

Lecture 3A • 04/16/12

If we took a carboxylic acid and reacted it with an excess of isotopically labeled water with some kind of acid source and heat, what would result? What's the mechanism that's going to be in place here? What would this be the most similar to? The Fischer esterification or de-esterification. This is different only that we are starting with something that's already a carboxylic acid and we're only using water, so we're not making an ester, but it's the same mechanism. If you let that mechanism keep going on, then eventually what's going to happen? Eventually, every time that water attacks it's going to be the isotopically labeled water. Every time that process of opening the carbonyl and it collapsing again, it would be water attacking. The point of this mechanism is that if you didn't go through the process where it opened first, if you had more like an S_N2 -style attack, then it would only be this regular hydroxide group that would be kicked out each time. Even in the basic version, if we had an carboxylic acid, and we did some reaction with just one equivalent of the 18-oxygen derivative, if there was no opening of the carbonyl and it was just an S_N2 -style reaction, we might imagine that this is the only product. No matter how many times this reaction occurred, if the carbonyl didn't get involved, you could only replace one of these oxygens with 18-oxygen. The point of this reaction is that, with a large excess, you're going to get both oxygens labeled, because the carbonyl bond does open, so you do have the chance for any of those three oxygens in that intermediate that forms to react. [Similarly,] we could start with an 18-oxygen-labeled ester and [saponify] it – the same kind of logic: if the carbonyl oxygen never got involved, the carbonyl, if it were labeled with 18-oxygen, would permanently stay labeled, it [doesn't], which prove[s] that a tetrahedral intermediate is involved. When we write something like saponification, that first step where sodium hydroxide would attack, it does push the carbonyl open; then there's a second step where whatever that's going to get kicked out – [since] this is saponification, it [will] be the alkoxide that gets kicked out at this point – that's going to happen separately. Whichever way you want to express it, the results of this 18-oxygen example indicate that carboxylates do go through tetrahedral intermediates. The above steps during saponification must be shown separately.

If I had an ethyl ester and I reacted it with a large excess of propanol, with an acid source and a long time, what will happen? What do the reaction conditions look like (ignore the fact that we're starting with an ester)? These are acidic conditions; they're actually the same conditions as Fischer esterification. The question is: in Fischer esterification conditions, what happens to something that's already an ester? The answer is: it reacts. If you had a large excess of this alcohol, you will kick out the original alcohol and end up with the longer one there; this is a process known as transesterification. It does not mean 'trans' as in cis/trans, it means transference, you could say, you change the type of ester. Let's say that we had this kind of situation: what reaction(s) could happen? S_N2 ; where? With the the bromide – primary alkyl halide, strong, basic nucleophile, S_N2 reaction. What else unwanted is going to happen? You could get this instead. Why? What if, instead of attacking the bromine, it attacks the carbonyl? You end up with this tetrahedral intermediate, and you'll have two different alcohols that are also attached. Which one's going to get kicked out? It depends on how much ethoxide you have around and how much time you give it, but there's no real big difference between the stability of ethoxide versus methoxide, so there's no reason that methoxide could not be kicked out, which means you've changed the ester [and failed to carry out the S_N2 reaction]. Even if you had enough methoxide in to make sure that you did the S_N2 [in this example], you'd be guaranteeing that transesterification would occur. For esterification or saponification, the actual attack of the carbonyl, because the basicity of what you start with and end with is so similar. If I had put methoxide here, you wouldn't know if methoxide had attacked the methyl ester because it would just make a methyl ester, because the base was compatible with the ester that you had there. The reaction, in principle, is not bad, but I'm going to get byproducts if I'm not aware the transesterification is possible.

Transesterification happens all of the time. There may be billions of times that carbonyl got opened and closed, you just don't know it because you didn't see any change in the product.

