Lab 7B • 05/07/12

D versus L configuration of carbohydrates

One of the important things that happened in the mid- to late-1800s was the idea that carbon, when it's fully bonded, does have a tetrahedral shape, which the mathematicians then said: oh, that means that you could have two versions of the same molecule that have all the same substituents but are mirror images of each other. It turns out that those mirror images have identical properties to each other – melting point, boiling point, density, index of refraction, everything you can think of – except optical rotation. That means, though, that if optical rotation is the only way to distinguish between the two, and there's not necessarily any way to predict which one's gonna have which optical rotation, then without being able to say exactly where the atoms are located, there's no way on the basis of optical rotation alone to identify which one is which, if you don't already know which one is which. In other words, if I gave you a molecule and you figured out it rotated light counterclockwise, so what? What if it have five stereocenters? How do you know what the configurations of those five stereocenters are, versus if you had its mirror image? You can't.

Glyceraldehyde, that's the simplest of the carbohydrates. This is [the d form]. That d designation has to do with optical rotation; it means that this is + itself [verify]. When this compound was first studied, they didn't know what the configuration of that -OH group really, so Fischer, as part of his stereochemistry proof, guessed – he just guessed what that configuration was, which meant that .... You can synthesize a whole bunch of other molecules from this d-glyceraldehyde; this is not the only molecule that has that designation; there's quite a broad range of molecules that have that d or l designation. But that meant that from that point where they first came up with that designation until the 1950s, that configuration was just a guess. At that point, we then had x-ray crystallography, [through which we also] got the structure of DNA. It also gave us the configuration not of this compound, but another compound that had stereocenters that could be related back to glyceraldehyde. What they discovered is the guess that Fischer made was correct, which, fortunately, that meant that all organic molecules in every textbook everywhere that had that designation didn't need to be changed, because in the 1950s if they had done that experiment and found out that he guessed wrong, then every molecule would have to be inverted – but that didn't happen. In other words, it's a monumental lucky guess. That's the origin of this d-glyceraldehyde.

To show why this is used to designate of classify different sugars, let's go through a small sequence of reactions. What would happen if we took glyceraldehyde and reacted it with HCN, hydrogen cyanide? You'd protonate the carbon, cyanide would come in to attack, [producing] a cyanohydrin. Of course, the bottom stereocenter never gets affected by this reaction; it doesn't get involved. But we have done something with the carbonyl, attacked it, and we're going to turn that carbon that was part of the carbonyl into a tetrahedral carbon, which means we've made a new stereocenter. Ignoring any kind of sterics, in principle, that carbonyl could be attacked from either side, which means we actually get two different products. To demonstrate that, I'm going to use a wiggly line, which could mean you don't know or don't care what the configuration is but you're trying to show that it may be variable. Maybe it's not a 50/50 distribution, maybe there's some kind of steric effect, but at least we are going to get two different products. Up at the top here, we're now going to have a nitrile. Nitriles, we know, we can reduce, we can use a hydride agent to reduce them. What he hadn't yet talked about is you could also reduce them using hydrogen, but just like a triple bond, you could selectively reduce down to a double bond, the same thing can happen here. If we have hydrogen and a poisoned catalyst [does Lindlar's work], we'll bring that triple bond down to a double bond, which means I make what kind of functional group? An imine. What would happen if I hydrolyzed the imine; what would I get? What would be isolatable? An aldehyde. You can take an aldehyde or a ketone and turn it into an imine, which means when you go backwards, when you add water and acid, you're going to go back and make the aldehyde or ketone. In this case, since it's a terminal carbon, it means we're going to make an aldehyde, which means we've made a carbohydrate again. This is an example of what is known as chain extension – we've added one more carbon. This will allow us to make a relationship between different sugars, because I've taken a smaller sugar and I've made two specific larger sugars from it.

If we look at all of the structures I've drawn so far, that last stereocenter doesn't change throughout. Since the d-glyceraldehyde was assigned that d label, then all these other molecules that have that same configuration for the bottom stereocenter are also called d. The reason for that is that glyceraldehyde, if you invert its stereocenter, you still have glyceraldehyde; it has all the same physical properties – except optical rotation. That's the only difference between the molecules. For all other sugars, the same thing ends up being true: that there's going to be mirror images of each one. For example, glucose, a molecule that's blood sugar, only one form gets metabolized by the body; the other one is the same in every, except it's like having gloves and hands – only one glove is going to fit on one hand, only one enzyme is going to wrap around the right form of glucose. The difference between those two is that they're mirror images, so we use just that last stereocenter to say which one of the two mirror images it is. [what are the effects of l-glucose on the body?]

