Chapter 18 – Carbohydrates

18.1   <u>Biochemistry</u>

Before we get to carbohydrates, we need a brief introduction to biochemistry. Your book's definition of biochemistry is "the systematic study of the chemicals of living systems, their organization, and the principles of their participation in the processes of life." A more compact one found in a biochemistry textbook is "the study of the molecular basis of life." Both say the same thing.

Where do chemistry and biology diverge? A similar question could have been asked near the beginning of CHM 203. That is: where do chemistry and physics diverge? After all, you had to learn and use quite a bit of physics last semester. One answer to this question is the proton, neutron, and electron. Chemists care about these particles and things made up of them, but nothing smaller. Since they are completely understood, physics no longer cares much about them, so these particles form a fairly clear dividing line between chemistry and physics. We can look for similar such "particles" as markers in biological systems. Clearly anything larger than the cell won't matter to a chemist (under ordinary conditions). After this, the response enters a gray area. In fact within the cell, many molecules and structures have significant chemical and biological interest and fall under the broad umbrella of biochemistry and molecular biology. The subject matter is largely the same, but the perspective is different.

In the coming sections and chapters we will see the functional groups and stereochemistry discussed in previous chapters. One significant difference between what we have covered and what we will cover is that most, if not all, transformations will involve enzymes rather than traditional chemical substrates. We will also learn new naming systems that are significantly different from the ones we have already seen. One section you should go back and look over if

you didn't understand it is the polymer chemistry section (Section 12.6). Many of the molecules you will encounter in the coming chapters are polymers of one kind or another. You'll have to review specific functional groups on a chapter-by-chapter (or section-by-section) basis, but the polymer thread will run deeply through this material.

We will see how the body takes raw materials (food and oxygen), breaks them up into usable pieces, then reconstructs them into new chemicals. These new chemicals may be stored energy (e.g. fats, glycogen), structural materials (e.g. proteins), or ways of storing or transmitting information (e.g. DNA). We will begin our discussion with energy.

18.2   Introduction to Monosaccharides

There is no simple definition of "carbohydrate," although your book's description of them as "aldehydes and ketones with many OH groups, or substances that form these when hydrolyzed" is a good description of them. The word *carbohydrate* comes from the phrase "hydrate of carbon" because most, but not all, carbohydrates have the formula $[C(H_2O)]_x$ $(x \geq 3)$. (When x = 1 the compound is formaldehyde, certainly not something you'd want to sprinkle on your corn flakes!)

Carbohydrates are produced exclusively by plants and are their principal way of storing energy and their molecular building materials (e.g. cellulose). They result from photosynthesis. In this process carbon dioxide (CO_2) and water are combined to form CH_2O units with the release of molecular oxygen (O_2) as a waste product. As you can see, carbohydrates result from properly stringing together CH_2O units.

The simplest of the carbohydrates are the monosaccharides. They are sometimes called *simple sugars*. All of these compounds possess the generic formula $(CH_2O)_x$. Two broad

categories they may be broken into are aldoses and ketoses. As you might guess, those sugars incorporating an aldehyde group are called <u>aldoses</u>, while those including a ketone carbonyl are <u>ketoses</u>. Another way of classifying monosaccharides is by the length of their carbon chain. Thus, <u>trioses</u> are 3 carbons long, <u>tetroses</u> are 4 carbons long, etc. These terms can even be combined. Thus, a 5 carbon sugar ending in an aldehyde groups would be a aldopentose. We will find a number of sugars of all types up to 6 carbons long important for humans. Examples include (ignoring stereocenters for now):
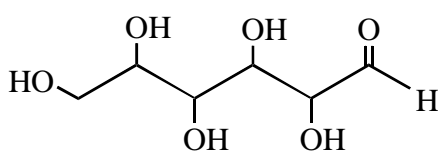
glucose   fructose
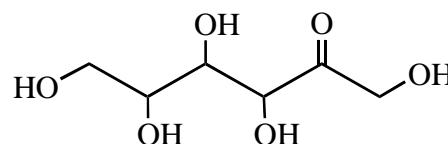
an aldohexose   a ketohexose

Remember that in reality these molecules exist mostly (>99.9% at room temperature) as rings. We'll come back to this later in the chapter, but the cyclic system formed by glucose appears in the notes on p. 9 of the Chapter 14 notes.

