Lecture 16B • 05/18/12

What is a disaccharide? When we've got two individual smaller sugar units that are stuck together. The smallest sugar unit is one that only has one carbonyl group in it. So far we've seen two disaccharides: one of them was maltose – what's in that one, what are the sugar units in maltose? Two units of glucose. What about lactose, the other sugar we did? Galactose and glucose. Do you know what sucrose is? Fructose and glucose, but the fructose is actually going to be in its furanose form.

Before we do sucrose proper, I'd like to take an aldohexose and make a furanose out of it, because it is a little trickier than making a pyranose. We're doing this as an exercise, then we're going to switch into sucrose proper. Let's work on drawing alpha-d-glucofuranose. Glucose: from top to bottom, where do the -OH groups go? [right, left, right, right] If I want to make the furanose what does that mean? Five-membered ring. It happens to coincide in this case with nomeclature, but I'm not numbering for nomenclature, I'm numbering for number of atoms in a ring. Whenever we do make a cyclic form of a sugar, the carbonyl is automatically a member of that ring, so I'm going to start numbering there. We go down the chain, position 2, 3, 4, and then if I move over from that point, then that particular oxygen, that's the fifth atom, that makes it the five-membered ring. I'm going to cyclize through that oxygen. We then need to figure out which side is alpha on, which side is beta on. In order to do that, we're going to have to twist the stereocenter around, like we've done previously. Then, we'll tip it and dump it into a Haworth projection.

Unlike all the examples we had done before, we're not twisting the last stereocenter, which means there'a complex group that's going to get rotated one way or the other, when we do try to put the oxygen into the backbone. But, if I did more it one way or the other, isn't that effectively turning it around 90°? It is, and so if it is, isn't that an improper transformation of a Fischer projection? It is also, but we're going to ignore that, because we're doing it on purpose just so we can see which side of the ring is this whole mess on. To make that whole process similar, what I'm going to do is rewrite it, because it's not involved at all in terms of reaction, in terms of mechanism. I'll call it R for the moment; this is just for ease of writing the structure over and over. Not to confuse us, but there's another R that I'm going to ascribe to this. What is the configuration of the bottom stereocenter, the one that I am folding into this R designation? Most important substituent is the oxygen itself, so that's 1; up top, we have a carbon that's connected to [O, C, H}. Down below, we have a carbon that's only attached to [O, H, H]. Carbon has greater priority than hydrogen, so that means substituent #2 is the rest of the sugar up above. Substituent #3 is the CH2OH group down below, and the hydrogen is the least-important substituent. They appear to be counterclockwise, but because hydrogen's on the side, it's really pointed towards us, so that means it is an R configuration. [need to know context; R abbreviation versus configuration]

I'm going to take that oxygen [fifth atom] and make a ring. I add a stereocenter, and for just a moment, I'm not going to try to assign that alpha/beta position, because R is still in the bottom of the structure, the oxygen that's part of the ring is not written in the backbone, so without excellent visualization skill, we could potentially get where to put the alpha/beta -OH group in the wrong place. I'll rotate the bottom stereocenter to precess those substituents around; that now gets the oxygen of the ring into the backbone, makes the hydrogen go to the right, that R group go to the left. Because the R group is on the left, and I want the alpha form, that means the top stereocenter, the -OH group, is going to be on the right, to make it trans. Let's put it into ring form, the Haworth projection. Since this is only a five-membered ring now, it's going to look a little bit different. Frequently, it's drawn symmetrically like this. Still, the oxygen's in the back, because the anomeric position is still placed to the righthand side. The things on the righthand side of the Fischer projection, when we tip it over, they're going to be on the bottom of the Haworth projection; the things that are on the left of the Fischer projection, when we tip it over, they're on the top. On the righthand side, we have [-OH, -OH, -H, -H]. Normally, I would just write one kink at this point and put an -OH group on it, but there's an additional carbon here, compared to the examples we've seen in the past, because we made the five- and not the six-membered ring form.

Many times an asterix to designate a stereocenter. We need a wedge or a dash here; which one should it be? There's a way to cheat, but it does require that you have reasonably good visualization skills. What if I looked down upon the molecule that way? In other words, here is that branch, and I'm looking at it like this. Relative to my viewpoint, from the stereocenter, which direction does the carbon-carbon bond, both of them, appear to point? Away from me. Whether my eyebrow's below or above, in this case it doesn't matter, the two carbon-carbon [bonds] are away from me. That would mean that the dash and the wedge are pointed towards me. Isn't that the way that we would normally visualize a Fischer projection. In the Fischer projection, we already have the configuration of that stereocenter. If I'm looking at it, and the carbon-carbon bonds are pointed away from me, and the carbonyl's up top, then -OH group's on the right, hydrogen's on the left. [demonstrating live how to visualize] From you position, though, which way is the -OH group? It's a wedge; because that's on the right, and because we're looking down this way, it's to you, so it's a wedge. Another way to do it is to just draw something – put the wedge, the figure out if it's R or S. You know it's supposed to be R, so if you get S, you know you did it backwards. It's unusual because I'm giving you a visualization point where my eyebrow is not oriented with the paper, it's opposite. That eyebrow means that my head is looking down this way.

