Lecture 2B • 04/13/12

If you have a carboxylic acid that has an oxygen that's part of the carbonyl and an oxygen that's not part of the carbonyl, why is it that it's the carbonyl oxygen that does get protonated, and not the single-bonded oxygen? If you recall, when we protonate the carbonyl, that carbonyl can open; that's a form of delocalization. You could even then have this single-bond[ed] oxygen stabilize that carbocation. But, if we had this single-bond[ed] oxygen protonate in the first place, then you make an ion out of it, but there's we could do to stabilize it. Even if we allowed resonance to happen, that would put a second positive charge on the oxygen; it'd be horribly unfavorable, so there's no stabilization of this [cation], so it's even less likely to form than protonation of the carbonyl.

We saw Fischer esterification, which is a reversible, cationic, acid-catalyzed mechanism. We're going to see the reverse which, by the principle of microscopic reversibility, is going to be step-by-step identical to esterification, just everything backwards.

A brief note about nomenclature. I'll start with carboxylic acids first. We, of course, know this as acetic acid, but that's its common. The more IUPAC-style name, where we name things by numbers, this would be ethanoic acid. The -oic acid is the standard ending for carboxylic acids. Because many, many carboxylic acids have a biological source, many carboxylic acids have common names. You look at the back of your shampoo bottles, if you see anything with laurate, palmitate, myristate, all these are long-chain carboxylic acids that have been derivatized. The one-carbon carboxylic acid [is] formic acid, also called its propername, methanoic acid.

Now about esters. We name an ester by addressing the two main parts of an ester's structure: what kind of alkyl group is attached to the oxygen, and then how many carbons are in the carboxylate portion. Think of this: when we had nitric and sulfuric and all these other acid names that you learned in Chem 1, when you made the counterion, when nitric acid deprotonates, then you make nitrate; if you have phosphoric, you have phosphate; if you have acetic, then it turns into acetate. Same way, we have a carboxylic acid from which we get the term carboxylic, meaning the negatively-charged portion of it. We're going to name this as the alkyl group, followed by the carboxylate. This particular compound would be called propyl – because of its alkyl group – then either acetate, or it could be called propyl ethanoate.

Let's look at that reverse esterification. As with many of the carboxylic acid examples I give, in terms of mechanism, I'm often going to use ethyl acetate as my sample compound, just because it's a relatively small compound to have to write over and over and over and over again if you're doing a mechanism. Similar reasoning as we saw at the opening of class as to why is it that one versus the other of these positions is going to get protonated, if the carbonyl gets protonate, there is favorable delocalization possible, so our first step is to protonate [the carbonyl]. Notice the revers[ible] reaction arrow – you must use reverse arrows for this reaction. You protonate. To retain that acronym, I show an open step, although it is possible to combine the first two steps together – you'd have an arrow coming from the double bond to H+. Remember that delocalization, that's just resonance, it's not really a reaction step, so if you ever combine resonance with something else, that's actually acceptable; it's a shortcut mechanism, it just doesn't fit this acronym any more, that's why I normally don't do it. We have protonate, we have open. If we're trying to go from an ester back to a carboxylic acid, we would make sure to flood the reaction – as much as we could and still make everything soluble – with water, so water would be what would come in an attack at this point. And then we'd have a deprotonate step.

The intermediate I just wrote is much like a hemiacetal or hemiketal – [functional group name?] Part of the reason I'm making a big deal of this intermediate is that, like the hemiacetials and ketals, this is normally not isolatable. We have three different oxygens that could potentially react right now. A reasonable question is: which one? The answer is: all of them. There's not that much reactivity difference between any of the three oxygens, not much. But if either of the hydroxides, OH groups, were the ones that would react at the this point, that would drive us back to the ester again. This reaction could go back and forth and back and forth, until eventually it's the ether portion (or what looks like an ether) that ends up getting protonated. How do we know the reaction's going to forward then? Because we can change the reaction conditions to favor either going forward as [it's being] presented here, going back to the carboxylic acid, or the way I'm going to express it is, how to make the esterification happen. We have one more round here of protonate, open, then we show resonance as a form of attack, and that's followed by one last deprotonate step. Just to be clear: I stopped showing it up above, but one of the end byproducts is that extra alcohol that used to be part of the ester. I point that out just anticipating that, sometime soon, we're going to start seeing more synthesis questions. If I gave you this ester as a starting material, realize that I'm giving you four carbons – not just the carboxylic acid – for you to do some synthesis with.

