Chemistry 5.07SC Biological Chemistry I

Fall Semester, 2013

Lecture 13 Introduction to sugar chemistry and polymers of sugars.

I. We have already discussed the chemistry of carbonyls (aldehydes and ketones). We will see in glycolysis, gluconeogenesis and the pentose phosphate pathway that there are two variations on the carbonyl transformations that are essential to understand in carbohydrate metabolism.

Outline of Carbohydrate Lecture:

A. Addition of nucleophiles: carbonyl + H_2O ⇆ carbonyl hydrates (rapid/reversible)

carbonyl (aldehyde or ketone) + ROH ⇆ hemiacetals, hemiketals (rapid/reversible)

carbonyl (aldehyde or ketone) + **Excess ROH, H^+** ⇆ acetals, ketals (stable)

B. For carbonyl compounds with C_α-H → enolization is important

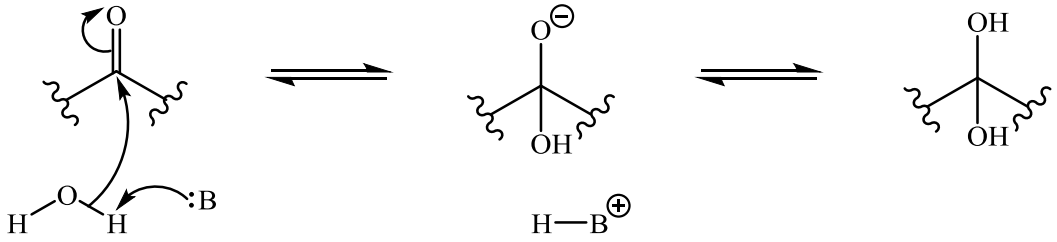
aldose ⇆ ketose example: glucose ⇆ fructose

C and D. Introduction to glucose and polymers of glucose (cellulose and glycogen)

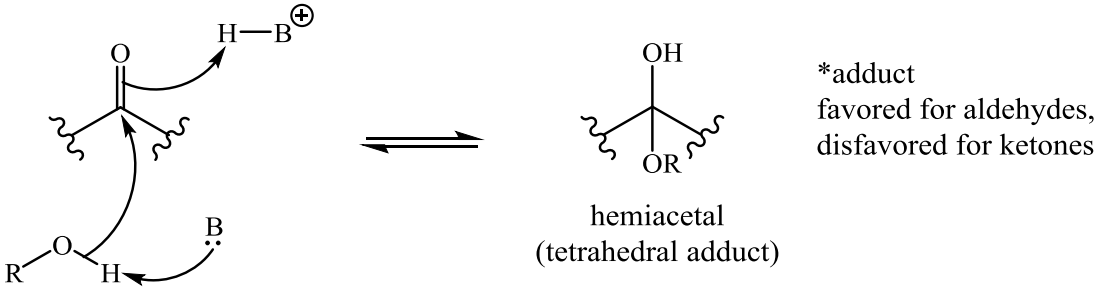
E. Inside the cell, most sugars are present as phosphate monoesters. Phosphate is largely a dianion and it keeps the sugar from diffusing out of the cell.

A. **Carbonyl addition reactions (think electrophile and nucleophile)**

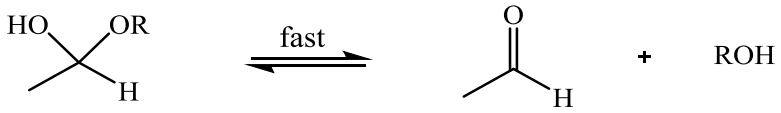
Carbonyl hydrate



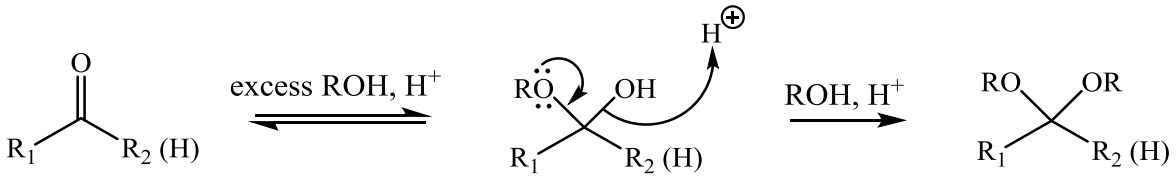
Addition of ROH to form a hemiacetal or hemiketal



