

Lecture 1B • 04/10/12

Carboxylic acids and their derivatives

[presentation of aldehydes, ketones, carboxylic acids, and carboxylic acid derivatives together in text]

First, an overview of the different types of carboxylic acid derivatives. First, let's put up the structure of a plain carboxylic acid. To keep it simple, I'll say R = alkyl, although technically the simplest carboxylic acid is one where you just have a hydrogen in the place of the R group; that would be formic acid. If we take the hydrogen of a carboxylic acid and replace it with some other R group, maybe the same as the first R, maybe not – to highlight that it's independent, that's why I'm going to call it R', it's an ester. The nitrogen equivalent of that is an amide. [Previously, we had] amine, imine, and enamine; this quarter we'll have amide and its close relative that has two carbonyls, the imide. There are two other derivatives that have this common motif of having a carbonyl in them. One of them [we saw when we] did Friedel-Crafts reactions: an acyl halide. Remember that the term acyl refers to some kind of R group attached to the carbonyl, but not what's attached to the other side of the carbonyl. For acylation, it meant to put a carbonyl with an R group on to the molecule. One last derivative of this type is somewhat the oxygen equivalent of an imide, but they have very, very different reactivity: anhydride, which literally means without water. If you take two different carboxylic acids, you take an -OH group off of one, a hydrogen off the other, then put the remaining pieces together, that's what an anhydride looks like. Since water was removed, that's why it's called an anhydride. It might make sense that this compound very much reacts with water. There's one last derivative: nitrile. You might think: that's kinda odd to throw in with all the rest of these, cause all the rest of these compounds do have a carbonyl. The thing is, under the right conditions, nitriles can react to form amides, [and] you can take amides and backtrack to carboxylic acids. Nitriles, indirectly, are part of the carboxylic acid family.

Before we discuss reactions of these compounds, [let's discuss the] order of reactivity. Ignore nitriles; since nitriles react to make amides, they're less reactive than amides. Let's ignore imide[s], since [they're] just a special case of an amide. We have five other groups we're looking at: carboxylic acid, ester, amide, acyl halide, and anhydride. Which of these, do you think, is the most or the least reactive? I'll let you answer either way. Take a look at those compounds and see if you can guess which one's the most reactive or which one's the least reactive. The acyl halide is the most reactive; the amide is the least reactive. Why [is] the acyl halide the most reactive? Halogen[s are] leaving group[s]. This is the one place where carboxylic acids really differ from aldehydes or ketones, all you had on the carbonyl was an R group or a hydrogen, neither of which normally functions as a leaving group. But, there's also the carbonyl itself: what is the charge distribution on that carbonyl? Chlorine does donate by resonance, but it's electronegative, so overall it pull electrons away; that would make the delta positive on that carbonyl carbon even stronger, which would make that more want to be attacked by a base, or it might mean that the oxygen, in response, is more easily protonated – either way, it means the carbonyl's more reactive? Why might the amide be the least reactive then? There's a lot of conjugation that can occur with the lone pair on nitrogen, because a positive charge on nitrogen is not nearly as bad as a positive charge on oxygen. Nitrogen easily delocalizes that lone pair; that lone pair, in fact, is so tied up in that carbonyl bond it makes the carbonyl bond very unreactive – which we would hope that would be true since all of our proteins are made up of amide linkages, that's what a protein is, an amide bond followed by another amide followed by another amide in a chain.

In terms of order of reactivity, there's two ways to think about it: whether there's charge stabilization or destabilization on the carbonyl carbon. Think of it this way: if you had something like an ester, why is an ester something that's less reactive? Even before it reacts, you do have a lone pair on that singly-bound oxygen which, although it's not favorable because we're separating charge, it's able to delocalize. Effectively what's happening is you're partially stabilizing the carbonyl by delocalization. The more that the carbonyl is stabilized, the less reactive it is. Halogens are deactivators, even though they're ortho-para directors. That's because, for one reason or another, even though halogens undergo resonance, they take more electron density than they give. Remember there are two cases of that involved. First, the general statement that halogens can undergo resonance or delocalization; they can do that because they have available lone pairs. Overall, however, more electron density is withdrawn than donated. The two subcases were: for fluorine, that has the same size, roughly, as carbon and therefore has good orbital overlap, so it does provide by resonance, but it's the most electronegative element on the periodic table, so it steals that electron density right back again. The situation's slightly different for the other halogens. They have the ability to delocalize, but they're larger than carbon, so they don't have the same orbital overlap, so that stabilization by resonance is not as significant. Even though they're less electronegative than fluorine, they still end up having more inductive effect than they do by the provision of resonance.

This is just one way, though, to explain the difference in reactivity of the derivatives. To get at the other explanation, I want to show you just a portion of a mechanism that you might find in a cationic reaction, and one that you might find in an anionic reaction. [related to textbook presentation of carbonyl compounds] First, let's say that we have a generalized carbonyl compound, not even worrying about it's functional group, just the fact that it has a carbonyl. Recall that that carbonyl has a negatively charged or slightly negatively charged end, cause oxygen's more electronegative, and electron density, one way or another, is going to be drawn from the carbon it's attached to, so there's a delta positive there.