Imagine that these are the two carbon-carbon bonds, so I'm looking down this way. Here's one carbon-carbon bond away from me, here's the other one. Carbonyl's up here, because there's the carbonyl, so it' above my viewpoint. On the Fischer projection, the -OH group is on the right; on the right, from where you're sitting, is pointed towards you; that's why it's a wedge. If you want to verify if that's correct: oxygen, priority 1; the rest of the sugar, priority 2; CH2OH priority 3; implicit hydrogen in the back, priority 4; those three substituents are in clockwise order, so it's R, so I did do it correctly. [furanoses of aldohexoses tougher because of stereocenter to draw] This 2-dimensional structure, you have to always, always, always remember that this Fischer projection is supposed to be rolling away from you. [careful not to invert what you're seeing by looking at ring line incorrectly] The middle of the Fischer projection should be pointed at you. [visualization] [It is easy to view the molecule incorrectly so that] this oxygen looks like it's in the front of the molecule. This oxygen, because it's vertical, is pointed away from you. You'll accidentally perceive this to be the back of the ring, so when you try to translate to the structure, you're going to get your groups backwards, because if you swap the front and the back, you make the mirror image.

Sucrose

Sucrose is 2-O-(alpha-d-glucopyranosyl)-beta-d-fructofuranoside.

Carbon that has oxygen and another carbon attached is more important than a carbon that only has oxygen and hydrogen attached. If you compare the priorities, we have [O, C, H] attached here; we have [O, H, H] on the bottom. Hydrogen's less important than carbon, so we take the top substituent instead.

Alpha=d-glucopyranose [trying to not go through linear structure] This sugar followed the normal pattern for aldohexoses, which is that d sugars always have that back CH2OH group pointing up [in the pyranose form]. In the previous example, it just happened to work out the same way where that back group was also pointed up. But, that's only because the stereocenter where that carbon was happened to have the -OH group on the right, just was we would for the last stereocenter of any d sugar. But, there are four d-aldohexoses where this stereocenter's on the left – gulose, idose, galactose, talose – all four of them have that stereocenter, which means when we get to this point of twisting around, we don't automatically twist to the right like we would for a d sugar, because it doesn't matter what the last stereocenter's configuration is, it matters where does the ring connect. That quick-and-easy rule about which way does the back group point and which way to alpha and beta point only works the way I've described it for d-aldohexopyranoses. Since I now want to draw a d-aldohexopyranose, we can follow those quick rules, which [are]: alpha's going to be pointed down, the back CH2OH group will be pointed up. Glucose is [right, left, right, right]. So there's alpha-d-glucopyrnaose.

Now I need to draw the beta-d-fructofuranose. Fructose and glucose are interconvertible; why? We could take glucose, make a double enol out of it; we could do a tautomerization. When we come back out of that tautomerization, we can move the position of where the carbonyl had been. In fact, if I take glucose, this form of it, and put it into water, what's going to happen to the optical rotation? If take this alpha-d-glucopyranose, measure its optical rotation in solution, and then measure it an hour later, what are you going to notice? It's changed; why? Protonate-open-attack-deprotonate, protonate-open-attack-deprotonate. We have the ring able to open and close, open and close, open and close, because, what kind of functional group do we have? Not a full acetal; it's a hemiacetal. Because it's a hemiacetal, it's in equilibrium with its open, linear form. Once it opens, if you're in the right condition, glucose and convert to mannose, or it could also convert to fructose. Glucose, mannose, fructose, and arabinose all share the same configuration for the bottom three stereocenters. So, fructose is this.