Let's talk about favoring the products, because if we now switch back to talking about esterification, not deesterification, esters and carboxylic acids, they're very close to each other in reactivity. [which one is truly more reactive or stable] They are so close to each other in terms of thermodynamic stability that, in an equilibrium situation like this, if you just had equal amounts of the two materials, you might not push the reaction much one way or the other. But, esterification, you might recall, has water as one of it's products. Let me write out the set of conditions that are often used in real life to do a large-scale Fischer esterification. We could have some form of carboxylic acid. Let's say I want to make the ethyl ester, so I'll used ethanol.

You need an acid catalyst. [Grad school story of waking up to remember catalyst] If you don't put the acid catalyst in, the reaction [has a high activation barrier] and it's not that favorable. One other thing that's often included is toluene. The products are going to be an ethyl ester, but you also produce water.

What are the definitions of equilibrium? Same rate of the forward and reverse process[es], can't see any change in the concentration of reactants and products, and delta G = 0, no observable change in energy because you're already at the lowest-energy point of the system. If you were to remove water, the forward rate of reaction is still going to be what it was, because water's a product, but that means the reverse rate of reaction's going to drop, because you removed a product, which means more product's going to be formed, because the forward reaction keeps on going, and so you make more product. Energetically we could analyze it and say that by removing product, you effectively make the reactants a higher energy, which means it reacts forward to lower the energy and makes more products. In other words, whatever way we stress an equilibrium, the reaction's going to respond to undo that stress. We remove a product, more product forms. If we keep removing the product continuously, then the reaction never settles, the reaction continuously moves forward, and that's how for these two things, the ester and the acid, if they were at the same energy, we could still make the reaction go forward, if we keep removing water as it happens.

[A Dean-Stark trap is often used to facilitate the removal of water in this kind of reaction] You might have a set-up somewhat like this: you have your reaction flask on the bottom, the Dean-Stark trap in between the reflux condenser and that reaction flask. What happens is you heat this whole mixture up to the boiling point, which, given that you have ethanol, the ethanol's probably going to be thing that boils at the lowest boiling point. Carboxylic acids tend to form dimers are pure compounds; the -OH group from one interacts with the carbonyl of the other and vice versa, so they tend to have much higher boiling points that just plain alcohols. This most likely will boil significantly below the boiling point of water. As it boils, what reflux means is it heats up and then condenses on the side of that side arm, falls back down, heats, falls down, heats, falls down ... but some of it, as it's falling down, is going to get trapped in that side-arm, just because it's physically falling down that piece of glassware. In the side-arm, if we blow up what it looks like, you'll have an accumulation of water an organic; the blue I'm using to represent water, and the organic in red. I put the organic on top because generally, in esterifications, the two compounds you use and the product are all less dense than water. What happens is: over time, the solution bubbles up, refluxes, recondenses, collects in the tube, water and organic separated. The water's more dense, and so it collects at the bottom of that side trap. As the reaction keeps on going, both of the levels build, both of the water and the organic. At some point, the organic will end up spilling back into the reaction flask, which is great, cause in case the reaction wasn't done, then that reaction has a chance to keep on going. But since water never makes it back over, water is removed as a product, which is what's draggin the reaction to the right, which is what causes the product to form.

The role of toluene is that it forms an azeotrope. An azeotrope is a vapor mixture which is made of two components that, if they were liquid, would be immiscible with each other – in other words, water and toluene won't dissolve in each other, but, for whatever bizarre reason, they do end up making some kind of solution with each other in the vapor phase. As this reflux is going on, the toluene helps effectively remove water from solution. Once it recondenses again, water and toluene separate, and again you get that separation of layers. That side arm, generally, on the nicer traps has a valve on it so you can drain the water out to help further ensure it won't build up enough to splash back, or, the nice onces generally have calibration marks to let you know the volume of water that's been collected, so you have a chance of calculating how far in the reaction that you are. That's the Deak-Stark trap.