When two monosaccharides couple, the product is a <u>disaccharide</u>. <u>Polysaccharides</u> form when more than 10 monosaccharides couple. Sucrose, lactose, and maltose are disaccharides, while cellulose and starch are polysaccharides. Both cellulose and starch have many hundreds of monosaccharides in their structures. Structures containing 2 – 10 sugar residues are called <u>oligosaccharides</u>.

All monosaccharides give positive Tollens' and Benedict's tests (p. 3 Chapter 14 notes). Most disaccharides do as well (sucrose is an exception). No polysaccharides give positive tests. We'll see why later in the chapter.

There are 4 stereocenters in glucose (the 4 internal carbons bound to hydroxy groups). This

translates into 16 stereoisomers (8 pairs of enantiomers). Only one of these [(+)-glucose)] is nutritionally important. This one stereoisomer is used to make starch, cotton, and cellulose. As you know, humans can't digest cellulose but we can digest starch. Why the difference? We'll see that the molecules are put together slightly differently, and that one difference renders one non-digestible by almost all creatures.

18.3   D- and L-Families of Carbohydrates

It turns out all of the aldoses have a common ancestor as do all of the ketoses. By this we mean that if we start with the three carbon aldose, glyceraldehyde, all other aldoses of interest may be made by inserting a CHOH group after the carbonyl carbon. For example:

glyceraldehyde   erythrose or threose
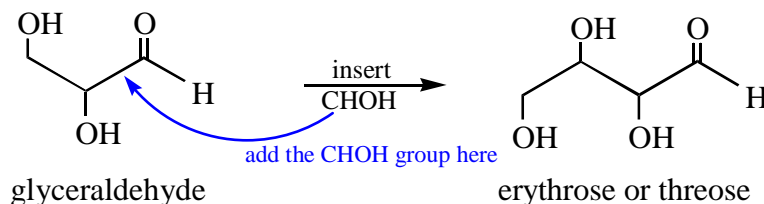
(depends on the orientation of the CHOH group)

Ketoses are built up similarly from 1,3-dihydroxypropanone (1,3-dihydroxyacetone). We'll return to this shortly.

In all of these sugars, each of the carbons except the end carbons (and carbonyl carbon in ketoses) are chiral centers. In glyceraldehyde there is only one stereocenter, resulting in two enantiomers. As with all chiral molecules, one enantiomer rotates plane polarized light in the positive direction [(+)-glyceraldehyde] and the other in the negative direction [(-)-glyceraldehyde]. For reasons we don't need to consider, (+)-glyceraldehyde is the parent of the D-family of aldoses, and (-)-glyceraldehyde is the parent of the L-family of aldoses.

There are three things important to remember here. First, only the D-family of

carbohydrates occurs naturally. Next, belonging to the D- or L-family depends only on the chiral carbon farthest from the carbonyl carbon. Finally, the +/- sign has nothing to do with the D/L-family the compound belongs to.

Until now, there have been only two pictures in this chapter's notes. Visualizing these molecules is very important in understanding how they react. Unfortunately, trying to draw a realistic 3-dimentional picture on paper is somewhat challenging, although your book does a nice job on p. 521. Chemists have developed alternative methods for straight chain and cyclic molecules that work very nicely, if you remember a couple of short rules. We'll discuss the straight chain method here and the cyclic method later.

Let's use glyceraldehyde as an example. The figure below attempts to show a 3-dimensional representation of the D enantiomer.

$$O$$
$$\|$$
$$CH$$
$$H \quad OH$$
$$CH_2OH$$
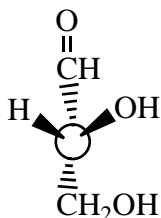
Remember the solid triangles are coming towards you out of the paper, while the dashed triangles are fading away from you. All angles are about 109.5°. Now imagine that you can pick the molecule up and set it on a sheet of paper. If a light sat directly above each atom what would the shadow look like. Another way of thinking about this is, what would it look like if you took your hand and pushed straight down on the molecule? This is how chemist's represent such figures. The method is called the <u>Fischer projection</u>.

