

Lab 2A • 04/16/12

Alpha chemistry – the chemistry of hydrogens attached to the alpha position, relative to a carbonyl.

This first reaction involving alpha chemistry is the aldol condensation. If we wanted to use the common name terms for the position going away from that carbonyl, the closest one is called the alpha position. That's because alpha's the first letter of the Greek alphabet. Beta position would be the next one, for the next one; then gamma, delta, etc. Sometimes the very last letter, omega, is used because it's the last letter of the [Greek] alphabet. Instead of counting exactly how many carbons there are, if you just want to refer to the end of the chain, you could say a phrase like: that omega-hydroxyacid. Omega-hydroxy acid would mean start with a carboxylic acid at one end, and at the very other end put a hydroxy group. We're going to focus just on that alpha position, which we've seen used before. You've seen [this reaction's] reverse reaction.

Imagine we took an aldehyde, and we threw a base like sodium hydroxide at it. Even more generally, let's just say strong base; let's not get hung up on the type of base doing this. If it attacks the carbonyl, what functional group could we, in theory be trying to produce, if the hydroxide attacks the carbonyl directly? Then we'd have one -OH group on that carbonyl, wouldn't we? And we'd have the other oxygen left over that, if it got protonated, what would it become? A hydrate, because we've added water across the carbonyl. In other words, I'm saying that if the carbonyl were attacked, we'd end up with something like this, which is just short one hydrogen from being a hydrate. Are hydrates normally thermodynamically favorable? No, they're not normally isolatable; that's why we're normally not worried about them. On top of the fact that they're not normally thermodynamically favorable, we can't even fully make the hydrate, because notice that H⁺ there. That means we'd have to exit basic conditions in order to be able to produce the hydrate, so it's just not going to happen. What other thing besides making a hydrate could happen, then?

You notice that I have another hydrogen that's been written here. What is the pKa of that hydrogen? 16. For an aldehyde, the average is 16; for a ketone, it's 19. But, isn't 16 pretty low? What's an alkane's average pKa? 60. Huge difference in acidity then, right? Why? What's so special that that proton is all of a sudden so much more acidic? Induction, partly, but it's more than just that. Resonance; from what? What if that hydrogen did come off? A base pulls off that hydrogen. Depending on the base used, that removal is reversible. I put a reversible arrow here, but there are some subtle details I need to weave into this discussion. Whether or not that is reversible depends on how strong the starting base was. If the starting base was similar to basicity to this thing we just produced – in other words, if we used hydroxide that had a pKa also about 16 [for its conjugate acid], that means the base strength of what you produced and what you started with are about the same, which means the reaction can easily float back and forth. If we used a Grignard reagent right here – of course, we can't use a Grignard reagent because it'd attack the carbonyl – but if we used something basic like a Grignard reagent, then it would deprotonate and have no chance of going in reverse.

[This leads to the question:] when is a basic reaction reversible, when is it irreversible? You make have been programmed to say: basic reaction, irreversible; acid reaction, that means it's going to be catalyzed and multistep and a bunch of arrows going every reaction. Basic reactions can be reversible; you hadn't seen it before because this is the first [reaction] where we're going to have products and reactants that are similar in strength. I'm drawing this as a reversible arrow; for today's lab, it really is a reversible arrow, just recognize there'll be times where it's a forward arrow only, and there'll be a darn good reason for it.

Once I've made this anion, we need to acknowledge the fact that yes, it is delocalized. Even more than induction, that delocalization is what provides enough stabilization to this anion that that's why that that position is so acidic to begin with, because anything that stabilizes the product makes the product easier to form, means the reactant's more reactable. Since we're quantifying that in terms of an acid dissociation, if the anion, the base, is more stable, the acid is more acidic, so lower pKa. If I put a hydrogen on this product, what functional group would that be called? Enol. But it is not an enol, because it doesn't have that hydrogen; it's the conjugate ion which is called enolate, using the common -ate ending for a negative ion. Of course, this is all occurring under basic conditions. We encountered this in the opposite direction when we tried to do hydroboration of alkynes. When we hydroborated an alkyne, we ended up with an enol, and enols are not thermodynamically stable. That's an enol formed under basic conditions, so we saw this base conversion into a carbonyl. At some point, we also did it under acidic conditions, [for which there was an acidic mechanism]. Since we're approaching this from a different perspective, from the carbonyl's perspective, let me also show you that reaction mechanism under acidic conditions to get us to the same point.

If, for example, we had some strong acid source, then the first likely step of the reaction – as many of the carbonyl reactions are – is for that carbonyl to become protonated. Once protonated, we could highlight its delocalized nature by writing a resonance structure. If we didn't have water around – even if we did, remember forming hydrates is not favorable – at some point, what if we had a base come along and pull off the hydrogen here? We've now made an enol, which is unfavorable, but if an equilibrium can happen it will happen. What does that mean? If an equilibrium is balanced so that it heavily favors reactants, that still means a little product has to form, otherwise you can't have equilibrium. Even though enols are unfavorable to form, in traces they will form, then they'll react.

