Lecture 17B • 05/22/12

Fischer stereochemistry proof

0) Glucose is an aldohexose

What are the five other steps, in the way that I presented this proof? [1] The last stereocenter is a guess. What specific molecule can we refer to to tell clearly what the difference between a d and an l sugar is? What would be the best example of a sugar to use and say: here's the d version, here's the l version. That's a subjective question. d-talose. Why not glyceraldehyde – the only molecule that the only difference between the d and l forms is that they are enantiomers. The point of bringing that up as the example of a d and l sugar is, the very second step, we talk about the Kiliani-Fischer chain extension: the fact that we can make some kind of stereochemical relationship between a smaller sugar and a larger sugar that it's able to produce. For step one, that wouldn't be so much the focus; the focus would be on the fact that you can create larger sugars from smaller ones, and if the simplest sugar of all, glyceraldehdye, that if that compound is used to establish what is d or l, then all of the larger sugars can be synthesized from it, which is why they're also called d or l. What is d and what is l is determined is by the [configuration] of that last stereocenter; it is because of glyceraldehyde that that determination is made, and the chemical reactivity of all the sugars is determined by the rest of the stereocenters effectively, not that last one.

Second point. Glucose and mannose are epimers. What two ways do we have to know that that is the case? You can synthesize both of them from arabinose, which, asides the fact that glucose and mannose are epimers, the importance there is that the three stereocenters that are in arabinose are automatically the three stereocenters of those larger sugars, because it is by adding only one stereocenter that you make glucose and mannose. What's the other way that we know that they are epimers? Osazones [hydrazone derivatives]. Those osazone derivatives – yes, it is three equivalents of hydrazine that react, because there's a redox reaction that one of those equivalents causes; it's that unusual reactivity of the nitrogen-nitrogen single bond that ends up causing it. Osazones, you get the same exact one from both glucose and mannose. That's because the bottom three stereocenters of the two sugars don't get disturbed when making an osazone, but the top stereocenter does. Since that's the only stereocenter that differentiates between glucose and mannose, that's how we can demonstrate that they are epimers, cause once you get rid of that difference, they form the same derivative.

Point three. Arabinaric acid is optically active. What [is] the consequence of that? HCN is the Kiliani-Fischer chain extension. Arabinaric acid is what kind of sugar derivative? An aldaric acid, which is synthesized how? From nitric acid. [mechanism?] Nitric acid oxidizes on the primary alcohol in a sugar, and an aldehyde, which is how we end up with one of these aldonic acids. How many stereocenters should I write down? Three stereocenters. Whatever acid you have, not the sugar, cause no sugars are ever meso, because they have not the same functionality on the top and the bottom of the molecule. It's the aldaric acids we're talking about. If we're talking about these aldaric acids, one of these stereocenters is not up for discussion, because that was established by point one of the discussion, that the bottom stereocenter is going to be configured to the right. What is the only way that this much of the structure can be meso? If the top stereocenter's also on the right – so it can't be on the right. End of point 3. If one stereocenter's already assumed, then the other one, you already know what it can't be, cause if it were, then it would be meso, which it can't be. Since the aldaric acid of arabinose is optically active, the acid cannot be meso. Since the configuration of one stereocenter is presumed in an earlier step of the proof, the configuration of another stereocenter must be determined, since it must avoid being meso, or, a meso molecule must be avoided.

Fourth step. Glucaric and mannaric acids are optically active. What would you suggest as a molecule structure to write down to have a discussion over it. You get some situation where you start with what you know, and then you discuss about the stereocenters you're going to fill in. We know this much of the molecule. Coming back one more time to step 2, if we know something about arabinose, it is because of that connection through the Kiliani-Fischer chain extension that we also simultaneously know something about glucose. Does that mean that Fischer proved arabinose at the same time he proved glucose? Yes, and a least [eight or nine of the other sugar configurations], not just glucose he figured out; but, since glucose is blood sugar, and since not all of the sugars are naturally-occurring, this one is the one most heavily-discussed – also since it does have some interesting, tricky bits of logic to it. If that is what we're looking at, which of the next stereocenters are we going to determine and why? The third stereocenter – why? You have two pairs of possibilities, and you're eliminating one pair. You have to always return to the idea that glucose and mannose are epimers of each other. You do not have the freedom to have glucose with one configuration for its third stereocenter, and mannose have the other. Both of them share the bottom three configurations; they only differ by the top. Don't worry about the top configuration, since both sugars differ by it; work on what they have in common, the three stereocenters they have in common. If we put the third stereocenter on the left, the we have a situation where you potentially have a meso molecule. Of course, that depends on the configuration of the top stereocenter.If it's on the left, which means talose, it's not going to be optically active once you oxidize [talaric acid]. If we put it on the left, it would not be meso. Galactaric acid, put the top stereocenter on the right, then it would be meso. Since either one, if one of those two choices are wrong, they're both wrong, because they share the same three bottom stereocenters, which glucose and mannose do. Once you determine that the third stereocenter can't be on the left, you know it has to be on the right, so those three stereocenters are correct for both glucose and mannose.