$$O$$
$$\|$$
$$CH$$
$$H \quad OH$$
$$CH_2OH$$

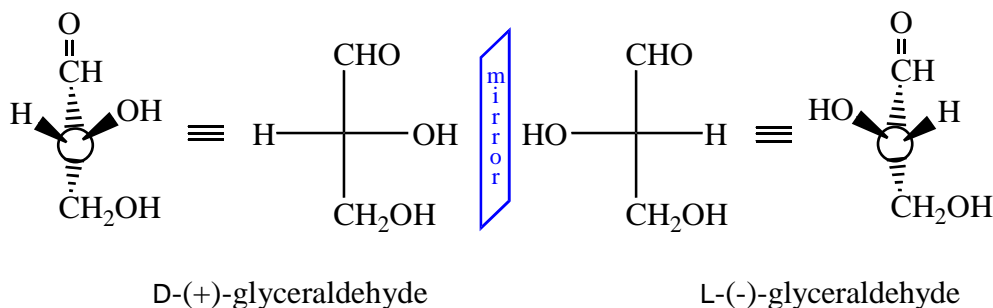$$CHO$$
$$H \longrightarrow OH$$
$$CH_2OH$$
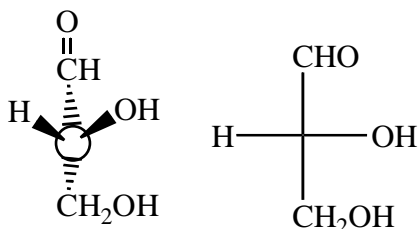
Do you see the similarity? To do this in general, line up the carbon chain down the sheet of

 paper. Then do this for each carbon. Thus for an aldotetrose:
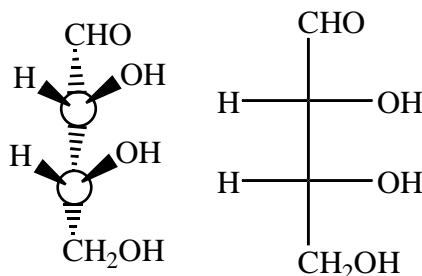
The beauty of this is that it lets one represent chiral molecules simply and without confusion.

Let's go back to glyceraldehyde.

D-(+)-glyceraldehyde   L-(-)-glyceraldehyde

   In all Fischer projections C1 goes at the top of the figure. For aldoses this is the aldehyde

carbon. The complete set of rules is put down in tabular form by your book on p. 522. When the

stereocenter furthest from the carbonyl group has its OH group on the left side of the Fischer

projection one has the L enantiomer. If the OH is on the right, one has the D enantiomer. While

henceforth we will only use D enantiomers, you should be able to distinguish between the D and

L forms.

   Figures 18.4 and 18.5 (p. 525-26 of the book) show all of the D enantiomers for carbon

chains up to 6. Notice how in each case a CHOH group is added after the carbonyl carbon, one

on the left, the other on the right. Each gives a different sugar. You should be careful to

remember that the differences between these sugars are not simply cosmetic.

18.4   Cyclic Forms of Monosaccharides

An interesting feature of glucose that your book discusses at length is that when solutions are made, their optical rotations change with time from an initial value to a final value. Recovery of crystalline glucose from the final solution shows it to be identical in every other way to the starting glucose. Redissolving causes the same cycle to reoccur. Under the right conditions a different set of crystals can be obtained, but these two move from an initial optical rotation to the same final value. So what is happening? First a definition. Mutarotation occurs when the optical rotation of a substance changes with time but there is no other *apparent* change in the solution. We'll elaborate on this further in a few paragraphs.

Recall from Chapter 14 (p. 7 of the notes) that a hemiacetal forms from the reaction of an alcohol with an aldehyde. The generic reaction is:
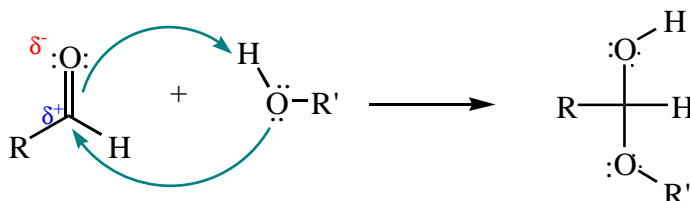
All of the aldoses have both groups within the same molecule and can engage in the generation of a hemiacetal internally. The result is a cyclic structure. At this point you should open your book to p. 528 and look at the figure at the top of the page. The center drawing shows the formation of the hemiacetal. As you can see two different products can form. Although the difference is subtle in appearance, it is huge in practical terms. More about this later. First assume the hydroxy group and carbonyl groups lie in the plane of the paper. In this the aldehyde hydrogen must lie perpendicular to the plane of the paper. Either it points straight up or down. This results in the α-form (straight down) and β-form (straight up). This designation applies to all of the sugars that we will encounter. These isomers are called anomers. Anomers are

isomers that differ only in the spatial configuration of the hemiacetal or hemiketal carbon.

