Lab 6B • 05/03/12

[lab directions]

Benzocaine

Benzocaine, lidocaine, cocaine – why is it that these are pain-killing compounds? [It is related to the] action of a nerve cell. Nerve cells communicate through electrical signals within the cell, but not between cells. [There is an action potential] generated by ion flow. The general shape of a nerve cell has a main part to it that have [branches] that come off of it, dendrites. There's a gap, and then there's another nerve cell. If we were to zoom in, we have a series of ion channels. Ions go one way or the other across a barrier. If you only let ions in in one direction, you're separating negative and positive charge, which causes a potential, which causes a signal to be generated; there's this cascade that occurs all the way down the cell. It's principally sodium ions that do this, although potassium ions are also involved. They're different-sized ions, so they generally go through different channels that can control which type of ion is going through. That's the portion that's generating the electrical signal – ions moving through these channels.

What benzocaine and these other 'cains do is they block that channel. It's not that you don't have pain, it's not that the cells aren't necessarily damaged, it's just it sends that signal or starts to, and it [may start] that electrical signal, but it never resets. It's like you're permanently stuck in one position or the other, and therefore there's not this constant generation of a signal. Eventually, these compounds can decompose. For example, benzocaine's an ethyl ester; there are deesterases – they are enzymes that specifically deesterify compounds that eventually might cause that compound to disappear. There are also monoamine oxidizers, [related] to MAOIs – monoamine oxidase inhibitors that prevents that kind of thing. You can decompose amine compounds by other types of enzymes, so eventually, the compounds go away, then that means the sodium channels can have the flow again, which means the electrical signal gets generated, which means ouch. When you go to the dentist and you get the shot, everything's blocked for a while, then slowly, as the compound decomposes, then you can tell [that something happened].

There are a whole bunch of other compounds that affect this portion right here. This gap here, called a synapse, has a couple of parts to it. On one side, you have several receptors, and on the other side, you have something that will release a set of chemicals called neurotransmitters. These neurotrasmitters come in all kinds of classes, and there's all kinds of neurotransmitter systems in the body. For example, across a lot of the muscular system, there are nicotinamide neurotransmitter sites, which nicotine is one of the activating chemicals of that, which since it's all over your body and your body uses that as a messenger, that's why nicotine is particularly addictive, because your body gets very, very quickly used to having that extra amount of signaling agent around. Some of these neurotransimtters are agonists, which means they enhance the action of that system; some of these neurotransmitters are antagonists, which means they mitigate the action of that system. Besides the nicotinamide system, there's the opiod system – where compounds like morphine affect for pain mitigation, we have the amphetamine sites, we have the serotonin sites – which is one of the most important ones that regulates moods, sleep patterns, and your daily cycle. Once the nerve's signal gets to the end of the cell, it causes the release of these chemicals, which then have to bind to the appropriate receptor site in order the next signal to be generated and then to be communicated on down the chain. An awful lot of [psychoneuralpharmaceutical] chemistry these days involves that little bit of the process right there: either allowing those chemicals to be prolonged – that's what an MAOI would do, to allow these compounds to stay in the synapse for longer, [for serotonin, there's one specific [for it], that's called a serotonin-specific reuptake inhibitor (SSRI); or you might have other compounds that might cause them to be decomposed more quickly.

[synthesis problems]

First problem, I had said one molecule somehow turns into this unsaturated, bicyclic ketone. Hopefully what observed is that there is an alpha,beta-unsaturated ketone, which is the normal product of an aldol condensation. How do we disconnect this molecule to get at what was there before the aldol condensation. The carbonyl after an aldol is the carbonyl that made the enolate to start with. That means that new bond was created at the alpha position relative to that carbonyl. What we need to do, then, is to cut the double bond at the alpha,beta position, because at the beta position, that's where the old carbonyl was. This does mean that the molecule was formed as an intramolecular aldol condensation.

The second one, you had to have two molecules. It's the same situation to start with: we have an alpha,beta unsaturated ketone, which means it could have been formed from an aldol, but that would just open the ring up and it wouldn't allow us to further separate the ring. If this was two molecules that somehow came together in some kind of ring-forming reaction, that would be the Robinson annulation, which is two things: a Michael addition and an aldol condensation. First, we're going to take the molecule apart going reverse aldol. Once we get there, then we need to figure out a way how we could have synthesized that intermediate with a Michael addition. This is an alpha,beta-unsaturated carbonyl-containing compound, which means an aldol. I'll chop the carbon-carbon double bond apart, because that's what was formed during the aldol condensation. When I do that, here's what results. Let's count carbons to make sure.

Notice at the top, because we had a carbonyl there that was the carbonyl that was there as the enolate, which means the alpha position of where that double bond is, that was part of the original compound next to the enolate that formed. Then, on the other side fo the double bond, that's where the new bond was formed, so that's why I broke open the ring at that point. Wherever the beta position of where the bond was formed to, that is where the other carbonyl was at.

Now, I need to do a reverse Michael. Michael addition we can recognize by there being a delta carbonyl compound. If I chose the top carbonyl to be the one where the enolate was formed, then I could say, why yes, I do have another carbonyl at the delta position. From that carbonyl, we backtrack again. There had to have been a double bond at the alpha and beta position from the carbonyl that got attacked. What that means is the beta and gamma positions, relative to the original carbonyl. If this was the carbonyl that was the enolate, the alpha position is where the attack occurs. From the other carbonyl, we need a double bond, so that would be the beta and gamma [positions], so we again would cut the bond at the alpha,beta position, relative to that first carbonyl, which means we would end up with acetone and this unsaturated aldehyde.

