## Lecture 7B • 04/26/12

What kind of functional group is this? Carboxylic acid and an alcohol. What two things do you need to make an ester? A carboxylic an an alcohol. Don't we have both of those things right here? The problem tells you you make a cyclic compound. You're going to make a cyclic ester; what's that called? A lactone. It's protonate-open-attack-deprotonate, protonate-open-attack-deprotonate; the product is going to be this. If we labeled our carbons, we could confirm I've got the right connectivity. [problems with cyclic compounds tend to unnerve][delineation of lab and lecture topics]

Let's discuss alpha halogenation under acidic conditions. We start with something like acetone and we react it with an acid [why is acetic acid often used], then we're going to have bromination. Is it likely that this reaction is going to occur multiple times? No, not under acidic conditions. You have to form a carbocation at the position of the carbonyl as part of the mechanism. You have bromine which, overall, is an electron withdrawer; it may have resonance, but it's a withdrawer atom. That puts a delta positive one position over from where that carbonyl is that wants to form a positive charge. Situations in which you have a positive and a delta positive next to each other aren't favorable. Any time that you have like charge being brought together, not a favorable situation. Because the bromine is electron-withdrawing, it makes that carbocation less likely to form, which means the reaction doesn't want to happen. [We could take] the opposite, the flip view of that. Instead of focusing on the carbocation stability, [we could focus] on the oxygen and [say] it's less basic, but they're tied together. In this case, under acidic conditions, halogenation only occurs once; that's because the halogen, by withdrawing electron density, makes the intermediate harder to form.

Let's go on to the base version. Let's say that we have something like this, an aldehyde, and we react it with sodium hydroxide and bromine. SInce it's under basic conditions, the enolate – not enol – will be formed by removing the alpha proton. Once the alpha proton is removed, a halogen is placed on there. What does that halogen do to the possibility of a further reaction under basic conditions? Is it going to happen in this case, a secondary or subsequent reaction? Yes, because it's the opposite behavior of what we had under acidic conditions. Whatever destabilzes the acidic mechanism – because you have a carbocation forming – stabilizes the basic mechanism – because you instead have a carboanion forming. Carbocanion likes having a delta plus right next to it, cause that encourages the negative charge to form. If I put one bromine on, it makes the alpha proton even more acidic, an the next reaction happens more easily. But in this case, there are only two protons on the alpha position, so the [haloform reaction is] a special case. You don't always have the haloform reaction, because in this, no haloform – in this case, specifically bromoform – is formed. The product's just going to be a dihalogenated aldehyde. In this case, multiple halogenation occurs since the inductive effect of bromine increases the acidity of alpha protons. Since only two alpha protons are present, only two are replaced, and no haloform reaction occurs.

If we did have a methyl ketone (special case), in that case, we initially form a tri-substituted compound. I'm putting this in brackets, because you can't isolate this. [pKas of chloroform, bromoform, iodoform] are close enough to water that when hydroxide interacts with this intermediate, it can attack the carbonyl. It can actually do that at any point in the reaction, but it won't do anything productive until you have the three halogens on here. Once you do and once that carbonyl is pushed open, it can reform. If hydroxide was the better leaving group, we'd just go right back to where we came from. The point is, these haloforms are acidic enough that their bases are weak enough that they can be expelled at this point. Reform the carbonyl, the bond breaks. That portion would still be technically reversible, because if they're comparable in basicity, why can't they go back and forth? Problem is, this is just like the saponification of an acid, because if the haloform ion is kicked out, we form a carboxylic acid. That haloform ion, although not as strong as a base as other organics, it is still basic, and the carboxylic acid (in organic terms) is fairly acidic, so you get an instant neutralization, which prevents the reversibility of the reaction.

Alkylation is significant because it's a carbon-carbon bond-forming reaction, which is really important if we're trying to build up larger organic molecules. There's an issue with the type of base that's appropriate to use in this kind of reaction. Let's ignore that for the moment to focus on the reaction itself. We could start with a ketone; not worrying about what kind of base, we will use a base. This kind of reaction is effectively base-only; I'm going to show you an alternate reaction that avoids the need to form an enolate. We've made this enolate; it's basic, and carbon, when negatively-charged, is nucleophilic, so if we had a primary alkyl halide around at this point, we'd be able to do Sn2. It looks more complicated than Sn2 because I've combined a resonance step in it [combining resonance]. This is a delocalized Sn2, and we end up with an alkyl group at the alpha position. It's important because you're able to form a new carbon-carbon bond.