α-D-glucose
36%

D-(+)-glucose
0.05%

β-D-glucose
64%
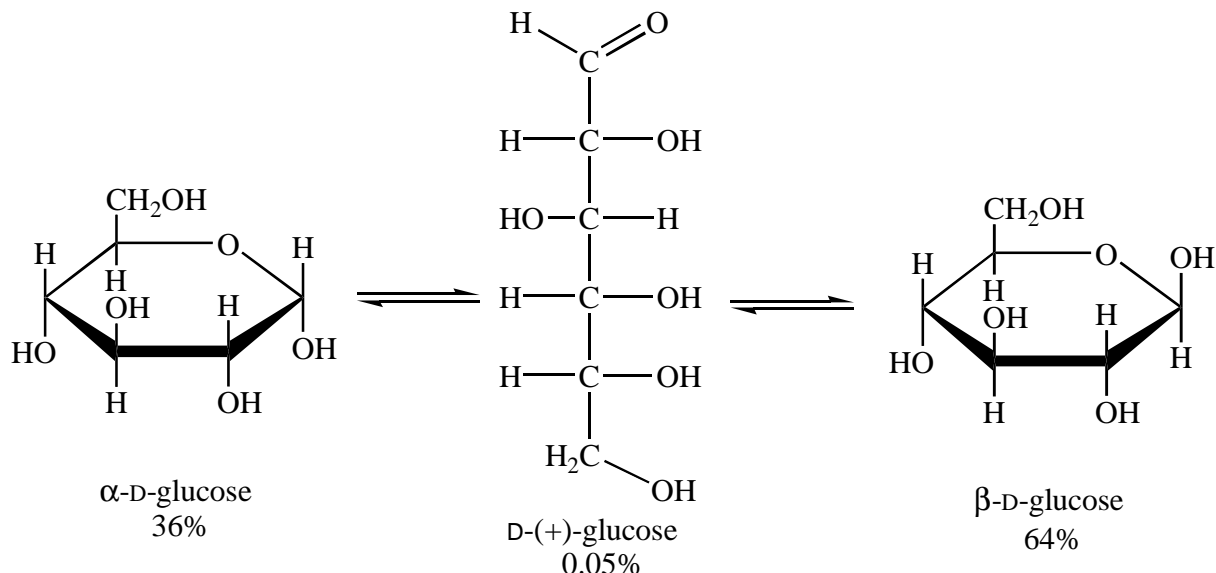
Your book correctly notes that these rings are not actually flat. Fortunately for most

purposes the actual 3-dimensional geometry isn't needed. Instead we can use drawings like

those above which show clearly the relative orientation of the various groups attached to the ring.

These drawings are called Haworth projections and are only used for the cyclic forms of

molecules. By convention, sugars are always drawn with the oxygen in the upper right hand

corner of the molecule (6-membered rings) or top-center (5-membered rings). You should get

used to writing and understanding them. The CH_2OH group(s) will always be above the ring.

The other hydroxide groups are placed using the rule that groups on the right side in a Fisher

projection lie will be placed below the ring in a Haworth projection. When interconverting

between Fisher and Haworth projections make sure you keep the numbering of the carbon atoms

straight. You can skip the highly condensed structures shown in Figure 18.7.

This equilibrium explains the mutarotation described earlier. When either pure α-D-glucose

or β-D-glucose is dissolved in pure water it slowly equilibrates to a mixture of all three of the

species shown in the previous figure (34% α, 66% β, 0.05 % open at room temperature).

Other important monosaccharides include galactose, the ketohexose fructose, and the aldopentoses ribose and 2-deoxyribose (like glucose all have α-, β-, and open chain forms). β-D-ribose and β-D-deoxyribose are important because of their roles in the structure of RNA and DNA, respectively.

