

## Lab 1B • 04/10/12

[emergency situations; exits; earthquakes; fire alarms; fire extinguishers; emergency phone; eyewash stations; emergency shower; backup clothes]

[appropriate clothing: no shorts, closed-toe shoes, lab coats; goggles; first aid supplies; health services; pre-existing condition; food and drink]

[chemical trays; waste; broken glass; acid and base cart; closing chemical bottles; lab cleanliness]

[class structure; pre-lab format; A/B/O waste designation]

### Aldol condensation

This is a reaction that's related to what's called the alpha position of a carbonyl. If we look at a carbonyl-containing compound, there is a common way to refer to positions of different carbons at different distances from that carbonyl. The immediate neighbor is referred to as the alpha position, then the position next to it is the beta position, gamma, delta, and so on and so forth. Sometimes, for convenience, the last position of a chain is referred to as the omega position, because omega is the last letter of the Greek alphabet. We're going to be concerned about that alpha position for today, because imagine I had something like the following: let's say that I had some kind of base that was really strong, but it was really, really sterically hindered. The reason I put in that bit about being sterically hindered is I don't want the carbonyl to be attacked in this case. But, it's still going to be really, really basic. What do you think could happen between that really strong base and this aldehyde? Is the hydrogen attached to a carbonyl going to be all that basic? Would there be any kind of delocalization possible of a lone pair that would result from the hydrogen of a carbonyl being deprotonated? Not really, that's not really favorable carboanion at all, not particularly. Versus the alpha position. What would happen if the base were to successfully pull a hydrogen off the alpha position? You've got the carbonyl right next door that it could undergo delocalization with. In terms of molecular orbitals, this would be similar to an allyl case. If that was not a negatively-charged product, if we did have a hydrogen on that oxygen, what kind of functional group would we call it? If the oxygen didn't have a negative charge, if it had a hydrogen instead, what functional group would we call this? An enol. Because it is an ion, though, we call it enolate.

What if we didn't have basic conditions, though? What if we had acidic conditions? Same starting compound. Let's say that we have a strong acid source, but no water. What possible reaction might occur here? Really the only thing possible is for the oxygen to react with a hydrogen, which means I need a reversible arrow. That carbonyl, we could show on paper as opening up; really this is just delocalization, it's resonance. We could have the counterion, the conjugate base of that acid we used, come along and pull a hydrogen off. Now we do make an actual enol. The difference between these two mechanisms is in the first case, the carbonyl is forced open by something happening next door, by a base coming in and attacking. In the second case, the carbonyl is made active by protonating it first. This is that anionic-cationic dichotomy that we've seen before when we discuss carbonyl compounds. What is this process called? Tautomerization. Specifically, when we go from a carbonyl, which usually this is shown with a ketone first, to the enol is called the keto-enol tautomerization. Why does this matter? Because enols and enolates react.

Let's go back and stick with just the basic conditions for a moment. I'll take that same aldehyde. I'll mention on the side that the circled proton has pKa value of roughly 16. How does that compare to the pKa of an alcohol? What is, roughly, the range of pKas for an alcohol? 16 - 18. This is 16; that's right in that same region. That means in theory, if we used a strong, concentrated solution of sodium hydroxide, we'd have a reasonable chance of deprotonating this compound. [memorize the pKa values that are quote] Many of these alpha chemistry reactions depend on knowing whether deprotonation is successful or not, meaning you're going to have to compare the strengths of [acids or bases]. [Henderson-Hasselbalch; half-equivalence point][warning to study ahead] Let me show you on the side that water has a pKa of 15.7, which means these two compounds are about the same acidity as each other, so you would need to use an excess of sodium hydroxide to assure deprotonation – or, I could show you a reagent that's often used to force deprotonation. Since an aldehyde, on average, has the same acid strength as water, a concentrated solution of sodium hydroxide can often be used to form enolate ions. Since the acidities are so similar, though, technically any arrow I write would be a reversible arrow, because the compound could push back, try to reform itself, and generate hydroxy therefore. For today, I'll write everything as a forward arrow.

I will rip the proton off that alpha position; [that can be followed up immediately] with showing the delocalization of the negative charge on the carbonyl. That's not necessary; it's just showing that delocalization. If you want to write a more compact mechanism, you could just stop right here – at least as far as the formation of the enolate. But if you have a negatively-charged carbon, what's gonna happen to another carbonyl. Isn't a Grignard reagent effectively a negatively-charged carbon? It's more basic than this kind of compound, but if you had another molecule of the same aldehyde sitting next door, then couldn't that first compound attack and open up the carbonyl? That's exactly what happens: an aldehyde can end up forming an aldol – therefore the aldol condensation – condensation because we're taking two of the same molecule and they end up stuck together [but not as dimers]. Let's see the rest of the mechanism. [reversible] Notice that this is the formation of a new carbon-carbon bond. You might remember how important carbon-carbon bond formation is; the fact that we have another way to form it means that this is going to show up a lot in synthesis problems.

