Lecture 14A • 05/14/12

If you had "real" Coke versus the diet version of it, if you were to spill one or the other on your floor or carpet or whatever, which of the two are you going to be more annoyed at cleaning up? I'd say the regular; why? Which one's actually going to be really that sticky afterwards? The regular one with sugar. By extension, what I'm really getting at is that sugars, in general, are difficult compounds to work with, because you get just a little bit of water in them, and they make this sticky message that doesn't necessarily easily crystalize out. Let's roll back to the 1800's where things like melting points were really important determinations. Some of these compounds were identified just on the basis of their melting points. If you ended up with some kind of gel or goo that you couldn't turn into a crystal to melt, how could you identify the compound? The answer is: you couldn't. So, carbohydrate chemistry was something of a difficult endeavor – until this reagent came along: phenylhydrazine.

Why does this molecule? If you take something like d-glucose [right, left, right, right] and react this with three equivalents of phenylhydrazine, you make a product. The bottom three stereocenters of this product are unaffected. The top stereocenter ends up getting converted into a hydrazone – but not just with that carbon, but with the neighboring carbon as well. The synthesis of this hydrazone is a fascinating mechanism. It's a variety of protonate-open-attack-deprotonate steps, along with some tautomerization, along with a little bit of [something resembling] decarboxylation. The point of this osazone – which is a particular kind of derivative – an osazone is a double phenylhydrazone that comes from [a] sugar, that's why it's got that -ose [ending] in it. These osazones are crystalline. So what? If it's a crystal, we can melt it and measure its melting point, which means we can identify a compound by it. Derivatives in general used to be prepared to help you identify a compound. If we weren't dealing with sugars, if we had just some other random compound that didn't have a nice, measurable melting point – even if you had that, you might have ten other compounds that have that same melting point. Make a derivative, though, and match that derivative's melting point as well – that's comfirmation[al] evidence of the compound that you're trying to identify. That's how these were used as well, because you got these nice crystalline materials out of this otherwise sticky message that you would get when you did carbohydrate reactions.

But there's one issue with this: what is the structure of g-mannose? [left, left, right, right] Notice that, if I took the same three equivalents of phenylhydrazine and make the phenylhydrazone, I get the same compound out, because the bottom three stereocenters in glucose and mannose match each other, and those three stereocenters are the only stereocenters that survive in this product. Since they're the same, two different compounds can make the same derivative – not unheard of, but structurally important, because if, back in the 1800's they didn't know what the structures of any of these things were, this is a piece of evidence that shows that these two compounds are structurally related to each other. In fact, it was from the fact that the osazones of d-glucose and [d-]mannose are identical that Fischer realized they're epimers – because there's one stereocenter that's left, and if it's that stereocenter disappearing, that stereocenter disappearing that identifies that makes these the same – that's an epimer right there, one stereocenter difference.

This is not the only way that he knew this to be true – the Kiliani-Fischer chain extension. What is the structure of arabinose? [left, right, right] Arabinose is chemically related to both glucose and mannose, because its three stereocenters match those same three bottom stereocenters that are in glucose, mannose, and their common osazone. This is [a modified version of the Kiliani-Fischer synthesis] to use more modern reagents. First thing is: hydrogen cyanide, which makes what kind of functional group out of the carbonyl? A cyanohydrin. What does it do to the carbonyl's configuration? We get one more carbon, and we get one more stereocenter.

To remind us what a cyanohydrin is, we could have a protonation, which means cyanide can now attack [open combined with resonance]. When I attack, I'm creating a tetrahedral carbon, which means I've got a new stereocenter, which means I'm going to have two different compounds, which we would almost recognize as being glucose and mannose. Of course, right after the reaction, they're not quite glucose and mannose yet, because we have a nitrile up top instead of an aldehyde. If I then use palladium with lead sulfate – that is one of those poisoning reagents that will diminish the reactivity of palladium and allow you to stop at the double bend when you reduce the nitrile. When we neutralize an imine – that's what we've made now – we'll make d-glucose and d-mannose.

There are two ways in which the structures were demonstrated to be related somehow: if you take glucose and mannose and make this osazone derivative of the two, it shows they must have somehow come from some common carbon source. We've just now shown that, by chain extension, by adding one more carbon, it causes glucose and mannose to be made. From both directions, it shows they're epimers, because arabinose, you're only adding one carbon, you're adding one stereocenter; it's by the difference of that one stereocenter alone that you make glucose versus mannose. When you remove that stereocenter by making the derivatives, you again make them the same compound again.