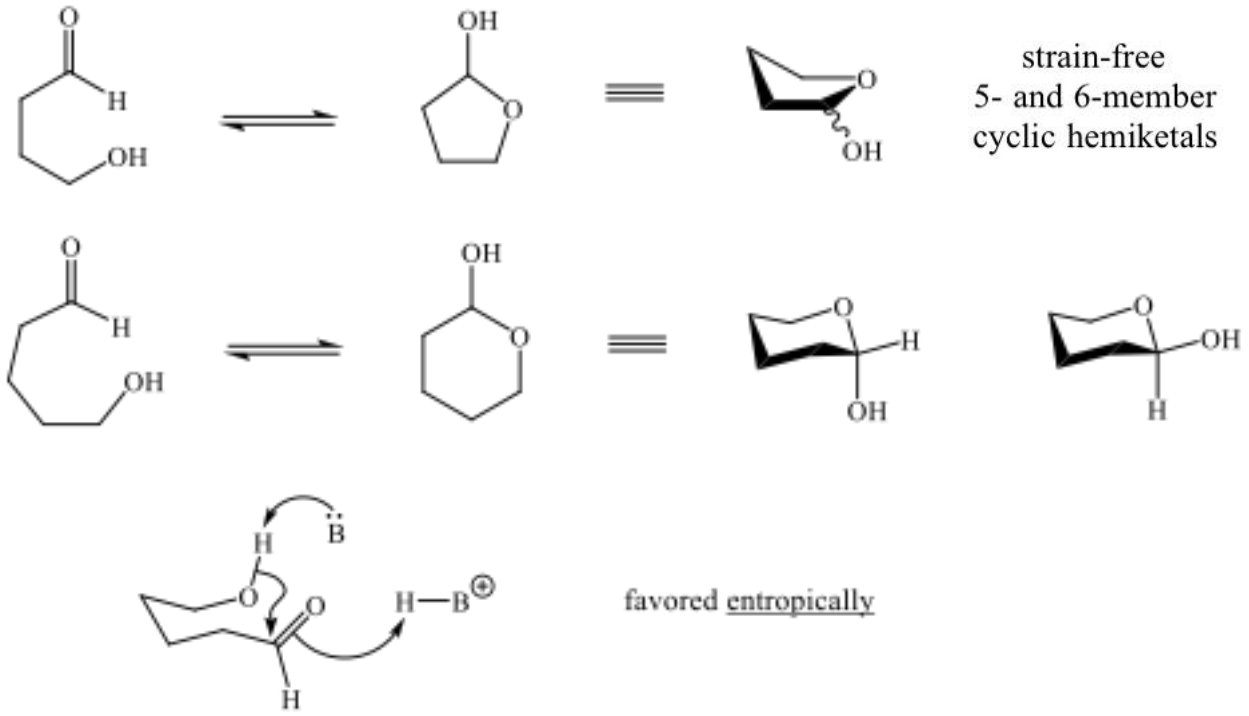
Hemiacetals at pH 7.4 are in rapid equilibrium inside the cell



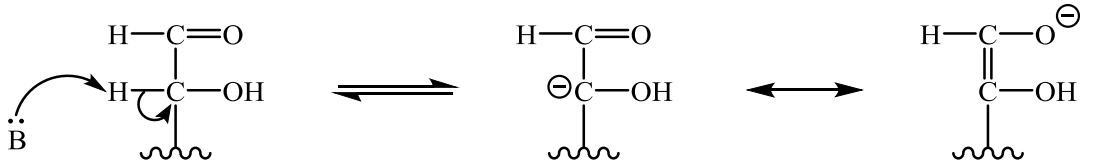
Ketals (R1/R2) and acetals (R1/H) can be generated chemically starting with a ketone or aldehyde in the presence of an excess of alcohol (ROH) and an acid catalyst, H^+. Ketals and acetals, in contrast with hemiketals and hemiacetals, are **usually stable and are not in rapid equilibrium under physiological conditions**.



Sugars involved in glycolysis and nucleic acid metabolism are predominantly six and five membered rings where they form **intramolecular** hemiacetals and hemiketals.

