Lecture 17A • 05/21/12

There are six steps to the [Fischer stereochemistry] proof. We can start with the assumption that [glucose] is an aldohexose. What [is] the first bit of the proof – what [is] the significance of it, which stereocenter's established, what are the pitfalls behind this first step? The first step is a guess: what is the guess? In the compound glyceraldehyde, the d configuration is such that, when you right the Fischer projection so that the carbonyl is up top and the rest of the molecule follows the normal pattern, the -OH group is going to be on the right. The first step was a guess; why was it a guess? Do you remember what it was that finally allowed them to make that termination? It was x-ray crystallography, it was being able to take a snapshot of where the positions of the atoms were, and then figure out, geometrically, where is it to say ah: it is R, it is S. Did he turn out to be correct? Yes. Why is that assumption important for the determination of glucose's structure? The guess was that, for glyceraldehyde, the d form is such that the -OH group is on the right. What connection is there between that and glucose?

What's the next step? Kiliani-Fischer chain extension; what's the importance of that? From arabinose. But in general, you can take a sugar and add one more carbon to it. Which portion of glyceraldehyde does not get affected by the Kiliani-Fischer chain extension? The last stereocenter, the one that he guessed was the d configuration. If you have the d configuration set, and you build a sugar by adding more carbons onto it, then all of the d sugars, including d glucose, have that bottom stereocenter on the right. As a larger picture, we can say that there's 16 aldohexoses, but 8 of them are mirror images of the other 8, and chemically they differ by all of their stereocenters – except that last one. We use that last one to say which one of these two sets is it. That's the full explanation of that first step – it was a guess, it had something to do with the configuration of glyceraldehyde, but because glyceraldehyde can be made chemically related to all the other aldohexoses, then by extension, any sugar with the d designation has that bottom stereocenter configured to the right.

There's a second little wiggle to that second step. We talked about the Kiliani-Fischer chain extension synthesis, but what other way did Fischer demonstrate that glucose and mannose are somehow structurally related to each other? The phenylhydrazones – more specifically, the osazone, which is a double phenylhydrazone. When you react phenylhydrazine with a sugar, the aldehyde, if it's an aldose, and the next stereocenter down from it both react to form a hydrazone. Since that stereocenter disappears, it removes the difference between two sugars, the two sugars that are related by the remained of their stereocenters. Because glucose and mannose only differ on the basis of that top stereocenter, get rid of it, and the derivative is the same. Because the osazone[s] for glucose and mannose were equivalent, that shows they're epimers, and because they're both synthesized from arabinose, it shows they're epimers, with the same stereocenters as arabinose in common between the two of them. That's step two.

Step three. The aldaric acid ... what's the difference between an aldonic acid and an aldaric acid. In the aldonic acid, is the aldehyde or the bottom of the molecule that gets oxidized? it is only the aldehyde that gets aldehyde. [mechanism] Nitric acid makes the aldaric acid. What's the third form of derivative I showed you? Alditol; what do we use to make an alditol? What is an alditol? Where everything's an alcohol, so how do you get from an aldehyde to an alcohol? Reduce, using sodium borohydride. Sorbital is another name for glucitol, which is glucose reduced. Aldaric acid – the aldaric acid of arabinose has three stereocenters to it. Which one of these stereocenters can we automatically write down, based on the previous assumptions or steps in the proof? The last stereocenter, because the assumption that the d stereocenter means it's configured to the right. Which stereocenter does the observation that aldaric acid is optically active [let us establish]? The top one we can now establish. Why does the top stereocenter have to be configured to the left? ... It has an internal mirror plane, which means within the same molecule, it's symmetric. If the two stereocenters shown were configured as shown, the molecule would be meso, and therefore optically inactive. Arabinaric acid is optically active, so it cannot be configured as shown. That means we know these two stereocenters for arabinose, which, cause of that same Kiliani-Fischer chain extension, we now know two stereocenters of glucose.

