Lecture 15A • 05/16/12

There are five steps to the [Fischer glucose stereochemistry] proof. The first is the assumption of the d configuration. The second is the realization is that glucose and mannose are epimers that can be synthesized from d-arabinose. [Third,] that arabinaric acid is optically active. [Fourth,] that glucaric and mannaric acids are also optically active. [Firth,] d-glucose and l-gulose both form the same aldaric acid.

These are the five steps that are going to get us the configurations of the four stereocenters of glucose through observation of optical activity as the sole way of physically characterizing the compounds.

Point one the proof: in glyceraldehyde, Fischer made a monumentally lucky guess. Fischer guessed he configuration of d-glyceraldehyde. From that, we get this: that out of all the configurations that are possible for glucose, we eliminate half of them, because we're going to assume that that last stereocenter is the same as the sterocenter in glyceraldehyde. The Kiliani-Fischer chain extension reaction [could be used] three times in a row to add three more carbons to glyceraldehyde in order to be able to synthesis glucose. There's also the Wohl degradation, where you could take a larger sugar, chop it apart, and end up with a smaller sugar. There's two directions – by building up and breaking down – to demonstrate the relationships between the different sizes of sugars. Step zero is that Fischer knew it was, glucose that is, an aldohexose. Once you know that, you know there's four stereocenters. He assumed one of the stereocenters, so the rest of these steps are the proof are to try to figure out the configurations of those remaining centers.

The next observation is that glucose and mannose are epimers that can be synthesized from arabinose. Recall arabinose's structure [left, right, right]. We have a threefold sequence of reacting with hydrogen cyanide, which forms a nitrile, which we then selectively reduce – palladium and hydrogen with a poison catalyst to control and make just the imines. Then those imines are hydrolyzed, which gives us our two new sugars. There's a new stereocenter created, and since that stereocenter, regardless of the actual percentage of each compound is formed, since there's two configurations possible, we make two different products – once of which we know is glucose, one of which we know is mannose, but at that time, they didn't know which was which, they just knew that the both could come from arabinose. This is important because there's only three stereocenters in arabinose; those three stereocenters are the same bottom three stereocenters that are in glucose and mannose, and so if you can figure out anything about the configuration of arabinose, you automatically know what one of the configurations in glucose and mannose is. Since glucose and mannose can be synthesized from arabinose, if the configuration of a stereocenter of arabinose is established, then its stereocenter in glucose and mannose is established as well. Besides the fact osazones were useful at that time because they allowed for the formation of crystalline products. They also showed, in another way, that glucose and mannose were epimers of each other, because you lose one stereocenter when you take either of those sugars – the top stereocenter you lose – when you're making the osazones. Since again the bottom three stereocenters are identical, then that means that you get the same osazone product from either sugar. [1984]

Arabinaric acid is optically active. There is a set of reagents – nitric acid – that can be used to oxidize the primary alcohol at the bottom of the molecule and the aldehyde at the top. This is an aldaric acid – specifically, this is d-arabinaric acid. Let's say that we didn't know what the stereocenters were; I'm showing you the end result. It is optically active, but let's see what that means. What Fischer knew going into it was this: arabinaric acid, he assumed the configuration of one stereocenter and was trying to guess the configuration of the other two. Arabinaric acid is optically active. Here's why this proof is an elegant piece of work: out of these two stereocenters, just by knowing that the compound is optically active, we automatically know the configuration of one of them. Which one is it and why? It's optically active so its mirror image is not the same as itself. It's not meso – that's the only way that this would be optically inactive. That's the way that we could get at this: how do we make this optically inactive? Make the top stereocenter on the right. The only way this compound could be optically inactive is if it is meso, which would require an internal mirror plane – which means the -OH group would have to be on the right.

