Lecture 18B • 05/25/12

[exam 2 – structure: pentose/hexose, furanose/pyranose, aldose/ketose, alpha/beta, d/l; name of monosaccharides: aldo-trioses, -tetraoses, -pentoses, -hexoses, fructose]
[disaccharides: maltose, lactose, sucrose; exhaustive methylation; Tollens' reagent; enolate interconversion of glucose, mannose, fructose; mutarotation]
[derivatices: aldiol, aldonic acid, aldaric acid; Kiliani-Fischer chain extension; Fischer stereochem proof; osazones; Fischer projections]

Exhaustive methylation

Lactose has galactose as one of its units; what's the other unit that's part of lactose? Glucose. If we were to draw the sugar from left to right, then we have galactose on the left, because it ends up being a substituent to glucose. What was the configuration of galactose in lactose? It's beta form. beta-d-galactopyranosyl-alpha/beta-d-glucopyranose. Since it's a d sugar, for all d aldohexoses, the beta form, the -OH group's going to be pointed up at the anomeric position, as well as the CH2OH that would normally be at the bottom of the Fischer projection. Galactose is [right, left, left, twisted right]; glucose [right, left, right, twisted right; alpha form]

Imagine you had methyl iodide and silver oxide react with this. The silver oxide was a way of sneakily introducing hydroxide into solution without it being a solution of hydroxide. The available -OH groups will all get deprotonated over time and then perform Sn2 with the methyl iodide. Because methyl iodide can't undergo elimination, it's a fantastic substrate for Sn2 reaction. What do you recall about the stability of hemiacetals and [hemi]ketals in basic solution? Do acetals and ketals react with base? No, which is why we use them as protecting groups [THP]. We have one acetal here, as well as one hemiacetal. As for as those oxygens are concerned, the ones actually trapped in the rings, those will not be alkylated. They won't be alkylated because the rings, which are an acetal and a hemiacetal, are not sensitive to base. The connection between the rings is not itself a ring, but since it is part of this acetal, it's trapped as part of the acetal, it won't react either. Notice I excluded the -OH where my finger is currently located, because there's no reason that couldn't get deprotoanted, cause it's not trapped in a ring. When we exhaustively methylate, here's what we're going to get: a whole mess of -OCH3 groups. [model sets]

Now imagine, after doing all of this methylation, that we hydrolyze. Ethers normally require strong conditions in order to cleave them. When I show H+, it really is meant to be an acidic solution, but not of any particular acid. You would really need something like HI, hydroiodic acid, in order to successfully cleave an ether. When we hydrolyze it, the hemiacetals and hemiketals, those will fall apart. As far as the left-hand side of this molecule, the galactose portion, what are we going to end up with? If we're hydrolyzing, then we're going to lose the anomeric -OH group, when it converts back to a carbonyl. That would correspond to where the two oxygens connect together. The next three positions have -OCH3 groups instead of -OH groups. But, notice what I just wrote as the final structure: the bottom stereocenter, that has an -OH group on it. Why? Because it was trapped in the ring, that oxygen, at the time the alkylation had occurred, the methylation. Since the ring was not sensitive to the base, it didn't get popped open, didn't get alkylated. Once you did finally break open the ring, because you switched to acidic conditions ... hemiacetals, hetmicetals, acetals, and ketals all open and close in acidic conditions; now we release that oxygen that didn't have the methyl group, which means we could figure out how big the ring was, because the -OH group that was part of the ring is the one that survives this methylation, so find where the -OH group is, you find what the size of the ring was. From this, we know that the galactose portion of lactose was in its pyranose form, its six-membered ring form. Since the indicated oxygen was part of the ring during methylation, it did not get methylated, since the ring was resistant to base conditions. Once the methylated sugar was hydrolyzed, the fact that one oxygen on the galactose fragment was not methylated can be used to established that galactose was in its pyranose form when part of lactose. If we did a more careful hydrolysis, it is possible to separate the two rings without necessarily being fully hydrated into their linear forms. The galactose portion of lactose only has one oxygen that's going to end up non-alkylated; for the righthand portion of it, the glucose portion of the molecule, it has an oxygen that's tied up in the glycoside as well as an oxygen that's part of the ring. The substituent in a disaccharide, how we could figure out what its ring size is.

Tollens' test

[lactose][sucrose – alpha-d-glucopyranosyl-beta-d-fructofuranoside][ways to write molecules] If we react them both with the Tollens' reagent, diaminesilver, we get contrasting results. From lactose, we end up with the silver mirror; for the sucrose, we don't end up with that. What's the significance? In terms of the terminology we're learning, we would say lactose is a reducing sugar. What reduces, get's oxidized. The sugar's providing electrons to silver to cause silver to fall out of solution an make the mirror. That means, in turns, lactose is the thing losing those electrons and it gets oxidized. For sucrose, there is not mirror, which means sucrose is not getting oxidized. Sucrose is not a reducing sugar. What's going on here? Two things. Recall that ketones normally shouldn't react with the Tollens' test anyways; there's one notable exception: when we have alpha-hydroxyketones, you can have tautomerization occur in solution. Even if we had a ketose, ketoses are automatically alpha-hydroxyketones, which means they could isomerize in solution into an aldehyde and then get oxidized.

Aside from that, under the conditions of the Tollens' reagent, these hemiacetal and -ketal rings can open and get oxidized. The pure acetal or ketal cannot. The beter way of putting it is: in solution, in these conditions of the Tollens' test, the cyclic and linear forms of aldoses and ketoses are in equilibrium with each other, but because sucrose has an acetal and a ketal, neither of them are hemiacetals or hemiketals, they don't exist, either of those two sugar units, in equilibrium with their linear forms, so they never get oxidized, which is why sucrose is not a reducing sugar. Under the conditions of the Tollens' test, hemiacetals and hemiketals are able to exist in equilibrium with their linear aldehyde or ketone forms. If they're in aldehyde form, on in this case because of the alpha-hydroketone form, they can be oxidized. Ketals and acetals, full ketals and acetals, do not exist in equilibrium with their linear forms, so they do not get oxidized.