The type of sugar, whether it's d or l, is defined by the configuration of the stereocenter that is furthest away from the carbonyl, [otherwise known as] the anomeric position. The anomeric position is that carbonyl carbon. Let me show you an example of d and l sugars with glucose. I keep using glucose because it's a biologically-important molecule, but I also want to use something that has multiple stereocenters to show you what d and l means.

If you're looking at what's on the righthand side of this, from top to bottom, glucose is -OH, -H, -OH, -OH, or if you want to focus on the -OH groups, it's right, left, right, right. Because of that configuration of the bottom stereocenter being on the right, then this is d-glucose. The other form of glucose is the mirror image – mirror image means what? What are enantiomers? Non-superimposable mirror image, that's the phrase that you're programed to say. We have to remember that these are stereoisomers, so all of the atoms are hooked up to the same atoms, it's just that they're arranged differently in space. These are non-superimposable mirror-image stereoisomers, which means that every stereocenter that's S on one molecule is R on the other, and every stereocenter that's R on one molecule is S on the other. One might incorrectly, to produce the l sugar, flip just the last stereocenter, but that's not an enantiomer; the enantiomer would be all the groups reversed.

What [are] diastereomers? Only some of the stereocenters are inverted, so if we wanted to talk about them being mirror images or not, are they mirror images of each other? No, because only some, but not all, of the stereocenters are inverted, so we could say they're non-identical, non-mirror image stereoisomers. Again, this means that some, but not all, of the stereocenters are inverted. If we wanted to think of it this way, diastereomers is a somewhat broad category; there are more specific types of diastereomers known as epimers. Do anybody remember what an epimer is? Where one stereocenter – specifically one – is change, but it's still a diastereomer, so it can't have just one stereocenter, because if we only had one stereocenter and we invert it, that's an enantiomer. An epimer is a diastereomer – meaning I've got at least two stereocenters – but out of all the ones that might be there, only one is changed. But there's a subset of this; that's the point of what we're getting to – anomers. An anomer is an epimer that only appears in carbohydrates.

I want to present to you the first set of sugars that you need to memorize. Glucose has four stereocenters to it. If you have four stereocenters, that means, potentially, you have sixteen different molecules – 2 times 2 times 2 times 2. But, half of them are mirror images of the other, so if you have four stereocenters, you only have eight unique types of sugars. The bottom stereocenter will be the same for one set or the other, the d set or the l set; therefore, there's only three stereocenters left that these sugars differ by, so 2 times 2 times 2 gives us eight different sugars. I'm going to write out the eight sugars. [leaving out lone pairs, except when showing mechanism][commentary of fossilization of binary system]

In our normal decimal counting system, we go 0, 1, 2, 3, 4, 5, 6, 7, 8, 9; we run out of numbers, so we start over again, so we add another digit to show that we ran out of numbers. The first digit that we normally count is the 1's, then we have 10's, 100's, 1000's – that's base 10, that's decimal. Not all cultures have always used the decimal system. In computer terms, there's three systems that are used – binary, octal, and hexidecimal, because they all have to do with how many digits of off and on do you have, because that's the way that computers store things – in terms of 1's and 0's. In octal, for example, we count 0, 1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 14, 15, 16, 17, 20, 21, 22, so on and so forth. Binary, first digit is 1. There's only one [number] in binary – binary, two, means counting in sets of two, so it's either off or on, so once you turn it one, you turn it off and you turn the next one on. So the numbers go 0, 1, 10, 11, 100. [one of favorite t-shirts: there's 10 types of people in the world, those who undertand binary, and those who don't]

The point of all of this is: how did I write all of these structures down so quickly? Look at the righthand side of each structure. Call the position of that -OH group on the righthand side zero, calling on the lefthand side one. Read the structures this direction, from left to right, but looking at it this way. This would be like a rack of zeroes: 0000, 0001, 0010, 0011, 0100, 0101, 0110, 0111 – binary numbers zero through seven. I don't have to memorize those structures; I know that they're binary numbers zero through seven, and I memorize just their names – allose, altrose, glucose, mannose, gulose, idose, galatctose, talose. [usefulness of binary pattern to memorize sugars]

Let's take glucose and see what happen to it when it [is] put in water. D-glucose. What's the functional group at the top of the molecule? An aldehyde. What are the rest of the functional groups? Alcohols. What happens if you take an aldehyde and an alcohol and put them together? What could you get? Hemiacetal or acetal. How does that occur? Protonate, open, attack, deprotonate. Attack of what? An alcohol. If you've got an aldehyde and an alcohol on the same molecule, couldn't you have an intramolecular attack? Yes. Resonance is not a step, so [this is] a shorthand for the oxygen attacking the hydrogen and then the subsequent resonance structure we always draw; since effectively that double bond opens up by resonance, we could show the double bond itself doing the attack. [reduces number of times Fischer projection is written] Now, we count the carbonyl position, 1, we count from there, we see that position six would be the second-to-last -OH group on the molecule, so it can come around and attack, because six-membered rings are favorable. But, again, ignore sterics, ignoring any intramolecular forces – if you've got all of these -OH groups, there's some complicated hydrogen bonding going on in these molecules that we don't normally have to consider but that do have an effect here – there's a 50/50 change that -OH group is going to attack that carbocation, because the carbocation is flat.