A little bit of an aside here: are these compounds both meso? Yes they are, because there's a mirror plane in both. They're both meso because of the configuration of the top stereocenter. How many stereocenters are in this molecule? What's our fallback definition of what a stereocenter is? For tetrahedral carbon, it's if you had four different substituents attached. Do we have four different substituents attached to the central carbon? No we don't, so I'll ask the question again: how many stereocenters are in this compound? Two. But are these the same compound? No. Then what about the middle carbon, isn't it a stereocenter? But if it was, these couldn't be meso, could they? So what is it? This is called a pseudostereocenter, which is created when you do have similar substituents that have different configurations. Here's another way of putting it: a pseudostereocenter is a carbon that produces stereoisomers but cannot be formally assigned a configuration of R or S, since two of the carbon substituents are equivalent. For a pseudostereocenter, instead of capital R and capital S, we have the configurations little r and little s. How do we determine that? The top stereocenter of the first of these compounds, is it R or S? Alcohol is priority number 1; carbon with three oxygens – notice that is the equivalent of having three oxygens on it – versus a carbon with one oxygen – this is the second importance, this is the third importance, this is the fourth. It looks like it is S, but because the hydrogen is pointed towards you, it's really R.

Since the bottom half of the molecule is the mirror image of itself, the bottom stereocenter is S. Both of those arms are less important, when we now look from the viewpoint of this middle stereocenter. Both of these arms are less important than the oxygen group, so from that middle stereocenter – the top is R, the bottom is S, we know that automatically the priority of the oxygen is number 1. In stereoconfigurations, R is given higher priority than S. On the basis of that tie-breaker, that makes the top group now priority 2, the bottom group priority 3. It's counterclockwise, but the hydrogen is pointed towards us, which means it's not being viewed correctly, so it'd be the equivalent of R, but it's little r, because it's not really a stereocenter, but it is, but it isn't, but it is – that's why it's a pseudostereocenter. That means that he configuration of the middle stereocenter up here is little s. To determine the pseudoconfiguration of a pseudostereocenter, R is given priority over S. You can meso compounds that have internal planes of symmetry, but odd number of carbons.

What's the point of all of this? That it didn't matter what the configuration of the middle stereocenter was, cause in both cases, it gives you a meso compound. The observation that Fischer made is that this compound is supposed to be optically active – arabinaric acid is optically active. That means it can't be either of these two compounds, so that means whatever compound it is, the top stereocenter is on the left. That leaves two possibilities for what arabinose is. We don't know the middle stereocenter, but we know the top one. We figured out the second stereocenter of glucose. One more stereocenter down, two more to go.

We make this connection chemically between arabinose and glucose and mannose, so that we know that if we establish a stereocenter on arabinose, the same one could be established in glucose or mannose. We know that arabinose makes an acid upon oxidation that has the same functional group at the top and bottom, which means, just on the basis of the number of stereocenters alone, it is technically possible to have meso compounds, but Fischer observed that this acid is optically active. The only way that it could be optically active is if the top and bottom stereocenters are configured oppositely from each other – not in terms of R and S, but in terms of direction, because if they were the same, then regardless of the middle stereocenter, it's going to be meso. Since it's not meso, cause it is optically active, that means the top stereocenter has to be opposite from the bottom, which is how we get one of the configurations in glucose.

The next step is exactly the same type of logic: glucaric and mannaric acids are optically active. What does that mean? That means we take glucose and oxidize it, and we again end up with the same [functional group] at the top and the bottom. With just the two stereocenters we have so far determined, that means there are four possible molecules left. Here are the aldaric acids of them. There are the four possibilities. Are any of them meso? Which one is meso? The second one, which means it cannot be the aldaric acid of glucose [or] mannose. What is the only difference between glucose and mannose? The top stereocenter doesn't matter; that means the third stereocenter cannot be on the left. That's the fourth step of the proof. There four possible compounds; only of them is meso. The one that's meso can't be glucose and it can't be mannose, which means it doesn't matter what the configuration of the top stereocenter; on either side, have that top stereocenter on either side, if either one of the cases make the molecule meso, both of them are wrong. In other words, the third stereocenter's configuration is also wrong. Once we eliminate those two choices, we're left with what we now know to be glucose and mannose.