Water and toluene form an azeotrope, which is a vapor mixture of two or more compounds that, in the liquid phase, are immiscible. Toluene is often added to refluxes such as this to help assist the removal of water.

[problems]

Imagine that you have a carboxylic acid that you react it with an acid source, heat, and water, but not just any old water: isotopically labelled water. 18O is just an isotope meaning it has a different number of neutrons than the 'standard' oxygen. It's pricey stuff, but it's used in what are called labeling experiments, because you can, with the right methods, track and trace regular oxygen versus 18-oxygen. What would happen if you were to extensively hydrate a carboxylic acid with an excess of 18-oxygen water? A related questions is if we take an ester and we react it with an alcohol that was not used to make the ester. Alcohol, acid catalyst, heat, and time: what would we get?

Let's switch to anionic reactions

I want to now get into saponification. Some of you might recognize a word that's related to it: soap [sabon, savon]. It's related to the old school way of making soap where you take lye – this stuff that's really caustic, really basic – mix it up with animal fat, it would decompose the animal fat and make carboxylic acid salts, or what are called carboxylate salts. Why is it that these carboxylates have any relationship to soap? Let's look at an example molecule of something that could be used as soap. [laurate 12; myristate 14; palmitate 16; stearate 18] If you look at the back of shampoo bottles, you might see some of these names. Why is it that it's these long carboxylic acids that are often used as soaps?

There's two portions of it that have contrasting solubilities. We have what is often called the head group, which is ionic. Because it's ionic, that means it's hydrophilic – compatible with water – but that also means that it is lipophobic – meaning fat-fearing, meaning it doesn't like organic layers. You also then have this long, very non-polar tail; because it's organic, that means it's hydrophobic, but therefore lipophilic. When you take a compound like this and add it to water, once you reach a certain concentration called the CMC – the critical micelle concentration – it makes a micelle, which is a structure composed of several molecules – in this case, of the soap – where the polar headgroups all migrate to the exterior of the structure while the lipophilic tails, the organic portions all end up in the interior of it. If you have some aqueous solution that's got a bunch of grease in it, when you drop the soap in, the grease will be compatible with the tails, will end up on the interior of these micelles, but the outside surface of this whole structure is polar, and therefore water-compatible. Even though the interior's grease, the whole thing's able to float through water – that's how you clean grease out using soap. That's why saponification historically was important because it produced the compounds that could act in this way. [Similar compounds] with this split behavior, they're called surfactants – surface active agents – because they operate at the interface between the organic and aqueous phases.

It's called self-assembly – the attractions between molecules that make these different shapes. If you change the amount of organic and water, you can actually change the micelles into lamellar sheets, meaning flat layers; you can also turn them into inverse micelles, where the water forms the interior and the organic forms the exterior. That's all based on polarity; it's not a chemical reaction, it's just the way that things congregate in water.

Let's see the reaction mechanism itself. There's two key portions of this particular mechanism, because part of the saponification reaction is technically reversible, and part of it is absolutely not reversible, and you need to know when and why it's not reversible. Saponification is where we use sodium hydroxide, a strong base; Grignard reaction is a stronger base; otherwise, the reactions have a lot of similarity. How does the mechanism start? Hydroxide is the main reagent in saponification. There's only one thing useful that can happen between hydroxide and some kind of carbonyl compound, which is: to attack the carbonyl itself. Hydroxide is going to displace something, but I'm going to show this as opening up the carbonyl first [tetrahedral intermediate]. The big deal here is that I am using a reversible arrow. We could compare some pKa values. [The pKa of water is 15.7]; as a side note, that is the pKw of water – which is 14 – multiplied by the [base 10] log of 55, which is the molarity of water. A primary alcohol in solution [has a pKa of roughly 16]. In solution, less substituted alcohols tend to be less acidic than more-substituted alcohols – something like ethanol has a pKa of 16, where something like t-butanol is more like a pKa of 18. Hydroxide and this alkoxide that we just made are not that different from each other in terms of how basic they are [or are they? look up pKa value], because their parent acids are not that different from each other either. If they're not that different than each other, then why does it want to be one of these versus the other? Couldn't this negative charge just kick the hydroxide back out? In theory, yes; that's why this step of the reaction is reversible.