Alpha positions [undergo] a sequence of extremely useful reactions – carbon-carbon bond-forming reactions. What is this called, these two portions of reaction mechanisms? Tautomerization. This is one specifically called the keto-enol tautomerization, [should show ketones first to mesh better with name] which is how we make enols and enolates to do these condensation reactions.

Let's see an example of an alpha reaction: the aldol condensation. Why is it called the aldol condensation? Because if you're doing a real, true, pure aldol condensation, you're only starting with aldehydes as starting materials, and unless you use strong enough conditions to cause a secondary reactions, the product is going to be an alcohol. So, an aldehyde making an alcohol [or is it because you're making a combination aldehyde alcohol] – aldol. How does the reaction start? Normally under basic conditions. Hydroxide works [as a base in this case] because water's pKa is 15.7, an aldehyde's pKa is roughly 16, that means an aldehyde is slightly less acidic but only that much less acid than water is. That means hydroxide is generally just about the same strength but just barely short of the same strength of base once we deprotonate that aldehyde. [Often, concentrated solutions are used] to force the deprotonation fully to occur.

Mechanism-wise, we draw it like this. Deprotonate that position; because hydroxide's comparable in base strength, it's going to be a reversible process. It is optional to show the delocalization. Why is it optional to show the delocalization? Because delocalization happens regardless of how we write it – our writing system's inadequate for delocalized systems, so writing the delocalization is just giving more evidence of our poor writing system [in this case and] not really illustrating anything useful chemically. When learning about this topic, writing the structure might be useful to emphasize the fact that it is an enol-type system. If you wrote it delocalized like that, you'd show it collapsing straightaway again. What's going to happen next, regardless the way we write it? A negatively-charged carbon is nucleophilic; a negative charge on carbon would be even more likely to substitute than if you had a negative charge on oxygen, so it attacks the carbonyl of another molecule and pushes that carbonyl open. What do we get as a result? The compound that had formed the enolate, that carbonyl's going to reform again, so one carbonyl retains its carbonyl in this reaction; the other molecule clearly just got attacked. We also have a new carbon-carbon bond. That is one of the most important aspects of this reaction synthetically, that we're able to make new carbon-carbon bonds. A new carbon-carbon bond is formed at the alpha and beta positions relative to the enolate's carbonyl, the one that survives the condensation reaction. How do we know which one is beta? Relative to the carbonyl, there is only one alpha position [in this case], but there are two beta positions. It doesn't mean I can't still call one of them the beta position and say the bond formed there; it's not that you have to identify the most important chain and that's called beta, it just means two positions way from the carbonyl.

[We have made] a new functional group at the beta position. Right now, it's just an alkoxide. As soon as we allow the next part of the mechanism to occur, it's an alcohol. A very common byproduct [or alternative] is to dehydrate that alcohol, so you might end up with a double bond, but it will always, in one of these condensation, be something that includes that beta position. The beta position is key to recognizing this kind of condensation.

Let me finish the mechanism. Obviously, the alkoxide's going to be neutralized. The not-so-obvious thing is that we're in basic solution, which means we can't show H+. So many times, we just H+ when we want a proton – not when you've got concentrated hydroxide around. You have to show water being attacked. If we used hydroxide as the base, then once it did pull a proton off, we made water, so even in a purely organic mixture, there's going to be a little water around; that will allow us to protonate the alkoxide. There are situations where that's not the end of the story, because if an alpha proton's acidic once, is there anything to stop it from being acidic again? No; it will [can] react again, but this time, before it has a chance to condense again, there's an intramolecular process that can occur: it kicks off hydroxide as a leaving group. How many times have we seen hydroxide being a leaving group? [very few, hydroboration] Why would that even be favorable to occur in this case? Because you make an unsaturated product, a conjugated, unsaturated product – an alpha,beta-unsaturated carbonyl-containing compound, another telltale sign of an aldol condensation. Key bit of mechanism: you might condense a mechanism on paper to make it take up less space, but it might be not how a reaction occurs. This deprotonation is a separate step from the elimination. It would be equivalent to E1, [meaning] it's unimolecular, meaning only one molecule is involved in the rate-limiting step of that reaction. The elimination is intramolecular, it is only involving itself; that would be a unimolecular process. E2 means bimolecular means you have two molecules involved [in the rate-limiting step]; hydroxide pulling off the hydrogen, two molecules are involved. If both of these steps happened together, then the overall reaction would have two molecules in its rate-limiting step, and so it would also be bimolecular. But, the fact that I have these written as separate steps must mean that, in real life, the reaction is only unimolecular, meaning the base is not involved in the rate-limiting step, meaning only the molecule itself is involved, which is why these are two separate steps. This is a flavor of E1 [known as E1CB, for conjugate base]. That's an ideal aldol condensation. Why is it ideal? Because only one product forms.