α-D-glalactose

α-D-fructose

β-D-ribose


note the oxygen has been removed here

β-D-deoxyribose
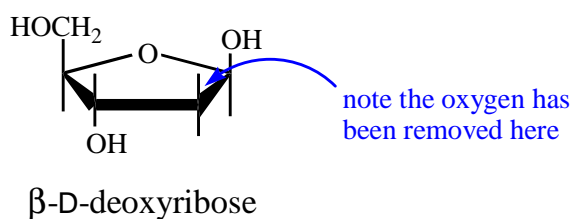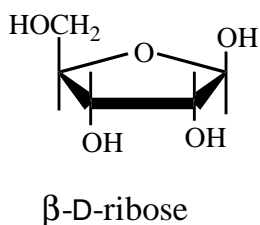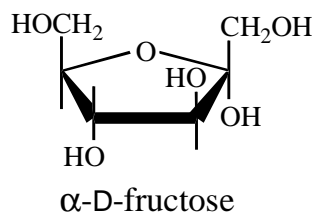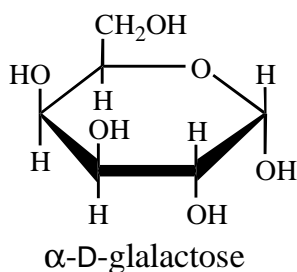
Interaction 18.2 – The Boat and Chair Forms of Saturated, Six-Membered Rings

We need to digress briefly from our discussion of sugar molecules. While the Haworth projections we just learned about are a convenient way of drawing these molecules, they don't accurately portray what the molecules actually look like in solution. In order to accommodate 109.5° angles into a six-membered ring, the ring must have a 3-dimensional shape. Research has shown the shape below as the most stable geometry for cyclohexane (and almost all similar molecules, including hexoses).
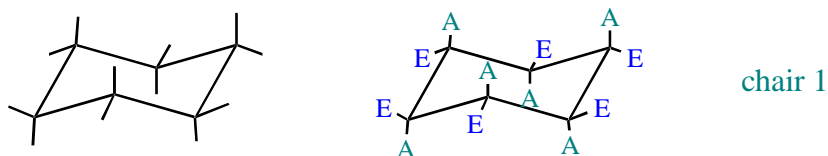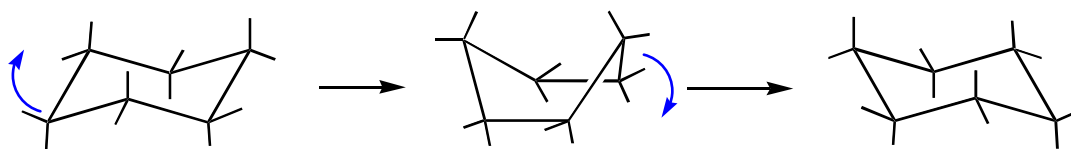

chair 1

This shape is called a chair form because when tilted and viewed properly, it looks rather

like a chaise longue. In this orientation, the 12 atoms bound to the carbons are not all in equivalent positions. Six lie in identical axial positions (labeled A) and six lie in identical equatorial positions (labeled E). If all substituents are the same, its mirror image has an identical energy.
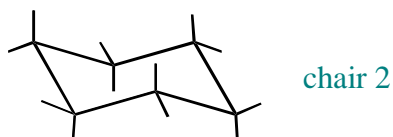
chair 2

These chair forms usually interconvert readily. Let's use the chair 1 cyclohexane molecule we saw above. Step 1: Take the far left carbon and flip if from a down position to the up position we see in chair 2. Step 2: Take the far right carbon and flip it down to the same position as seen in chair 2.

The middle structure is called a <u>boat</u> form and is somewhat less stable than the chair form. You may be able to see that things are a little more crowded in the boat structure than the chair structure. When converting from one chair form to the other, the axial substituents move to equatorial positions and vice-versa.

If all of the substituents on the ring are not identical, then both chair forms will not have identical energies. The axial positions point in parallel directions, while the equatorial positions point away from each other. The result is that the largest groups bound to the ring prefer to reside in equatorial positions. When there are several groups attached to the ring, it will usually twist so that the largest number possible like in equatorial positions. As the book notes, one chair form of β-glucose has all substituents axial and the other all equatorial. The latter is much more stable and predominates. It also accounts for the higher percentage of β-glucose than α-

glucose in the equilibrium we saw earlier. This is because unlike β-glucose, α-glucose must

have at least one group in an axial position regardless of which chair form it assumes.

