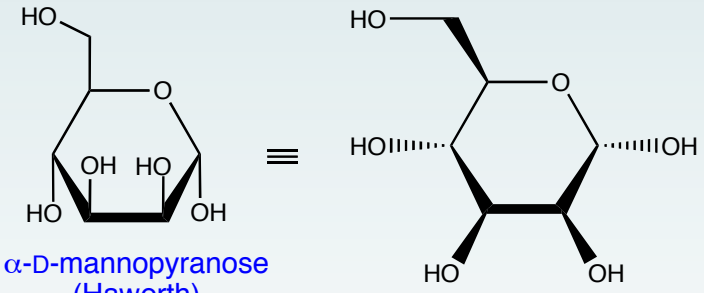
Fall 2014

Interpretation of Haworth projections



β-D-ribofuranose
(Haworth)

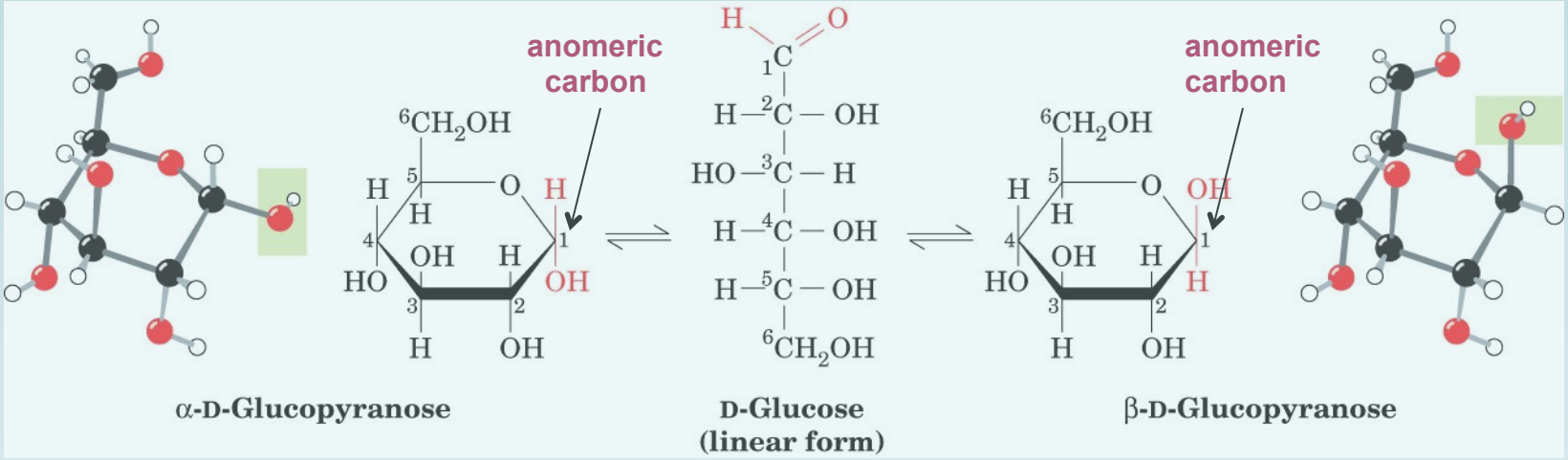
furanose rings



α-D-mannopyranose
(Haworth)

pyranose rings

Formation of anomers upon cyclization



The anomeric monosaccharides, α-D-glucopyranose and β-D-glucopyranose, drawn as Fischer and Haworth projections, and as ball-and-stick models

Upon cyclization, the carbonyl carbon becomes chiral and is referred to as the anomeric carbon. In the α-form, the anomeric OH (O1) is on the opposite side of the ring from the CH_2OH group, and in the β-form, O1 is on the same side.

The α- and β-forms are referred to as anomers or anomeric pairs, and they interconvert in aqueous solution via the acyclic ("linear") form (anomerization). Aqueous solutions of D-glucose contain ~64% β-pyranose and ~36% α-pyranose.

Monosaccharides in aqueous solution

Hexoses (C_6), pentoses (C_5) and tetroses (C_4) can form pyranose (6-membered) and/or furanose (5-membered) ring forms, depending on which OH group within the structure reacts with the anomeric carbon (intramolecular hemiacetal/hemiketal formation).

Equilibrium composition in solution depends on monosaccharide structure:

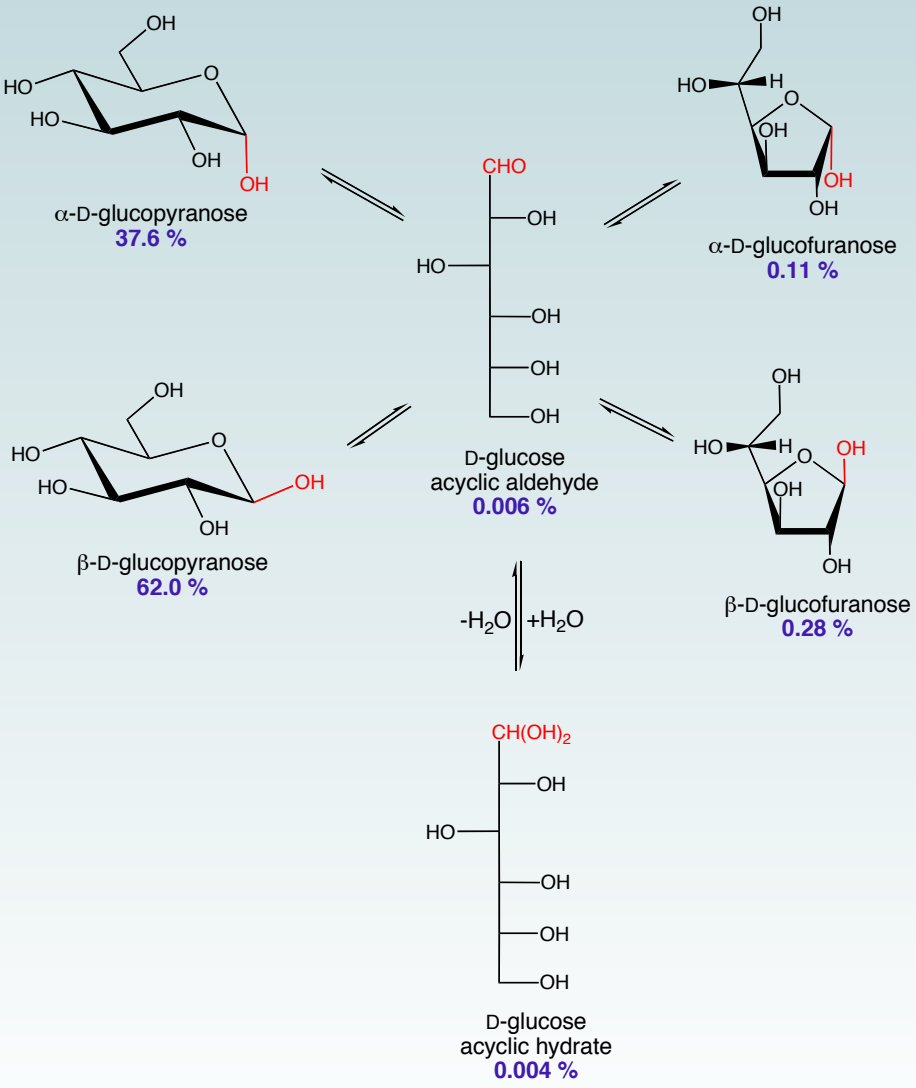
D-glucose: >98% pyranose
D-fructose: ~67% pyranose / ~33% furanose
D-ribose: ~79% pyranose / ~21% furanose

