Lecture 5B • 04/20/12

[Quiz 1 – relative reactivity of carboxylic acid derivatives; cationic versus anionic mechanisms; Fischer esterification; acid hydrolysis; saponification; reduction; alkylation]

Why is it that cationic reactions are usually fully reversible? Whether we protonate one oxygen versus another, there's usually not very much energetic difference between the different oxygens we might protonate. There's not much energy difference between the various intermediates – makes it easy to go between the different intermediates. [Carboxylic acids and esters] are so close in energy that it's not difficult to go back and forth between one or the other. The intermediates are so similar in energy, the products and reactants are so similar in energy, that that's why the reaction is so reversible. Think of an example such as esterification. Often the products and reactants are very similar in energy and, more importantly, the intermediates are similar in energy – one protonated oxygen does not greatly differ from another protonated oxygen in terms of energy.

That's for cationic mechanisms; what about anionic mechanism – why is it that they are sometimes reversible? Of course, the word 'sometimes' means that they are not reversible in other situations. Let's look at saponification as an example. Part of the saponification reaction is reversible; of course, part isn't. Let's start with some simple ester – ethyl acetate. It reacts with hydroxide. Hydroxide pushes that carbonyl open. We do end up with an alkoxide. Hydroxide is the conjugate of water; that conjugate pKa is 15.7. We make an alkoxide as a product. If we ignore the fact that there are other oxygens attached to the same carbon as that alkoxide – which means they would potentially have some form of inductive [or resonance] effect, but let's ignore it for now – we could guesstimate that a secondary alkoxide – or this is quasi-primary – it's probably got a pKa [for the conjugate] of around 17, let's say. [what is the real value?] The point here is that the base strength of the hydroxide we start with is not appreciably different than the base strength of the alkoxide we end up with. Therefore, since there's not that much difference, this portion of the mechanism is reversible.

Why are we worried about the pKa values of the conjugate[s]? Realize that pKa means how likely a proton is to come off; in these two cases, it's already come off. The number you use to describe pKa is not associated with the base; it's associated with the acid itself. If I wanted to directly compare base strengths, I would need to use pKbs [which causes cringing]. If there was a big difference in pKa, that means there's a big difference in their conjugate bases. In this case, there's not that difference, so the bases are similar, which is why it's reversible.

Let's look at a situation where it's not reversible. What if we did, for example, a Grignard reaction instead? The mechanism looks very similar. We start out with an ester. Let's keep our reagent generalized; I'll say R–MgX. It attacks the carbonyl, pushes it open, the same way hydroxide would. [We] end up with a similar-looking intermediate; we have R instead of hydroxide, of course, but we still have an alkoxide. But, if we still argued that that alkoxide had a conjugate with a pKa of 17, the Grignard reagent, its conjugate, is an alkane, which means its pKa is somewhere around 60. 60 means it's so much less acidic than an alcohol would be – 43 orders of magnitude lower. Even if we were to work some kind of ICE problem with that and establish that some changing concentration might occur of ten to the -21st, it means that even if one mole of the stuff reacted, that only a dozen or so molecules would try to go in the reverse direction. Although, on paper, whenever you say equilibrium, technically that means reversible, it's so imbalanced that this really is just not a reversible reaction. This step is, for all purposes, not reversible, since the reagents differ greatly in base strength.

[Saponification of amides]

We're still dealing with hydroxide and an alkoxide at first in this saponification. The first part of this mechanism is reversible, again because of the comparable base strengths. But now look – if we have this alkoxide (let's again assume its conjugate has got a pKa of roughly 17), how's that going to compete when trying to kick out an amine if it technically is true, that the conjugate of that amine has a pKa as high as 40? Is there any way that this reactions going to want to happen? We have an acid with a conjugate pKa of 17; we have another product that gets made whose conjugate has a pKa of 40. That means the base that's expelled in this reaction is a heck of a lot more basic than what we start with, in terms of either the hydroxide or the intermediate that we make, so if we were to write an arrow, if we were being really technical about it, this is the type of arrow that we would use, to show that, on paper, this process is reversible but it doesn't really want to happen. But now we switch back into equilibrium mode and say that if equilibrium can happen, it will happen. Even if it is only a few molecules that get generated at any one time, if this thing happens, there's instantly a neutralization, because we have an acid with a pKa of roughly 5 and a conjugate of an acid that's roughly 40 – instantaneous acid-base neutralization. If that neutralization happens, then there's no way the reaction can reverse from this point. The reaction's not favorable to occur, it doesn't want to go forward, but if it does go forward, it's trapped, it gets caught up by that neutralization, and now it doesn't reverse. So, the overall mechanism in this case is irreversible, even if there is a portion of it that doesn't want to happen. Because both and acid and base are formed at the same time, before the reaction step that formed them can reverse, they neutralize each other, preventing that very reverse reaction.

