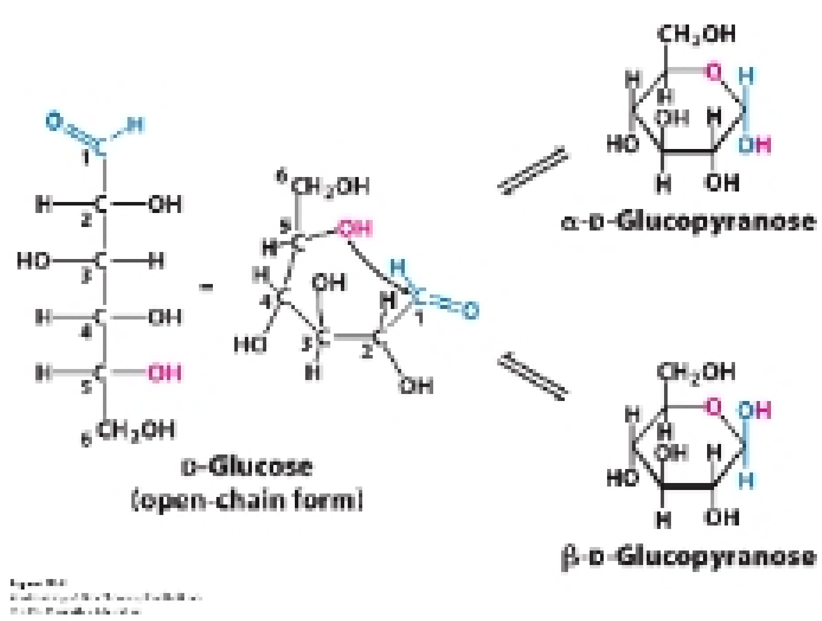
CMB 311 Fall 2017
Monday, October 16
Lecture 15 Notes
Carbohydrates and Glycolysis I

In this lecture, we discussed carbohydrates and glycolysis. Carbohydrates are the preferred carbon sources for many organisms. First we covered the nomenclature and classification of carbohydrates:

- The term 'carbohydrate' comes from the formula $C_m(H_2O)_n$ suggesting 'hydrates of carbon', but...
- Later found to be polyhydroxy aldehydes and ketones
- Range in size from 3 to 6 carbons
- Carbohydrate names contain the suffix 'ose'
- Also referred to as 'saccharides' and 'sugars'
- Present as monosaccharides (1 sugar), the smallest unit, disaccharides (2 sugars), polysaccharides (many sugars), linked together

Carbohydrates can be classified into two groups, **aldoses** (that is, they are aldehydes, with a carbonyl group at the end of the molecule) or **ketoses** (ketones, with a carbonyl attached to two carbon atoms). Different carbohydrates are distinguished by the relative orientations of their hydroxyl groups. In aqueous solution, most carbohydrates form cyclic structures by the formation of **hemiacetals** and **hemiketals**, involving the reaction of the aldehyde or ketone group with one of their hydroxyl groups. This creates a new asymmetric carbon atom, creating two isomeric forms known as **anomers**, designated α and β. Cyclic forms of carbohydrates are presented as Haworth projections, indicating the stereochemistry of the hydroxyl groups. Note here that for some carbohydrates, a mixture of 5-membered and 6-membered rings can form, depending on which hydroxyl group forms the hemiacetal or hemiketal. 5-membered ring forms are called **furanoses**, while 6-membered rings are called **pyranoses**, after the compounds furan and pyran, respectively. Carbs with 5 carbons are called **pentoses**, those with 6 carbons are called **hexoses**. Thus, there are **aldopentoses** and **aldohexoses**, **ketopentoses** and **ketohexoses**. Glucose is an aldohexose, while fructose is a ketohexose. *Do not confuse the number of atoms in the ring with the number of carbon atoms in the sugar.* Thus, glucose and fructose are both hexoses, but glucose forms a 6-atom ring while fructose forms a 5-membered ring (since glucose is an aldose and fructose is a ketose, and both form cyclic structures by reaction of the carbonyl with the OH of carbon number 5). These are also chiral molecules, and are classified via their stereochemistry. This is most easily visualized by Fisher projections, shown at the left in the figure. Based on the orientation of the OH group on the



asymmetric carbon furthest from the aldehyde or ketone group, they are classified as either 'D' or 'L' isomers, with the OH group drawn to the right for D-sugars and to the left for L-sugars. For D-glucose, the hydroxyl group on carbon 5 is drawn to the right (carbon 6 is not asymmetric). For the Fisher projection of L-glucose, all the hydroxyl groups would be drawn in the opposite direction. In the Haworth drawings on the figure, you can see that glucose adopts a 6-membered pyranose ring. By convention, the Haworth projection of the α anomer (α-D-glucopyranose) shows the OH group pointed downward, while that of the β anomer (β-D-glucopyranose) shows the OH pointed upward.