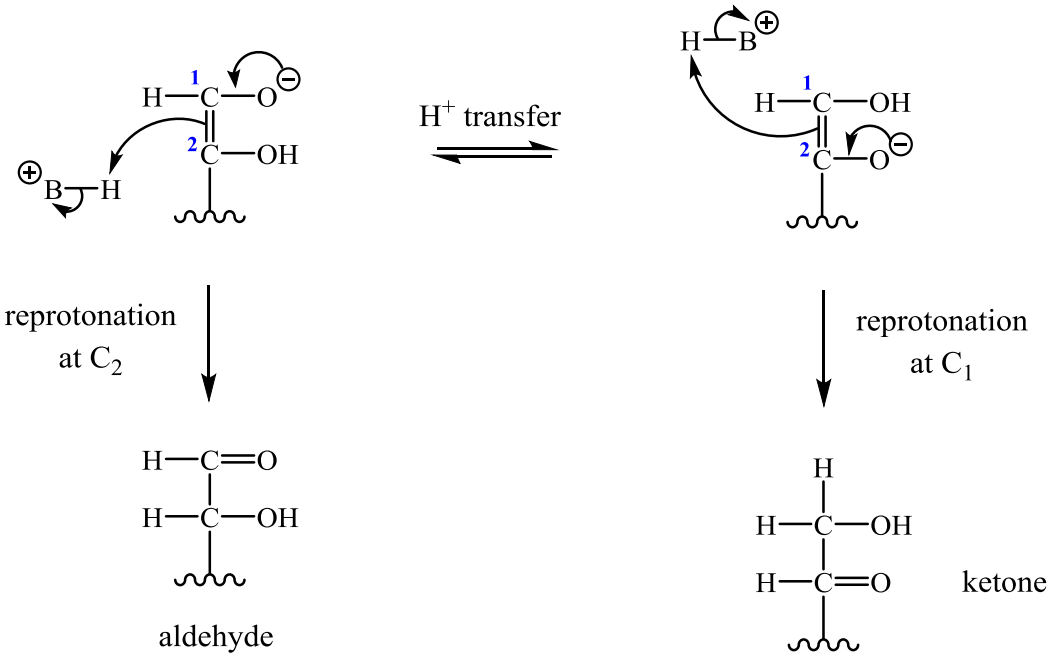


B. Enolization is very important:

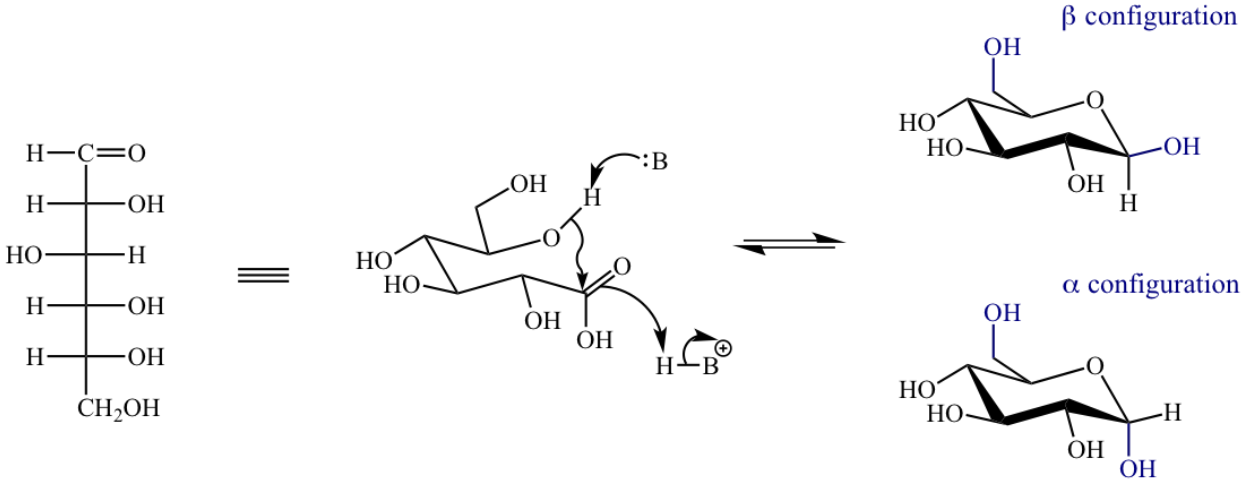


cis ene diolate

The dienolate anion (cis-ene diolate) shown above is resonance stabilized and kinetically accessible. This transformation is essential in conversion (isomerization) of an aldehyde to a ketone (glucose to fructose). [see Problem Set 5 for an example]



