## Lecture 15B • 05/17/12

Fischer stereochemistry proof.

There's five steps to this proof; kinda like the laws of thermodynamics, there's a zeroth step as well. Here are the 5+1 steps of the Fischer stereochemistry proof. First, glucose is an aldohexose. There were a number of ways this could be determined. We've so far learned the Kiliani-Fischer chain extension reaction – if we started with glyceraldehyde, the simplest of sugars, and if we were to do that chain extension three times, that would put on three more stereocenters, which, yes, means we're going to make all eight sugars, but one of them's going to be glucose. There is also something known as the Wohl degradation; it's a way you could take the sugar and chop it apart. One way or another, he did establish that glucose is an aldohexose. The first real step them is that the configuration of the bottom stereocenter was arbitrary, that he guessed. The next step is a little bit more concrete: it's the fact that glucose and mannose are epimers are each other, and they both can be synthesized from arabinose. This is important because, one, it does mean they – glucose and mannose, that is – have all but one stereocenter in common, and those three stereocenters that are in common come from or are the same as those in arabinose. By making a tie to arabinose, if we were to establish any piece of the structure of arabinose, we automatically establish some of the structure of glucose. The next step, then, is that arabinaric acid is optically active. We're going to see what the geometric consequence of that is; it allows us to establish the configuration of one stereocenter. After that, we'll see how glucaric and mannaric acids are also optically active, which allow another stereocenter to be established. The final step is a realization that glucose forms an aldaric acid that another sugar forms as well.

We know it's an aldohexose. This d/l designation, the configuration of the last stereocenter of a sugar, is, in fact, random; it is a guess. It was a very good guess, because he ended up being correct, but it was just a guess. We then have the chain extension that allows us to get from arabinose to both glucose and mannose. Of course, we know what the configuration of arabinose is; even if we didn't know it, though, we could recognize that a new stereocenter's created, and it's the only difference between glucose and mannose. Recall that we make cyanohydrins. [old versus new procedures] An amalgum, by the way, is when you have a mixture of two metals; mercury is often used to form those kinds of amalgums. Since mercury's not exactly the safest chemical, though, that's why some of these more modern techniques have gotten away from that very old-style chemistry. This is one of those examples of a modified, more modern version of the synthesis. Make the cyanohydrin first, selectively reduce with a poisoned catalyst to get imines, then hydrolyze the imines to get aldehydes again. Yet one more time, Fischer didn't know what these configurations were at the bottom, but he did know that this reaction resulted in epimers. One of the aspects is that glucose and mannose contain three stereocenters that are identical to those in arabinose. Glucose and mannose are epimers, which means they're differing by only one stereocenter.

Let's start getting to the juice part of the proof, which is the next step: arabinaric acid is optically active. Arabinose, if we started from scratch, this is what FIscher knew – actually, he didn't know it, he guessed it. Remember, step 1: guessing the configuration of the last stereocenter. Step 2, he made a chemical relationship between arabinose and glucose and mannose. Step 3, we use arabinose to figure something out about itself, which then let's us automatically figure out something about glucose and mannose. If you have nitric acid that's used not in its super-concentrated form and if it is not heated, we can selectively oxidize the aldehyde and primary alcohol both. The first compound, arabinose, is there any way arabinose can be optically inactive? What would be the only way, other than totally bizarre coincidence – one could imagine there must some example molecule that the stereocenters have exactly the right effect to somehow cancel each other out just randomly – what way would we guarantee that we would have no optical activity? If it is was a meso, so what I'm really asking is: is there any way for arabinose itself to be meso? No. Why not? The top is an aldhyde, the bottom is an alcohol, they're never been the same, there'll never be a mirror plane. Arabinose itself is going to be optically active; all sugars, unless by coincidence, are optically active. We established it can't be meso because the groups are different.

