

Lab 4B • 04/26/12

Robinson annulation

Annulation from annulus which means ring, so this is the Robinson ring-forming reaction. It's a combination of two different alpha reactions. One of the reactions involves conjugate addition. If you think back to dienes, we talked about 1,2- versus 1,4-addition. We're going to see a different 1,4-addition today. It's going to be followed up by an aldol condensation. The combination of this new Michael addition [then] followed by an aldol condensation, that's a Robinson annulation.

[First,] I want to revisit conjugation a bit; more importantly, I want to talk about charge distribution. For unsaturated ketones and aldehydes, those compounds can have two different modes in the way that they react: there is 1,2-addition and 1,4-addition. Which one happens is going to depend on what kind of reagent you have, what kind of charge distribution you have on that reagent.

Let's visit this topic of charge distribution. You might recall [the concept of] polarizability; it came up in the context of nucleophiles. For example, if you have OH⁻, and SH⁻, which one's the better nucleophile? Even though oxygen [is] basic, and even though there's this close relationship between nucleophilicity and basicity, they're not the same thing. It turns out that sulfur, even though it's not as basic, is the better nucleophile because its charge is squishy – it has not-as-densely packed charge, which meant that it was able to begin the process of bond formation more easily than oxygen did; that's what make[s] it the better nucleophile. There is some terminology used to describe ions that have a broader distributed charge, versus ions that that charge – which might be the same in magnitude – but it's more compact: hard and soft ions – hard ions meaning ones that do have that compact charge, and soft ions where the charge is squishier. Using that terminology, hydroxide would be, by comparison, a hard ion, and the SH⁻ minus would be a soft ion.

Why do these hard/soft designations matter? It's all about charge interaction. Let me draw a couple of pictures up and talk about charge interacting. Let's say that up here we have what are referred to as hard ions, which means charge density is high, which means the ion is compact. Let's not worry about whether these are real physical objects or not; the way I've drawn them, this is just for argument's sake. Here are broader charges; let's presume that these are of equal magnitude to the first set of charges I drew up: +1, +1; -1, -1. It's that shape of that plus or minus that's different between these two. These other two would be referred to as soft ions; the charge density is lower and squishy.

Let's talk about different interactions between ions. If we had the two compact charges interacting with each other, there's only a very small volume right near the charge where its charge density has the maximum effect. How strong an interaction between charges you have depends on how close those charges are to each other. If the ion itself is small, then ideally you'd want some other small ion to interact with it so you'd have the maximum amount of interaction between those two charges. Similarly, for the distributed charges, if those two charges line up in the correct way, then even though at any one point there's not as much interaction between the charges, given the whole interaction that's going on, adding up surface there, then there'd be a good interaction between those two objects. What if we mismatched the objects then? Again, it's wherever the objects are going to be closest to each other that that interaction between charge is at a maximum. If you have a broad charge interacting with a compact charge, it's only where those two objects are closest that you have the best charge interaction, and as that broad charge gets further and further away, yes there's an interaction, but the less of an effect there is. There's not going to be as much overall interaction, even though the two charges are the same magnitude, because it's a matter of geometry. So, hard ions tend to interact with each other; soft ions tend to interact with each other; but, hard/soft interactions are not necessarily as productive.

The first set: in this case, the charges interact well, because they have the maximum possible physical (geometrical) interaction with each other. In this other case, because you have a small charge interacting with a distributed charge, the amount of interaction is reduced, because it's only effective locally. Because you have part of the charge that's further away, not as good an interaction. The point of this discussion is that charges of similar charge density prefer to interact with each other.

Switching gears, let's get into the mechanism. We have [an] unsaturated ketone, plus two methyl propanal. Which of these compounds would you guess is more reactive? Normally aldehydes are more reactive than ketones. What do you think the pKa of the ketone is? What's the standard pKa of a ketone? 19. But things that somehow stabilize the ketone make them less acidic, so what's the double bond going to do? It's going to do conjugation, which makes me think it's going to be less acidic than it'd normally be. If this is providing electron density into the carbonyl, then if you form a negative charge here, you'd have competition between the double bond and that negative charge as far as being in resonance with that carbonyl. [what is the pKa] It is the aldehyde in this case that does react first. It does form an enol through [an] acid-style tautomerization. Enols instantly tautomerize [when formed] because the enol is unfavorable. Since what we're making is thermodynamically not favorable, this whole reaction has to be [technically] reversible, every portion of it.