So, there's a dichotomy, a set of opposite reaction mechanisms that are created due to this separation of charge. One way to get it to react is to focus on the oxygen, to use an electrophile; something that wants electrons would therefore want one of the lone pairs from oxygen [and] would then cause the carbonyl bond to break and something to attack the carbon. We saw that when making hydrates or ketals or acetals, that protonate-open-attack-deprotonate cycle. The other possibility, though, is that we have something like a Grignard reagent that comes in and it attacks the carbon directly because it's delta positive.

A portion of a cationic mechanism that will look familiar is for the oxygen to become protonated, technically reversibly. The carbonyl can be shown to open up, which is really just delocalization, although we normally call it resonance. Some kind of nucleophile – water, an alcohol, something not a very strong nucleophile, but still nucleophilic – could come in at this point and, in many cationic reactions, the process would stop here. For example, when we make ketals and acetals, it was two rounds of this kind of mechanism. Oxygen gets reacted upon to tease the carbonyl into reacting.

How about a refresher of a general anionic reaction: think Grignard reaction. In this case, we'll have some sort of base. I'll make it negatively charged to make clear it's a much stronger reagent. We could still call it a nucleophile, but it's actually more important in this case that it's something really basic, something that will cause an anionic reaction. In the case of a Grignard or a reduction reaction, something attacks the carbonyl, pushes that carbonyl open. Last quarter, that was the end of the story – you would make an alkoxide; if it was a Grignard reaction, you would then neutralize it, reprotonate that oxygen to isolate your alcohol. But here's the main point of showing you these mechanisms, the one thing that's really different this quarter – once we see a more complete cationic mechanism, we'll see it there as well: what if Y, this arbitrary group on here, is a chloride? What if this was an acyl halide? Then we have a leaving group. We also have a negatively-charged oxygen right next door. Don't you think it might be possible, then, that the negative charge could collapse to try to create a carbonyl, at the same time kicking off this group Y? The answer is: yes, it certainly can happen.

Now that I've given you the general mechanism for an anionic reaction, let me show you a more specific example. Since I just named acyl halides, let's say that I had acetyl chloride. Acetyl chloride, if you were to throw hydroxide at it, will undergo this process of first pushing the carbonyl open, and then once that carbonyl's opened to form the alkoxide, it recollapses to kick chloride out as a leaving group, making a carboxylic acid. I want to point out something about this intermediate, which is referred to as a tetrahedral intermediate, which means what it sounds like: four things connected to a carbon, ignoring the differences between the groups, that would have a tetrahedral shape. What's so important about this that we bothered referring to it as the tetrahedral intermediate? Cause there's some discussion as to whether or not the reaction happens the way I did show you, where first the carbonyl gets pushed open and then it reforms, or whether all of this happens in just one step. Think of tosyl chloride or thionyl chloride: exactly the same situation, where in both of those cases, we could show a sulfur-oxygen double bond being opened and then closing to reform, or we could show all that at once. Whether we do show it as two separate steps or whether we show it as one, there might not be a right answer; the answer could very well be that both happen. Now that I've thrown that out there, we'll temporarily ignore it cause I want to come back first to reactivity.

Back to the reactivity point. Let me just throw up what the real order of reactivity is, and let's see if we can identify what would be a leaving group in each one of those functional groups if it was to do this type of anionic reaction. Here they are: acyl halide more reactive than anhydride, more reactive than a carboxylic acid, which similar in reactivity to an ester, and they're both more reactive than an amide. Let's think about that charge stabilization argument. Earlier, we were talking about how chlorine, even though it has resonance, overall it withdraws electron density, so it makes a bigger delta positive, which helps explain why this compound is the most reactive of these. Look at the next compound over, the anhydride: there's an oxygen there, but the oxygen's attached to a carbonyl. Maybe it won't electron density overall, but because the oxygen's tied up with two carbonyls, it's not possible to donate as much either, so it's still reactive. Carboxylic acid: there we have an oxygen that is more able to provide electron density; remember that oxygen groups are activators, if we're talking about electrophilic reactions with benzene. An -OR group, having that alkyl group there, does do a lot to the oxygen; that's partly why these have similar reactivity. But then move to nitrogen, which is less electronegative than oxygen and able to easily delocalize, that's why it's the least reactive.

But now imagine that we're doing one of these anionic reactions. What would be the effective leaving groups? A chloride, versus a carboxylate (like acetate), versus hydroxide, versus ethoxide or an alkoxide, versus a negatively charged nitrogen, which is really, really basic. Which of these is the best leaving group? Chloride. Which is the worst, the nitrogen. Follows exactly this pattern of reactivity, in the sense that those functional groups that the least basic are associated with the most reactive functional groups. Remember that we talked about leaving group ability in general as being where the leaving group is the conjugate base of a strong acid. We could put a few more trends here. The increase in reactivity is coupled with an increase in leaving group ability, which is opposite of leaving group basicity. So there's our second way to explain it.