Let's now talk about the kind of base that we should use. When we did the ideal mixed aldol condensation, we were able to get away with using sodium hydroxide; that was because only one of the two compounds even had alpha protons, and once it formed an enolate it [was] able to react primarily with just one substrate, the more reactive one. But in this particular case, let's think about the consequences of using hydroxide to deprotonate this cyclohexanone. I'll get at this concept in this way: I'll write a neutralization reaction, where I leave out the arrow in between. I'll show the products, which are going to be the enolate and water. What kind of arrow should go here? Why would you think that it would not be a forward arrow? What's the pKa of water? 15.7. If cyclohexanone is a normal ketone, what would roughly be the pKa of it? 19. Which of these two is the stronger acid? Water. Out of the negatively-charged compounds, which one is the weaker base?

Hydroxide, because if water's the stronger acid, it's conjugate is the weaker base – which means, automatically, cyclohexanone is the weaker acid, and the enolate is the stronger base. If you were going to put any kind of arrow, and you wanted to be technically correct, we would use a lopsided reversible arrow, like this. This arrow does communicate the fact that it is reversible; the product will form, because if it can form, it will form, but it also indicates this is not a likely process. Now imagine that you had a combination of these two things – the cyclohexanone and the hydroxide – but you also had the alkyl halide around, or wanted to. If you added hydroxide to this reaction, it does not go to completion. That means there's a significant amount of hydroxide around. Hydroxide could easily react with the alkyl halide, so you'd get a byproduct. Since hydroxide cannot irreversibly form the enolate, it would be a poor choice of base in this reaction, since you could get a side Sn2 reaction that occurs. I'll add a stipulation to that: hydroxide is a poor base in alpha reactions of mono-carbonyl compounds, since it normally cannot produce the enolate irreversibly. This means a significant proportion of hydroxide will be present, which means a side substituted reaction could occur.

We need some kind of base that's strong that can force this thing to happen, but we have to be careful about what base we select, cause if we just used [n-]butyllithium, [it is a strong base] but something like that's going to directly attack a carbonyl. So, we play a trick: we make a base that's really strong, but also sterically hindered. That base is LDA: lithium diisopropylamide. Amide in this case doesn't mean the [carboxylic acid derivate] functional group; it just coincidentally in this case just means negatively-charged nitrogen. [LDA} looks like this: two isopropyl groups attached to a nitrogen which is negatively charged so it has two lone pairs, with a lithium counterion. Normally, this is not bought – at least if you do this reaction routinely – because it is easy to make this base from cheaper components of [n-]butyllithium itself and the amine, the conjugate acid of this. Synthetically, we cake [n-]butyllitnium, react it with the amine, which would have a hydrogen, and that makes LDA. The lithium base is a stronge base than this; that's why I wrote this with a forward arrow. [pKa of diisopropylamine is 35]. We could again compare cyclohexanone, with time with LDA. Same situation: we're going to wonder whether LDA can deprotoante the carbonyl and make the enolate. Now we have an acid that has a pKa of 36, versus a pKa of 19. We now have the weaker acid on the right as a product, and the stronger acid on the left, which means we have the stronger base on the left – because it's the conjugate of the weaker acid – and then the conjugate of the better acid is itself the weaker base, which means, especially given the broad difference in pKa values, this is going to be a forward and effectively irreversible reaction. Strong base means a high likelihood to dissociate, which also means negative delta G. The more likely it is to dissociate, the more negative that process is in terms of delta G. If you go from strong to weak, you've going downhill in energy, cause you're allowing those dissociationgthat want to occur to occur. If we tried to go from weak to strong, weak acids are ones that don't want to dissociate, which means they have a more positive delta G for dissociation, so when you go from weak to strong, you're going uphill in energy, which doesn't want to happen. Another way to express it is: remember that delta G = - RT ln K, so we can come up with an overall equilibrium constant based off these pKa values, and from that still prove that, in this case, it's going to be negative delta G and if we tried to reverse it it would be positive.

We have our irreversible base. In terms of synthesis, I could do an alkylation reaction by reacting with LDA to form an enolate, then use whatever primary alkyl halide I want to do substitution. Why is it that it has to be a primary? Not sterically hindered. We do have hydroxide, which for secondary can cause elimination, and if these are stronger bases than hydroxide, that means elimination's even more likely, especially since these enolates are generally going to be slightly more sterically hindered than something small like hydroxide. The reaction, in this case, only works well with primary substrates.

