

Lecture 1A • 04/09/12

Welcome to Chem 12C

[goggles, lab book, pre-lab, clothing][waitlist][textbooks]

What is the structure of a carboxylic acid? How would identify something as being a carboxylic acid? COOH. Some kind of R group attached to a carbon that is both a carbonyl and an alcohol, you could say. We have carboxylic acids, but there's a bunch of other compounds that you just change a little structural feature, and so therefore they're very related both in terms of structure but in terms of reactivity as well. [Uniqueness of Bruice textbook due to treating all carbonyl compounds as two classes of the same molecular family] We're going to learn certain types of reactions like reduction or hydration, throwing water at it, and instead of memorizing the same mechanism for each of these different functional groups, I recommend that you try to see the patterns. Let's see how many different functional groups we're going to have to worry about.

Here's a carboxylic acid. What would it be called if I put an alkyl substituent on? An ester. What if, instead of just an alkyl group, I substituted the oxygen with either an alkyl group or a hydrogen, but on a nitrogen, what functional group is that? It's an amide. We've had amine, enamine, imine, and now we're going to have amide and imide. If we replaced the singly-bound oxygen with a halogen, [that's an] acyl halide; acyl refers to the portion including the carbonyl but not what's attached to the carbonyl. [One functional group has] essentially two carboxylic acids that have been joined together through one oxygen. If you wanted to take two different carboxylic acids and join them together like this, what would you have to take out? Water. That's why these are called anhydrides, literally meaning without water. I might as well show you the imide; an imide is kinda like the nitrogen equivalent of an anhydride, but there's a big difference in the reactivity of oxygen versus nitrogen, which is partly why this critter has its own functional group name. Amide is when you put one acyl group on a nitrogen; imide is when you put two. There's one more functional group that actually belongs to this family, but it might be a surprise: a triply-bound carbon-nitrogen [bond] – a nitrile. You might say that there's no carbonyl in there, but what you're going to learn is that, under the right conditions, this could be converted into an amide, which then could be converted back to a carboxylic acid. That's why nitriles are part of the carboxylic acid derivative family.

[You should learn patterns of reactions] instead of memorizing. Here are seven functional groups. Let's say that we wanted to learn about hydration, that's one reaction; there's reduction, there's alkylation, there's solvolysis, which is kinda like hydration except using an alcohol. There's four reactions I've named right there, and seven functional groups. Throw into that whether it occurs under acidic or basic conditions – [although] not all of those reactions can occur under those conditions, but let's just for [argument's] sake say that they could. So, seven functional groups, four reactions, two conditions: $2 \times 4 \times 7 = 56$ mechanisms in one week – one lecture really. If you wanted to treat each functional group differently, fine, but are you going to want to memorize fifty-plus different mechanism? The reality is that you do learn over 20 reactions in these first few lectures, so the first couple of weeks are kinda rough.

Shall we see some of these different reactions, then, cause here are the functional groups; this is where we're going to be living the next few weeks is this group of carbonyl-containing or, in the case of nitrile, triple bond-containing compounds. We should talk about the fact that some of these [functional groups] are more reactive than others; we should talk about the order of reactivity. Let's use some educated guesses. Out of these, which might you guess is the least reactive – leave nitriles out: nitriles, I'll just tell you, [are] less reactive than the rest of these. Out of the remaining carbonyls and therefore related compounds, which one do you think might be the least reactive? Let's talk about the imide. Why would [that be a good guess]? We talked about how aldehydes are more reactive than ketones; we used an argument of hyperconjugation to explain why it was that aldehydes are more reactive, because they lack the stabilization provided by hyperconjugation. One could imagine that there might be something similar going on here. The better question, then, would be: what is the reactive part of that molecule: is it the nitrogen, or is it the carbonyl? It is the carbonyl that's still reactive in all of these cases. Which of these groups can have any stabilization of the carbonyl using what's attached to the carbonyl? In other words, by resonance, which one of these have any stabilization? In other words, what I'm asking is something like this: if I have an ester like this, I could in theory write a resonance structure where I push a single bond lone pair to the carbonyl, forcing the carbonyl open and making something that, admittedly, not stable. If this was a carboxylic acid salt – if we take an acid and neutralize it, you make a carboxylic acid salt or a carboxylate. In those carbonates, there is resonance stabilization that occurs cause there's always a negative charge; here, we end up with something that has both charges. But it still happens. Even though oxygen's electronegative, it provides more electron density through resonance than it draws by it's electronegativity.