In later sections, we will usually use Haworth projections, but occasionally will include

drawings such as these to remind you of the 3-dimensional shapes of molecules.
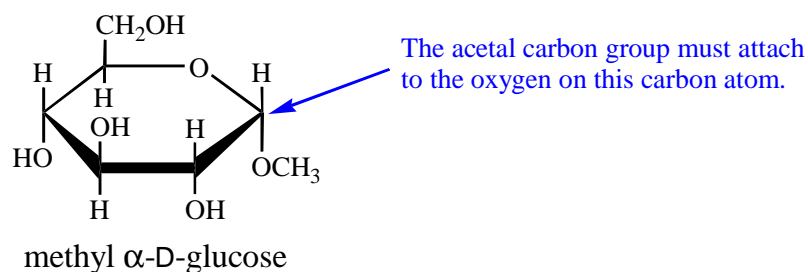
18.5   Disaccharides

Hemiacetals react with alcohols in the presence of an acid catalyst and heat to form acetals.

This reaction was discussed in Chapter 14 (p. 7 of notes). For generic reactants this reaction

looks like:
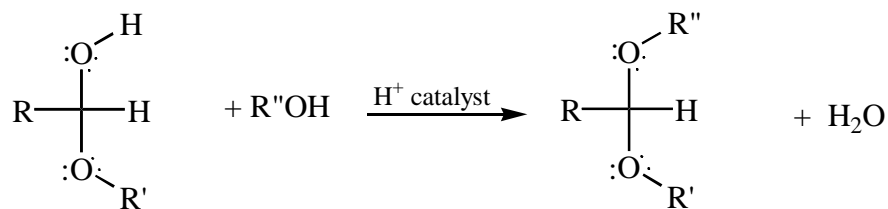
Such a reaction can occur between sugar molecules because they are both hemiacetals and

alcohols. Thus monosaccharides are able to self-assemble into larger units. One difference is

that in the body the coupling is accomplished enzymatically, rather than by heating in an acidic

solution.

Sugar acetals carry the special, generic name glycosides. They are named by taking the

sugar name and changing "-ose" to "oside." Thus glucose becomes glucoside.

Glycosides refer to any sugar acetals, including those in which the organic fragment is not a

sugar. A simple glycoside is methyl α-D-glucose. Note that the methyl group must go on the

indicated carbon for the molecule to be an acetal. Glycosides readily hydrolyze (react with

water). They do not ring open and don't give positive Benedict's tests.

CH$_2$OH

The acetal carbon group must attach
to the oxygen on this carbon atom.

H   H
H
OH   H
HO   OCH$_3$
H   OH

methyl α-D-glucose

While this simple glycoside is not particularly interesting chemically, such glycosides are

widespread in nature. An example is salicin, which is found in the bark of willow trees.

CH$_2$OH

H   O   O
H
OH   H   CH$_2$OH
HO   H
H   OH
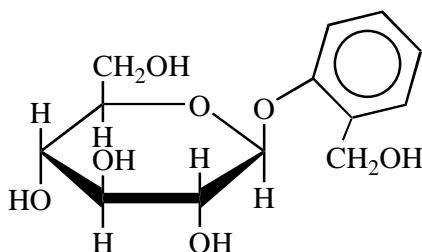
Since antiquity, civilizations in China, Greece, and North America have known that boiling

willow bark produces a solution that relieves pain (in addition to other health benefits). In 1829

the active ingredient in the bark was isolated and identified by a pharmacist named Leroux. In

1859, Charles Gerhardt of France first prepared acetylsalicylic acid, but didn't pursue it further.

A German chemist, Felix Hoffmann, rediscovered the compound in 1897 while seeking

treatment for his father's arthritis. The Bayer Corp. first marketed this material in 1899 under

the trade name Aspirin. Bayer lost the trade name as a result of the Treaty of Versailles that

ended World War II. Interestingly salicin is converted to aspirin (acetylsalicylic acid) in the

body itself. Your book discusses how aspirin work in Chapter 19 (p. 548).

O
OH
O
O   aspirin
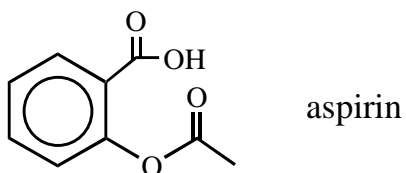
For what it's worth: It is now possible to purchase willow tree bark extract on the web as either a

liquid extract or in tablet form. However, for the true experience one can also buy dried

bark/flowers and brew your own "tea."

The glycosides we are really interested in are those that form between two sugar molecules. Glycosides made of two sugar molecules are called disaccharides. There are three nutritionally important glycosides: maltose (glucose/glucose), lactose (glucose/galactose), and sucrose (glucose/fructose).

When glycosides form, the bond is usually between the acetal hydroxy group and the hydroxy group on the opposite side of the ring (the #4 position if the acetal carbon is #1 in hexoses). β-Maltose appears below in both Haworth projection and in a chair view. It is the acetal of two β-D-glucose molecules.