[First, the carbonyl] gets protonated. [can combine resonance] I'll show the resonance separately. We've made the carbocation. Notice that I've got two hydrogens drawn in (ignoring the hydrogen on the oxygen). Be careful which one you eliminate at this point. I drew the hydrogen on the bottom right only because I'm acknowledging that we came from an aldehyde. That's not an alpha proton; that is the proton on the carbonyl itself, so that proton will not be the one eliminated; it's the one next door that is the true alpha proton that you must eliminate at this point. Notice that to make this happen we had to protonate the carbonyl first. In all the other steps you're going to see, whatever reaction occurs happens by first protonating the carbonyl. This enol, in terms of electron density, would you say that it's compact or distributed on this molecule? [Although] the carbon is delta plus, doesn't the oxygen also have a lone pair on it? Even though it would end up making a charge-separated structure, isn't there resonance possible here? That's the whole idea behind the tautomerization; there's somehow this tendency for the charge to get delocalized. If we were in basic conditions, this whole discussion would be easier, because if you have an enolate, that's by definition a distributed ion. I'm going to write in a different color to the side the fact that we have a possible resonance structure here to [emphasize] that this is a delocalized or squishy compound.

What other material do we have in here? We have the ketone, which for the same reasons we could call squishy, cause this is not just resonance, this is conjugation. If you had just a carbonyl that's the only functional group on the molecule, of course the carbonyl is what would be attacked by the enolate. Even in this kind of conjugated system, if we had a Grignard reagent, it would still attack the carbonyl, because of that difference in polarity. But there are other alkylating reagents [such as dialkyl cuprates] that are softer bases, and these softer, squishier bases are rather reactive, in a distributed way, so they add not to the carbonyl, but to the end of the double bond, pushing it into the carbonyl; if something then adds to the oxygen that's on the other side, it's a 1,4-addition. The point of telling you that about alkylating reagents is that the enol, which is squishy, is going to react with this ketone, which is squishy, in this delocalized fashion. Because this an acidic mechanism, we're first going to protonate that ketone to activate it. That means we're adding to the 1 position, you could say. We have the enol, [which] tries to reform the carbonyl; that's what always happens in these alpha reaction: whichever compound made the enol or the enolate reforms into the carbonyl. This is going to push the carbon-carbon double bond open, which, because we have this squishy interaction, it's going to attack the end of the molecule, not the carbonyl. That will push the double bond into the carbonyl, which, since it's protonated, simply opens up. If we call the oxygen the one position, and we call this carbon here the four position, this is 1,4-addition, conjugate addition.

What do we get? A carbonyl[, which is going to be protonated at first right after this reaction]. We form a new carbon-carbon bond. Like an aldol reaction, a new bond is formed at the alpha position relative to the carbonyl that is retained. That would be equivalent to the 4 position of the ketone (the way that I've labeled it here). We then have one more carbon; that's where a double bond's going to be now because we made an enol, our first intermediate, which we won't be able to isolate. Why? Because it's an enol. [summary up to this point] Michael addition is conjugate addition, because you have two systems that are distribute in their electron density, and they would prefer to interact in a way that maximizes that interaction between electron density, which is why they add 1,4-style in this case.

From here, we're going to do an aldol condensation. [Since this is called an annulation reaction,] we know this thing is going to somehow fold up together. What's one possible way we could guess that that might happen? We have an enol. Remember that enols or enolates are the things that do aldol condensations. We have a carbonyl right next door. What if an aldol reaction was going to happen with the molecule just the way it is? How many atoms would be in the ring? Remember that here where the enol is, it is the alpha position that creates the bond. If you were looking at the carbon where the alcohol is, that is not in the ring, it would be exterior to the ring. The alpha position would be 1, the carbonyl up above would be 2, we have two more atoms in between them, so we'd have a four-membered ring. Are four membered rings likely to form? No, but it [can/will] but it won't be isolatable, cause the whole reaction is reversible. There are a zillion side reactions I could write mechanisms for here. Everywhere where there's neutral oxygen, you could show it being deprotonated. Everywhere you have a protonated oxygen, you could show it being deprotonated, and back and forth and back and forth. Where you have an enol, you could show tautomerization, and you could show it being tautomerized back again. We could show this condensation to make a four-membered ring, and we could show it opening up again. There's a whole variety of things we could show, but we want to write the most compact mechanism we can.