What would happen if this carbonyl tried to reform and, instead of hydroxide, it kicked the ethoxide out? Ethoxide is slightly more basic than hydroxide because hydroxide's parent is more acidic than ethanol is. But, if it does get kicked off, now something else happens: we have a reaction that's no longer directly because of the carbonyl; it is indirectly, though, because we just made an acid, but we also simultaneously made a base, so before anything else is really possible, an instant acid-base neutralization is going to occur. Let me put two stars on here to show the two places in the mechanism that we need to pay particular attention to: the first is where the reaction is reversible. The first portion of this mechanism is reversible since the base used and the intermediate formed are similar enough to each other in terms of basicity. I will say practically the same statement again [for] the Grignard reaction, only there the difference beween bases is going to be dramatic, so then the reaction will be irreversible. We do have irreversibility that turns up in this case, and that's at the end of this process, because at the end of the mechanism, both an acid and a base are formed, which instantly react with each other and prevent the reaction from being reversible.

[summary]

We talked about the two ways in which the [carboxylic acid derivatives] differ in reactivity: induction or resonance, and leaving group ability. Because they're carbonyl compounds, these carboxylic acid derivatives tend to have two flavors of reaction: cationic and anionic – cationic are generally stepwise and acid-catalyzed, ionic [are] generally concerted and base-promoted. Esterification/de-esterification [is an] example of a reversible cationic reaction; saponification [is an] example of an anionic reaction. We've seen how to go back and forth between carboxylic acids and esters, and we've seen how in certain cases there can be both a cationic and an anionic version of a reaction: to go from an ester to an acid, we saw we could water and acid, or we could use sodium hydroxide. But, we've also seen that carboxylic acids themselves can break these patterns of reactivity because the carboxylic acid itself is acidic. For example, even though we could successfully use a cationic mechanism to produce an ester – if we took a carboxylic acids, and alcohol, and an acid catalyst, we've seen how that kind of reaction occurs. But if we tried to take the basic version of that reagent, using an alkoxide instead, the only thing that will happen is neutralization. Esterification's not possible due to the fact that neutralization will happen first. Acid-base reactions are generally some of the fastest reactions that can occur. Throw this set of reagents together before the alkoxide has a chance to attack the carbonyl, it just rips the hydrogen off, reaction's over with.

[There is one exception to this.] It is an anionic method for making esters. It's using a very special reagent known as diazomethane. Diazomethane is so useful because it can produce a methyl ester, specifically, with practically quantitative yield – quantitative yield means 100% yield, it means every mole that reacts is successful. That's as long as you can keep the whole thing from blowing up, because diazomethane is a very, very, very reactive compound. Why? Look at the structure of it: it is nitrogen gas trapped on the carbon, effectively. This rapidly can decompose to form a very reactive intermediate called a carbene [is it, cause it's charged?] You make that and nitrogen gas if this falls apart. You can avoid it blowing up by using specially-coated glassware, pastic or teflon-coated. Why? Because the little cracks that are in any kind of glass are the right environment for this to start to decompose and initiate that explosion. If it doesn't explode, it undergoes this reaction mechanism. Having a carbanion in it, it's very basic; exposed to a carboxylic acid, you get exactly that kind of neutralization reaction [you would] expect. But, you now have a methyl group, which is normally an excellent substrate for Sn2, and you have nitrogen gas, which is an excellent leaving group. Even though a carboxylic is not that basic, you'll get Sn2 occurring, which means you make the methyl ester and nitrogen gas that bubbles off as a byproduct.

————

ic –> ate; carboxylic –> carboxylate

Esterification – Dean-Stark Trap

Water & toluene form an azeotrope, which is a vapor mixture of two or more compounds that in the liquid phase are immiscible. Toluene is often added to refluxes such as this to help the removal of water.

Saponification –> Formation of carboxylate salts
CMC – critical micelle concentration

* The initial portion of this saponification is technically reversible since the base used and the intermediate formed are similar enough to each other in terms of basicity.
* At the end of the mechanism, both an acid and base are produced, which instantly react with each other & prevent the rxn from being reversible.

————

Structures – Identical to those from lecture 2A (04/13/12)