Glucose and mannose have the same configuration for the third stereocenter. [numbering of carbons versus stereocenters] The third stereocenter in glucose and mannose are the same; they only differ by the first stereocenter. Therefore, if any structure is demonstrated not be either or mannose, then any structure that contains that same configuration for the third stereocenter cannot be either glucose or mannose. It means that I've got two choices: that stereocenter on the right or the left; at the same time, I've got two choices for the top stereocenter. One of these four compound I identified as being meso, when it's oxidized to its aldaric acid, cause then the top and the bottom are identical. That third stereocenter, if it was glucose, then that same stereocenter has to be in mannose; if this was mannose, that same stereocenter would have to be there in glucose. In either case, if one or the other is meso, they're both wrong, because they have to be related by having that same third stereocenter, so when I cross one of them out, I automatically cross the one that has the same configuration at that third stereocenter out.

Glucose and mannose that the same configuration for the third stereocenter; they only differ by the first stereocenter. Therefore, if the third stereocenter is shown to be incorrect for either compound, it is incorrect for both. This is why two compounds were eliminated as possibilities when one of the two was shown to be meso upon oxidation.

Therefore, what does that mean? We only have the top stereocenter left to determine, because: step 1 was to assume the bottom stereocenter; step 2 was to make a link to arabinose; step 3 was to realize that arabinose shows us the second stereocenter has to be configured a certain way; and then this observation about glucose and mannose, when you oxidize them, establishes the third stereocenter. Only one stereocenter is left unknown, which brings us to the last [and most difficult] step of the proof: that glucose makes an aldaric acid that another sugar can too.

What would happen if I were to flip the functional groups at the top and bottom of this molecule? In one case, nothing would happen. Here's mannose. Let's just imagine that something allowed the functional groups to be inverted; there is a way that we can chemically flip the two groups around. Imagine we had all 16 aldohexoses. If I now take this sugar and turn it 180°, what do I get? They're the same compound.

In other words, mannaric acid, which you would get from [mannose] with nitric acid, if I turn it 180° around, it's the same as itself. In other words, this is rotationally symmetric. The significance of that is: there is no other molecule that can give the aldaric acid that comes from mannose, because the only way we could generate some other molecule is to flop the functional groups. But when we flop the functional groups, we get the same molecule back again. Only one out of all 16 sugars can give us this particular aldaric acid, which means it mannose. The point of the last step of the proof is that some other molecule besides glucose can make the aldaric acid that glucose does. Why? Because glucose, in its glucaric acid from, is not rotationally symmetric.

Let's see why that matters. Let's take d-glucose. If you flip the functional groups, what molecule did I just make? Is it a d or an l sugar? l – which means everything you've memorized for the d, it's backwards. So flip them all around, what is it? l-Gulose [0100, 4, aagmgulose] But they both, if you oxidize them, make the same aldaric acid. This is the point: the difference between glucose and mannose is just the top stereocenter. For mannose, because of its configuration, when you oxidize it, it's rotationally symmetric, which is why there's no other compound that can give you that acid. For glucose, it is not rotationally symmetric, if you were to oxidize it. If somehow you could take from the acid and go back down to either one of these two compounds, the point is: you're going to get two possibilities, because which is the top and which is the bottom gets scrambled when you oxidize it. That's the last step of the proof: that because two compounds make the same aldaric acid, and only by putting the top configuration on the right gives us this situation, that is its configuration, so we know it's glucose. Then, in 1951, when the d/l question was resolved, it really was shown that that really is glucose.

That's the Fischer stereochemistry proof.