These molecules are identical. The only difference is in the way we choose to display them. The connection between the rings is called an α(1-4) glycosidic linkage. The α refers to the linkage pointing below the left ring (at the acetal carbon) and (1-4) refers to the position numbers of the connecting carbons.

β-maltose
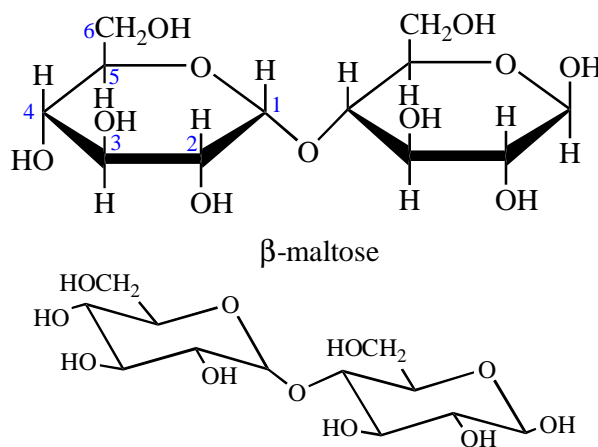
The disaccharide formed from two α-D-glucose molecules is nearly identical. The only difference is that a β(1-4) glycosidic linkage joins the molecules. The OH on the number 1 carbon is directed upward which makes this β-cellobiose. It is interesting that this small structural difference causes β-cellobiose to be non-digestable. This molecule does not appear

freely in nature.

β-cellobiose
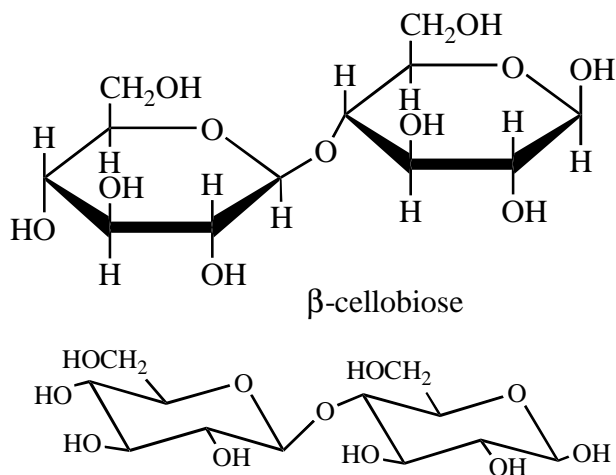
Your book goes over lactose and sucrose and you should read over these sections. Both

maltose and lactose mutarotate, but sucrose does not. Why? Both maltose and lactose are

composed of two aldoses, while sucrose forms from an aldose and a ketose. In sucrose an acetal

linkage bridges a glucose molecule and a fructose molecule. The bond forms between the

hemiacetal group on glucose and the hydroxy group on the number 2 carbon on fructose. The

result is that there is no way for the molecule to open up and interconvert forms. For the same

reason, sucrose gives a negative Benedict's test, while lactose and maltose give positive tests.


18.6   Polysaccharides

While stringing 3 sugars together to form a trisaccharide is possible, we needn't concern

ourselves until the chain reaches about a thousand units. The naturally occurring saccharide

polymers are starch, glycogen, and cellulose. None gives a positive Benedict's test.

Starch

Starch is actually composed of two related polymers amylose ($\approx$20%) and amylopectin

($\approx$80%). Amylose is a straight chain polymer of α-D-glucose with at least a thousand sugar units.

It looks a lot like a maltose molecule that goes on and on.