All else being equal, *pyranoses are usually more stable than furanoses*.

Larger ring forms (*e.g.,* 7-membered rings) are less stable than pyranose or furanose rings and are rarely observed.

Cyclization to give 3- and 4-membered rings is not observed (steric strain).

A more detailed view of solution composition: D-glucose



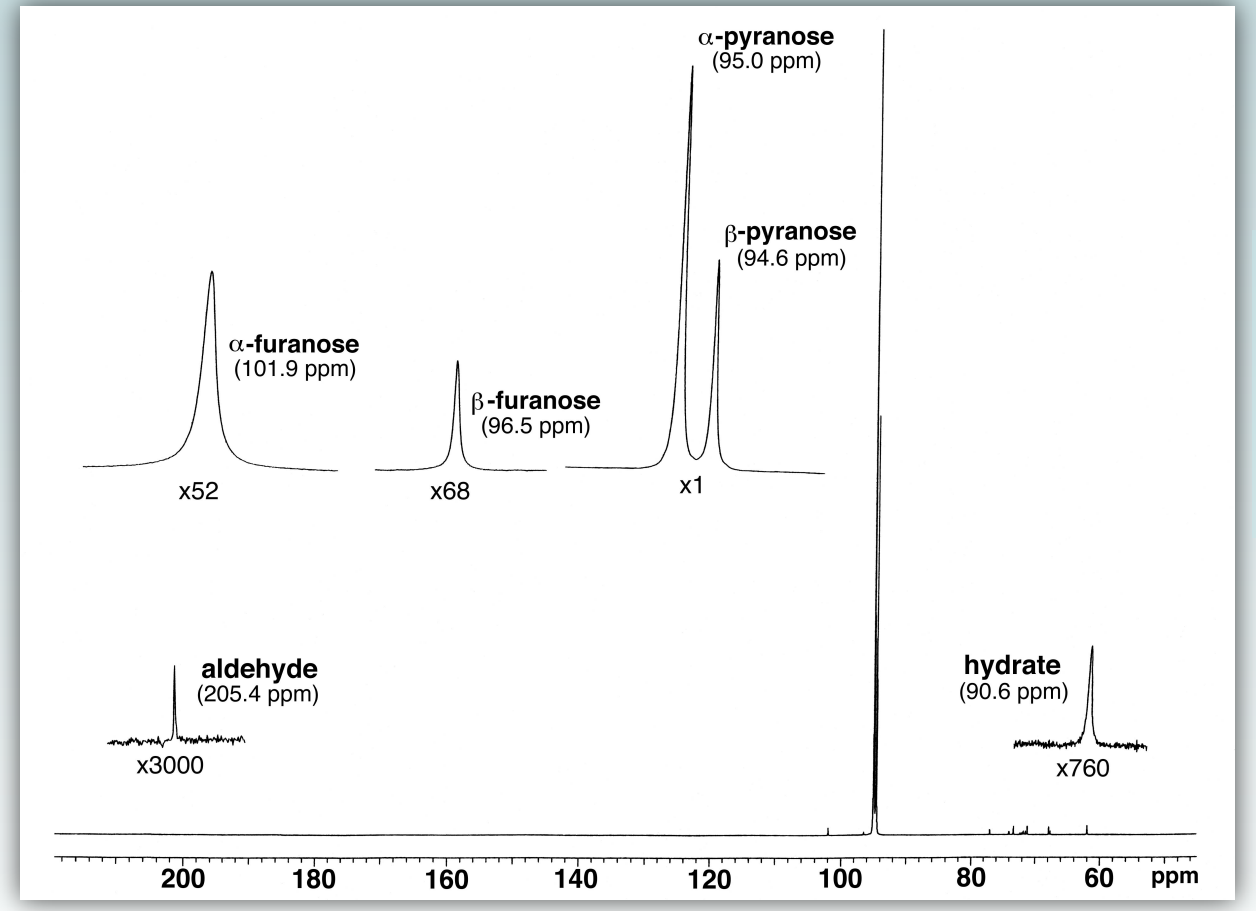
The rate of an enzyme-catalyzed reaction can be limited by the rate of anomerization of its monosaccharide substrate *in vivo*, since the enzyme may bind only one of the multiple forms possible in solution. Utilization of only part of the total monosaccharide forms has implications for the calculation of K_m values.

Some enzymes bind to specific monosaccharide anomers *in vivo*: anomeric specificity

Some examples:

- hexokinase: α- or β-D-glucopyranose
- fructokinase: β-D-fructofuranose
- phosphofructokinase: β-D-fructofuranose 6P
- galactokinase: α-D-galactopyranose
- G6P dehydrogenase: β-D-glucose 6P
- CMP-NeuAc synthetase: β-pyranose of NeuAc