Let's say that you have four cookies, and they're presented to you in pairs. You don't know anything about the cookies, except that one of them has been poisoned. You may have either one of either of the pair of cookies. You want to figure out which is the poisoned one, cause at least if you can't figure out which of the two cookies is poisoned, but you know there's poison in one of the pair, just throw both away and accept the pair that's fine. It's the same type of situation – you have a pair of molecules that you're looking at, another pair of molecules. They're related because they're epimers, so if one epimer is incorrect, because the other stereocenters are in common, the other epimer is automatically incorrect. I have here potentially meso. This stereocenter [the one in red] cannot be configured as shown, since both glucose and mannose both have the same configuration of that center and neither can be meso. This is the fourth step.

Fifth step. Glucose, when you oxidize it, makes the same aldaric acid as another sugar. In terms of 180° angle, is this rotationally symmetric? In the context of doing a 180° rotation, is this rotationally symmetric? If I turn it 180°, I get its opposite image; then they're not rotationally symmetric, cause you made a new shape upon rotation. What if I had a shape like this? Is that, relative to 180° rotation, rotationally symmetric? Here's the exact same situation with portions of sugars shown. If we were to imagine that the top and bottom were the same functional groups, imagine that were dealing again with the aldaric acids, then on the left, we see one set of stereocenters that, when we rotate 180°, we get a different configuration. If this was the aldaric acid, it wouldn't matter which way we wrote it; you turn it 180° again and you get back to the original molecule again. That's because the top and the bottom functional groups are the same. If we had a way to go back from the acid to a sugar, one of these will put the carbonyl on top, turn it 180° around, it'd be effectively as putting the carbonyl at the bottom, gives us two different molecules. Now look at the pair on the right, you turn 180°, you'd get itself again. There are three other molecules that also have this rotation symmetry. It's not that it's the only case that only one sugar makes that acid. If we presume that FIscher had all 16 sugars in play, and found that glucose oxidized to give the same one as something else. Since he had already determined the bottom three stereocenters, that part of it, he couldn't change, so he had to look at these two cases: one where you made a different molecule potentially, or the acid could be made from another molecule. In another case, there's only one source of it, because it has rotationally symmetry. If we were to put functional groups on, we see one combo gives different molecules; the other gives the same. The one that's different is glucose, which means we've figured out the structure of glucose.

Imagine that you wrote out all 16 sugars – oxidize them all. You're going to find there's a couple of cases where only one molecule makes one type of acid, and none of the rest can, and you'll end up with another case where it'll be more than one molecule that make the same acid. That's because if you have this pattern of stereocenters, for example, and do what I did here, if you put an acid at the other end, then you could turn the molecule around and the top and the bottom would still match each other. The point is: for this case, if you put acids at both ends and rotate it, you'd end up in the same molecule again. These would be the same if you carboxylic acids on the top and the bottom. Another way of saying it is that the one is just 180° rotation of the other. Glucose, because it's not rotationally symmetric, has a cousin sugar that will oxidize to the same thing. But mannose, if you turn it, you get mannose again, as far as the stereocenter are concerned. If we're talking about the acids you oxidize, both of these are the same just to start and are the same after rotation. Fischer knew mannose was the only source of mannaric acid, so once he figured out three of the stereocenters, he knew the fourth one automatically because of that observation. [riff]

Tollens' test – silver nitrate and ammonia under basic conditions

[chem 1C scheme; dissolving silver, mercury, lead; redissolve silver by adding ammonia, because of complex that is made] Silver is able to act as the center site for two ammonia ligands that turn it into a water-soluble ion, and therefore this becomes soluble again. This compound could decompose [and can] become explosive over time, so this reagent is prepared freshly. This process is done very frequently, because if you take this Tollens' reagent – oversimplifying and calling it just the cation – it turns out that that is a good oxidizing agent. Aldehydes are able to be oxidized, because that hydrogen can be eliminated. We're doing this under basic conditions, [so although we're] oxidizing acid, we get a salt. We also get silver solid as a product so the Tollens' test is sometimes called the silver mirror test, because if we take, for example, a watchglass, slap some [formaldehyde], pour a little bit of the Tollens' mix on it, you'll end up with a mirror out of that watchglass, because the silver metal gets deposited on the surface. This, therefore, is a qualitative test for aldehydes. The Tollens' test is often used in a qualitative way to distinguish between aldehydes and ketones, cause aldehydes can be oxidized, but ketones normally cannot – not in this kind of process. Of course, if you took a strong enough reagent, you could make a ketone oxide, but you do so by cleaving a carbon-carbon bond and ending up again with a carboxylic acid – means you're wrecked the molecular structure. A "normal" oxidation won't happen with a ketone. That's how you could do a qualitative test to determine whether or not you have an aldehyde or ketone, versus a carboxylic acid, an alcohol, some other totally different functional group.