Let's look at mixed aldols. You need to understand why [the following reaction] is an example of an ideal mixed aldol condensation. There's two very concrete reasons for it. [A mixed aldol] is when you use more than one type of compound. I have ethanal and propanal, two different aldehydes. I'm exposing them to sodium hydroxide, heat, and time. Given enough time for it to do whatever it's going to do, how many products am I going to get? Four. Why? Because either one of the starting materials can make the enolate. Then, the enolate can attack either one of the starting materials. Propanal can condense with propanal, propanal can condense with ethanal, ethanal can condense with propanal, and ethanal can condense with itself.

We end up with these four products. Mixed aldol condensations in which more than one compound – particularly when you have an aldehyde and a ketone involved – when you have more than one thing, you get a mess, because you can potentially get four products.

Let's look at a reaction [where even though we have two starting materials we're only going to get one product]. Acetophenone. A phenone is a benzene stuck to a carbonyl. Acetophenone means a two-carbon object connected to the benzene ring; in other words, this. The other reactive material is p-anisaldehyde, which is related to anisole. This is an ideal example of a crossed aldol because: how many of these compounds have alpha protons? One. The hydrogen on the carbonyl itself is not an alpha proton; there's no delocalization that would happen if you pulled the carbonyl hydrogen off, so they're normally not reactive. The other end of this particular carbonyl, on the p-anisaldehyde, you have a benzene ring there, which benzene, each carbon on benzene only has one hydrogen to begin with, so if you've stuck something onto the benzene ring, it took up hydrogen's position, so there's no alpha protons there. Only one of the two compounds has alpha protons, so only one enolate can form. That cuts in half the number of potential products right there.

Once the enolate forms, what's it going to attack? Another carbonyl. Which of these two compounds is more reactive, in terms of their carbonyl? The aldehyde. Ketones, by having two alkyl groups, automatically has more hyperconjugation between those alkyl groups and the carbonyl's pi bond. That hyperconjugation stabilizes the pi bond, which makes it less reactive. An aldehyde automatically lacks one of those alkyl groups, and because the hydrogen that is on an aldehyde is 90° to the pi bond, there's no way it can stabilize that pi bond. Less stabilization means higher reactivity. Aldehydes are more reactive than ketones. If we have an enolate that's going to attack one of these versus the other, it's going to attack the aldehyde. It's enough more reactive that it's the only thing that reacts. We'll only get one thing. We'll make the enolate, and because only one molecule reacts with the enolate, that's why we get 99% or whatever high percentage of just one product.

[Let's] see the mechanism for this reaction. Deprotonation. It's a good thing that the ketone is the only thing that has alpha protons, because it has a pKa of 19, which means that hydroxide does not instantly deprotonate it. Hydroxide is a weaker base than that enolate, but it's the only thing that can for, and if equilibrium can happen, it will happen. Some of this will form, and then it will continue to react. We help make sure that this happens by using [a] strong, concentrated solution of hydroxide. We form the enolate, which will now react with the p-anisaldehyde. The carbonyl that made the enolate remains intact; the carbonyl that got attacked is gone. After the initial attack, the condensation itself, that alkoxide gets protonated – remember, we're in basic conditions, so we have to use water, not H+. That gets us a beta-hydroxy carbonyl. It's not always true that heating is required to cause a secondary reaction. Hydroxide attacks; we make an enolate that doesn't condense again [steric reasons for that?]; intramolecular elimination [occurs], and we've made our alpha,beta-unsaturated carbonyl compound. Molecules with this structural feature are known as chalcones.

[lab procedure]

You throw everything together at once, with hydroxide being last. Why? Because the hydroxide could potentially start forming an enolate with the acetophenone, and if you only have acetophenone, in theory, it condenses with itself. That condensation is often reversible, which is why we're not worried about condensation products of ketones here.

Aldol condensation

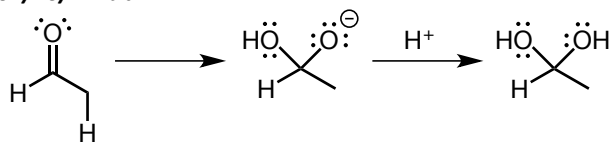
Mixed aldol – When dissimilar compounds are used in aldol condensations (mixed aldol), potentially four compounds can result.

This is an example of an ideal mixed aldol since:

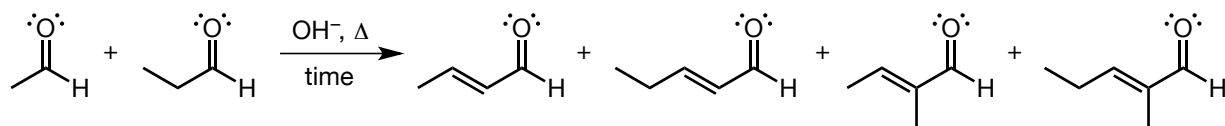
- 1) Only one compound has alpha hydrogens, so only one enolate forms
 - 2) Aldehydes are more reactive than ketones, so the enolate will likely react with only one starting material.
-

Structures (remaining structures identical to lab 1B)

04/16/12 lab • 1



04/16/12 lab • 2



04/16/12 lab • 3