This is what is called the Stork enamine synthesis. Let me draw you a general structure of an enamine. It is what it sounds like: partially ene (alkene), partially amine. Are enamines thermodynamically stable? What if both R groups are alkyl groups; does it have anything else it can convert into spontaneously? No. It's only if we do have a hydrogen on that nitrogen that this group is unstable. With both groups being alkyl groups, it is isolatable and stable. [review of enamines]

When will an enamine form? There are certain situations where you can make enamines, certain situations where you can only make only enamines, and certain situations where they would not want to be made because you would make an imine instead. If we have an aldehyde or a ketone and we have some kind of primary amine ... by being a primary amine, that means it has two hydrogens on it, which is going to be significant later. The first part of the reaction than the protonate-open-attack-deprotonate sequence that we've seen for most of these cationic carbonyl reaction. It's overall cationic because there is still an acid catalyst need, but too much acid prevents the reaction from happening because it would make a salt with the amine; too little acid nothing happens because you do need an acid catalyst. Because the amine is basic, that's the justification for showing this carbonyl being opened by the amine, along with the fact that the optimal pH for this reaction is 5, again implying that it's not necessarily the acid that's causing the thing to start. We have attack and open, followed by protonate/deprotonate. At those point, the oxygen and the nitrogen protonate and deprotonate respectively, although they do not occur simultaneously. I show the alkoxide being protonated, and now the nitrogen loses the first of the two hydrogens. We then form an intermediate which is called a carbinolamine. This much of the mechanism is exactly the same, whether you have a primary or a secondary amine. Tertiary amines don't even have hydrogens on them, so they can't even get this far in the mechanism. Only primary or secondary amines, or ammonia itself, could do this reaction.

Now, we have [another] round of protonate-open-attack-deprotonate. For both primary and secondary amines, the next two steps will be the same: protonate the oxygen, which will make water, which will be a leaving group.

Now, if we have a primary amine, we can show resonance, [and] once you make the resonance structure, you end up with a positive charge on the nitrogen, which can't be isolated – except that here, we can lose the hydrogen, and we end up with the imine. Let me show you the intermediates that are formed [from a secondary amine]. I'll take the same starting aldehyde, ethanal, then I'm going to react it with a secondary amine, which has only one hydrogen on it. We get as an intermediate the carbinolamine. Notice we now have no hydrogen. That means when we get to that pivotal part of the reaction mechanism, we can't form a carbon-nitrogen double bond, because we can't get it neutral. What happens instead is you have an alpha hydrogen come off instead, which is how we end up with the enamine, which has a resonance structure. Because positively-charged nitrogen is not the worst thing in the world, this makes this a non-trivial resonance structure. It's not going to be the best resonance structure, because we have charge separation, but it's not as bad as some other molecules in the same situation.

What is this product a little bit like? If we got rid of the nitrogen and put an alcohol in its place, what would we call this? An enol. Enols do alpha reaction; these sorts of enamines also do alpha reactions, but they do so under less drastic conditions. pH 5 is all that's necessary to make the enamine, and then you don't need a special base to get it [to] react. That's because the nitrogen's lone pair does such a good job delocalizing, that's why this resonance structure's not trivial and how we take advantage of this do to an alkylation reaction. Let me show you an example of this. I'll first react this with a cyclic secondary amine, only because it happens to be a common reagent. Please note it's not pyrrole; pyrrole has [what appear to be] double bonds in it. Why would pyrrole be a very poor base to make an enamine out of? It's aromatic; why? The lone pair becomes part of that delocalized system, and if you were to try to use that lone pair in some other reaction, it wouldn't be there to make the system aromatic, so there's a big energy penalty; this is a very non-basic amine. Most amines have pKbs that are similar to acetic acid's pKa, so their pKbs are about 5ish and the pKas of the conjugates are about 9. The point is, that lone pair doesn't want to do anything. Because it only has the one hydrogen, you are going to form an enamine first, which we could write a resonance structure for to show that there would be a build-up of charge at the alpha position. If we now were to throw an alkyl halide at it, it would react and after reacting reform the enamine. After you're done, you could react with water and acid to hydrolyze the enamine and get back the ketone. The Stork enamine synthesis is useful because no strong bases are used, which allows for more sensitive substrates to be used in the alkylation reaction.

Since an amine is a base with a pKb of about 5, it means that it's not that strong, but it's stronger than neutral, and it's strong enough to be able to do an Sn2 reaction. The problem is, for most amines, after you do this reaction, the product is more basic than what you start with, because if alkyl groups are electron donators, then you're donating electron density to the lone pair, which makes the lone pair even more basic, which makes the second attack more likely than the first, and the third attack even more likely than the second, then. This reaction keeps going on until you end up with a tetraalkylammonium salt. Once we get to amines, we'll be talking about ways to prevent this. We don't have this problem in the enamine synthesis because there's only one hydrogen at that position, so you can't get multiple reaction anyway. [summary]

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alpha-halogenation

special case: methyl ketone

alpha-alkylation – base only
* Forms a new C-C bond!!

Hydroxide is a poor base in alpha-reactions of monocarbonyl compounds since it normally cannot produce the enolate irreversibly. This means a significant proportion of NaOH would be present, which could react with an alkyl halide instead of the enolate.

LDA – lithium diisopropyl amide

Stork enamine synthesis

The Stork enamine synthesis is useful because no strong bases are used, which allows more sensitive substrates to be used in alkylation.

Claisen
Malonic ester synthesis

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**Structures** *(remaining structures identical to lecture 7A)*

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