Step four. Just like arabinaric acid is optically active, glucaric and mannaric acids are also optically active. We've established two stereocenters so far. We know that both of those acids are going to look something like this. Which of the stereocenters does this part of the proof get us? We get four different molecules; which stereocenter is the one that we're going to end up establishing? The third one. Why is it going to be that stereocenter that gets determined? When you pick one of the configuration of stereocenter 3, you do end up with two possibilities as far as what the top configuration's going to be. But, if you choose the wrong one for the third stereocenter, if you put it here, then one or the other of the possibilities is going to be meso. Only by putting it there does it reflect with that other one that's up there; the mirror plane wouldn't exist if that third stereocenter wasn't configured that way. Since it can't be meso, because they're both optically active, that means that third stereocenter's on the other side. When the third stereocenter's configured as shown, one of the two possible sugars, when oxidized, will be optically inactive. Since they both have that same configuration for the third stereocenter, they both must have the opposite configuration for that point. When the third stereocenter is configured as shown, when oxidized, one of the sugars will be optically inactive – that's because it's meso, since a mirror plane can be drawn through the molecule. Since both glucose and mannose have the same third stereocenter, they must be configured the opposite way for both compounds. Only one of the two is meso. Here's four possibilities; if I eliminate one, I eliminate two. That's why I divided the four possibilities up into pairs, because one pair has one configuration for the third stereocenter, the other pair has the configuration for the other.

So it’s not that both compounds will be meso – if you look at the d sugars, if you oxidized all the d-aldohexoses, galactose is the only one that’s going to be meso. But of that one is meso, then whatever compound shares the bottom three stereocenters can’t be that one either. Glucose and mannose share those three bottom stereocenters. If you show one configuration of the top one to be wrong, flip the top one around, it’s still wrong, because if the bottom three stereocenters.

All aldohexoses are always optically active. I choose the third stereocenter like that. If so, I don’t know which one is glucose an mannose. Put the top one on the right, the way that you choose to, now it has a mirror plane. But since they both must be one of those, if it’s wrong, it’s wrong for both. [red pill, blue pill] Let’s say I’ve got my twin over here, who’s also holding out two pills – a red one and a blue one. You don’t know which one is good and which one is bad [which one will take you deeper down the rabbit hole]. Let’s change that scenario a little bit. Let’s say that one of my twins, both pills are good; the other twin, one pill is bad, one pill is good. You would want to go with whichever twin only gives you good choices, so for one twin, you don’t know which one’s bad, but you know one’s bad, so you’re not going to go that way, no matter what. Which one of these is glucose? That’s the point. If I say this one is wrong, they’re both wrong, cause you don’t know which is which, but they both are related by the bottom three stereocenters. Since that doesn’t change between the pair of choices, the top stereocenter, no matter what it is, the bottom three are the same. Since they have to be correct, if one molecule is shown wrong, both molecules are wrong.

Step five. Out of the 16 sugars, how many of them, if you remove the top and the bottom functional group, are rotationally symmetric? Mannose, and that’s the only one. What did I just say? Rotationally symmetric – what in the world does that mean? Is this shape rotationally symmetric 180°? No. You turn it 180°, what happens? [C2V] It is not symmetric when rotated 180°. What about this shape? You know that if the first one is no, the second one’s gotta be yes. When I turn it 180°, what do I get? The same thing back again, so it is rotationally symmetric 180°. What does this have to do with the sugars? Because if somehow I could swap those groups by rotation, that has exactly the same form as this disc I just drew. In fact, if you fill in these with -OH groups, this becomes the molecule mannose. Mannose is [one] sugar that has this kind of configuration, where if you turned it 180°. Mannose is the only one that’s rotationally symmetric that has that configuration of the bottom three stereocenters.

Why does it matter whether it’s rotationally symmetric or not? Because, for the sake of argument, assume that Fischer had all 16 sugars to play with, and oxidized them all. The one that glucose made, when it oxidized, was the same as another sugar was. That’s not physically possible for mannose, because the reason that you have those two possibilities for glucose is – imagine that I start with the stereocenters for glucose and nothing else, but I take this two different directions: in case, I take exactly that same sugar and put the aldehyde and alcohol the way we normally would. But, I could also do the opposite way (there are ways chemically do to this, but that’s not really the point – the point is just to demonstrate why would two possibilities occur). Because when you oxidize either of these compounds they both turn back into the same aldaric acid, because the top and the bottom of the aldaric acid are the same. If you made them different, by taking them back down to the sugar level, that means that two different sugars would be involved: one of them is d-glucose, the other one is l-gulose. Taking mannose, which is rotationally symmetric, [I get the same thing when I turn it upside down]. No matter which end I put the aldehyde on, it's the same sugar; it's the only sugar that, when you oxidize it, gives you that particular aldaric acid, which is why that one is mannose.