But now, when we oxidize, and both the top and bottom are the same functional group, then we have the potential to be meso. Let's address this concern about the number of stereocenters. Does that middle stereocenter actually matter? Is that center position always going to be a stereocenter? In other words, what would be the one restriction that we must have in order for this molecule to be meso? If the top stereocenter was configured so that the -OH group was on the left, not matter what we do, it could never be meso, because we wouldn't have a mirror plane through it. That's one possibility. We'll have two cases: one where the top stereocenter is on the left; at this point, we are talking about these aldaric acid derivatives. [calling by names because it otherwise becomes combersome] If the groups are on opposite sides, then this molecule cannot be meso, regardless of the configuration of the middle stereocenter. What about the other possibility? Are not the top and bottom [functional groups] identical?

Is the middle stereocenter actually a stereocenter any more? We have a mirror plane that goes through this molecule. It is meso. You might be chopping a bond in half, but it would be symmetric at least; if it's symmetric, it's meso. What does that mean? That means that the top stereocenter must be configured this way, because the observation is: arabinaric acid is optically active. That means regardless of the middle stereocenter, the top one cannot be on the right, because it if were, it'd be meso, which means it wouldn't be arabinaric acid, because arabinaric acid is optically active.

He assumed that the d sugar was on the right; that's why if this one is assumed to be here, the top one must be opposite to prevent it being meso. The only way arabinaric acid can be optically active is if the top stereocenter is configured so that it does not form a mirror plane with the bottom stereocenter. That's the point. We have a mirror plane.

Let's back up for a second. Is the middle stereocenter a stereocenter or not? Are these the same compound? The how could it not be a stereocenter, because if we have a difference in configuration that makes two unique molecules, doesn't that make it a stereocenter? But is the compound optically active? So it's not a stereocenter. Which is it? Neither; it's what's known as a pseudostereocenter, because the top and bottom substituents, although mirror images of each other, are technically not identical. Why? For either compound, what is the configuration of the top stereocenter, R or S? R. What's priority 1 in terms of substituents? We have oxygen itself as the most important group; the carbonyl, 2, because it effectively has three oxygens attached to it; the carbonyl counts for two oxygens, and we have a third one; the rest of the compound, 3. It looks counterclockwise, but the hydrogen, by definition of the Fischer projection, is pointed out towards us, so that means we reverse what we see, so yes, it is R. Automatically, then, because the molecule is a mirror image, the bottom stereocenter's got a configuration of S.

Now we look to middle pseudostereocenter. In Cahn-Ingold-Prelog rules, if you ever come to a tie between two substituents, and they're exactly identical in every way, except the configuration of one of their stereocenter, then R is given greater preference than S. Now, we go back and re-evaluate. On the middle pseudostereocenter, the -OH group is priority 1; the top substituent, being R, is priority 2; the bottom stereocenter, being S, is priority 3. We would again make it look like there's a counterclockwise precession of substituents; again, the hydrogen is pointed towards us, so we reverse it, so it is r, written in lower case to indicate that it is a pseudostereocenter. [RS vs rs] You don't need an even number of stereocenters to make a meso compound.

The whole point of this step 3 of the proof is something to do with arabinose. This top stereocenter, we have established its configuration by looking at arabinaric acid; the bottom stereocenter was established by a guess. [KFC extra] The bottom three stereocenters are identical to those in arabinose, which means we've established another stereocenter of glucose. [burritose]

Now, since we've got this stereocenter, we can come back and address: could we establish the top stereocenter, through the same kind of logic. In other words: if before we used the bottom stereocenter and a trick of optical activity to establish a stereocenter, would it work a second time? The answer is yes; that's what the next step is. If we "know" the configuration of two stereocenters, and if there's two more stereocenters, that means we have four possible structures of what glucose could be. [blue, established; red, left to determine] Glucose and mannose are epimers; they only differ by one stereocenter, so the two structures on the left make a pair; the two structures on the right make a pair. If I find any one of these structures that I demonstrate cannot be glucose or mannose, then both of the structures in the pair are not glucose and mannose, [because] glucose and mannose are epimers. Which stereocenter do glucose and mannose differ by? The top stereocenter. So, this is glucose and mannose, or, this is glucose and mannose. You can't take this and say "that's glucose" and take one from the other pair and say "that's mannose", because then this third stereocenter would be different. They are the same, which is the point that arabinose can be used to make glucose and mannose. The bottom three stereocenters have to be the same for both compounds, that's why these form a pair.