The Kiliani-Fischer chain extension of arabinose demonstrates that glucose and mannose are epimers formed by adding one stereocenter to arabinose. The formation of osazones show[s] that glucose and mannose are epimers, since the stereocenter that differentiates the compounds is lost upon osazone formation. Fischer took this and several other observations, put them together, to come up with what is the structure of each of these sugars.

You already know the first step of this proof: that he made a random guess. But we've also just demonstrated this much: that, starting with arabinose, if you don't really know its structure is, but we're assigning it configuration for its bottom stereocenter, are creating two new compounds, where, because we're adding a stereocenter, we know one has its top stereocenter configured one way, the other has that top one the opposite way. That means there's just two more stereocenters that we have to determine the configuration of – at least to get the pair of glucose and mannose. Once we've figured out the pair, we've gotta figure out for the top stereocenter: which way is glucose, which way is mannose?

Is this compound meso? No, because what do you have to have to be meso? You have to have symmetry. Even though the two -OH groups, you might be able to draw a plane through there, the top and the bottom, they're two different functional groups. But what if I oxidized. What was this sugar I wrote? Erythrose. If I make erythrotic acid – which is what you get when you oxidize – this is what is called an aldaric acid. [Aldonic, aldaric, alduronic] Is that meso? Yes it is, because it's symmetric. Here are the types of tricks Fischer played: some sugars, when you oxidize them, will be symmetric; some won't. That he could determine. Tf we already knew the bottom stereocenter in this compound was on the right, if we know that when we oxidized it was optically active, then we know the top stereocenter is also on the right, cause that's the only way it could be optically inactive.

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Kiliani-Fischer chain extension

– The Kiliani–Fischer chain extension of arabinose demonstrates that glucose & mannose are epimers, formed by adding one stereocenter to arabinose.
– The formation of osazones shows that glucose & mannose are epimers, since the stereocenter that differentiates them is lost upon the osazone formation.

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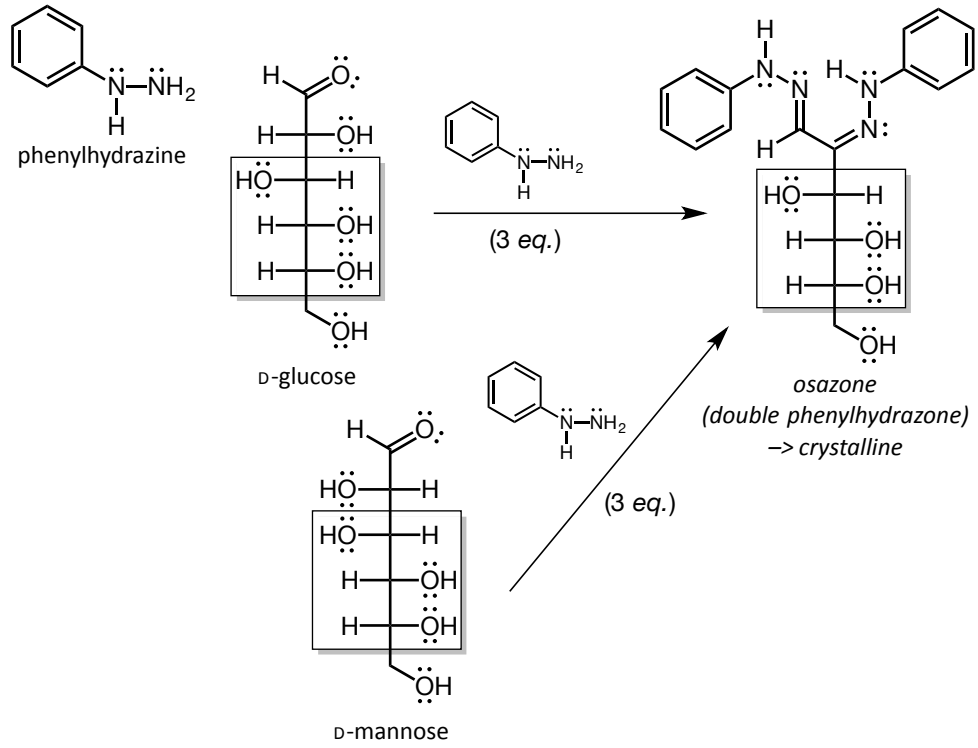