If the pKas are similar, reversibility happens; it they're hugely different, they're not reversible.

What would happen if you have a carboxylic acid and you exposed it to excess 18-oxygen water and acid? The first step of that's reversible, because it's going to be a round of protonate-open-attack-deprotonate: protonate the carbonyl, the carbonyl opens in resonance, the isotopically-labeled water can attack, and because we had neutral water – even though it was an isotope – we're gonna have a deprotonate step. When you have three oxygens connected to the same carbon like this, it's not a thermodynamically-favorable molecule. Think of hydrates – a hydrate's just a carbonyl that got turned into a double alcohol. Normally, that's not a favorable process, so if you end up with two alcohols on one carbon [and there's therefore removable hydrogens], it's going to form a carbonyl. We've got three alcohols on one carbon; this thing's really not that favorable, so it's going to form a carbonyl. But now, which one of the oxygens will get protonated to start that process? Any of them really. Is there any difference in the energy of protonation of a regular oxygen versus 18-oxygen? Yes, a small amount, because 18-oxygen's a heavier atom, so there's a slightly different bond strength between oxygen and hydrogen if you have 18-oxygen. It shows up in what's referred to as the isotope effect, the kinetic isotope effect. If you wanted to try to figure out the mechanism of a reaction, you could start out with a compound with a regular hydrogen, start out with a compound that has a deuterium – if the two compounds have a different rate of reaction, it must be because you replaced that hydrogen with a deuterium, which tells you that it must have been involved in the rate-limiting step, cause that's the only way there'd be a difference in the rate of reaction, so it lets you figure out something about reaction mechanism. The main point is: no, there's not a big difference in energy if any of these get protonated. That's why this is reversible and that's why an excess of that isotopic water was used, to help push this reaction forward. Something productive, from our perspective, will happen if one of the regular oxygens gets protonated, cause that oxygen can then leave as water.

Normally at this point, you would expect [the reaction[to continue to making a carbonyl – one of the two oxygens would fall into the positive charge there, making a carbonyl, and then you'd have a subsequent deprotonation. That thing that we formed, if it continues to react, it's just going to get protonated and have its carbonyl open again – in other words, why can't I just attack this right here at this point? Do I really need to show the formation of a carbonyl? No, because making it's just going to be reversible, so you don't have to show it. Another molecule of isotopic water could attack at this point. it could come right back off again; this is all reversible. Once it does come on, we need to deprotonate, and now, to end up with what we really care about, the last regular oxygen gets protonated. Yes, one of the other oxygens could get protonated instead; that's the point of this all being reversible. But, if the regular oxygen gets protonated, we move forward; that protonated oxygen leaves as water; one or the other of the remaining oxygens falls into the positive charge; we form a carbonyl that will get deprotonated; and we end up with our isotopically-replaced acid. If there's enough excess [isotopically-labeled water], you push it to completion; but if you didn't have that, then yes, you could end up with a mixture of products. This is a Le Châtelier's principle-driven reaction.

[carboxylic acids only get alkylated once in Grignard reactions]

Acid hydrolysis of an amide

Here's an amide. We're doing acid hydrolysis, which means the first step's going to be protonation of the carbonyl, followed by opening of that carbonyl. At that point, since it's hydrolysis, it'll be water that attacks; then, of course, it deprotonates. At this point, we're at the equivalent stage as we would be with a carbinolamine – a functional group that doesn't normally want to be isolated, so we go through another round of protonate-open-attack-deprotonate. Same issue of multiple side-products, multiple reversible reactions being possible, in that if either one of the –OH groups gets protonated at this point, we're going back to the beginning. But, the nitrogen is actually more basic than the oxygen is [is it? what about resonance???] so at this point it's more likely that the nitrogen gets protonated. If it does, that makes an ammonium ion, which can leave. Once it leaves, we're in the same situation that we were in the reaction above – we have two –OH groups and a positive charge, so one or the other donates a lone pair in to make a carbonyl, which then deprotonates to become neutral.

In the base hydrolysis, part of that reaction's not favorable, because you use hydroxide to kick off a stronger base; that's part of the reason in real life we have to use harsh reaction conditions to saponify an amide – even more harsh conditions than you would for an ester. That matches the trend that amides are less reactive than esters. Same type of thing here: because the nitrogen lone pair is so heavily involved in delocalization with the carbonyl, the carbonyl doesn't want as much to be protonated; it is more stabilized. The nitrogen here: nitrogen is usually basic, at least a weak base, but it's almost not at all basic here, again because of that same delocalization. In other words, you need strong conditions here as well in order to get hydrolysis to work. Nitriles are less reactive than amides, so the same conditions that we're going to use – hydroxide, heat, and water; or acid, heat, and water – they need to be just as severe if not more severe when we're trying to react a nitrile. Nitriles form amides, [but] if those conditions can get a nitrile to make an amide, the same conditions are going to cause those amides that form to immediately react again. Nitriles go directly to carboxylic acids.