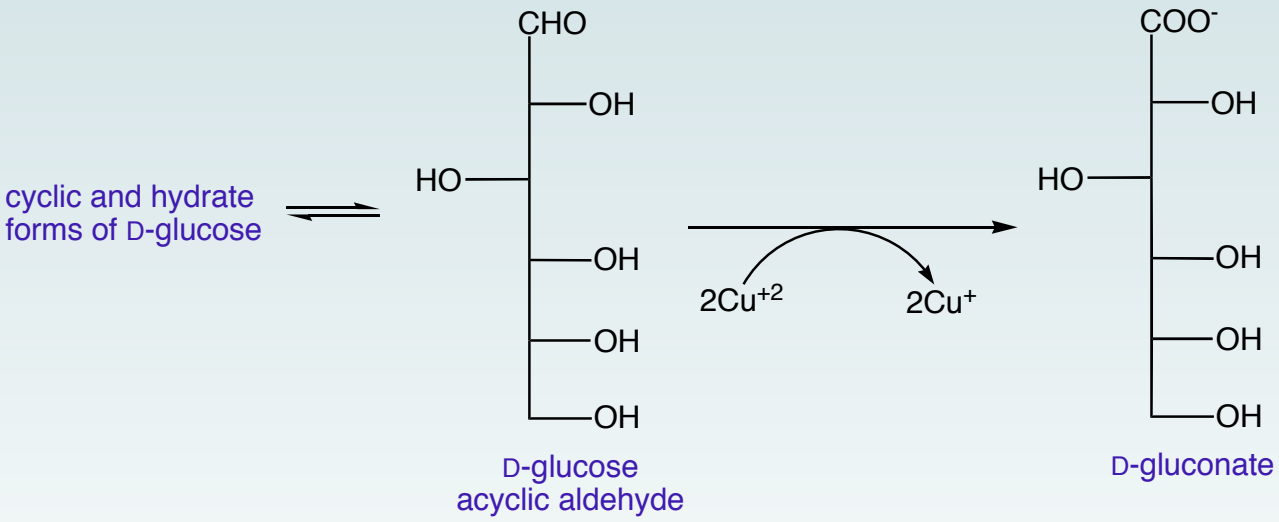
^{13}C NMR detection and quantification of monosaccharide forms in solution



D-[1-^{13}C]Mannose: An equilibrated aqueous solution contains six (6) monomeric forms.

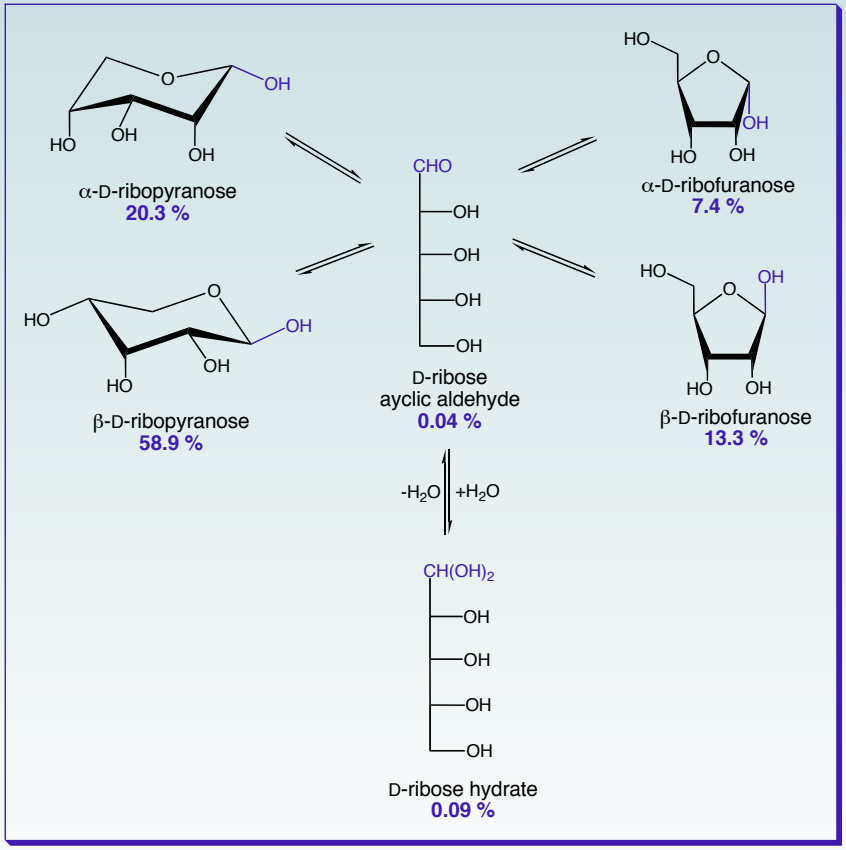
Definition of a reducing sugar

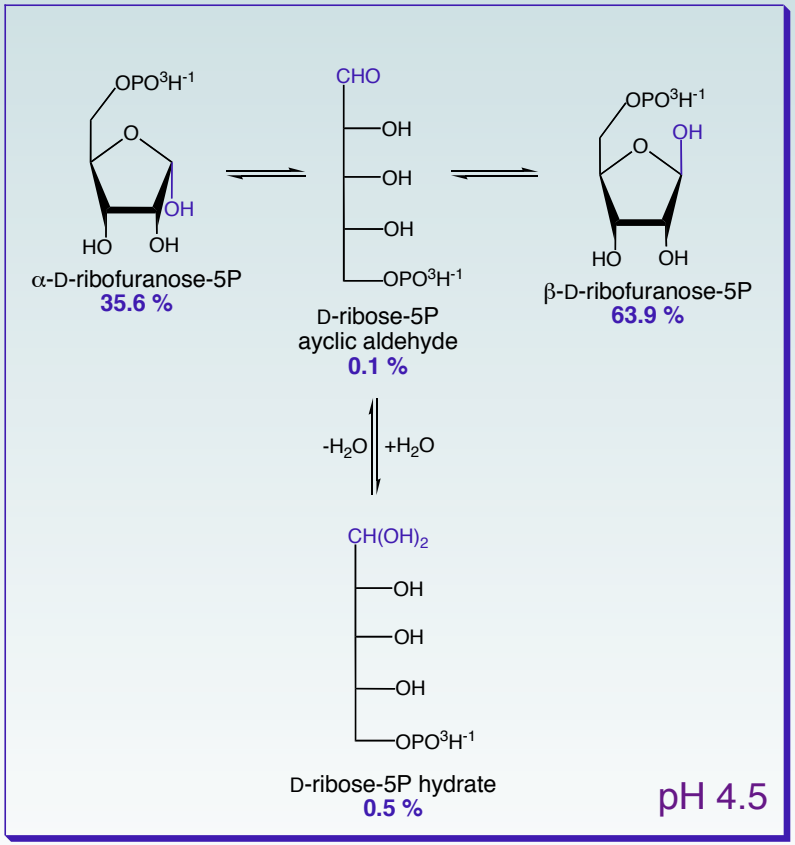
Monosaccharides that are capable of assuming a form in solution that contains a free carbonyl group can be oxidized by relatively mild oxidizing agents such as Fe^{+3} or Cu^{+2} (Fehling's reaction). The saccharide is oxidized and the reagent is reduced.