A four-membered ring is not favorable, but don't we have another alpha proton on the other side of what would have been the carbonyl there? In other words, if we could tautomerize and get the double bond to point out instead of in, we then would be able to take that carbon, wrap it around, and make a six-membered ring. That is favorable, and that's what happens. But, when I show the shift of that double bond, is it really necessary for me to show all the way to making the ketone, doing the full tautomerization, if, as soon as you make it, it's just going to un-react again. No. This is unfavorable, so you can add water to the double bond, and the whole thing unfolds in reverse. If equilibrium can happen, it will happen, just like things roll downhill [even at the Mystery Spot]. If this can happen, it's gonna form, but that doesn't mean it sticks around. Back up to the very start of the mechanism: enols don't like to form, but if it can, it will, so if a little bit of enol forms, it starts this whole process off. If equilibrium can happen, it will happen. But, this product is not favorable, so it will reverse.

What will happen? We could have tautomerization of this intermediate. If I wrote the full tautomerization mechanism, I first would show the double bond being protonated, which is going to generate a positive charge.

I could then reform the carbonyl and have it deprotonate. But, if an enol can form, it will form. Realize that where I just got to, that carbonyl is going to have to get protonated to make an enol, which means I'm back to this previous step. The carbonyl's going to open to make the carbocation, which means I back up to this previous step. So, if I'm going to end up here again anyways, why write four extra steps just to go forward and back to the same place; why not just pick the mechanism up right here and continue. That's the way that I recommend that you do it. I instead will show the forward process of the other alpha proton being removed. That gets us our new enol.

Let's number our carbons; in this case it's going to be both a set of numbers that will happen to match nomenclature numbers. Remember that the aldol condensation, which is what's about to happen next, a new bond is formed from the alpha position of one carbonyl to the carbonyl itself of the attacked carbonyl. The attacked carbonyl's going to be position 1; the alpha-proton's going to be position 6; that's going to give us our six-membered ring. Since this is still an acidic mechanism, we need to protonate first. Then, the carbonyl tries to reform. The carbonyl opens up as a response, attacks the carbonyl, which opens up as a response. One carbonyl disappears; turns into an alcohol. The other carbonyl is still there, but it's protonated, cause it started out with a hydrogen on it. Let's number our carbons to make sure I did this correctly. Where the carbonyl was, that's still position 1; the two methyl groups still at position 2; 5 is where the alcohol portion of the enol was and where the carbonyl's now reformed; and 6 is what's connected to the first carbonyl.

We deprotonate, so we have our beta-hydroxyketone. Aside from a new carbon-carbon bond, one of the ways to recognize an aldol condensation is the formation of an -OH group at the beta position. Then, since we're in acidic conditions, since we heated it for a prolonged period of time, the alcohol can get protonated, water leaves as a leaving group, and then an alpha proton can be eliminated to make our alpha,beta-unsaturated ketone. Overall we have a Michael addition plus an aldol condensation; the two of them together, when they make a ring, are called the Robinson annulation.

"hard" ions → charge density is high; ion is compact
"soft" ions → charge density is lower; "squishy"

In this case, the charges interact well because they have the maximum possible "physical"/geometrical interaction with each other.

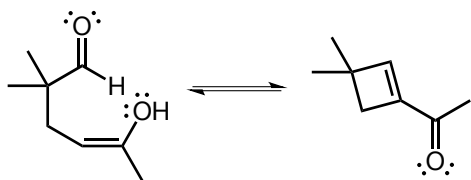
In this case, the overall interaction is not as favorable since the point of closest interaction does not involve as much charge (too much of the charge interaction is separated by distance).

Ions of similar charge density prefer to interact.

Michael + Aldol = Robinson Annulation

Structures

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