DNP derivate

What does DNP stand for? It stands for 2,4-dinitrophenylhydrazine. Technically, it should be abbreviated 2,4-DNP. What does it do? We react it with a trace of acid and a ketone, and we make a hydrazone. These products tend to be very easily isolatable, handleable crystals. The same reason that osazone formation was great for carbohydrates, this is great in general for making derivatives of ketones and aldehydes.

Since this kind of functional group can't form with other kinds of functional groups, this is a qualitative test for aldehydes and ketones. In theory, you could do this test first, you get some yellowish-orange crystal, you say: aha, I've got the DNP derivative, I've got an aldehyde or a ketone. You could then do the Tollens' to test to determine if you had an aldehyde versus a ketone

Unless you had something like a sugar. Even ketoses give false positives to the Tollens' test. False positive. Let's say I'm a plain, old ketone, and I do the Tollens' test, and you see at the bottom of the flask a silver mirror. That result is only supposed to happen for an aldehyde. I'm a ketone, but I had the reactive appearance of being an aldehyde. That's positive result – positive meaning you see the result, you get that silver mirror – but a ketone's not supposed to react, so it's a false positive. It means you get results that are not in line with the kind of molecule that you have. That's because there's an exception to the Tollens' test. That's because ketoses are alpha-hydroxyketones. Why [do you] get this false positive? Because I have the alpha hydrogen; why does that matter? Which of these two alpha hydrogens should be deprotonatable? Does oxygen donate or withdraw electron density? [in a benzene ring it's an activator] Donates, so it effectively adds electron density. That's because of resonance; if it had just electronegativity involved, it'd be a different story. So wouldn't that one actually be less acidic? Possibly. What if that's not what really matters? What if we formed an enolate here, what if nothing happens? Form an enolate here, what could happen? What about double tautomerization [same to interconvert between glucose, mannose, and fructose][mutarotation] In base, there is an equlibrium. [IECHIWH] As soon as that aldehyde appears, it gets oxidized, you get the silver mirror response, even though you didn't start with an aldehyde. That's something that only happens with these alpha-hydroxyketones, because of this potential to double tautomerize. [cliffhanger]

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3) Since the aldaric acid of arabinose is optically active, the acid cannot be meso. Since the configuration of one stereocenter is presumed at an earlier step of the proof, the configuration of another stereocenter can be automatically determined, since a meso molecule must be avoided.

4) potentially meso –> this stereocenter cannot be configured as shown, since both glucose & mannose share this configuration and cannot be meso once oxidized.

Tollens' Test – Silver mirror test

$AgNO_3 + 2\ NH_3$ –> [basic] $[Ag(NH_3)_2]NO_3$

The Tollens' test is often used as a qualitative way to distinguish between aldehydes & ketones, as aldehydes can be oxidized, but ketones normally cannot.

– Test for aldehyde and/or ketone: DNP

Ketoses return a "false positive" to the Tollens' test, because ketones are alpha-hydroxyketones

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Structures *(remaining structures identical to lecture 17A)*

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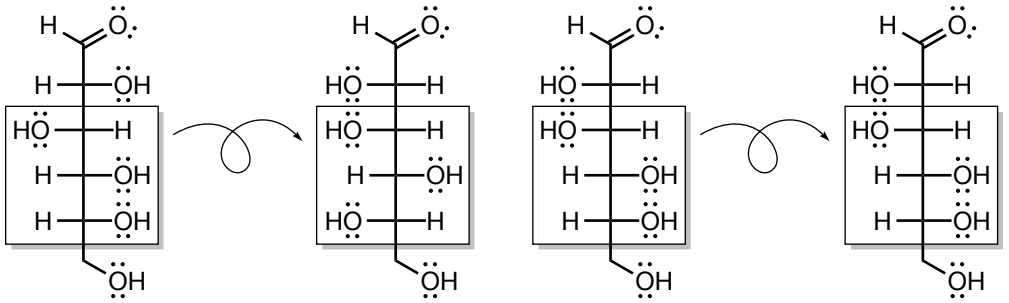

different *same*