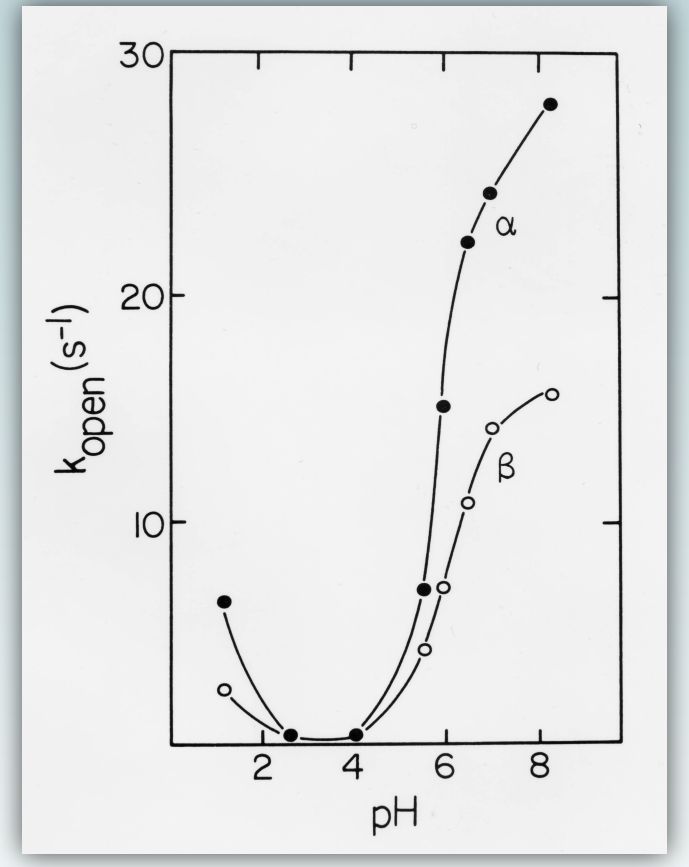
D-Ribose and D-ribose-5P anomerization: Effects of phosphorylation

- Phosphorylation can restrict the types of cyclization reactions of the acyclic carbonyl form.
- Phosphorylation enhances rates of anomerization.





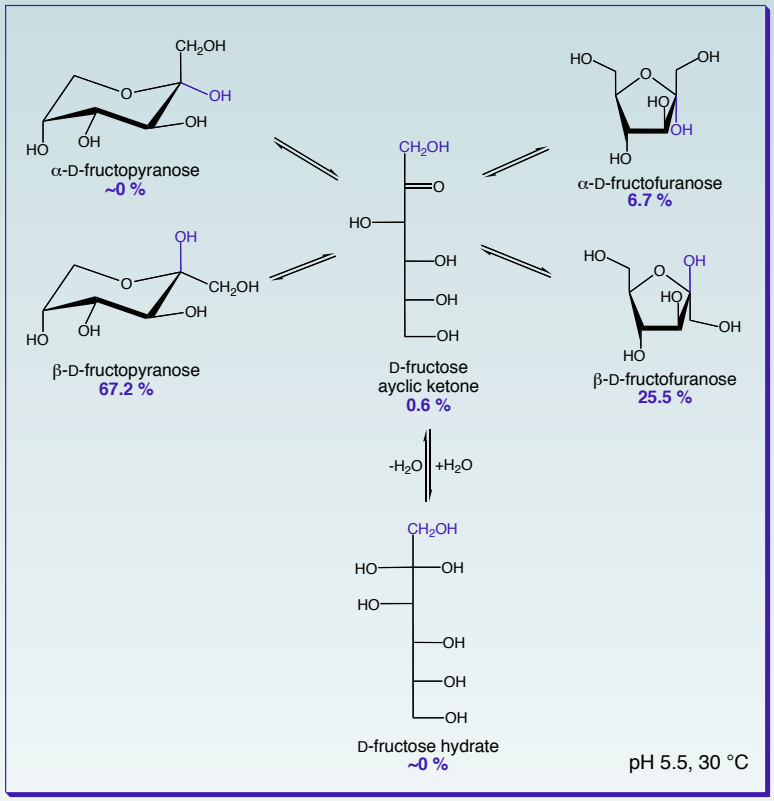
pH Dependence of the ring-opening rate constants for the α- and β-furanose forms of D-[1-^{13}C]ribose 5-phosphate

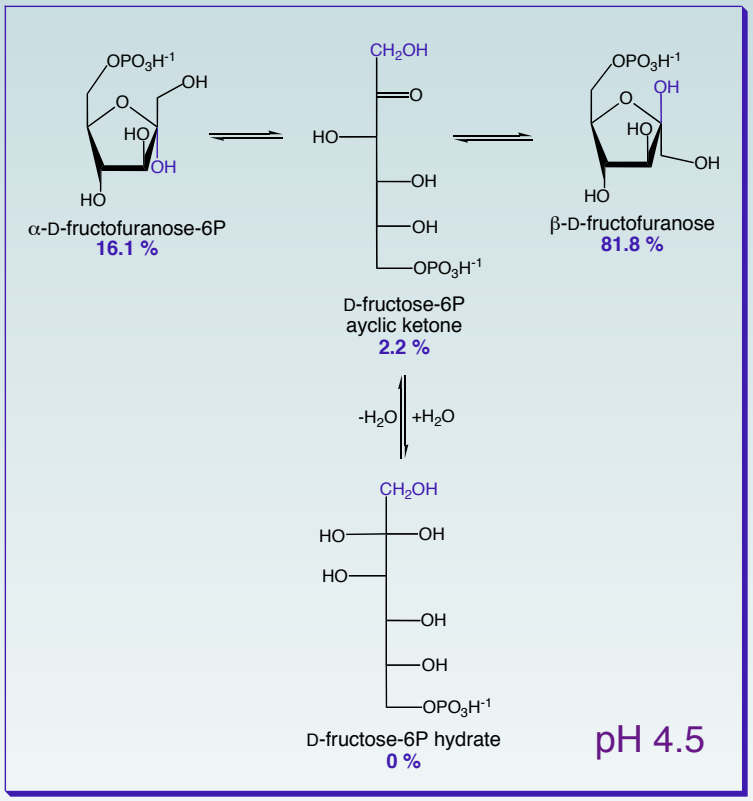


(solution conditions:
0.03 M sugar in 15% $^{2}H_2O$ at 24 °C)

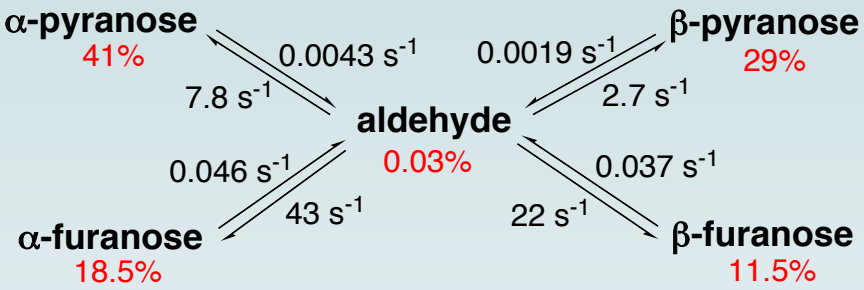
The two anomers show different sensitivities to pH, with the α-anomer generally more reactive than the β-anomer. Interestingly, the β-furanose is the more abundant furanose form in solution. If a similar study was done on unphosphorylated D-ribofuranose, the k_{open} values would be considerably lower; phosphorylation enhances anomerization rates, which may have physiological significance.