To help identify a condensation reaction, let me point out that the new carbon-carbon bond is formed on the alpha and beta positions, relative to the carbonyl that formed the enolate. Notice also that one carbonyl survives, the one that was part of the enolate; the carbonyl that got attacked turns into an alcohol. Because of the type of attack that occurs, that alcohol always forms at the beta position. As you see more and more of these condensation reactions, watch out for these kinds of tricks for identifying the condensation that occurred. [You need to be able to identify what kind of condensation reaction occurred][preview of quarter content and difficulty] This is not done, because we have an anion and you can't isolate an anion. We're also in basic solution still, so we can't use H+ at this point. We could imagine that if hydroxide the deprotonation that we have some water around, so we can use water as the thing that quenches this alkoxide. If an alpha proton was deprotonatable once, why can't it happen a second time, especially if we're using a hot, concentrated solution of sodium hydroxide? I again made an enolate ion. You might imagine that another condensation could try to happen, but here's something quite unusual: hydroxide leaves as a leaving group. Hydroxide leaves as a leaving group. When is the last time you saw that? Borane; hydroxide is spit out as a leaving group [because] there is this thermodynamic push for bond migration that allows that hydroxide to be kicked off. When you kick off hydroxide here, what do you form? You form an alpha,beta-unsaturated carbonyl-containing compound that's conjugated. When you form a conjugated system, remember that there's a stability that comes along with that that you would not get if the double bonds were isolated from each other; that why the formation of this compound is favorable, that's why hydroxide can be a leaving group in this rare situation. This is the other potential product that you could form from an aldol condensation. Under certain conditions, we might be able to isolate the alcohol, the true first product on an aldol condensation. But in this case, the conditions we will be using in this lab, where with heat and a concentrated solution of hydroxide, we'll push all the way to this alpha,beta-unsaturated compound. That is the aldol condensation. This is a pure aldol, where you take one compound and condense a second molecule of it.

What you're doing in your lab experiment is a mixed aldol condensation. Your two starting materials are p-anisaldehyde and acetophenone. What's anisole? An oxygen and a methyl group stuck on benzene. Anisaldehyde is where you add an aldehyde to that; it's the para position, that's why this is p-anisaldehyde. Phenone is a common name for a benzene compound that has a carbonyl directly fused to it. Acetophenone is where you have two carbons – including the carbonyl – stuck onto the benzene ring. You have two carbonyl compounds. Not knowing any better, we might worry that, were we to put a concentrated sodium hydroxide solution in this, we might get four products: the first one condensing with itself; the second one condensing with itself; the first condensing with the second; the second condensing with the first. As we'll see in lecture, there are situations where that can happen, where if you try to take two different carbonyl sources, you'll produce multiple products. But there's several gotchas about this case; this is a special case, because: which of these compounds actually has alpha hydrogens? [rant about no participation] Only one of them can start the process, only one of these two compounds can make an enolate. In a mixed-aldol reaction, often you can get multiple products, but in this case, only one is going to make the enolate. Only one of the two compounds can form an enolate, since only one compound has alpha protons.

In general, a ketone has a pKa of roughly 19. Why is it higher than an aldehyde? The carbonyl is definitely going to stabilize the anion that forms. Why is there a different amount of stabilization in this compound, though, versus the aldehyde. Both of them have a carbonyl, so both of them have that stabilization. Which compound is more acidic: an aldehyde or a ketone? Is a larger or smaller pKa value more or less acidic? Larger pKa means less acidic, which means that proton is harder to pull off, which means there's less stabilization there somehow. Why? Because you already have the benzene ring stabilizing the carbonyl, lowering the delta + that's there. This is why ketones are less reactive to begin with – if you have alkyl groups that provide hyperconjugation, or benzene that provides conjugation – some way that gives electron density to the delta + on the carbonyl, the carbonyl's less reactive – also less able to handle a neighboring negative charge. If you destabilize the carbon, increase that positive charge there, then that makes it more likely for its neighboring carbon to want to get a negative charge, because it could be tolerated. On a practical level, it's a good thing this is the only compound that has alpha protons because hydroxide's going to have a tougher time deprotonating it. This is a weaker acid than water, so you really do have to pound on this to deprotonate it with hydroxide. Only one of the two compounds can form an enolate, since only one compound has alpha protons. This is fortunate, since hydroxide is not quite strong enough to easily deprotonate the ketone.