The bottom three stereocenters in glucose and mannose must be the same, so the four structures above represent two possibilities, each of those possibilities consisting of a pair of molecules that have a common configuration for the bottom three stereocenters. The structures above represent two possibilities; each possibility, in turn, is a specific configuration of the bottom three stereocenters. If either structure of the pair is shown to be invalid, then both structures in the pair are automatically invalid, because they have the same configuration for the bottom three stereocenters. I wrote these four structures already in the form of aldaric acids; are any of these structures meso? The top and the bottom functional groups are the same. The third one is meso; the third one is galactaric acid. Since we figured out that one of those two compounds is incorrect, both of those are incorrect, so we know the pair on the left is glucose and mannose. We technically don't know which one is which, yet, because this allowed us to establish the third stereocenter.

We have two stereocenters that we have figured out; we have two stereocenters that we still need to figure out. What we do know is that glucose and mannose are related, that they only differ by one stereocenter. What I did is I arranged them in pairs, where you can see, the first pair, the top stereocenter, it's one way then the other; the second pair, the top stereocenter's one way or the other. Not knowing what the structure is, potentially, either pair could represent the combination of glucose and mannose. If we look at one pair, like the one on the right, and we see that this molecule is meso, this can't be glucose; it also means it' can't be mannose, because they have the same three bottom stereocenters, which are the same for both members of the pair, so if one's wrong, both are wrong. Since this is the one that has a meso molecule, that means that the configuration of this third stereocenter is incorrect. That means this is the correct configuration, which means we now only one stereocenter left that we have to establish. In real life, they were able to measure and find that both glucose and mannose, when you oxidize them, are optically active – optically active means it can't be meso. It's because the acids were optically active that he proved what the stereocenter was.

The last step is that there are two sugars that form the same aldaric acid as glucose, [glucose being] one of them. Glucose makes the same aldaric acid as another sugar [does]. If we have a sugar of some sorts, there exists, at least for these hexoses, a chemical process by which we can switch where the aldehyde and the bottom CH2OH group are; it involves the formation and destruction of lactones, but it is possible. To know that that route exists is to then understand how Fischer was able to make l sugars. If you had a mixture, a racemic mixture, of glyceraldehde, how would you separate the two compounds from each other? You can't, without using something else, because if I have just one stereocenter and it's 50/50 mix, those are enantiomers, so boiling point, melting point, density, index of refraction, everything is the same [except two properties]. But what if I took another compound that maybe somehow could make a salt; what if I took a chiral amine and made an imine from glyceraldehyde? Then I'd have the stereocenter from glyceraldehyde, and I'd have the stereocenter from the amine at the same time. What used to be enantiomers would become diastereomers; their physical properties would then become different, and I coud then separate the two compounds. If the same amine with its one stereocenter is combined with these two versions of glyceraldehyde, then this stereocenter may be different, but this one's the same between the two compounds. That means they're not enantiomers; they're now diastereomers. This is using what's called a chiral auxiliary to do this separation.