D-Fructose and D-fructose 6P anomerization: Effects of phosphorylation





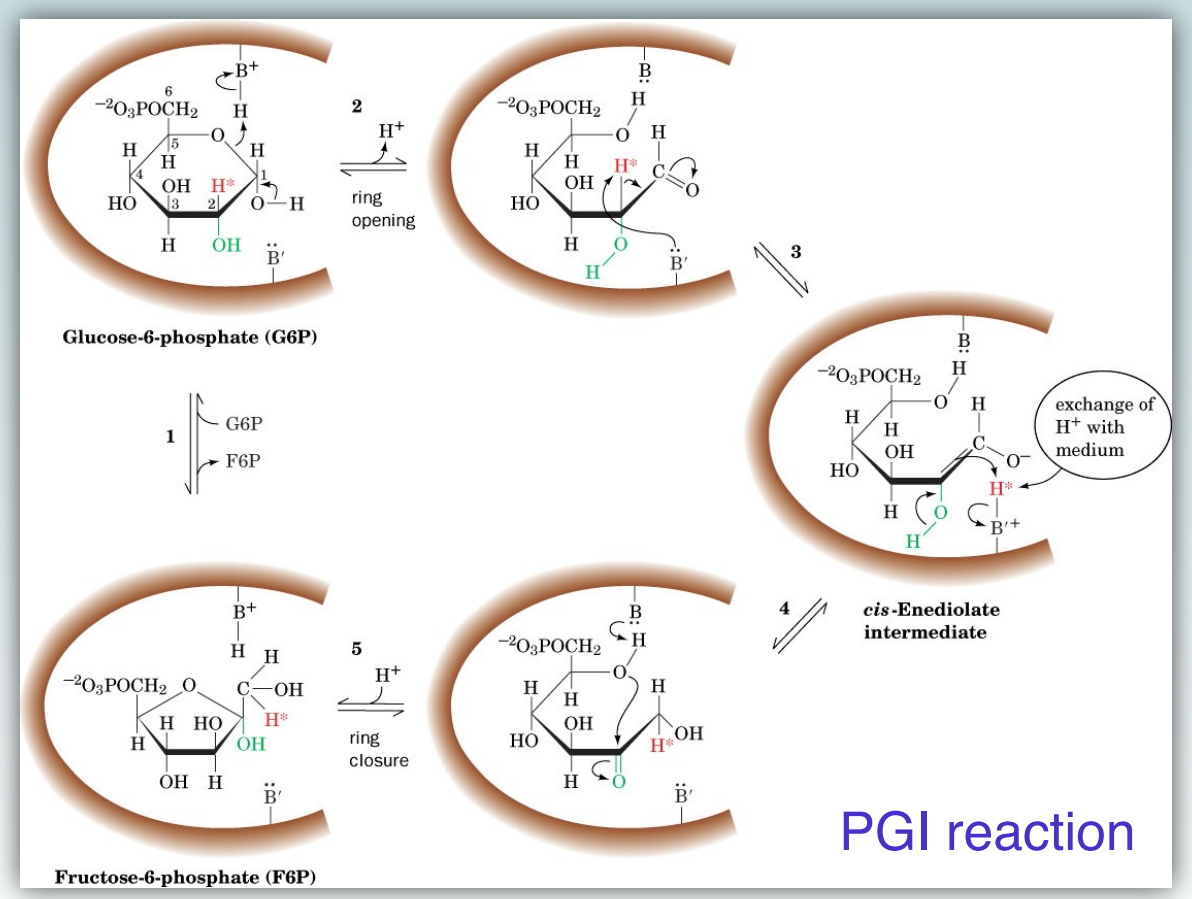
A more detailed view of anomerization kinetics: D-Talose



50 mM Na acetate, pH 4.0, 15% v/v $^{2}H_2O$, 28 °C

Talopyranoses are more thermodynamically favored than talofuranose, but talofuranoses are more kinetically favored than talopyranoses.

Enzyme-catalyzed anomerization: anomerases and mutarotases



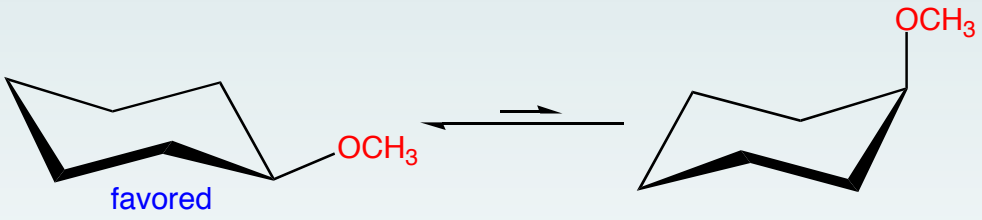
Stereoelectronic effects in monosaccharides: Anomeric effects

Endo-anomeric effect: a specific type of stereoelectronic effect; refers to the preferred orientation (axial *vs* equatorial) of the C-O bond involving the anomeric carbon of a monosaccharide

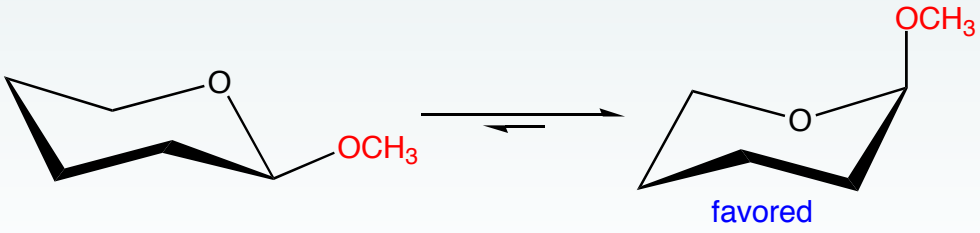
Major factors that influence C1-O1 bond orientation in aldopyranosyl rings:

- steric
- stereoelectronic
- solvation (hydration)

The relative contributions of these three factors in dictating preferred C1-O1 bond orientation vary with the structure and configuration of the monosaccharide and environmental (*e.g.*, solution) conditions.



