Lecture 10A • 05/02/12

[Exam 1 review]
[carboxylic acids and derivatives – relative reactivity; reactions: hydrolysis, saponification, solvolysis, Fischer esterification, reduction, alkylation, reversibility]
[nomenclature]
[alpha reactions – pKas; LDA; halogenation, haloform, aldol, alkylation, Stork, Michael, Robinson, Claisen, Dieckmann, decarboxylation; malonic ester synthesis]
[types of problems]

Example problem

If I tell you that one molecule and one molecule alone was able to make this product, what was that starting molecule? The point of this problem was that you look at it and say: oh, that's an alpha,beta-unsaturated ketone – aldol condensation. Which means what? That you need another carbonyl there on the starting molecule, because you need two carbonyls for an aldol condensation – one that survives because it was the enolate, and one that got attacked. If you cut at that alpha,beta-unsaturation, you can go back and you figure out that the starting material was this.

Problem set – problem 2 mechanism

LDA is going to deprotonate the alpha proton. I combine resonance with it. I'm going to say forward arrow: why? Here's a theory question: is the neutralization reversible or not? Why is it not? [huge difference in pKa values] We make an enolate. If all I give you is LDA and no other reagent, you know that the only thing left for it to possibly react with in solution is itself, so the carbonyl reforms, double bond opens up, we attack the other carbonyl, so we reform one ester, and we starting making a bond to another. We're going to finish the mechanism by an elimination occurring, which is going to give us a beta-ketoester.

Stork enamine problem

Started out with cyclopentanone; reacted it with morpholine. [pyrrolidine] Then we have propanal; then we have sulfuric acid, heat, and water. For the first part, I'll just jump to the product, which is the enamine. Then we have an aldehyde. [is aldehyde reactive enough] The whole point of this enamine synthesis is that the lone pair on nitrogen pushes enough electron density onto the double bond that it reacts. This is like an aldol [reaction]. We end up with both a positive charge and a negative charge. We can assume that there's some kind of solvent around that the alkoxide could get protonated by. Then, we have a problem of this positive charge on the nitrogen – but it's not really a problem, because the way that the enamine formed in the first place .... Once we get here, we do have another alpha proton, so if some kind of base was able to take that alpha proton off, we remake the enamine. That's all that could happen to allow this compound to be stabilized – remake the enamine.

At this point, we could then dehydrate the alcohol and break apart the enamine. Double bond gets protonated; carbocation, where water can attack; water that just attacked gets deprotonated, so we end up with the carbinolamine. Next, the nitrogen gets protonated; we make an ammonium salt, which then leaves, so that's the open; we end up with a carbocation that can undergo resonance, that's the attack; and then deprotonation. But, if we're still in acid and water, if you formed an alkene, you'd expect it to be hydrated. You could also argue, though, that if you heat it up enough, the water first is going to just hydrolyze the enamine, but then if the water gets driven off, you can dehydrate. Let's say I wanted to dehydrate, then this will get protonated, water will leave, and then, effectively, we have E1 elimination – proton alpha to the carbonyl gets removed, makes the double bond. There's our alpha,beta-unsaturated ketone.

Can a carbocation shift occur? Secondary carbocations are more stable than primary, and tertiary carbocations are more stable than secondary, but what will the delta plus on the carbonyl do to the stability of a tertiary carbocation? I don't know which one is worse – the stabilization caused by the hyperconjugation of the sigma bonds, or the destabilization caused by putting two positive charges next to each other. I don't know if you're going to get carbocation rearrangement. You might remember that, in the context of alpha-halogenation, we talked about how that would make an unfavorable carbocation. Over here, it may be secondary, but it avoids interaction with the positive charge. Can you actually have hyperconjugation with the carbon where the carbonyl is? Even though that is a tertiary carbocation, if I'm visualizing this correctly, it's only going to have interaction with two neighbors; you'd be trading a secondary for effectively a secondary; if I've got that right in my head, then no, it won't move.

Robinson annulation – what two reactions make up a Robinson annulation? Michael and aldol. For a Michael addition, what do I need? [An] alpha,beta-unsaturated compound of some sort, and something that likes to form a squishy base. [This] is a squishy base, because having that nitrile there is going to help delocalize, just like having the carbonyl, [so the pKa of this] is relatively low. If it's relatively low, that means it's a stronger acid, which means the base is the base is one of these delocalized, squishy ions which likes to do conjugate addition.

What would a basic mechanism look like? Between these two compounds, it's definitely going to be this first one that has the more acidic proton. Let's say that I use hydroxide. Why can I get away with using hydroxide? Because as long as the pKa here is greater than 15, even if I just drop-by-drop add it in, let a little bit of it get neutralized at a time, that way I can prevent any other side reactions that might happen with this hydroxide. Is saponification an issue with this particular example? Do we have to worry about saponification in this example? Why not? No leaving group; no ester. If I kept this at a reasonable temperature, is there a concern about saponification? What if I turn the temperature up? If I left sodium hydroxide in this solution for a long enough time, is saponification a worry? Yes, because what functional group do I have? A nitrile. Remember that nitriles can be hydrolyzed. But let's not worry about that just yet.

Let's see the mechanism first before we get into the details. I'm going to make the enolate like I had before by deprotonating and allowing resonance at the same time. I've made a conjugated ion; how many of the pi bonds in the nitrile are conjugated with this enol? One, both, or neither of them? It's one. Remember that in a triple bond, one pi bond is this way, one pi bond is perpendicular to it; you can never, therefore, have one other pi bond conjugated simultaneously with both of the pi bonds in a triple bond. Only one of the bonds is delocalized with the enol, but it is delocalized, which means it would prefer to attack the squishier compound, this one over here, the one that has itself delocalization. What happens next – we'll attack at the beta position, which will knock that over into the carbonyl, pushing the carbonyl open. I've remade a carbonyl; I made a new bond. Next to that bond, we have an enol. Since I used hydroxide to start with, I can presume that I have water now, in order for that enol to get protonated.

[Now] there is this swap from one alpha proton to another, as far as where the enolate form[s]. If I left the enolate where my pen is as is, I could make a four-membered ring by attacking through the alpha position to the carbonyl up above. But, remember that four-membered rings are not favorable. This reaction's reversible, because this alkoxide would be as basic as that alkoxide. Since it's reversible and since four-membered rings don't like to form, it's not going to happen. But, remember that if equilibrium can happen, it will happen, so if this enolate can form, so can the enolate by removing this other proton, which is what we show next. The carbonyl reforms; attack through the alpha position; open up the other carbonyl. Water can again be used to provide the hydrogen to neutralize this, and then we finish off by having one more alpha proton removed by hydroxide. The whole point of the E1CB mechanism is deprotonation is separate from elimination. To highlight the fact that we have delocalization, the last thing is intramolecular E1, which is the E1CB, which forms, therefore, a ring that is alpha,beta-unsaturated.

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Structures *(remaining structures identical to lecture 9B)*

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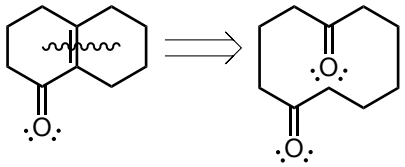

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