Lecture 5A • 04/20/12

[Quiz 1 – relative reactivity of carboxylic acid derivatives; cationic versus anionic mechanisms; reversibility; saponification; esterification; reductions and alkylations of acyl halides, esters, and amides]

Often, as in esterification, the products and reactants are similar in energy, and, more importantly, the intermediates are similar in energy. One protonated oxygen is not vastly different from another protonated oxygen [barring delocalization]. [example of saponification as reversibility of basic mechanism, ignoring subsequent neutralization, and Grignard as irreversibility of basic mechanism]

What would we call the reaction of a carboxylic acid derivative with sodium hydroxide? Saponification; what else could we call it? Basic hydrolysis. In that kind of reaction, if you have an ester with sodium hydroxide – we looked at the sodium hydroxide and we identified that the conjugate pKa of water is 15.7. We allow this reaction to proceed. Based on the result of the 18-oxygen experiment, we go through these tetrahedral intermediates, so we're going to end up with this situation where we end up with a new alkoxide that, if we ignored what ever potential effects there might be by having these neighboring oxygens – ignore the neighboring oxygens – based on the fact that this is otherwise a secondary alkoxide, we'd probably say it's pKa [of the conjugate] is probably about 17 [but what is it??] That means that the base we start with and the base that we end with are about equal in strength. That's why this is reversible.

When would we have a situation where this can't be reversed? Grignard reactions with esters [for example]. Technically, if we did consider the Grignard reagent as just an alkyl group – an isolated, a bare alkyl group – a conjugate of that, an alkane, that has a pKa of about 60. That is far more basic that whatever alkoxide that we do end up with, no matter what the neighboring effects of the other attached oxygens might be. You could get really really technical and say that in any equilibrium there's always reversibility, even if it's only one molecule of the stuff that reacts. That'd be the situation we'd be in in this case, because if we had a pKa of 17 versus 60, that's 43 orders of magnitude, which is a huge difference. Even if we took the square root of that [related to ICE problems], square root of ten to the 43rd is roughly ten to the 21st, which is roughly the size of a mole. So, even if you had one mole of material, that means you'd only have a handfull of molecules that would try even to go in reverse, and maybe not even then successfully. Since it's such a vast difference, that's why I've written this with a forward arrow; that's why I'll say, ignoring all of these fussy arguments about equilibrium, this thing is not reversible.

If a portion of an anionic mechanism ends up reversible but not all of it, when does the switchover occur? It occurs when there's a subsequent reaction, not involving the carbonyl. We saw that in saponification of an ester, and it also happens in saponification of amides.

Let's take a typical amide. Let's say that we did saponification. We'll take hydroxide, attack this carbonyl. This is reversible; it's the next part that gets tricky. If we're saying that the conjugate pKa of this alkoxide is roughly 17, then how likely is it that the following is going to happen: that when that alkoxide tries to collapse back down to reform a carbonyl that it will kick off this nitrogen group? What you'll form is a carboxylic acid, and you'll also get something on the way to a primary amine but not yet neutral; it's going to be negatively charged. Primary amines have a pKa of roughly 34. Which is the stronger base: the alkoxide that's the intermediate, or this ion of an amine that just got kicked out; which one's more basic? The amine, by far. Does this reaction want to happen? No. In fact, if we were being really fussy about it, we'd write it like this. It may be reversible technically, but it doesn't really want to happen. If it doesn't want to happen, why does it happen? If equilibrium can occur, it will occur, even if to some small extent. If this happens, then the reaction can't reverse. Why? Because we just made this horribly basic compound at the same time that we made an acid. That neutralization captures, you could say, traps the carboxylic acid. That is now irreversible, because there's an even huger difference between pKa values: 34 versus 5, approximately, for acetic acid. The same thing is true here [as for saponification]: because both an acid and base are formed at the same time, before the reaction can reverse, they neutralize each other, preventing a reverse reaction. That's where and when this particular mechanism becomes irreversible.

[why using pKa instead of pKb; make sure to refer to pKa as being associated with the conjugates of the bases being compared]

[Mechanism for 18-oxygen replacement in a carboxylic acid]

Acid mechanism: the first thing that's going to happen is protonation. The carbonyl is protonated; it opens. Recognize that this is identical to Fischer esterification. Water attacks; that would be an alcohol if this was solvolysis, another term for Fischer esterification. Of course, if we have neutral water to start with, that means it's going to lose a proton once it's attached. Now, multiple things happen next. We have three oxygens. If we protonate any one of these three oxygens, we have virtually the same energetic intermediate. Technically, 18-oxygen forms a slightly different bond with oxygens; it's called the isotope effect. If the 18-oxygen gets protonated, that means we're going to back to where we just came from. If either of the other –OH groups gets protonated, then we're going to go forward somehow. Let's see what that somehow could be. One of them gets protonated, becomes a leaving group, and leaves.