Let's look at the sugars. We can see that lactose has an acetal and a hemiacetal, while sucrose has an acetal and a ketal. There's not hemiacetal or hemiketal in sucrose; there is in lactose. Since lactose has a hemiacetal, it reacts with the Tollens' reagent, but since sucrose only has a full acetal and ketal, it does not react. It's a ketal because there's two oxygens connected to one carbon; on that same carbon, there's a carbon, not a hydrogen attached; that makes it a ketal.

Amino acids

I've drawn an example of [an amino acid]. There's amino group on it; there's an acid group on it. That means we have both basic and acidic functionality on the same molecule, which gives them some unusual behavior. Let's talk about the different forms of an amino acid that might exist depending on the pH of solution. For example, if we had really, really acidic conditions, unless we had supremely acidic conditions, it is unlikely that we would protonate the carboxylic acid portion of this molecule. That amine is a base, it easily gets protonated, so under acid conditions, we're most likely to find an amino acid in this way – it's protonated or cationic form. As we decrease the acidity level, increase pH, eventually, we're going to have deprotonation occur. It turns out that the pKa for the acid is much lower than for the protonated amine, which means as you get more and more basic and we lose a hydrogen, it doesn't come off the NH3+, it comes off the carboxylic acid. Another way of expressing this is that this is an amino acid, which means you've got acid and base functionality. Once it's in solution, what's to prevent it from neutralizing itself? Nothing, so this has the same number of atoms as the neutral structure I wrote above. This would be what would exist under neutral conditions, it's just that you have this built-in positive and negative charge, which is why this is call a zwitterion [twin/hermaphrodite ion] Since it's a plus and a minus, that means it is overall neutral. Continue to reduce the acidity level, eventually, you're going to coax the ammonium salt to become deprotonated as well; that happen under basic conditions. That means we now have the anionic form of the amino acid. The more acidic, the more protonated it gets; the more basic, the more deprotonated it gets. What we'll talk about after the exam is we quantify all of this with pKa values. If I throw an acid at something already protonated and already with an octet, is it really going to want to get protonated? No. The reverse direction: this is a carboxylic acid, so a base is going to react with the acid portion first.

Avoiding any of the quantitative discussion, though, let's at least talk about what distribution of these three forms would we expect to see in solution. Our body has a certain pH; blood pH, for example, is right about 7.2. Deviation of much more that 0.2 pH is fatal. That means that just much change in pH, there's an awful lot of sensitivity in these acid/base equilibria. Let's find a way to discuss what would the proportion of these things look like in solution. It's going to be a graph of two things. In this case, we're going to make the x axis pH. Recognize that if we're going a titration curve, normally pH would be the [y] axis. But this is not a titration, this is us trying to figure out what's the proportion of these different forms of the amino acid as a result of the pH, so pH is therefore our x axis, and it's going to be mole fraction that ends up being our y axis. Mole fraction has a maximum of 1. What is a mole fraction? It is the number of moles of one species vesus the total moles of all things in solution; it's not just the ratio between the two of them, it's like a percentage if you wanted to say. Since we could start with just the cationic version, for example, and since these interconversions are just 1:1:1, the total number of moles is never going to change, so we can treat this a little bit like percentage. We will have three things in solution: the acidic form, the neutral form, and then the basic form. It might make sense that if we were in extremely acidic conditions, like pH 0, that 99.999% of that molecule is going to be in its protonated, acidic form, so we expect to have a mole fraction of 1 for that acid. Similar logic, is we're in really, really, really basic conditions, we could expect to have 100% of the base form. What might make sense is that somewhere between the two, we're going to maximize the neutral form of this molecule. I've left off any specific pH values, because once we do talk about different amino acids, each of them has their own structure, there's extra groups that can influence the acidity of the amino or the acid portions of that molecule. This is a generalize discussion.

Starting out with an extremely acidic solution, we only have the acid form, but as we add base to the solution, eventually that amino acid's going to start getting deprotonated. Eventually, you add enough base, one equivalent's worth, where the whole deprotonate, that first deprotonation, is complete. In terms of how much of the acid [form] were around, it might look something like this. At the same time that that acid form is decreasing, the neutral form is increasing. Once you've added one equivalent of base and removed one of the two protons available, you're going to start deprotonating the second one. Deprotonating the second one means you're making the basic version, which means you're destroying the neutral version, so this is what the curve looks like.

[significance of two points just marked, where the curves cross] If this was a titration, that point would be the half-equivalence point. There's something special that happens at that half-equivalence point. [idealization for simplification to occur; Henderson-Hasslebach equation]

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Since the indicated oxygen was part of the ring during methylation, it did not get methylated, since the ring was resistant to base conditions. Once the methylated sugar is hydrolyzed, the fact that one oxygen on the galactose fragment was not methylated can be used to establish that galactose was in its pyranose form when part of lactose.

Under the conditions of the Tollens' test, hemiacetals & hemiketals (of sugars) are able to exist in equilibrium with their linear aldehyde or ketone forms, which can then be oxidized (remember alpha-hydroxyketals tautomerize & can then be oxidized). Ketals and acetals do not exist in equilibrium with their linear forms, so they dod not get oxidized. Since lactose has a hemiacetal, it reacts with Tollens' reagent, since since sucrose only has a full acetal or ketal, it does not react.

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Structures – Identical to those from lecture 18A (05/25/12)