What about halogens, though? We have acyl halies here as one of the functional groups. What is the reason a halogen is a deactivator, even though it's an ortho/para director? It withdraws more electrons than it donates: why? There's two different cases: what's fluorine's story? It's the same size, roughly, as carbon, so it has good orbital overlap, but it's so darn electronegative that it's going to pull electron density away. If you had an acyl fluoride, you've got oxygen and fluorine both pulling on the same carbon – that makes that carbon super duper delta positive, which is why acyl halides are the most reactive of these. What about the other halogens? What about a chloride?

Chlorine is less electronegative than bromine is, but why is it still in electrophilic aromatic substitution a deactivator? It's a big atom, so it has poor orbital overlap, so it does do resonance, but not very well, and it's still electronegative, so it pulls more than it supports. Acyl halides are the most reactive of the functional groups.

First, I'm going to talk about how halogens donate by resonance, but as they give, they take away. I'm going to link that to the acyl halide being the most active of those functional groups, and we're going to use similar logic to decide amongst the rest of these which are the less and then less and then less and less reactive, because there's one other way to consider all of these. I want you to think of another way that we can argue whether one of these functional groups is more reactive than the other.

First, about halogens. Halogens can undergo resonance. There is no such thing as resonance. Resonance is the fact that we can't write a structure on paper because our writing system is inadequate. It's the fact that bonds can cover more than just two atoms, but we have no way to write that. So we write these things called resonance structures and then say, it's really in between the two of these things, or three or our five. That means no one structure itself is real. That argument, we don't care much about until the next time we do a SMOG. You can undergo resonance – but the better word is delocalization. Halogens can undergo resonance since halogens have available lone pairs. However, overall, more electron density is withdrawn by halogens than donated. That splits off, then, into two cases: fluorine, it is similar in size to carbon so it has good orbital overlap, but it is the most electronegative element. The buzz word to describe what happens is induction. Because of that electronegativity, it induces charge to move about. In the case of the other halogens [Cl₂, Br₂, I₂], they're less electronegative, but they have poor orbital overlap since they're not the same size of carbon. That means they don't donate as much through resonance.

This is one way explaining that acyl halides are the most reactive carboxylic acid derivative because how is it that carbonyl compounds react? Why is it that carbonyl compounds react? If I come up with some general group Y to stick onto the carbonyl, we could suppose that there are two things that might happen: either that Y is so darn electronegative that it's going to cause the carbonyl to be delta positive. We know that the oxygen's going to be delta negative anyways because oxygen's more electronegative than anything else except fluorine. Just how delta positive the carbonyl is depends on what Y is, what's attached to it. Since you're going to end up with a delta plus on that carbonyl carbon no matter what, that's why there's two ways that a reaction can occur. One way is to be sneaky about it, to throw an acid in that will affect the delta negative portion of the molecule, but which will therefore lead to a proper carbocation. If you had something, some group Y, that donated a lot of electron density at this point, that means it's going to be less reactive. If you're making this a nice, stable carbocation, why would the carbocation want to react? But there's another way that this reaction could begin. You could have some really strong base that comes in to force the carbonyl open. Again, we have the delta positive here that would attack something like a Grignard reagent, for example. I'll keep it more generalized and just say B⁻ for the moment. The other possible mechanism is for something to force that carbonyl open.

What if group Y is a leaving group? We have an alkoxide that maybe could collapse back down and kick Y off. So it's not S_N2; we didn't kick something off at the same time something came and substituted, but there's still substitution occurring. Notice that what I've shown you is a cationic mechanism and an anionic mechanism. These are the starts of all of the mechanisms that we're going to learn; this is the crux of the mechanisms we're going to learn. There's going to be a way of activating the carbonyl by pre-protonating it, so you're kinda teasing the carbonyl into reaction; that's where you're using a weaker base like an alcohol to attack. Think of making a ketal from a ketone – works by exactly that same top mechanism: protonate, carbonyl opens and then at that open point, something attacks. Think of the Grignard reaction and that's like the anionic mechanism here: something comes in and attacks and pushes the carbonyl open, making an alkoxide. [Previously,] we didn't see this next step; that's how carboxylic acid derivatives are different.