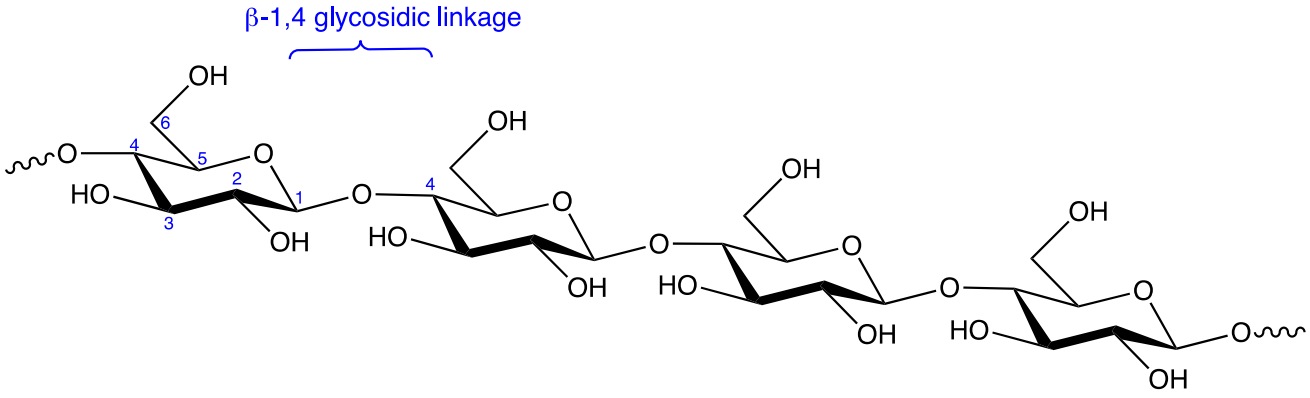
C. Introduction to the structure of the sugars we will deal with in glycolysis, gluconeogenesis and the pentose phosphate pathway (PPP). Glucose shown below is a polyhydroxyaldehyde.



Glucose (whose structure you need to remember) rapidly forms intramolecular hemiacetals where the C5-OH attacks the aldehyde. The attack of the C5 OH can occur from the top face of the aldehyde to give the HO in the α configuration at C1 or from the bottom face of the carbonyl

and which gives the β configuration at C1. The C1 position is the **anomeric carbon** and the α and β conformers rapidly interconvert through the ring opened aldehydic species. (For practice draw the mechanism of this interconversion).

D. Just like we showed in Lecture 2, that amino acids are the building blocks for polypeptides by a dehydration reaction. Monosaccharides are also the building blocks for polysaccharides by dehydration reactions. Two examples of very important polysaccharides are shown below: cellulose (poly-β-1,4-glucosyl units, several hundred to 10^4) is the major constituent of wood (cotton) and glycogen, the storage polymer of glucose in humans (plants).



Cellulose is the most abundant macromolecule on earth. The polymers of cellulose form microfibrils via H bonding interactions that possess great tensile strength. The structures differ from organism to organism (Figure 1A).

A. B.

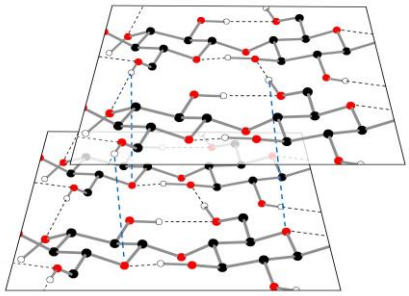
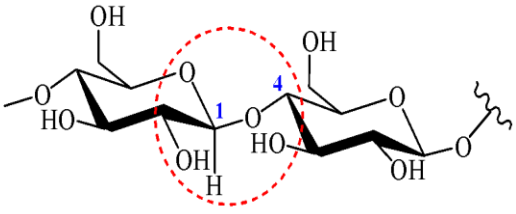


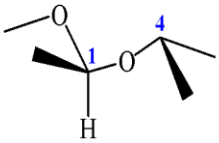
Figure 1B by O'Reilly Science Art for MIT OpenCourseWare.

A. Courtesy of Elsevier, Inc., http://www.sciencedirect.com. Used with permission.
Source: Kirby, Andrew R., A. Patrick Gunning, Keith W. Waldron, Victor J. Morris, and Annie Ng. "Visualization of plant cell walls by atomic force microscopy."*Biophysical Journal* 70, no. 3 (1996): 1138.
B. PDB: 4FER.
Georgelis, Nikolaos, Neela H. Yennawar, and Daniel J. Cosgrove. "Structural basis for entropy-driven cellulose binding by a type-A cellulose-binding module (CBM) and bacterial expansin." *Proceedings of the National Academy of Sciences* 109, no. 37 (2012): 14830-14835.