Tollens' silver mirror test

Why is it called the silver mirror test? It makes a mirror. You can perform the formation of a mirror chemically by mixing a solution of formaldehyde, wash it on the inside of a test tube, wash it with this reagent, and you're going to get silver film, solid silver, deposited as a thin layer all on the inside of your test tube; it's purposely done to make mirrored objects in that way. What's going on here? Take a solution of silver nitrate and ammonia. What would happen if I added hydrochloric acid at this point? Silver chloride would precipitate. But if I had a silver compound like silver chloride, if I take it out of acid and put in into basic conditions and put it into ammonia, that silver salt dissolves, because it forms a complex ion; it forms this. This silver-ammonia complex is an oxidizing agent. If you take an aldehyde and you react it with Tollens', you get a carboxylate – which is oxidation. The product is silver metal – silver is the oxidizer (whatever oxidizes gets reduced).

If we have a ketone, there's no reaction; why? No hydrogen. Aldehydes, because of the ability to form hydrates, can be oxidized. Ketones – even if you can form hydrates – you can't make another bond, because it's already got four connections to it; you need the ability to remove a hydrogen from that carbonyl position. In order to be able to oxidize. Why is this important? Historically, if we didn't know whether we had an aldehyde or a ketone, we could show that we had one or the other by making a hydrazone. This is 2,4-dinitrophenylhydrazine – when you react it with something like acetone, [you make] a derivatized hydrazone; it's short name is DNP. DNP derivatives – very crystalline, very isolatable; means they're great for doing melting point tests. It also let you know whether you have an aldehyde or a ketone, because those are the types of functional groups that can make this. Just on the basis of the DNP derivative alone, you don't know: is it an aldehyde or is it a ketone – except if you do the Tollens' test. The Tollens' test lets you distinguish between an aldehyde and a ketone – unless you have a sugar, more generally, unless you have an alpha-hydroxy group – that'll give you a false positive. Why? Normally, the Tollens' test is positive for aldehydes, negative for ketones. Why? Aldehydes can be oxidized, ketones can't.

The Tollens' reagent is an oxidizing reagent; it oxidizes aldehyde, it doesn't oxidize ketones. You see if it happens or not because of the silver film produced, so it's a qualitative test for a functional group.

It's got a drawback to it: a ketone that is not supposed to react with because it's not oxidizable, it gives that positive indication for; it makes the silver, which is only supposed to happen for aldehydes. Why is this happening? The primary alcohol by itself wouldn't reagent; you need a carbonyl. If you're in basic conditions – if you have ammonia around, that usually implies you've got basic conditions. You can double tautomerize and turn this into an aldehyde; that's how glucose and fructose are related. In solution, this tautomerizes; once it does, it oxidizes, gives you the false test. Why does this matter?

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If the two stereocenters shown were configured as shown, the molecule would be meso & therefore optically inactive. But arabinaric acid is optically active, so it cannot be configured as shown.

Glucaric & mannaric acids are also optically active – When the 3rd stereocenter is configured as shown, when oxidized, one of the sugars will be optically inactive (meso), since a mirror plane can be drawn for the molecule. Since glucose & mannose have the same 3rd stereocenter, it must be configured the opposite way for both compounds.

Tollen's silver mirror test – used to distinguish between aldehydes and ketones – Silver itself is the oxidizer, so silver gets reduced

$AgNO_3$ (aq) + 2 NH_2 (aq) -> $[Ag(NH_3)_2]NO_3$ [oxidizing agent]

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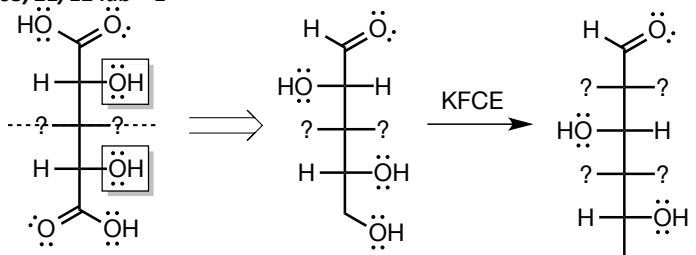
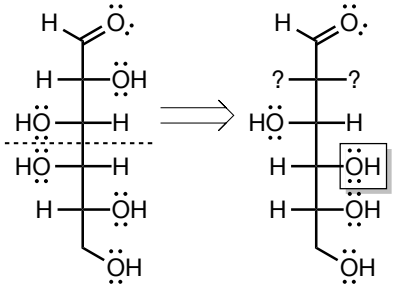
Structures