I've only given you one of the reasons why this condensation is favorable: once you make the enolate, which compound is more likely to be attacked? What's more reactive: aldehydes or ketones? Aldehydes. If you provide electron density to the carbonyl, it stabilizes it, makes it less reactive. Having a hydrogen versus a methyl group, the methyl group stabilizes the carbonyl because you have hyperconjugation, the hydrogen can't because it's perpendicular to the carbonyl. The aldehyde's more reactive, so it's the one that gets preferentially attacked once the enolate is formed. Because only one compound can form the enolate, and because only one compound would preferentially react with the enolate, only one product forms.

Let me write the complete mechanism for the formation of that product. The alpha position gets deprotonated. Optionally, you may show the delocalization of that enolate. To save space, we just continue on with the reaction. It's going to attack the aldehyde. Look at the alkoxide I just formed, and imagine that it wanted to reform its carbonyl, that negative charge tries to attack the carbon. Normally, we ignore something like that because we presume carbon-carbon bonds won't break. But what's the pKa, roughly, of the parent acid of this alkoxide? What's the pKa of an alcohol usually? 16-18. What is the pKa of this parent of the ketone, the ketone itself? 19. If one's 18, one's 19, couldn't this potentially be a leaving group to the carbonyl reforming? That's why the reaction could be reversed. For now, we're ignoring that detail.

This alkoxide that I just formed is going to do exactly what I showed you with the example molecule, where it will get reprotonated – we can assume some water around [since hydroxide was used as a reagent]. There'll be a second deprotonation at the alpha position, and a separate step, an internal elimination can occur. I want to emphasize that separate step element of it. [A common mistake that is sometimes made is to combine reaction steps] to save space on mechanism, but it's actually incorrect, at points, to combine steps. This is one of those cases: the deprotonation is separate from the elimination, which we could prove using a kinetic study – to find out whether it's first- or second-order, for example. If it were second-order, the elimination, then that would mean the base and this compound would be required at the same time [if the reaction is first-order in each reagent]. If it's first order, you only need one molecule, which would be this one.

[lab directions]

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keto-enol tautomerization

Aldol condensation

Since an aldehyde (on average) has the same acid strength as water, a concentrated sol'n of NaOH can often be used to form enolate ions.

\*A new C-C bond is formed at the alpha & beta positions relative to the C=O that was part of the enolate. The carbonyl not part of the enolate turns into an alcohol at the beta position.

Mixed aldol condensation

In mixed aldol reactions, often multiple products can result. However, in this case, only one product will result.

– Only one of the two compounds can form an enolate, since only one compound has alpha protons. This is fortunate, since OH<sup>-</sup> is not quite strong enough to easily deprotonate the ketone.

– Since aldehydes are more reactive than ketones, once the enolate forms, it will far more likely attack the aldehyde.

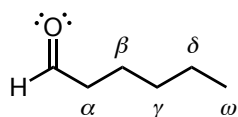
Only one product forms.

\*All rxns written as irreversible for now.

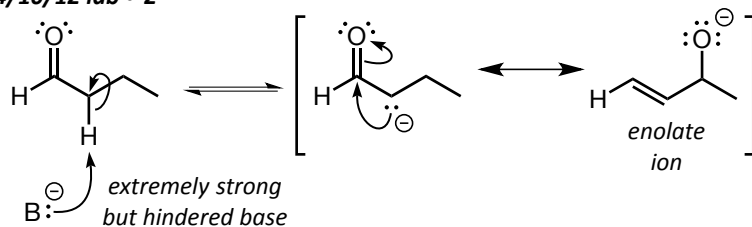
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Structures

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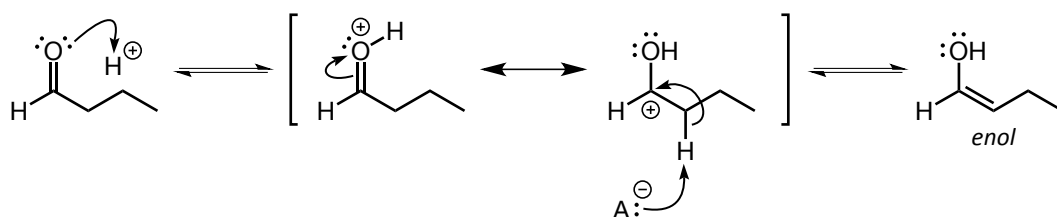


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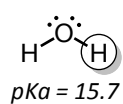
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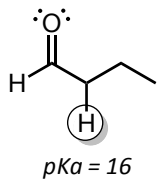


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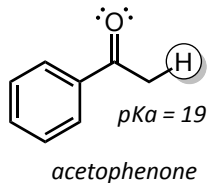
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