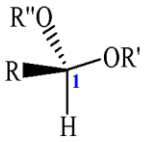
Figure 1. Cellulose. A. Micrograph of cellulose fibers of the cell wall of *Eleocharis dulcis* L. plant cells. B. Schematic of cellulose fibers from *Bacillus subtilis*.

Note in the cellobiose linkage (two sugars, Figure 1B) shown above, the **acetal linkages are stable** under physiological conditions as the sugars possess stable carbonyl protecting groups. Non-enzymatic breakdown is negligible under physiological conditions. We saw with polypeptides where the amides provide stable linkages, proteases play an important role in CONTROLLED proteolysis. Similarly glycosidases (breakdown of polymers of sugars) play an important role in breakdown of sugars. Many scientists are interested in the breakdown of cellulose to make feed stocks to generate economically competitive biofuels. We will look in some detail at glycogen phosphorylase, the enzyme involved in the breakdown glycogen that is the storage form for glucose in humans.



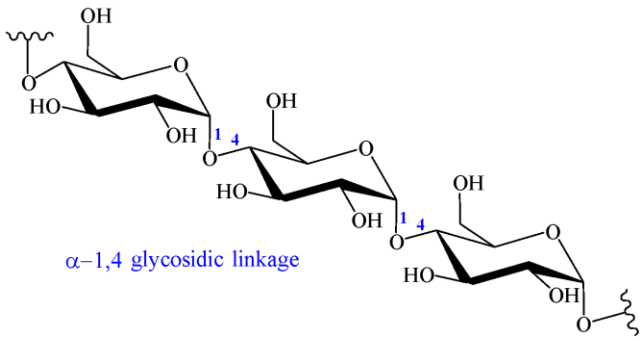


Look at C_1:

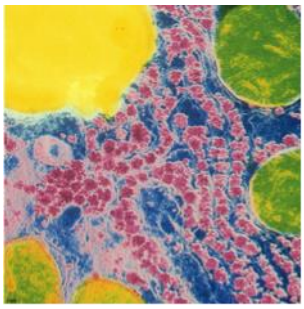


The structure of **glycogen** (poly-α-1,4-glucosyl units with α-1,6-glucosyl branches) is shown in Figure 2: Note the α−1,4 glycosidic linkage gives glycogen a distinct structure from cellulose. The micrograph shows the insoluble glycogen in dark blue that is deposited in heart and brain cells (Figure 2B).

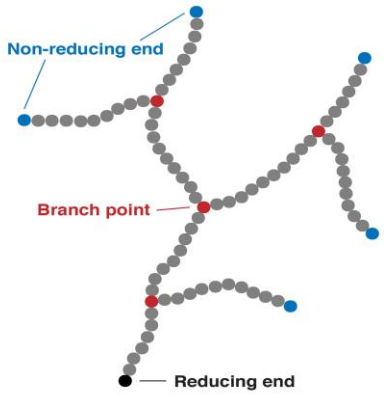
A.



B.



C.



D.

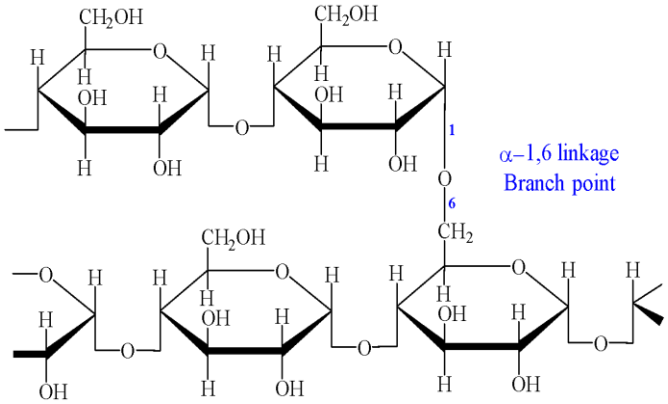


Figure 2C by O'Reilly Science Art for MIT OpenCourseWare.