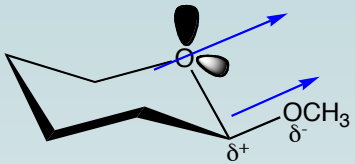
controlled mainly by steric factors



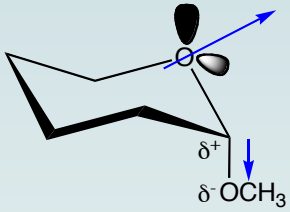
controlled mainly by stereoelectronic factors; axial orientation more favored with increasing electronegativity of the ring substituent.

Two physical descriptions of the origin of the *endo*-anomeric effect

1. Electrostatic (dipole-dipole) model

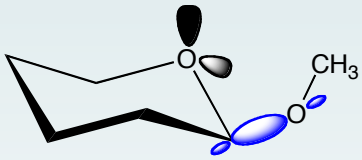


two dipoles approximately parallel; energetically unfavorable

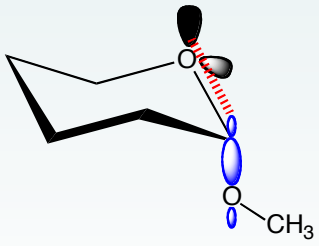


two dipoles approximately perpendicular; energetically more stable

2. Orbital interaction model



no orbital overlap in the β-anomer

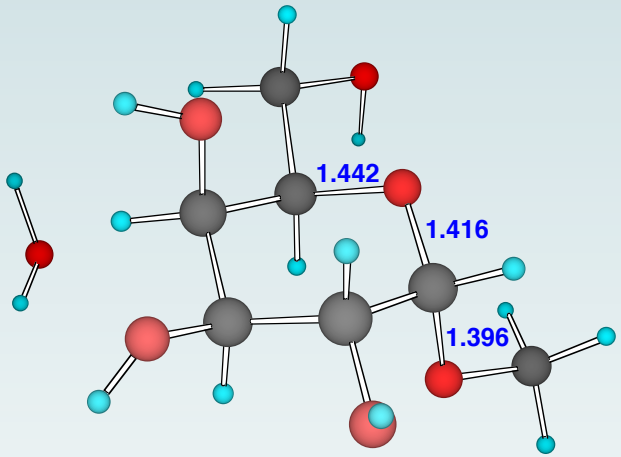


orbital overlap possible in the α-anomer ($n_{O5} \rightarrow \sigma^*_{O1}$); a stabilizing effect; geometric implications are that (a) the C1-O5 bond shortens, (b) the C1-O1 bond lengthens, (c) C1 acquires more sp^2-character, and (d) the O5-C1-O1 bond angle increases relative to the β-anomer.

X-ray structures of an anomeric pair of glycosides

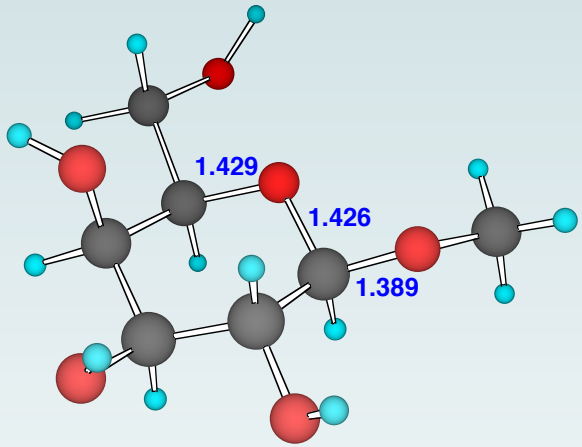
Evidence for the orbital interaction model

O5-C1-O1 angle: 111.4°



methyl α-D-galactopyranoside

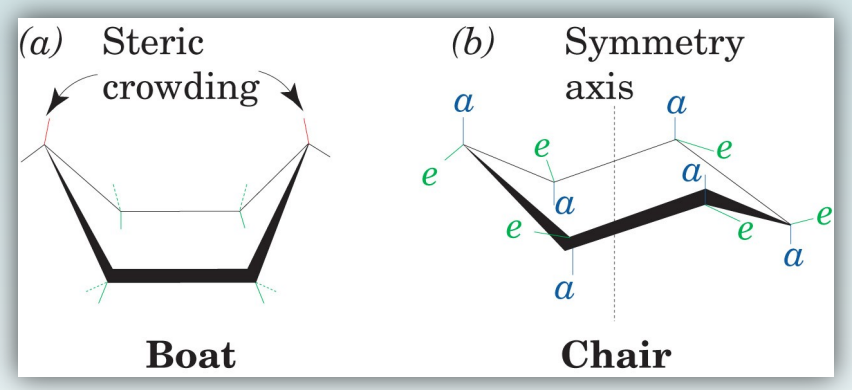
O5-C1-O1 angle: 107.9°



methyl β-D-galactopyranoside

Monosaccharide ring conformation

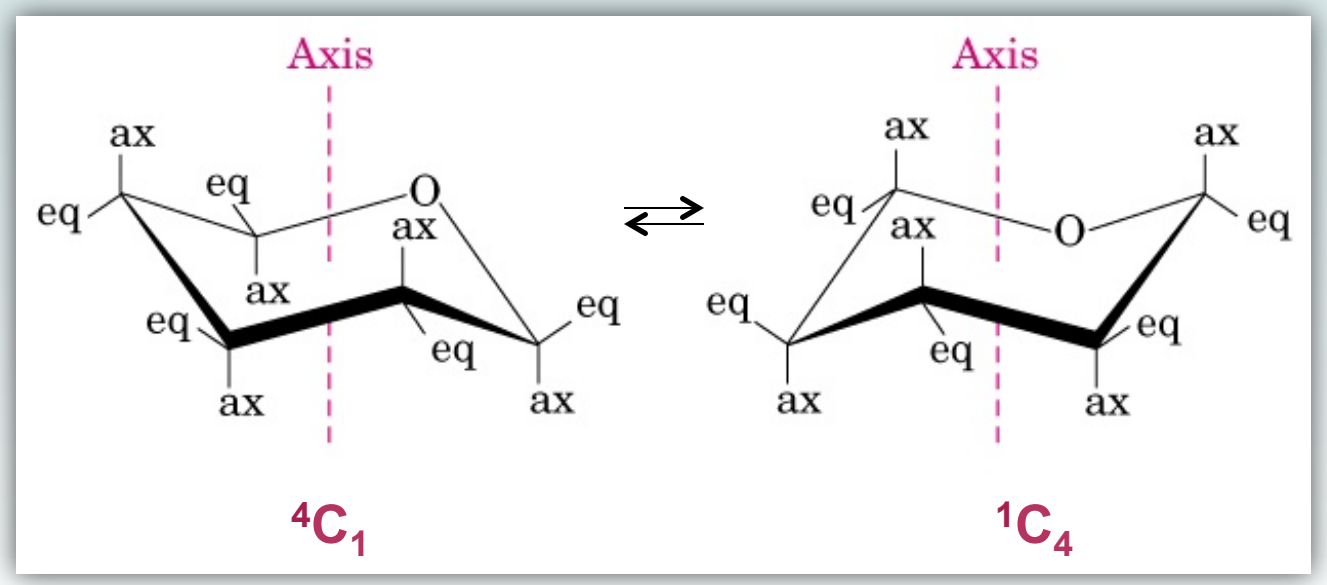
Rings can adopt different three-dimensional structures in solution and in the solid state.