If this was Fischer esterification, the next thing that we would try to do is to reform a carbonyl. Technically, it could be either one of these oxygens that becomes the carbonyl oxygen. After the first addition, you can't specify where the 18-O's going to end up; it's got a 50/50 change. But who says you even have to form a carboxylic acid? There would be an attack and deprotonate step here normally. But, if this is flooded with 18-oxygen water, couldn't it just go ahead and attack now? You could go to the carboxlic acid at this point, drop a lone pair into the positive charge, lose a hydrogen off the carbonyl, which then gets reprotonated and opens again if you did another protonate-open-attack-deprotonate, so why go to the carboxylic acid? This could react right here at this moment. If it does, then it deprotonates. We're back again at that same situation of three oxygens. Again, any one of these three oxygens could get protonated, but the whole point of this is the 18-oxygen water was in excess, so over time, statistically, eventually, the plain –OH is going to get protonated and leave. It could come right back again; there's nothing to prevent it. But, that's the whole point of this being a reversible reaction. Now, if either one of these oxygens forms a carbonyl, it could get deprotonated. Because of Le Châtelier's principle, we'll end up here eventually. Once this deprotonates, we end up with our fully-18-oxygenated carboxylic acid.

It is possible to do an acid hydrolysis of an amide. Part of the reason this amide is unreactive is because that lone pair on the nitrogen is tied up with the carbonyl. Even if you were to protonate the carbonyl, it's just not as reactive. Because that lone pair on the nitrogen is tied up with the carbonyl, it is unlikely that that nitrogen gets protonated. Amines normally are weak bases; this not, because of delocalization. The whole point of this story is that you don't use just nice, dilute solution of acid to do this reaction. No, you use concentrated acid, water, heat, and time. It's a very harsh condition-reaction. But, with harsh enough conditions, it will occur, and it occurs by our standard cationic mechanism – protonate, open; this is hydrolysis, so the attack will be from water, and then we have a deprotonation. Before I continue, look at this carbocation, realize that nitrogen can be donating into the carbocation, making the carbocation less attractive to water, making this process more difficult. We're at the halfway point. Now, another round of protonate, open, attack, deprotonate. If you get here, the rest of the reaction is relatively favorable, because it is likely for the nitrogen to get protonated. We end up with ammonium, which can leave. If it does so, then we're in the same situation we were in the previous reaction: a carbocation with two –OH groups around it. One or the other we show delocalizing and then deprotonating. This is acid hydrolysis of an amide.

Solvolysis is not that favorable for an amide, because amides are not that reactive. Solvolysis would be like transesterification, it's just that in this case one alcohol would come in and the amine would be kicked out.

Let's finish up with nitriles.

Nitriles – how can we synthesize them? Use sodium cyanide. Cyanide might be an ion, but once it makes a carbon-carbon bond, it turns into a functional group – a nitrile. There is another way, technically, that you could make nitriles, although it's not exactly just a nitrile. If you use hydrogen cyanide with a carbonyl source, you could make what's called a cyanohydrin. That cyanohydrin does contain nitrile functionality. There is also a way to dehydrate an amide to make a nitrile. What are reactions of nitriles? Hydrolysis. Technically, they could be used in alkylation. What would happen if you reduced them?

Since we're not going to worry about complexation in this case, I'm not going to write out the aluminum hydride in full; I'll be lazy about it and just show hydride attacking this carbon-nitrogen triple bond. It generates a negative ion which could be attacked by another hydride; lithium aluminum hydride is reactive enough. Certainly not a favorable product, something with a double negative charge. After protonation, we end up with an amine.

What about hydrolysis? Let's do base hydrolysis first. Base hydrolysis would be hydroxide attack, which is not a favorable process. This requires even harsher conditions that saponifying an amine. This means that, once we're done with this reaction, we're not going to be able to stop a follow-up reaction. This hydroxide pushes the carbon-nitrogen triple bond open. If there's hydroxide around, we can reasonably assume that there's water around; if there's not, we can imagine that there's another molecule around to grab hydrogen from. What we've now made is the nitrogenous equivalent of an enol. The next portion of this mechanism is tautomerization. The –OH group gets deprotonated. Because that proton gets removed, even if there's not water, this is the proton that could have been used in the previous step. Since resonance is not really a reaction step, it's fine to combine resonance with another step. Having deprotonated here, I'm going to go ahead and show the resonance that occurs. We've now made a carbonyl. We've now made another negatively-charged nitrogen. We can presume there's some quantity of water around, which means we've just made an amide. But, since nitriles are less reactive than amides, if we were able to hydrolyze the nitrile, that means this keeps on reacting until we get to the carboxylate salt. You then do have to do a secondary acidification, and we get out a carboxylic acid. This is why nitriles are related to carboxylic acids, because eventually you can turn nitriles into [them].

The last thing that we have is the acid hydrolysis of a nitrile. It's kinda everything reversed from the base hydrolysis. The base hydrolysis, the nitrile bond gets attacked then there's protonation; here, protonation occurs, then the nitrile gets attacked. Once the attack occurs, we have a deprotonation step, and we again end up at the nitrogenous equivalent of an enol, which we would call an iminol. There'll be another round of the same thing happening; there'll be a tautomerization. We do the acid tautomerization mechanism, starting with protonation, then delocalization. Now we've made our carbonyl, which, for the moment, is protonated, and we get the carboxylic acid.