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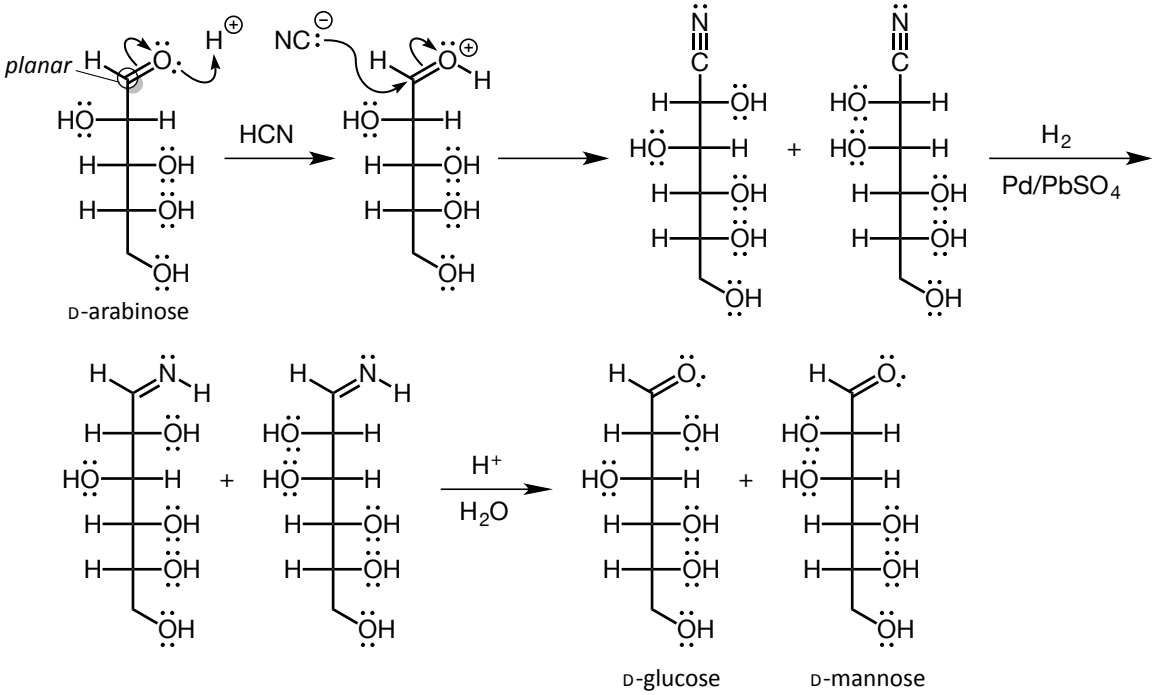

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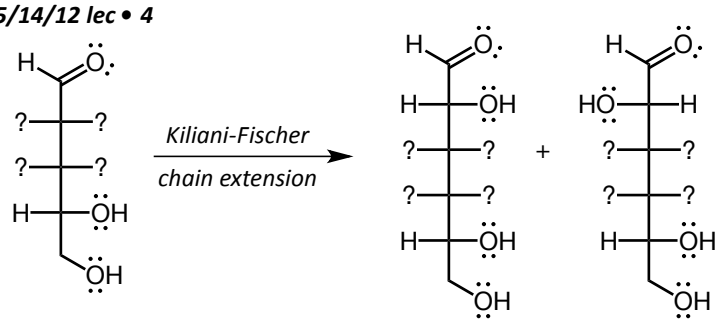

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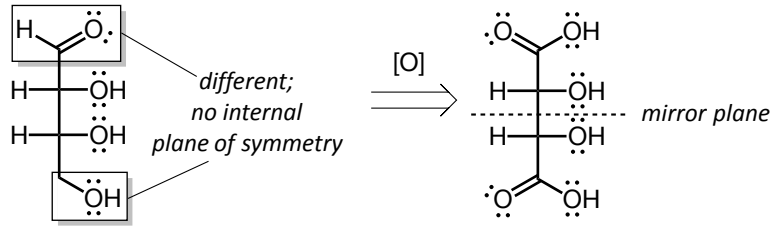

meso? no, not symmetric

meso (symmetric)