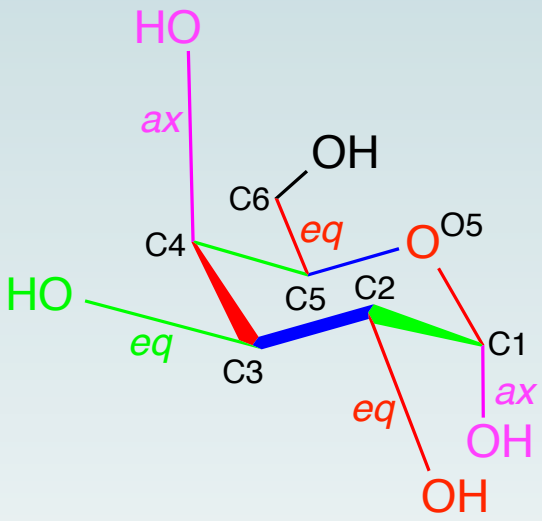


Conformations of the cyclohexane ring. (*a*) **Boat** conformation; (*b*) **chair** conformation. In monosaccharides, the chair conformation is the most common conformation (3D form) of pyranose rings in solution.

Monosaccharide ring conformational dynamics

Different chair conformations interconvert spontaneously in solution, and the rate of interconversion is very rapid. More stable conformations orient bulky groups in **equatorial** (eq) rather than **axial** (ax) positions (excluding substituents at the anomeric carbon where stereoelectronic effects occur).





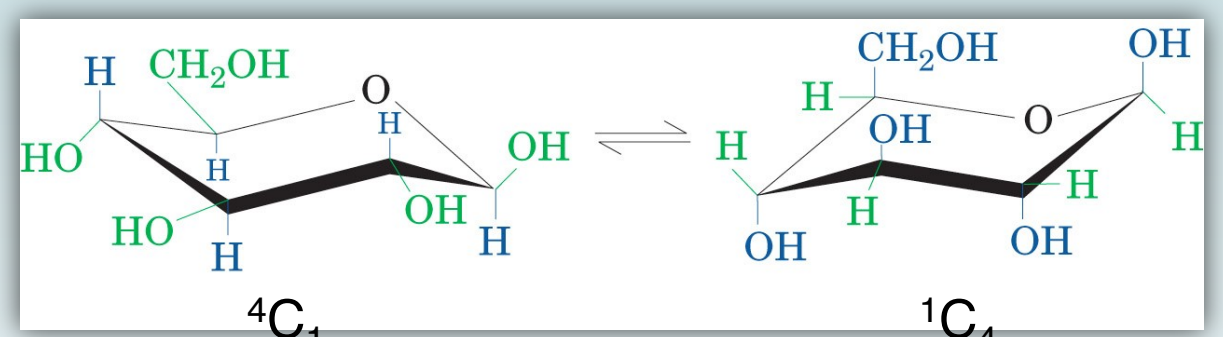
Pyranosyl Ring Drawing Hints

(a) axial (*ax*) bonds (pink) are always orthogonal to the ring plane shown in blue.

(b) equatorial (*eq*) bonds are always parallel to two endocyclic bonds. For example, the C2-O2 and C5-C6 bonds (red) are parallel to the C1-O5 and C3-C4 bonds (red). The C3-O3 bond (green) is parallel to the C1-C2 and C4-C5 bonds (green).

Some of the exocyclic bonds are exaggerated in length in this rendering to emphasize their proper orientation. Normally these lengths are similar to those within the ring, as shown for the C1-O1 and C5-C6 bonds.

Idealized chair conformations of β-D-glucopyranose



$^4C_1$ $^1C_4$

more stable

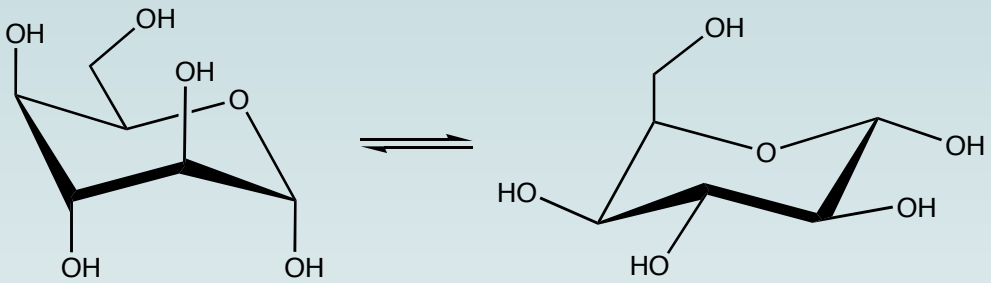
less stable

5 equatorial substituents
0 axial substituents

5 axial substituents
0 equatorial substituents

Note that equatorial and axial substituents exchange orientations upon ring interconversion.