Before I show you any more mechanisms, I've shown you enough to now have this discussion: I just made one argument where I said the acyl halide is reactive because there's not much electron density being put into the carbonyl. If there's not a lot of electron density being put into the carbonyl, then this carbocation that would form would be less stable, and it would be a more attractive carbon for something already negatively charged to attack. But isn't chloride a good leaving group, too? I'll show you one anionic mechanism. If I had an acyl halide, whatever that halide might be, and hydroxide, you could show the following two-step reaction: that first, hydroxide attacks, you form this tetrahedral intermediate. That's an important buzzword in this series of reactions. From this tetrahedral intermediate, because a halide's a good leaving group (let's say we're not using fluorine), it can get kicked off. Notice, we then made a carboxylic acid out of an acyl halide, which is why carboxylic acids are less reactive, cause they're the products you get from an acyl halide reactive. That halogen's a leaving group; why don't we look back at the other functional groups and see what's a leaving group. A halogen, that's a leaving group; acyl halides are reactive. An anhydride: the leaving group would need to be a carboxylate; is that a good leaving group or a bad leaving group? It's not great; it's kinda in between. What's the pK_a of acetic acid, roughly? 5. If the pK_a is 5, then what does that mean about the basicity of its conjugate? It's high, but not as high as hydroxide. It's not a great leaving group; it's worse than a halide, but it's better than a hydroxide, which is why anhydrides are more reactive than carboxylic acids but less reactive than acyl halides.

There's two ways to argue this. Let me summarize all of these different thoughts I've thrown at you. I've shown you lots of little bits of things; let me put the package together.

Carboxylic acid derivatives are carbonyl-containing compounds, which means they normally react due to the partial positive charge on the carbonyl carbon, or due to the partial negative charge on the carbonyl oxygen. That gives us our two classes of reactions: cationic reactions, which are normally stepwise. You might recall that there's two flavors of mechanisms: concerted, which means everything happens at once; stepwise, which means one thing happens, and then the next thing happens, and the next thing happens. It's usually stepwise and it's usually acid-catalyzed. Normally, protonation occurs to cause the formation of a carbocation. Then there's anionic, which is normally something like a Grignard reaction: it's concerted, and it's base-promoted. [The] reason acid catalysis is called acid catalysis is you start with an H^+ , and at the end, you lose an H^+ , so H^+ came, H^+ went, no overall difference, that's one of the classic ways of describing what a catalyst is. In the base reaction, the base gets used up one way or the other; that's why it's called base-promoted. Cationic is corresponding to taking advantage of the oxygen, making the oxygen react to get at the carbonyl carbon. Anionic is where you attack the carbonyl carbon directly. But because this has to do with something with the carbonyl, then any factors which stabilize the positive charge on a carbonyl carbon will reduce the reactivity of that carbonyl compound. Any factors that reduce the positive charge on the carbonyl carbon will decrease the reactivity of the carbonyl.

Here is the order: acyl halides, anhydrides, carboxylic acids, esters, and then imides and amides, since they just differ by the number of carbonyls but otherwise are the same type of reactivity, I'm just going to discuss amides. They're the least reactive, which we hope would be true since all of our proteins are made of amide bonds. When they say amide bond, it's not a bond, it's a particular kind of connection, exactly what I've got shown here, a carbonyl connecting to that nitrogen. Why is that so unreactive? What's more electronegative, oxygen or nitrogen? Oxygen's on the left here. Oxygen's more electronegative, pulls more electron density. Nitrogen, less electronegative, less electron density. Also, that lone pair is super-duper delocalizable. Remember pyrrole, how easily nitrogen's lone pair can be pulled into an aromatic system? This isn't aromatic, but it's the same type of thing: nitrogen pairs delocalize easily. If it delocalizes easily, it supports the carbonyl, it reduces the positive charge on the carbonyl, makes it less tasty to a base coming from the outside, less likely to react, versus over here, we talked extensively earlier about how a halogen, even though it is something that can participate in resonance, it withdraws more electron density than it gives. If it withdraws electron density, it makes the delta positive more intense, makes it more reactive; that's way number one of expressing the difference in reactivity of these compounds.