Further reaction between the carbonyl of one sugar and an OH group of another can lead to formation of acetal or ketal in a condensation reaction. This leads to disaccharides linked together by an *O*-glycosidic bond. One important disaccharide is lactose, found in milk. Lactose is hydrolyzed in humans by the enzyme lactase (β-galactosidase). Ancestral humans produced lactase only during infancy, and stopped producing it in adulthood. Some modern human populations persist in producing lactase into adulthood, mainly in areas where dairy products remain part of the adult diet. People in other populations are unable to digest lactose, so it passes into the lower GI tract where bacteria can hydrolyze it with unpleasant consequences.

Sugars can form many higher-order structures, called polysaccharides, and many of these are very important. These include starch, glycogen and cellulose, all polymers of glucose. They differ in their linkages and the degree of branching.

Glycolysis

The bulk of this lecture focused on glycolysis. Glycolysis is the process by which glucose, a 6-carbon molecule, is converted to 2 molecules of pyruvate, a 3-carbon molecule. This takes ten steps, divided into two phases. The preparatory phase requires the investment of two ATP molecules. The payoff phase is where ATP and NADH are produced.

Preparatory phase:

This involves the conversion of glucose to two triose phosphate molecules, driven by the hydrolysis of two ATP molecules.

1. Phosphorylation of **glucose** to **glucose-6-phosphate** by the enzyme **hexokinase**. Uses 1 ATP molecule.
2. Isomerization of **glucose-6-phosphate** to **fructose 6-phosphate** by **phosphohexose isomerase**. This step is necessary for the later cleavage reaction (step 4) to produce two triose molecules.
3. Phosphorylation of **fructose 6-phosphate** to **fructose-1,6-bisphosphate** by **phosphofructokinase**. Uses a second ATP molecule.
4. Cleavage of **fructose-1,6-bisphosphate** to **glyceraldehyde-3-phosphate** and **dihydroxyacetone phosphate** by **aldolase**. This is the actual 'glycolytic' reaction, or splitting of glucose.

Payoff phase:

5. Isomerization of **dihydroxyacetone phosphate** to **glyceraldehyde-3-phosphate** by **triose phosphate isomerase**. This results in two molecules of glyceraldehyde 3-phosphate per molecule of glucose. This isomerization drives the reaction forward, since it removes dihydroxyacetone phosphate thereby preventing the back reaction.
6. Oxidative phosphorylation of **glyceraldehyde-3-phosphate** to **1,3-bisphosphoglycerate** by **glyceraldehyde-3-phosphate dehydrogenase**. This uses inorganic phosphate and *not* ATP. It does reduce one molecule of NAD^+ to NADH per molecule of 1,3-bisphosphoglycerate formed. The large negative $\Delta G^{\circ\prime}$ for oxidation drives the reaction forward.
7. Conversion of **1,3-bisphosphoglycerate** to **3-phosphoglycerate** by **phosphoglycerate kinase**, with a phosphate being transferred to ADP to produce the first molecule of ATP generated by glycolysis. This is called *substrate-level* phosphorylation. A total of two ATP molecules are generated per molecule of glucose at this step. This reaction is thermodynamically favorable because of the resonance stabilization of the resulting carboxyl group of 3-phosphoglycerate. Note that this molecule differs from glyceraldehyde-3-phosphate in having a carboxyl groups instead of an aldehyde. Thus, it is the oxidation of that aldehyde to a carboxyl that provides the energy for the formation of ATP.
8. Conversion of **3-phosphoglycerate** to **2-phosphoglycerate** by **phosphoglycerate mutase**. This reaction simply moves the phosphate from the 3 position to the 2 position, setting up the final steps of the pathway.
9. Dehydration of **2-phosphoglycerate** by **enolase**. This produces the high energy compound **phosphoenolpyruvate** (PEP) that adopts a high energy enol tautomer.
10. Transfer of a phosphoryl group from PEP to ADP to produce the second pair of ATP molecules per molecule of glucose. This reaction is catalyzed by **pyruvate kinase**. The result is **pyruvate**. PEP hydrolysis is driven by the tautomerization of pyruvate from the enol form to the more stable keto form and by resonance stabilization of the free phosphate (if there were one...) and resonance stabilization of the carboxylate ion. Tautomerization also prevents the reverse reaction, thus driving the forward reaction.

Some important principles

- Carbonyl groups are important for reactions that form or break C-C bonds.
- ATP provides energy by group transfers, *not* by simple *hydrolysis*.
- ATP concentration is held high above the equilibrium concentration by catabolism.
- Important factors in driving reactions forward:
  - Resonance stabilization
  - Reactivity of bonds in the α-position relative to carbonyls
- For reactions with an unfavorable $\Delta G^{\circ\prime}$ reactions can be driven forward by removing the reaction product, i.e. by the next step in the pathway.