Even though amides are more reactive than nitriles, which means we wouldn't really want to go in this reverse reaction, it's because we have an acid-catalyzed mechanism that these arrows are technically reversible. There is a reagent that could be used to force an amide to dehydrate and go back to the nitrile. After more water and H+, then we would have a carboxylic acid.

[Fill-in-the-blank problems]

If I have this, for example, what would you put in the middle? That's Fischer esterification. Or, start with thionyl chloride and react with an alcohol. If you look at the way that these problems are worded, the blank where the reactants would go does not imply how many reactants go there. If you have an answer that requires you going from one through eight in that box, you might be able to guess that you're a little bit on the wrong track. But, it's perfectly acceptable to have a simple two-step reaction like this.

What's 2 eq mean? Two equivalents, which means two molecules of it are used, which means you have to use them in whatever [substrate] you start with. What would be the name of this starting material? Carboxylic acids only react once. It does use up two Grignard reagents, but it gets a ketone, not an alcohol, so that means we have to have an ester or an acyl halide. This is either acetyl chloride or some kind of acetate [like] ethyl acetate.

Reduction of an amide is like erasing a carbonyl.

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– Cationic vs anion mechanisms –> reversibility

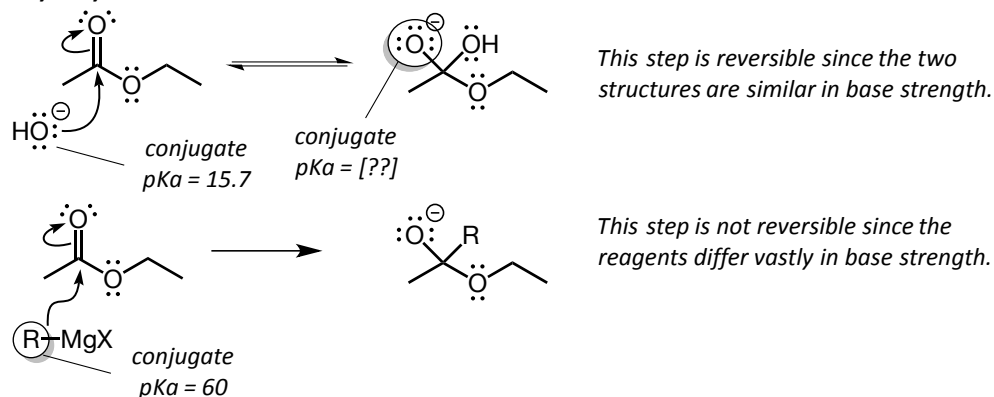Why are cationic mechanism normally fully reversible?
– Often (such as in esterification) the products and reactants are similar in energy and, more importantly, the intermediates are similar in energy (one protonated oxygen is not vastly different from another protonated oxygen).
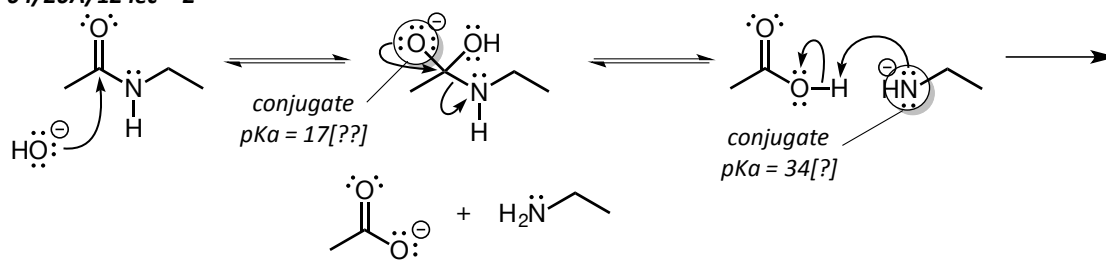
Why are anionic mechanisms sometimes reversible?
– Because both an acid & base are formed @ the same time, before the rxn can reverse, they neutralize each other, preventing a reverse rxn.

Nitriles

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Structures *(remaining structures identical to lecture 4A)*

04/20A/12 lec • 1

conjugate pKa = 15.7

conjugate pKa = [??]

This step is reversible since the two structures are similar in base strength.

This step is not reversible since the reagents differ vastly in base strength.

R—MgX conjugate pKa = 60

04/20A/12 lec • 2

conjugate pKa = 17[??]

conjugate pKa = 34[?]

$+ \ H_2\ddot{N}$

04/20A/12 lec • 3

H$^+$

H_2O (*excess*)

$H_2{}^{18}\ddot{O}$:

$H_2{}^{18}\ddot{O}$:

04/20A/12 lec • 3

$H_2\ddot{O}$:

824

04/20A/12 lec • 4

NaCN

04/20A/12 lec • 5

HCN

cyanohydrin

04/20A/12 lec • 6

1) LiAlH₄

2) H⁺

H⁺

04/20A/12 lec • 7

H⁺

H₂O

H₂O
H⁺

04/20A/12 lec • 8

OH , H⁺, Δ

or

1) SOCl₂   2) OH

1) MgBr (2 *eq*)

2) H⁺

or   *not*

1) LiAlH₄

2) H⁺