What's the 1st step of the proof? Step 0 – glucose is an aldohexose, which can be determined by successive degradation of a sugar to get it down to glyceraldehyde. We can do three degradations to get there, which, since glyceraldehyde has three carbons, three carbons plus three degradations make six. There's another test that shows it's an aldose, so it's an aldohexose. If I call that the zero step, then what's step 1 of the proof? Guess the d configuration. What's step 2 of the proof? That glucose and mannose are epimers and they from arabinose, which means we know that three of the stereocenters in arabinose are the same as glucose and mannose. What is the third step? Why do we care that arabinose is related to glucose and mannose? Cause we're going to use arabinose. The third step is that arabinaric acid is optically active. Why do we care? It's not meso, which means what? That there's only one possibility as far as the configuration of the top stereocenter: it must be opposite of the bottom, otherwise you couldn't end up with an optically-active aldaric acid. [notice it doesn't take five paragraphs to give me the answer]

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0. Glucose is an aldohexose
1. Assumption of d configuration
2. Glucose & mannose are epimers that can be synthesized from arabinose
3. Arabinaric acid is optically active
4. Glucaric & mannaric acids are optically active
5. d-glucose & l-gulose form the same aldaric acid

1) Fischer guessed the configuration of d-glyceraldehdye – ∴ The last stereocenter in glucose is assumed and was a guess.
2) Since glucose & mannose can be synthesized from arabinose, if the configuration of a stereocenter in arabionse is established, the configuration of a stereocenter in glucose & mannose is established.
[3)] Arabinaric acid is optically active
The only way this compound can be optically inactive is if it is meso, which would require an internal mirror plane
pseudostereocenter - r,s – A carbon that does produce stereoisomers but cannot formally [be] assigned a configuration of R or S since two of the carbon's substituents are equivalent. To determine the pseudoconfiguration of pseudostereocenter, R is given priority over S.
Since both of these compounds are meso, neither can be d-arabinose.
4) Glucaric and mannaric acids are optically active.
Glucose and mannose have the same configuration for the 3rd stereocenter; they only differ by the 1st stereocenter. Therefore, if the 3rd stereocenter is shown to be incorrect for either compound, it is incorrect for both. This is why two compounds were eliminated as possibilities when one of the two was shown to be meso (upon oxidation).
5) Two sugars make the same aldaric acid as glucose.

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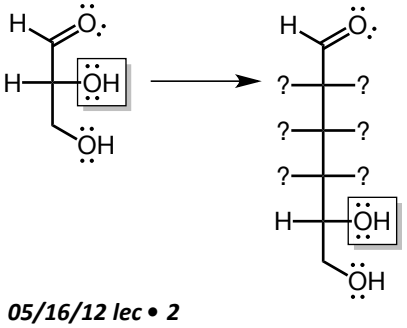

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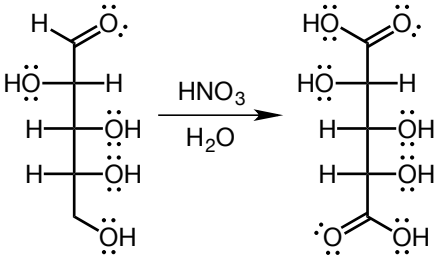

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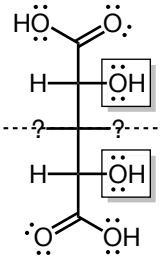

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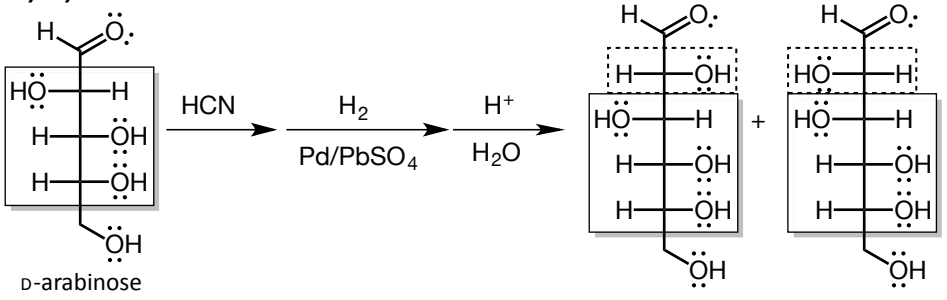