Here's what he showed: the aldaric acid he made from mannose, mannose was the only molecule that could make it. Let's discover why. Up to this point, we've now established three of the stereocenters; coincidently, that means he figured out the structure of arabinose, cause it only has those three stereocenters [glucose more important since it's blood sugar, that's why we focus on it][didn't really set out to prove structure of glucose itself; multiyear research into multiple sugars, which he compiled to deduce structures] This is going to be mannose. What if we somehow swapped the groups? I did not turn the molecule upside down; all I did is swap where the aldehyde and alcohol were. Now, I'll turn the molecule 180° around; in Fischer projections, 180° degrees is allowed, 90° is not. When I turn it around, what do I get? Mannose again. So what? If we take mannose and mannose – its swapped structure, which happens to be identical – they both make the one and only one version of this aldaric acid. There's only type of sugar that can make this aldaric acid, because it is rotationally symmetric. That why when we flip it around, we get the same molecule again, because it's got this rotational symmetry.

What would happen if we had glucose? Let's say we oxidized it to make glucaric acid. Let's say that we swap that around 180°. If, somehow, we could backtrack and go from the aldaric acid to the sugar itself, that no sugar no longer matches glucose at all. This is d-glucose; I just make l-gulose. But, because once you oxidize both the top and bottom, you lose the distinction of what is the top and the bottom. Then, we can return just to the set of stereocenters itself and show that that set of stereocenters is rotationally asymmetric. As a consequence purely of symmetry, there's only one aldaric acid that can be made from mannose; out of any sugar, there's only one that will match that; that is made from mannose. But, there are two sugars that can make the same aldaric acid that glucose makes. That means the top stereocenter is now established. His observation was – presume he had all 16 sugars to play with – he found that two had the same product, d-glucose and l-gulose. We can use geometric arguments to prove that the stereocenter must be on the righthand side for that first position; that's the only way that we end up with something that does not have symmetry.

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Fischer stereochemistry proof

0) Glucose is an aldohexose
1) The configuration of the last stereocenter was a guess.
2) Glucose & mannose are epimers, and they both can be synthesized from arabinose.
3) Arabinaric acid is optically active
4) Glucaric & mannaric acids are optically active
5) Glucose forms an aldaric acid that another sugar does as well

Glucose & mannose contain 3 stereocenters that are identical to those in arabinose.
Glucose & mannose are epimers (differing by only one stereocenter).

3) Arabinaric acid is optically active – The only way arabinaric acid can be optically active is if the top stereocenter is configured so that it does not form a mirror plane with the bottom stereocenter.

4) Glucaric and mannaric acids are optically active – The bottom 3 stereocenters in glucose & mannose are the same. The structures above represent two possibilities; each possibility, in turn, is a specific configuration of the bottom three stereocenters. If either structure in a pair is shown to be invalid, both structure in the pair are invalid.

5) Glucose makes the same aldaric acid as another sugar.
Only one sugar can make this aldaric acid because it is rotationally symmetric

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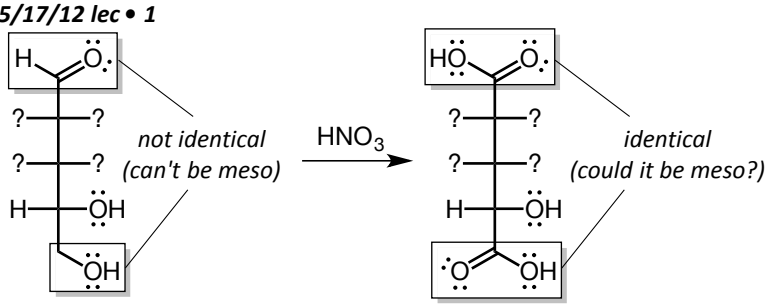
**Structures** *(remaining structures identical to lecture 15A)*

***05/17/12 lec • 1***

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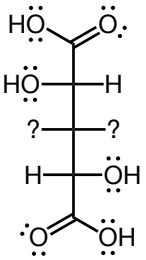
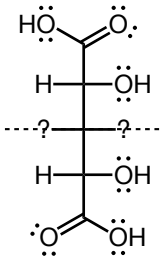


*cannot be meso regardless of the configuration of the middle stereocenter*



*mirror plane –> meso*