Before I move on to specific reactions, let me return to this anionic versus cationic split that I was talking about a moment ago. Carboxylic acid derivatives, other than nitriles, are carbonyl-containing derivatives, which means they have the potential to undergo both cationic and anionic reactions [nitriles can too but don't have carbonyls].

Carboxylic acids and derivatives are carbonyl-containing compounds, which means they normally react due to the delta positive on the carbonyl carbon – that's the point where we were talking about stability a moment ago, those would be anionic reactions, since that carbonyl carbon is partially positively charged – or the reactions due to the delta negative on the oxygen of the carbonyl, which means you'd have a cationic reaction. In fact, there's general tendencies for both of these classes of reactions: aside from it being anionic or cationic, generally if you have a cationic reaction, it's often something that's acid-catalyzed. Think of the POAD mechanism that we had for ketones and aldehydes. We're going to see the same type of thing happens with carboxylic acids. For the anionic reactions, think of things like Grignard reagents. They're normally concerted reactions, and the base in these reactions is normally not a catalyst. The reason we call it an acid catalyst for these cationic reactions is, like in the POAD mechanism, you start with protonation, but at some point deprotonation occurs, so the hydrogen you throw in at the beginning, you get back at some point. For something like a Grignard reaction, that Grignard reagent gets used up, but it is the thing that forces the reaction to happen. So, instead of saying base-catalyzed, there's often the phrase base-promoted – not as in going up in the world, not a new job, but as in causing it to happen.

Example reactions

The first one's going to be Fischer esterification and de-esterification. This is Fischer with a 'c', Emil Fischer, the person for whom Fischer projections are named. [warning for upcoming material] Fischer esterification is a cationic mechanism. [flashcards] Excluding imides, you have six different carboxylic acid functional groups: carboxylic acids themselves, esters, amides, acyl halide, anhydrides, and nitriles. All of them can undergo alkylation, in theory; all of them can undergo reduction. You can throw water at all of them; maybe not necessarily something useful happens, but you could try to hydrate all of them. You could try to do solvation, which means to throw a solvent – specifically an alcohol – at it. If we just studied those four reactions right there, with those six different functional groups, that's 24 different reactions. Of course, there is this cationic versus anionic difference. What if every one of those reactions that I named had both a cationic and an anionic equivalent; they don't, but if they did, that'd be 48 reactions. [flashcards]

[six aspects of a reactions re-explained][reactions to be responsible for]

The overall process is to take a carboxylic acid, react it with an alcohol, usually in large excess, along with an acid source and heat. I've chosen ethanol only because it's a very popular alcohol, but in principle, any alcohol could be used here. What's my favorite acid catalyst? Tosic acid, p-toluenesulfonic acid. [birthday cake] Why? It's organic-soluble. The conjugate base is weak and non-reactive; that's one of the most important things. It's a strong acid, and it's cheap; there's nothing wrong with that if it works. What's the mechanism? If all you have is a carbonyl and H+, what's going to happen? The carbonyl's going to get protonated. I have these two oxygens. Why is it that it's the carbonyl that preferentially gets protonated and not the -OH group? Protonate. If this is like what we did with ketones and aldehydes, after protonate, what comes next? Open; followed by attack, which in this case would be the alcohol. We use a whole bunch of that alcohol to help influence the reaction to move this way. After attack of a neutral oxygen-containing compound, we're automatically going to have a deprotonate step. At this point, which is kinda like the equivalent of a hemiacetal, this thing we can't isolate, so there's going to be another protonation event that occurs. Which oxygen's going to get protonated? The answer is yes. All three of them are going to get protonated, but one of them would turn us back to the starting material; this is a reversible reaction. Eventually, one of the -OH groups gets protonated, and if it does, then we'll have another cycle of protonate; we made water, so it can be a leaving group, so that bond opens; what's different about this than an aldehyde or a ketone is we still have an -OH group left, so the attack is intramolecular. We reform the carbonyl, which then deprotonates to make the ester.

Carboxylic Acids & Derivatives

Order of reactivity

– Charge stabilization/destabilization on C=O carbon

*The more a C=O is stabilized, the less reactive it is.

Halogens – Can undergo resonances (delocalization) since they have available lone pairs. Overall, however, more e- is withdrawn than donated.

– Fluorine – Although F is similar in size to C and ·· has good orbital overlap, it is the most EN element on the periodic table.

– Chlorine, bromine, iodine – Less EN, but longer than C so they have poorer orbital overlap so they do not contribute as much by resonance.

– Carboxylic acid and derivatives are carbonyl-containing compounds, which means they normally react due to the delta+ on the carbonyl carbon (anionic) or due to the delta- on the carbonyl oxygen (cationic).

– Cationic rxns: normally stepwise, often acid-catalyzed.

– Anionic rxns: normally concerted, base-promoted

Fischer esterification/de-esterification

Flashcards: 1) Synthetic utility; 2) reagents; 3) conditions; 4) mechanism; 5) stereochemistry; 6) regiochemistry

Structures – Identical to those from lecture 1A (04/09/12)