Starch
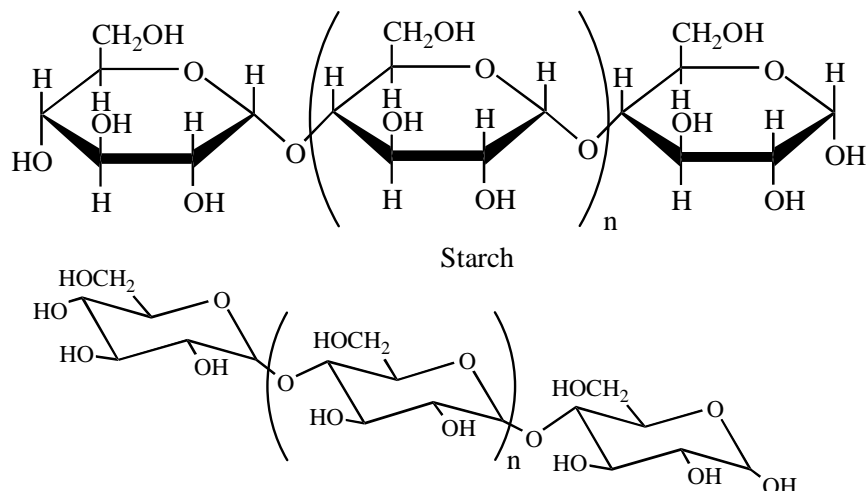
Amylopectin would look the same except that at about every 20th to 25th unit there would be a branch at the CH_2OH (an α(1-6) glycoside linkage). The book has a picture on p. 539.

Each "molecule" of amylose contains anywhere from (roughly) 1000 – 4000 glucose units. Thus these are heavy molecules (weighing from 150,000 – 600,000 g/mol). Amylopectin is even larger with anywhere from a few thousand to a million glucose molecules. Thus, amylopectin molecules can have molecular weights of over 160 million g/mol!

The large number of hydroxy groups in these molecules self-associate (they hydrogen-bond to each other) causing the molecule to wrap in on itself. The result is that relatively few –OH groups point outward. This causes the molecule to have low water solubility, which is important for a plant's ability to store glucose for the long term.
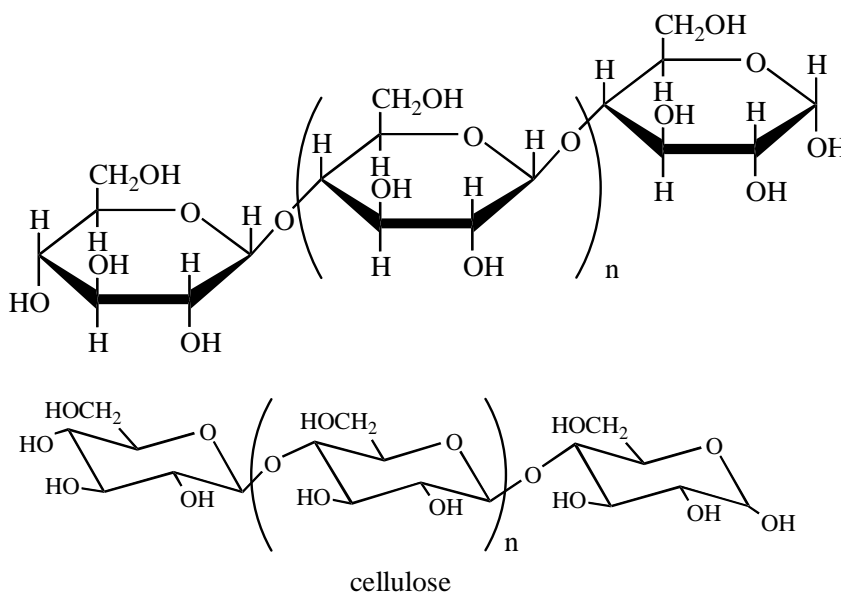
We begin digesting starch in our mouths, where the enzyme amylase begins breaking it down by attacking the α(1-4) glycoside linkages. The remaining α(1-4) linkages and all of the α(1-6) linkages are broken in the small intestine. The resulting glucose is absorbed into intestinal cells and passed on to the bloodstream there.

Glycogen

Animals store glucose as glycogen, which is very similar structurally to amylopectin. The difference between them is that the branching at α(1-6) glycoside linkages occurs about twice as often (every 10 – 12 glucose molecules). These molecules range in size from about 1700 to 600,000 glucose units.

Cellulose

Structurally cellulose is identical to amylose except that it has only β(1-4) glycoside linkages. Although you can't see it, the structural difference allows cellulose molecules to align themselves in a way that generates structurally valuable material. Cellulose provides the structural material used in plants. Cellulose accounts for more than half of all organic carbon easily making it the most abundant organic compound on the planet. What is interesting is that no higher animal has evolved the ability to digest cellulose. Only certain protozoa can (unlike us, they produce the enzyme cellulase). And calling a termite a higher animal may be a stretch, but even they use bacteria to accomplish this task (your book is incorrect when it says termites themselves digest cellulose). That we cannot digest cellulose accounts for its ability to clean the colon.

March 20, 2002

cellulose