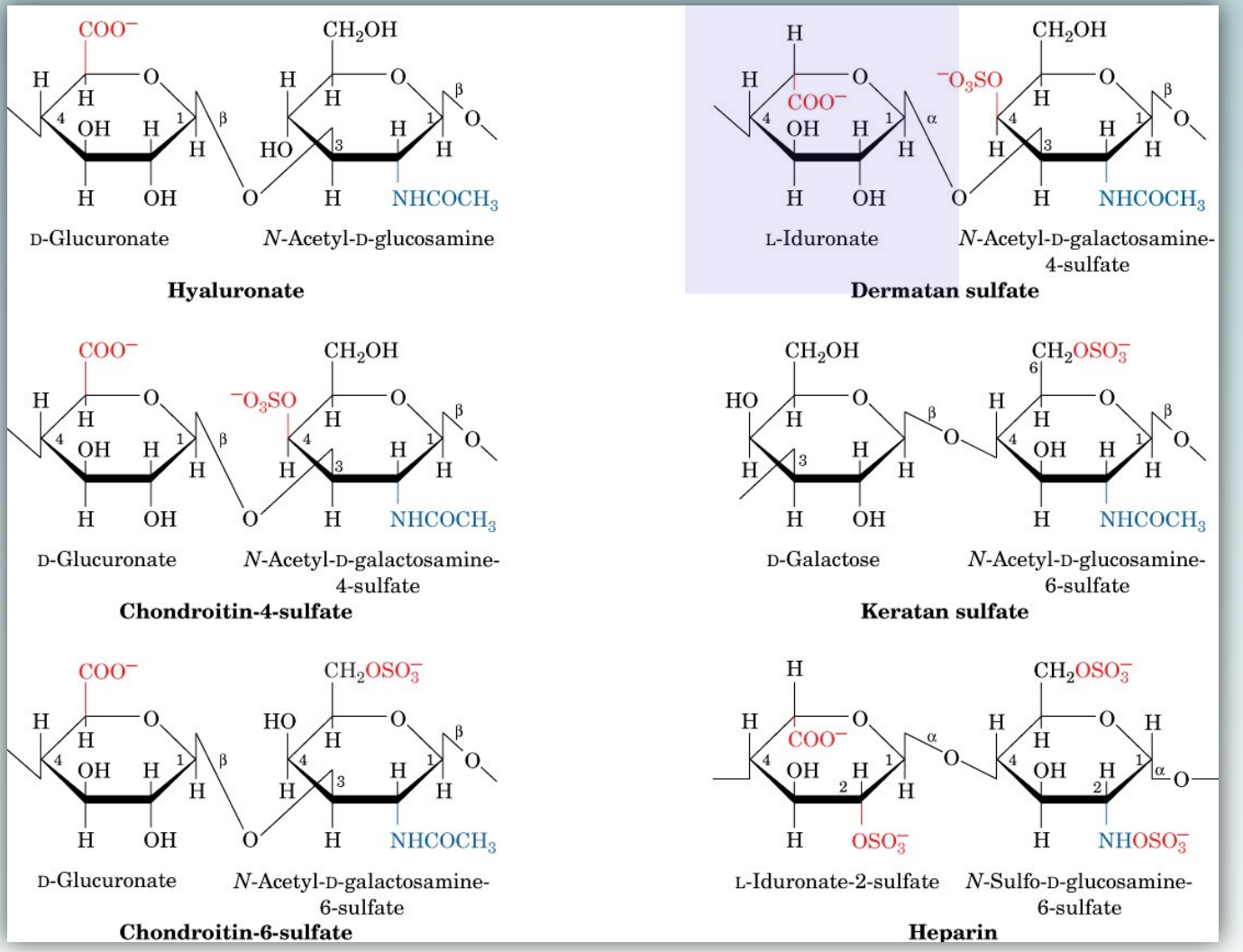
Conformational heterogeneity of the α-D-idopyranose ring



$^{4}C_{1}$
4 substituents axial
1 substituent equatorial
~20%

$^{1}C_{4}$
1 substituent axial
4 substituents equatorial
~80%

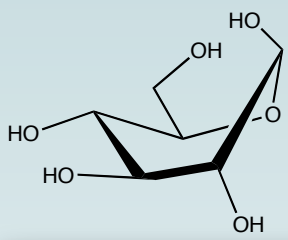
The ido(hexo)pyranosyl ring is observed *in vivo* in the L-configuration and with C6 oxidized to the carboxylic acid (α-L-idopyranuronic acid; IdoA); IdoA is a component of the proteoglycan, dermatan sulfate.

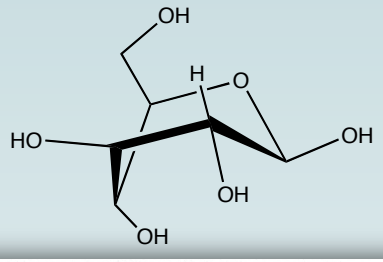


Disaccharide repeating units of the common glycosaminoglycans (proteoglycans): connective tissue; cartilage

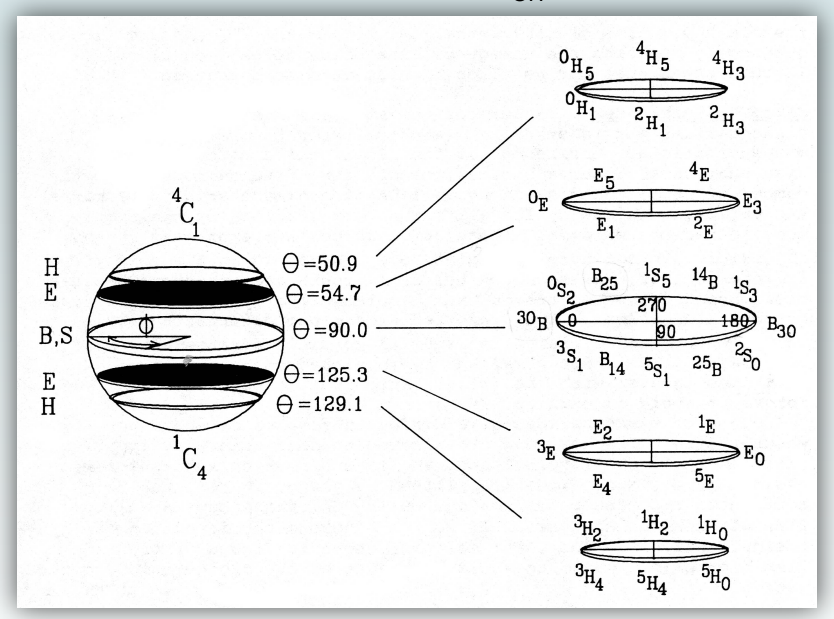
A more detailed description of pyranose conformational dynamics: pseudorotation

In addition to chair forms, pyranose rings can assume half-boat, half-chair, twist-boat and boat conformations.





Two boat conformations of β-D-glucopyranose (6 are possible)



C = chair (2)
H = half-chair (12)
E = envelope (12)
B = boat (6)
S = skew or twist-boat (6)
Total: 38

A pseudorotational model describes systematic interconversion between pyranose conformers.