If I had a triple bond instead of a double bond, how many of those pi bonds of the triple bond would be in conjugation with the carbonyl? Just one; why? Because the two pi bonds in a triple bond are orthogonal to each other.

[why is a vinyl hydrogen not a viable alpha proton?] Because if we have a double bond that's already in conjugation with that carbonyl, and anion you're going to form is going to be perpendicular to it, at an angle to it. Just in the same way that, in a triple bond, only one of the pi bonds can conjugate. Same thing here, if we put an anion on that carbon at the alpha position, it's not going to be in conjugation with the carbonyl because the double bond already is. In this case, we don't even run into that issue; if we have a methyl group, it can't make an enolate, no matter what. We deprotonate the ketone, it's a squishy base because it's delocalized, we have the squishy substrate, the unsaturated aldehyde, aldehydes are more reactive that ketones, so that should react to make this intermediate which continues on exposure to base. Now we have two alpha protons now, but if the alpha proton to the aldehyde gets deprotonated, it's going to make a four-membered ring, which is not favorable. This ketone, if that gets deprotonated, you make a six membered-ring, which gives us the product that we really do end up with.

What if the top is not where the enolate originally formed? If the bottom is where the enolate originally formed, I could cut between that alpha and beta position. What that would give me is propanal as my aldehyde, and then this unsaturated ketone as the other molecule. The aldehyde is more acidic than the ketone, so between the two of these you still could more easily deprotonate one versus the other. Even though the ketone is less reactive, it's also a squishy substrate, so the enolate that you form from an aldehyde still should want to attack the ketone even if the ketone is the less reactive compound because of that squishiness factor.

Third problem. Hopefully you recognized this as a beta-ketoester, which means: Claisen condensation. In a Claisen condensation, you have two esters, one of which makes the enolate and attacks the other ester. The ester that gets attacked loses its extra functionality; it has this "leaving group" that comes off. If we look at this product, we see that we have a ketone, so that's the carbonyl that got attacked. To get back to the ester it may have come from, we do not include the alpha position between the carbonyls, because that alpha position would have come from the other ester that had made the enolate. I pull the two back apart again, and in this case, I'm going to get ethyl acetate as one of the original molecules; I'll have some form of butanoate as the ester, but what kind of ester do I need to make it? It also needs to be an ethyl ester. Why? Because if you made the enolate and attacked this butanoate, and it was some other kind of ester, then that alkoxide can be kicked out and come back and attack the first ester; in other words, you'd be prone to transesterification. In order to avoid that, what ever thing might be kicked out by any of three of these compounds – either of the starting materials or the product – you want to have the same alkoxide around in solution – if there's going to be one – and that way avoid transesterification.

Next was a malonic ester synthesis. You were supposed to make this unsaturated carboxylic acid. All the products of [a malonic ester synthesis] are derivatives of acetic acid, because that's would be left over of malonic acid itself decarboxylated. Here is the acetic acid; that means the rest of the molecule is the R group of the alkyl halide that was attacked in order to make the ester. How do we get the double bond there? It's easy: start out with diethyl malonate, deprotonate it – a good base to use would be sodium ethoxide, since, if it attacks the ester, it just makes the same ester, and it's basic enough to remove the alpha proton. We need a primary alkyl halide, like allyl bromide. Why not use allyl bromide? The double bond won't be attacked, because if you make an anion from a double bond, that's a base that's got a conjugate pKa up in the [40s]. Why would such an incredibly strong base form from something that only had a conjugate pKa of under 14. The double bond will survive that Sn2 no problem; if fact, this is a really good Sn2 substrate; allyl substates make good Sn1 and Sn2 substrates. Once we've done the alkylation we then need to decompose the malonic ester. Here, we might want to be a little careful about conditions, cause if we subjected this to acid and heat and water for an extended period of time, then we might hydrate the double bond in addition to the ester. But, the double bond won't react with a base, so why not do saponification, after which we then could use a little acid and then a little heat, since 3-oxoacids are prone to decarboxylation.

The next one, we have pentan-2-one that somehow you're supposed to convert into butanoic acid, to lose a carbon. We've only seen really only one carbon-carbon bond-breaking reaction, which would be the haloform reaction. After the haloform reaction, you initially have a carboxylate; if you want the carboxylic acid, you need a follow-up acidification step.

The last, we had a part aldehyde, part ketone. What we should notice here is this a delta-carbonyl carbonyl; in this case, we could call it a delta-oxoaldehyde. That is the telltale sign of Michael addition. Same thing as before: from one carbonyl or the other, we want to break the bond at the alpha,beta position to pull it apart to figure out which one was the enolate and which one was the unsaturated carbonyl compound. If I take the alpha and beta the way I've written it and break it apart, I'll end up with ethanal and an unsaturated ketone. I could have also done it where I broke at the other alpha,beta position. We end up with an unsaturated aldehyde and acetone. What about cis and trans? In this specific case, it doesn't matter, because even if we have a stereocenter – which we do right in the middle of the molecule: the methyl group, where it is, that's a stereocenter, because even though on both sides it looks like you've got the same thing because on both sides you've got a carbonyl, on the other side of one carbonyl it's just a hydrogen, on the other side of the carbonyl, it's just a carbon, so that middle carbon with the methyl group is a stereocenter. We don't care what the double bond's configuration is, because [it wasn't specified whether the product is R or S].

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Na2CO3 wash – neutralize sulfuric acid and to remove unreacted starting material by converting it into a water-soluble salt. It is a stronger base than NaHCO3, so it can help ensure the compound is not protonated (at the amino group). NaOH is not used to avoid any chance of saponification.

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Structures – Identical to those from lab 5A (05/02/12)