05/21/12 lab • 1



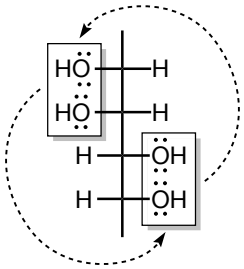
arabinaric acid
(*optically active*)

05/21/12 lab • 2



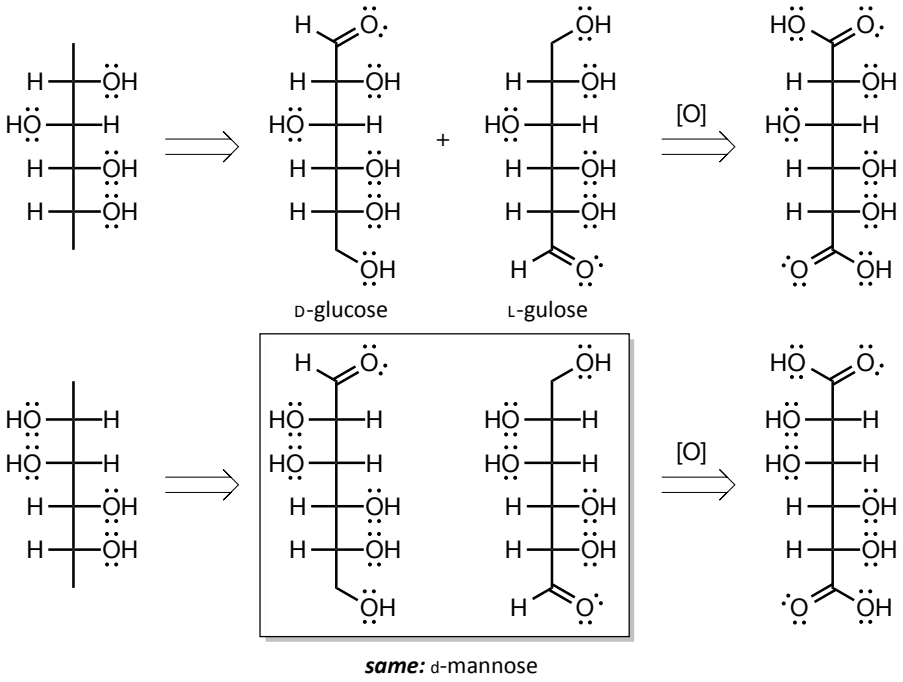
(*meso*)

05/21/12 lab • 3



mannose

05/21/12 lab • 4

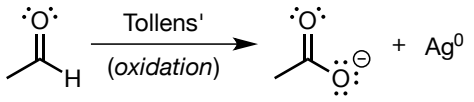


D-glucose

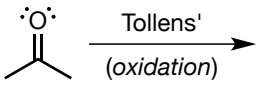
L-gulose

same: D-mannose

05/21/12 lab • 5

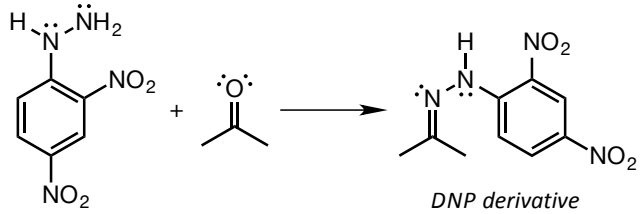


05/21/12 lab • 6



(*would form 5 bonds to carbon*)

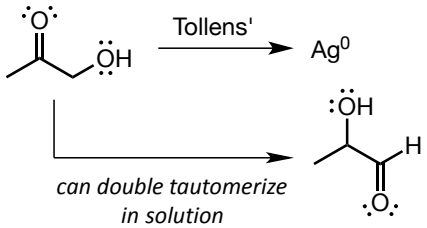
05/21/12 lab • 7



2,4-dinitrophenylhydrazine

DNP derivative

05/21/12 lab • 8



can double tautomerize in solution

false positive – only "supposed" to happen for aldehydes