Now there's way number two of demonstrating the reactivity of carbonyl carboxylic acid derivatives is focusing in on this type of substitution, this carbonyl substitution. As a reminder, the overall transformation was a carbonyl compound reacting with a base to displace some sort of leaving group. Listing the carbonyl carboxylic acid derivatives, let's look at what would have to be the leaving group. There's the different functional groups; there's what would be the leaving group. Notice that the basicity of the leaving group increases as we go left to right, which, think of S_N2 reaction: good leaving groups are the conjugate bases of strong acids, so the conjugate acid strength increases as you go to the left. [need to know acid-base chemistry] The leaving group ability, the basicity of it, that's bad for a leaving group, so the reverse of that is the increasing reactivity. So we've got two ways to explain why it is that the carboxylic acid derivatives have the order of reactivity that they do.

Cationic and anionic reaction examples

The first one is Fischer esterification or de-esterification. The overall transformation is the following: a carboxylic acid is flooded with an alcohol; I'm using ethanol just because it's a very popular example, plus some kind of acid source. $TsOH$ stands for tosic acid. Why is tosic acid my favorite choice of an acid catalyst? It's cheap, organic-soluble, it's a solid so it's easily measured out. What are it's most important chemical qualities? Strong acid that the conjugate base is weak and non-reactive. Once it does its acid catalysis, it doesn't do anything else. The result we get from this is an ester. Let me very quickly show you the mechanism. It's going to sound very familiar. If you're putting an acid in acid – notice this, we're trying to protonate an acid. Why is it that it's the carbonyl that gets protonated first and not the $-OH$ group? Notice the reversible arrow; the whole darn reaction's going to end up reversible. After protonation occurs, the carbonyl opens – well, it doesn't, cause there's no such thing as resonance, but on paper we do it. After that point, that means that ethanol can come into attack. What do you think the next step's going to be, if I've had protonate, open, attack? Deprotonate. POAD. Which is exactly the same mechanism we learned to make a hydrate or make a ketal. Notice that if we drop the $-OH$ group, this is exactly the same mechanism as making a ketal. But, this is a carboxylic acid, which is why there's a little twist at the end. If we've got three oxygens here, how do we know which one's going to react next? The answer is yes; all three of those oxygens react. One of them will bring us back to the starting material; the other two will bring us forward. Depending on how we influence the conditions, using Le Châtelier's principle, we could make the product happen. Protonate again, we make water; the bond to water opens; we have, unlike [previously] a second oxygen at this point, so instead of another molecule coming in to attack, the carbonyl reforms. The last thing to occur is for deprotonation.

Carboxylic Acids & Derivates

Order of reactivity

Halogens – Halogens can undergo resonance (delocalization) since halogens have available lone pairs. However, overall, more e- density is withdrawn by a halogen than donated.

– Fluorine – Similar in size to C → good orbital overlap; but, most electronegative element → induction
– Chlorine, bromine, iodine – poor orbital overlap (not same size as carbon) → do not donate as much e- density by resonance, yet still have induction.

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

– Cationic: normally stepwise, acid-catalyzed – protonation occurs to cause the formation of a carbocation

– Anionic: normally concerted, base-promoted

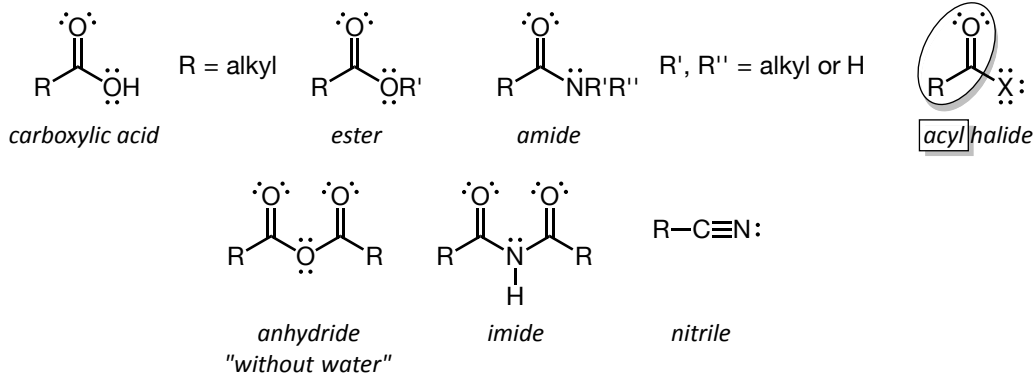
– Any factors that reduce the delta+ on the carbonyl will decrease the reactivity of the carbonyl