There are two ways that we'e learned to make nitriles. One is sneaky: it's an Sn2 reaction involving sodium cyanide. When it does Sn2, we do end up with a nitrile functional group. Another way we learned to do it was to use hydrogen cyanide on a ketone, which is going to make a functional group called a cyanohydrin [which appears in carbohydrates]. Let me quickly show you reduction. If we write it synthetically, it is a 1/2 reaction: reduction followed by acid work-up.

Mechanism-wise, because we don't have the complexation of the intermediates with aluminum like we do in the reactions [with amides and carboxylic acids, or the complexation has no bearing on the reaction], I'm not going to write the aluminum hydride out; I'll base lazy and space-conservant and just show H- attacking. If you're using lithium aluminum hydride, you're not going to have a protic solvent, so there's not really nothing to grab a proton from at this point. It turns out that lithium aluminum hydride is reactive enough [maybe because of complexation] it'll just react again. We make a dianion which, as soon as we introduce acid, we get a double protonation, so the product of the reduction of a nitrile is an amine.

Let's see the acid and base hydrolysis. Let's start with the base one first. Base hydrolysis starts out with hydroxide attacking the nitrile. We make a negatively-charged nitrogen, which is really basic, and since we have hydroxide and since we're doing hydrolysis, we can assume we have some water around, which can provide the hydrogen for that negatively-charged nitrogen to get reprotonated. There's going to be a big difference of pKas, so that much of it is pretty much irreversible. Notice that we've just made the nitrogenous equivalent of an enol, so the next part of the mechanism is tautomerization. To write the mechanism in a slightly more condensed way, I'll show this being deprotonated, but remember that delocalization doesn't count as a reaction step, so I'm going to do some resonance at the same time, showing the bond that just got released collapsing back towards the carbon, kicking open the carbon-nitrogen double bond. When that happens, that means we now have a carbonyl. We again have a negatively-charged nitrogen, so again we can show water neutralizing that, which will get us an amide. Nitriles are less reactive than amides, so if we were successful in making a nitrile into an amide, those same reaction conditions would cause the amide to continue to react and make, in this case, a carboxylic salt. As a separate step, with acid work-up, we could get to the carboxylic acid.

This is base hydrolysis; this is saponification. Now let's see the acid hydrolysis. In acid hydrolysis, everything happens backwards from the base. The base version, the bond got attacked and then protonation occurred. Here, protonation occurs, then the bond gets attacked. Protonation; since this is cationic, technically each step is reversible. After protonating the nitrile, the nitrile gets attacked by water, pushing open that carbon-nitrogen triple bond. Gives us a carbon-nitrogen double bond, which means we have an imine, but we also have the alcohol; makes it unstable, makes it like an enol. Technically, it would be called an iminol. Since we're in acid conditions, we'll do acid tautomerization. The nitrogen gets protonated; separately, I'll show the delocalization, which gives us a carbonyl again; of course, it's a protonated carbonyl, so we lose a hydrogen and we end up with an amide. Since [amides] are more reactive than nitriles, they'll continue to react under the same conditions to make a carboxylic acid.

[Fill-in-the-blank problems]

What if we have a carboxylic acid that react with something to make an ester. If you look carefully at the wording of this style of problem, when there's a blank where the reagents would go, there's no presumption about whether it's 1, or 1/2, or a mix of reagents. Of course, if in your solution you think you need to put 1/2/3/4/5/6/7/8, then maybe you're going the wrong track for your solution. There is more than one answer here. [One is] H+ and ethanol; that would be Fischer esterification. But, it would also work to first use thionyl chloride and then use an alcohol. Because the blank does not presume a certain number of reagents, this would be an acceptable answer; if you had eight steps, it would be a wrong answer, but two – that's reasonable.

Let's say that we have something that reacted first with a Grignard reagent – two equivalents – and then work-up with acid to make an alcohol. What does the two equivalent part mean? That you used – they weren't just there – two equivalents of the Grignard reagent. What functional groups have we learned that use two of them to make an alcohol? Esters or acyl halides. For both of them, after the addition of the first Grignard reagent, you make a ketone, which then reacts with another reagent to make an alcohol. It would not work with a carboxylic acid, because the first equivalent will pull a hydrogen off; the second equivalent would attack, but then you'd end up with a double alkoxide, which can't react any further, so a carboxylic acid would be a wrong answer here.

Let's do one with the product blank.

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– Cationic vs anion mechanisms –> reversibility
Why are cationic mechanism normally fully reversible? – (example: esterification) Often the products & reactants are very 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 the reverse rxn.
Nitriles

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Structures – Identical to those from lecture 5A (04/20/12)