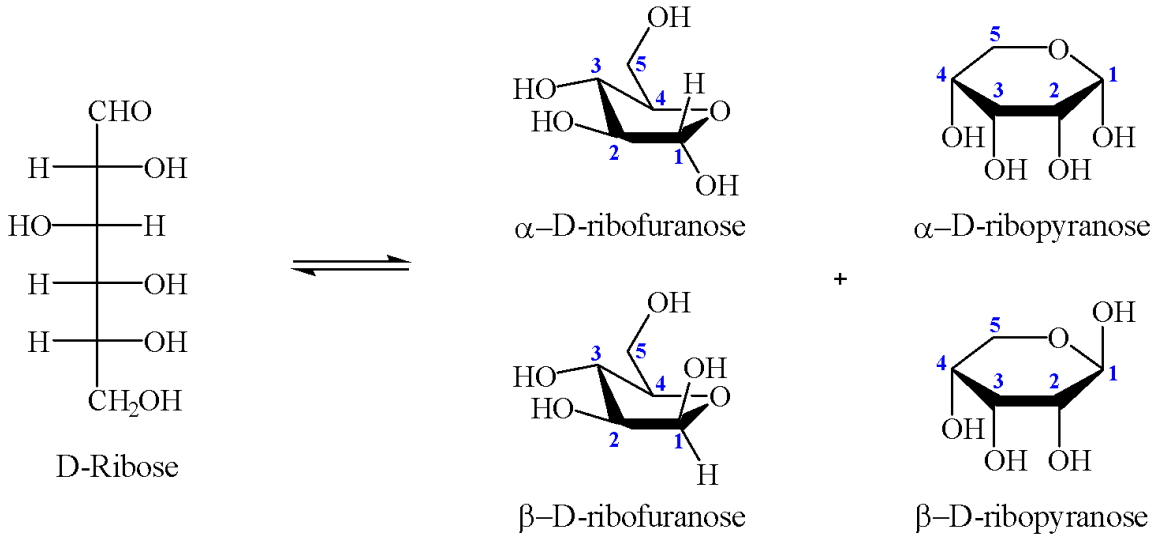
Figure 2. Glycogen. A. α-1,4 glycosidic linkages. B. Micrograph of crystalline-packed cellulose (pink) that has made a phase transition from soluble to insoluble polymer. C. Schematic of branched glycogen. D. Branching is the result of α-1,6 glycosidic linkages.

Given the differences in function of glycogen in the liver (storage) and in the muscle (rapid source of glucose when the Doberman pinscher chases you), do you think that the mechanisms of

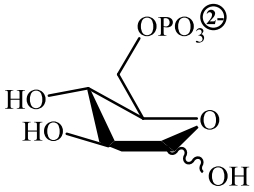
depositing this insoluble biopolymer in both organs is the same? One form of the polymer needs to be reused rapidly, while the other does not. Polymers of glucose have long been of interest as there are many glycogen storage diseases.

Type	Enzyme Deficiency	Tissue	Common Name	Glycogen Structure
I	Glucose-6-phosphatase	Liver	von Gierke's disease	Normal
II	α-1,4-Glucosidase	All lysosomes	Pompe's disease	Normal
III	Amylo-1,6-glucosidase (debranching enzyme)	All organs	Cori's disease	Outer chains missing or very short
IV	Amylo-(1,4→1,6)-transglycosidase (branching enzyme)	Liver, probably all organs	Andersen's disease	Very long unbranched chains
V	Glycogen phosphorylase	Muscle	McArdle's disease	Normal
VI	Glycogen phosphorylase	Liver	Hers' disease	Normal
VII	Phosphofructokinase	Muscle	Tarui's disease	Normal
VIII	Phosphoryl kinase	Liver	X-linked phosphorylase kinase deficiency	Normal
IX	Phosphoryl kinase	All tissues		Normal
O	Glycogen synthase	Liver		Normal, deficient in quality

E. Phosphorylated sugars. Five membered ring sugars are also prevalent in biology. You have seen the structure of ribose in the lecture describing the chemistry of ATP. Ribose is another structure you should know, as it will be encountered often. However, in addition to the furanoses shown below, ribose exists as a pyranose, a six membered ring with the hemiacetal formed between C1 and the hydroxyl of C5.



The structure of ribose-5-P is shown below. It maintains ribose in the furanose form inside the cell.



We are now ready to study our first metabolic pathway: glucose as a fuel in glycolysis. Where are we in the complex metabolic pathways chart from Lecture 1?

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