Carbonyl substitution

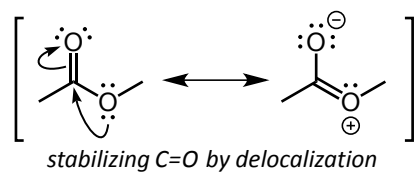
Fischer Esterification/Deesterification

Structures

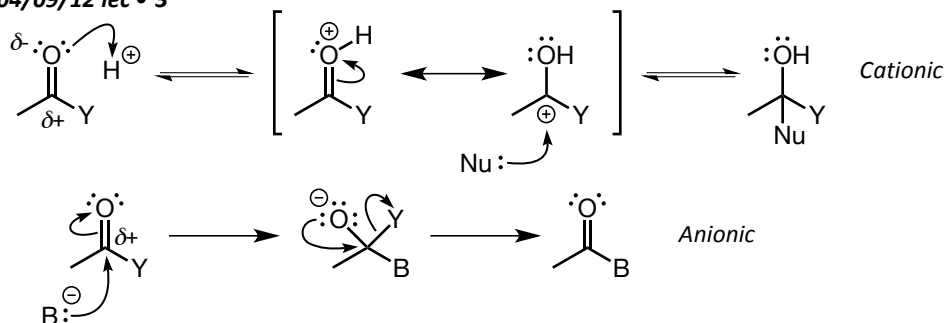
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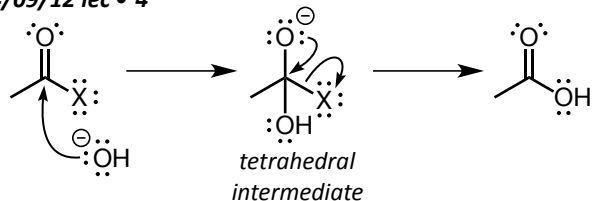
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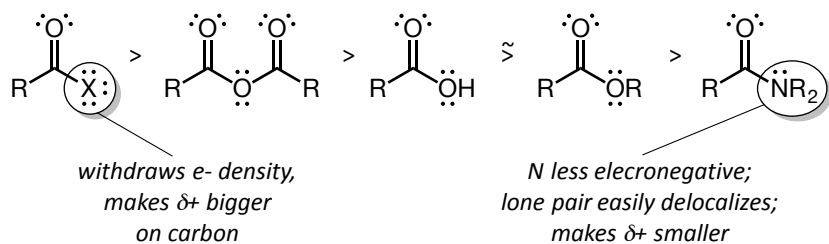
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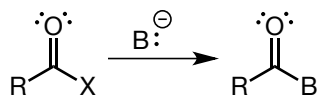
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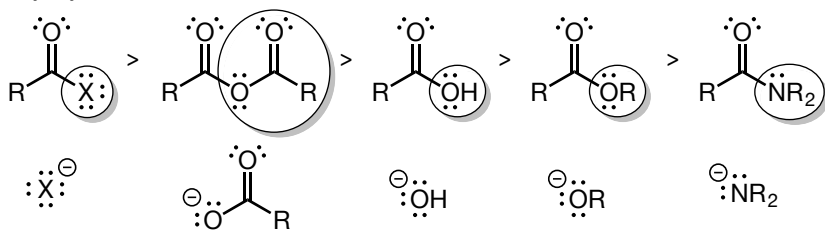
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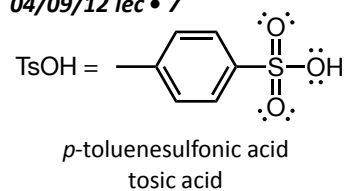


basicity of leaving group

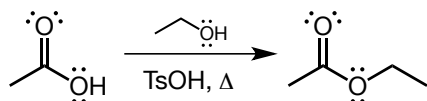
strength of conjugate acid of leaving group

increasing reactivity

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Why does protonation occur here?