D-arabinose

D-glucose D-mannose

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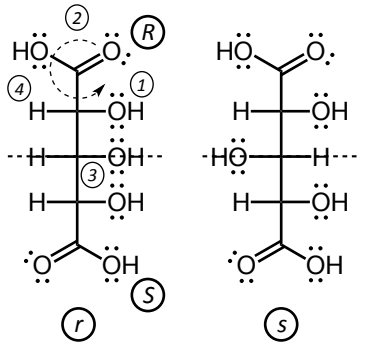

both are meso, because of the configuration of the top stereocenter, so neither can be arabinaric acid

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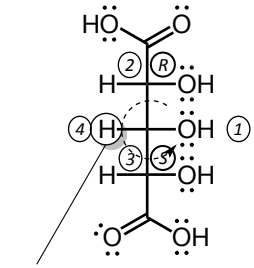

pointed towards observer

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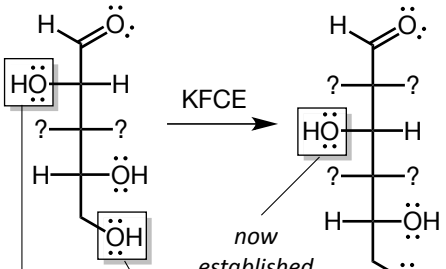

established by optical activity of arabinaric acid

established by a guess

now established [for glucose]

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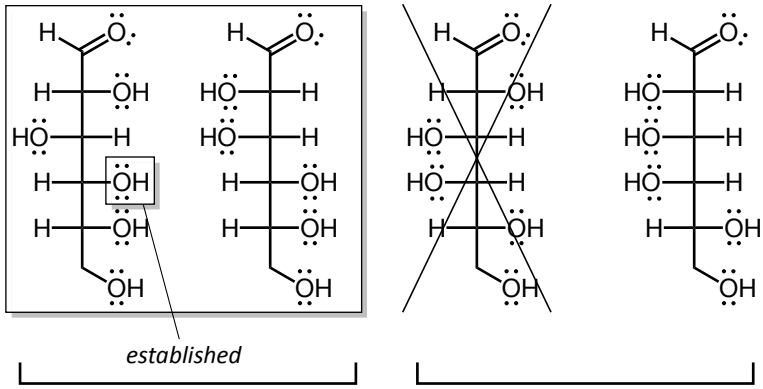

established

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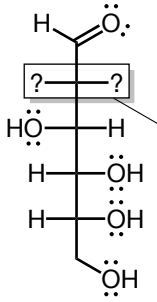

only one SC left undetermined

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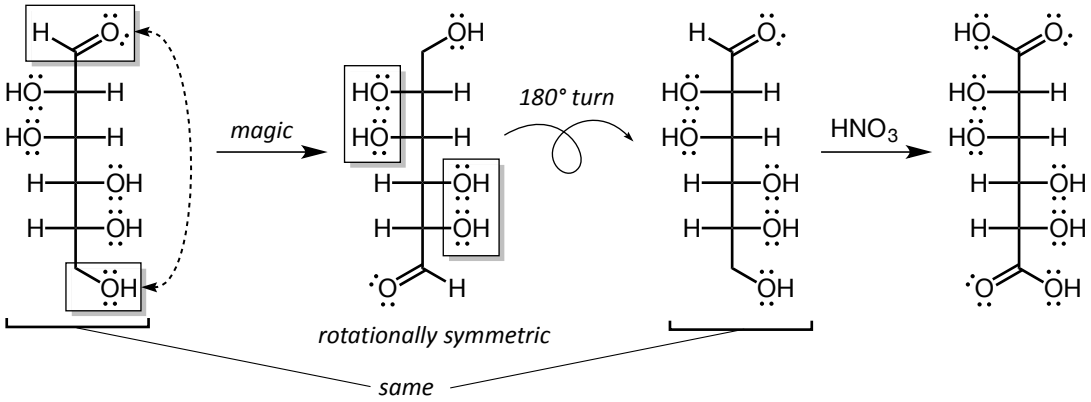

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