If I want to make fructofuranose, I want the five-membered ring. The numbers I'm about to write are not nomenclature numbers; they're numbers to count atoms. Now, because I have a ketose, a ketohexose, position 5 is the -OH group on the last stereocenter, so this is going to be an easier molecule to visualize than the one up above was. Let's go ahead and make the ring. When I make the ring, I have a new stereocenter at where the carbonyl used to be. The oxygen is not in the backbone; it's sticking off to the side, so if I want to move it into the backbone, because I am now dealing with a sugar where I'm using its last stereocenter and because it's a d sugar, it is automatically twisted clockwise to visualize correctly. That puts the part of the molecule sticking off the ring on the lefthand side. I want the beta form, so whatever I draw is going to be cis. [hadn't written anomer -OH yet cause needed to get in proper ring form] Now that I know where the -OH group is, I automatically know where the CH2OH group is. Now the only thing left is to tip this into a Haworth form, a cyclic form. Now I've made beta-d-fructofuranose. Because we have a ketose, which means the carbon that becomes part of the ring is not the top, that's why we end up with two of these "tails", two of these CH2OH groups.

There's one thing left to do, which is to connect the two rings. Notice that this is 2-O. In terms of nomenclature numbers, you still number from the top of the compound, because that's where the carbonyl was, but the carbonyl, because it's a ketose, is not carbon 1, as it was in all of our previous examples. Now, if we want to substitute at the two position, through that anomer, that's why it's 2-O. Notice what that's going to mean, though: we're going to take the anomer of one sugar and tie it to the anomer of another; that's going to have some consequences on the reactivity of this sugar. [When writing the molecule], the normal pattern is to try to keep the anomer position on the right, but if I do that for both of these molecules, I'm going to have to stack them on top of each other with a big, long bond with an oxygen connecting the two. I prefer to write the molecules side-to-side, but what that's going to mean is I'm going to need to spin this around.

If oxygen is in the back, and if I spin this 180° around, that means the oxygen's now in front. The way this is currently drawn, on my left, which is your right, you have an -OH group that's up; on my right, which is your left, you have an -OH group that's down, in front. That means that when I turn 180° and don't change anything else, I don't reflect or anything, in the back of the ring, I'm going to end up with an -OH group up on the left and an -OH group down on the right. Here is the glucose part, and now I'm going to do the fructose part. It's as if I took that ring and just twisted it 180°. In the back are my two -OH groups, and on the side I have my CH2OH group. [helping visualize][model sets] We're trying to take 3-dimensional objects on 2-dimensional paper and, in our heads, spin them in 3 dimensions, but still write them in 2.

From both sugars' perpectives, this is now an acetal. Acetals do not as easily open up into linear form, because acetals, although they can be hydrolyzed, are less prone to opening than a hemiacetal is. [The optical rotation of glucose changes] because it freely opens and closes, but since this sucrose is an acetal, not a hemiacetal, it does not easily open and close by itself; it does actively take hydrolysis to change the ring. [reducing sugars; tied up in acetal, no reaction]

If I take this compound, which is an acetal, and if I reacted it with a solution of silver oxide and methyl iodide, what's going to happen? [silver oxide seen previously in Hofmann elimination] Silver is still being used to trap a halide in this case. Will anything happen to the acetal? We're going to have hydroxide that's somehow produced; will hydroxide do anything to the acetal ring? Do we have protons in hydroxide? [DHP] What would happen to that THP-protected alcohol if we used a Grignard reagent? Nothing, which is the reason we used it as a protecting group. Aren't Grignard reagents pretty darn basic? That's the point of [DHP] – base won't hurt that acetal. Silver oxide won't do anything to the acetal. This is going to alkylate all those -OH groups, because if somehow, indirectly, hydroxide is produced, then you can make an alkoxide of an alcohol. Alkoxide with this methylating agent – it's one of the best Sn2 substrates [strawberries] – so you throw silver oxide at the sugar .... Notice we won't throw hydroxide, because if we had hydroxide and methyl iodide, all we're going to get is methanol; they'll react with each other. We use the silver oxide as a sneaky way of deprotonating the sugar. Every -OH group gets alkylated, so we end up with exhaustive methylation. Here's what our product would look like.

Notice it's every available -OH group that get alkylated. The oxygen in the ring, since the ring is not affected by basic conditions, [it] doesn't react. Why would we want to do such a thing? Let's say we had a sugar that we didn't know the identity of. Let's say we did exactly this reaction. When we do hydrolyze this, when we do force this to turn back into linear form, we're going to have the ring open, which means now one of the carbons has an available -OH group. If you identify which carbon that was, you identify the size of the ring that was in that sugar, because on the oxygen in the ring doesn't get a methyl group.

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alpha-d-glucofuranose

sucrose: 2-O-(alpha-d-glucopyranosyl)-beta-d-fructofuranoside

beta-d-fructofuranose

exhaustive methylation

NaOH + CH3I –> CH3OH

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Structures – Identical to those from lecture 16A (05/18/12)