Lecture 14B • 05/15/12

Back in the 1870's/80's when this carbohydrate chemistry was developing, melting point was one of the main ways to characterize a material. [Often, derivatives of compounds were made] in order to do melting point tests. The logic behind it was this: if you had a compound that you could measure the melting point for, there could easily be five, ten other compounds that might happen to have that exact same melting point. But if those were different compounds of different functional groups, for example, then if you were able to make a derivative that could only be made out of your particular compound you're interested in, that derivative should also have a very distinct melting point that, if you could match the original compound with its melting point and the derivative with its melting point, that would help more fully confirm that you got what you thought you got.

With sugar chemistry, there's an additional issue. Let me ask you this question: if you had a can of Coke versus Diet Coke, which one are you going to be more upset about falling over and spilling all over the place? [which one attracts ants] Coke sticks to things. Sugars, all these different carbohydrates, if you're trying to do synthesis with them, they make big, sticky, gooey messes, cause they're sugars. If you think of normal sugar and water, yeah, if you give it enough time, maybe you can drive enough water [off] that you recrystallize sugar out, but what if you've got just a little bit of impurity? Basically, these carbohydrates were difficult things to work with because they were difficult to crystallize. If you can't crystallize them, you can't take a melting, which, since they didn't have IR or NMR, that means you couldn't identify easily what was in your solution.

This was changed – and Fischer was one of the people responsible for this – by a reagent known as phenylhydrazine. This derivative has a benzene ring on it; we'll talk about why momentarily. If you take three equivalents of this phenylhydrazine and react it with a molecule like glucose [right, left, right, right], you get a derivative that looks like this. Three of the stereocenters, the bottom three, are retained. The top two carbons both are converted into another functional group – a hydrazone. This is a double phenylhydrazone – but that's not the name usually given. These derivatives are called osazones – the os- prefix means related to sugars, and then the -zone part is related to hydrozones in general. Why are these osazones useful? All of these benzene rings stack versus each other, very crystalline, it help crystallize the compound – makes a carbohydrate derivative that can be isolated. That was enormously helpful.

It also elucidated a certain issue in carbohydrate chemistry. Yes, the bottom three stereocenters of glucose and the osazone are the same, but that means there is one other sugar that has this configuration [left, left, right, right] that, if you also react with three equivalents of phenylhydrazine, you'll get the exact same product – again, the bottom three stereocenters match. It's only the top stereocenter that you lose. What sugar is this? Mannose. What this demonstrates is that glucose and mannose are somehow related to each other, because they both form exactly the same derivative. This was known to researchers at the time, which is connected to this whole puzzle of what are the structures of these sugars, and how can we prove that they're related to each other? This is a case of epimerization, where the top stereocenter in either sugar gets lost when reacting with the phenylhydrazine. The point is, these are related structures.

There's another way that we can demonstrate that there's a relationship between glucose and mannose. This is the modified Kiliani-Fischer chain extension [synthesis]. Let's say I started with this sugar. What is the name of this one? This is arabinose. What would happen if we took a carbohydrate and reacted it with hydrogen cyanide? To write the mechanism in a more compact form, in general, if you have an aldehyde, it can get protonated, and then cyanide can attack. We end up with a cyanohydrin. That's what will happen with arabinose's case. Notice that the anomeric carbon is planar in its linear form; it's not a stereocenter. If we do this reaction, we're adding a carbon, but we're also creating a new stereocenter. If we do the reaction with arabinose, we get not one product, but two. On all the structures on this page so far, all of them have this same common set of stereocenters on the bottom part of the molecule. Since we added a new stereocenter, that means two molecules are going to be made – except, it's not going to be an aldehyde; it's going to be a nitrile to begin with. Let's say that we knew arabinose's structure, [but] didn't know glucose['s] or mannose['s] yet. From this derivative's test, though, we could show that they're related to each other. But, we don't know which one is which without, ahead of time, knowing the structure. What we're going to learn is how to figure out which one of these two is glucose, and which one of these two is mannose.

We're not done with the reaction yet, because first, we're going to reduce it with hydrogen and palladium, but we'll used a poisoned one [catalyst]. Lead sulfate is one of those components that's often included in Lindlar's catalyst. [We previously learned] that this [set of reagents allows us] to selectively hydrogenate something, to go from the triple bond to stop at the double bond – that's exactly what happens here. That means the next thing that we make is an imine; it's a set of epimers that are imines. The last step would be hydrolysis – acid and water – from which we're going to get glucose and mannose. The formation of osazones from glucose and mannose shows that they are epimers, because the formation of the osazone itself causes the loss of just one stereocenter, and otherwise the derivatives are identical.

Synthesis from arabinose shows also that they are epimers, because again we start with one sugar and make two; we can identify, through derivatives, that they're related. We don't know yet which one is which. We also know, though, that the bottom three stereocenters in arabinose match those in glucose and mannose.

There's a way to make larger sugars from smaller ones, which [in the context of this proof] has a two-fold purpose to it: it show which stereocenters from the smaller sugar will be identical in the larger sugar, and we also know that those two larger sugars are epimers of each other.

Take a very simple sugar like this one – what is its name? It's erythrose. Is it meso? No, because to be meso, you have to have [a] mirror image within the molecule itself; another way of saying it is that there has to be an internal plane of symmetry. What if we were to oxidize, and oxidize in such a way that both the aldehyde turns into a carboxylic acid, and only the primary alcohol also turns into a carboxylic acid? Is this meso? Yes it is; that's because it's got a mirror plane. If you imagined threose, which is [left, right] for its -OH group configuration, if you oxidize it, it's not going to be meso, because it's not symmetric with itself. If we started with Fischer's first assumption, that the bottom stereocenter is fixed on the right by choice, arbitrarily, and then if we were to find out that that sugar, when oxidized, is meso, that means the top stereocenter also has an -OH group on the right, automatically, no matter what's in the middle.

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Modified Kiliani-Fischer chain extension

The formation of osazones from glucose & mannose show the two sugars are epimers, since they both form the same derivative and that process involves the loss of one stereocenter. The synthesis of glucose & mannose from arabinose demonstrates the close structural similarity of the three sugars and that glucose and mannose are epimers.

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Structures – Identical to those from lecture 14A (05/14/12)