If we were viewing this the way that we should be doing it as a Fischer projection, where the way that I've written that carbocation is essentially tilted a little bit away from our plane of view, but we could imagine that we're looking at it like this, the [-OH group] could come around and attack from on to top, or the [-OH group] could wrap around and attack from behind, giving us two possibilities. Whether or not they're really 50/50 in proportion doesn't really matter; the point right now is that you get the two possibilities. That means, though, we're going to generate a new stereocenter that did not exist and would not exist if and when the compound opens up again.

This new stereocenter, the position of the new stereocenter, is the anomeric position; it is this place where epimerization occurs, but only upon cyclization of a carbohydrate. Notice that the bottom four stereocenters don't get affected by this, which is why these products are just epimers. We have a deprotonation step, and we'll get two products – the names of which I'll give once we have them viewed correctly.

Let me define the anomeric position. When a sugar cyclizes, a new stereocenter is formed at the carbon that was part of the carbonyl. This cyclization produces two epimers – these are [anomers]. Open up the sugar, the stereocenter disappears because you have a carbonyl. Allow the sugar to cyclize, it forms one of these two forms. To properly name which one it is, we need to visualize this correctly. Let me show you where things are not quite correct at the moment. The way that we name the epimer is the position of the new stereocenter, that -OH group, relative to this last carbon, the CH2OH, which way it's pointed, as far as which side of the ring they're on. But we're not [currently] viewing the ring as a normal ring, because in a Fischer projection, we essentially treat a Fischer projection as something like this, where you have the structure written along like in a roll like this, and then we roll along and each time we're looking at it, the top and bottom are pointed away and the sides are pointed towards us. Most of the ring follows exactly that pattern to backbone, except we make this sudden turn once we get to this stereocenter. If we want to view this properly, we want to have the whole ring in the ring. We could use some of the work we did with Fischer projections to get us there. We've already seen before that if we swapped two positions on Fischer projection twice – which also means if we precess three substituents – we get the same configuration back again. I'm going to chose one of these possibilities to show the rest of this with. I'm going to turn the bottom stereocenter. That's going to put the oxygen that's in the ring in the backbone, so the whole ring is now in the backbone. I'll do that for this next one so I can more explicitly show the geometric relationship here.

Now that the ring is in the backbone, we can more clearly see that for the first structure, the bottom CH2OH group is trans to the top -OH groups, whereas in the other structure, that bottom CH2OH group is cis to this new stereocenter. When they're trans to each other across the ring, that is the alpha anomer; when they are cis to each other across the ring, that is the beta anomer.

[Now, we need to] turn this into what is known as a Haworth projection – a way of representing cyclic sugars. Rotation of a Fischer projection by 90° is incorrect; we're going to do it, though, but for a very specific purpose, so that instead of the -OH groups being horizontal, we're going to make them vertical. Imagine that we take the whole Fischer projection and let it fall 90° to the right. We're going to retain, though, the idea that this main part of the structure is pointed towards us, so it's still going to be pointed towards us, we're just going to have it laying horizontal now. The last thing we do is to stylize it – since we have a six-membered ring, we make a hexagon. We imagine that we have a flattened-out cyclohexane ring. We still put all the substituents in the same order, again in a fixed cyclic form known as a Haworth projection. By convention, we place the anomeric position at the righthand side of the drawing.

A saccharide is one of these simple, single-carbonyl containing sugar units. You can take two of those units and stitch them together, making a disaccharide. Once you do so, one or both of the sugars ends up in cyclic form. We've got to be able to take the simple sugars, cyclize them like this, and then put them together.

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The relative configuration of sugars and derivatives (d or l) is determined by the stereocenter furthest from the anomeric carbon (the carbonyl carbon).

enantiomers – non-identical mirror-image stereoisomers – all stereocenters are inverted
diastereomers – non-identical non-mirror-image stereoisomers – some, not all, stereocenters inverted
epimer – type of diastereomer in which only one stereocenter (out of two or more) is different
anomer – type of epimer that only appears in carbohydrates

When a sugar cyclizes, a new stereocenter is formed @ the carbon that was part of the carbonyl. This cyclization produces two epimers – anomers.

Haworth projection

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Structures – Identical to those from lab 6A (05/07/12)