How to move between the different carboxylic derivatives. If I start out with a carboxylic acid, and let's say I can't do Fischer esterification because I have some other acid-sensitive functional group on there, then how could I esterify? If I did have methanol, and an acid source and heat that one of the likely products of this reaction, besides the one you want, is for the alkene to be substituted. If we don't want the alkene to be substituted, do we have another way of making an ester? The answer is: yes. One of the ways [involves] thionyl chloride. What does thionyl chloride do? Turns an alcohol into an [alkyl] halide. Turns a carboxylic acid into an acyl halide. It has a somewhat similar mechanism. We attack the sulfur-oxygen double bond; that sulfur-oxygen bond can reform, kicking off one of the chlorines as a leaving group, we lose a proton off of the oxygen, get something neutral, and the carbonyl can get attacked by chloride, which in this case works because the sulfur-containing group is such an excellent leaving group. In other words, when chloride attacks, afterwards, when the carbonyl's reformed, instead of chloride getting kicked right back out again, it's the sulfur group. Part of the reason for that is that a lone pair doesn't just fall back to oxygen, it falls back, attacks the sulfur, and kicked chloride out. We've made an acyl halide, plus we have sulfur dioxide that bubbles out as a gas.

Now that we've made an acyl halide, didn't we identify that as the most reactive of all functional groups in that carboxylic acid series? So, I can make anything less reactive than it. How? If I want to make an ester, what kind of reagents could I use? Do I have a choice about whether I use acidic or basic conditions? Think about the reaction mechanisms we had: Fischer esterification would be an example of acidic conditions. Could we use those acidic conditions on this molecule?

We don't even need the acid; all we need is the alcohol. This reagent is a reactive enough functional group that it will appear to undergo an anionic mechanism, where it's not an anion, it's a neutral alcohol, but the neutral alcohol could attack the carbonyl by itself. If, in the general case, if I had an acyl halide, the most reactive thing I could do is throw an alkoxide at it. That'll go by an anionic mechanism that will look like saponification. In this example, the alkoxide attacks and kicks open the carbonyl – that's just like saponification. Also just like saponification, once we have this tetrahedral intermediate, the carbonyl's going to reform and something's going to get kicked out as a response. We have an alkoxide, which is the parent of an alcohol that has what kind of pKa? Primary alcohol like ethanol has what kind of pKa value to it, versus chloride, which is the conjugate of an acid that's got a negative pKa because it's such a good acid. Out of the two of these, it's only going to be the chloride that's likely to get kicked out; that is the second step of one of these anionic mechanisms – for that thing to become kicked out again.

I could, in theory, if I made rigorously sure that I had no water around, in theory, you could have acidic conditions, and you'd get the exact same product. This would be the more cation style mechanism. Which one in real life would you do? Normally, it's just with the plain alcohol, because the acyl halide is reactive enough. If you had easy access to it, the alkoxide, that would guarantee a vigorous reaction; that usually means an extra step to make the alkoxide. Normally this last method wouldn't be used in case you introduced water into the system, because water would make a carboxylic acid out of the acyl halide instead of an ester.

[review of reactions]

If we had water or hydroxide, that would get a carboxylic acid. What if we wanted an amide? What's an amide? An amide is when you have a nitrogen instead of an oxygen where the ester oxygen would be. In other words, if I took an acyl halide and reacted it with a primary amine, it's already basic, you don't need an acid catalyst, it is basic, it will attack the carbonyl; it'll be an anionic-style mechanism, and you'll end up with an amide. What is that? Lactone [has relationship to milk?]. Lactam – which are nothing more than a cyclic ester and a cyclic amide, but the fact that you cyclize will cause one of these functional group to have differing reactivity from its linear counterpart [upon reduction]. [water reacts, hydrolysis; alcohol reacts, solvolysis; amine reacts, aminolysis]

Anhydrides are one of the less-useful functional groups. There's a good practical reason why. First, how to make an anhydride. One reagent that's sometimes used is [di]phosphorus pentoxide. The reason it's used is cause it's really, really hygroscopic – hygroscopic enough that with heat and a carboxylic acid, you'll the water out of two carboxylic acids and make them an anhydride. There's also a trick. Acetyl anhydride. If you have an acid like acetic acid, then to name its anhydride, the you just stick the word 'anhydride' in instead of 'acid'. Methanoic anhydride would be an anhydride of carboxylic acid containing how many carbons? One. When acetic anhydride decomposes, it makes acetic acid. Acetic acid is a relatively low boiling point compound, so if you have a large-chain carboxylic acid, if you distill at the same time that you react – so that you pull the acetic acid out that forms as it forms – then you can use one anhydride to dehydrate another. But, anhydrides outside of this [meaning mixed] are not always useful; why? BEcause you could have the possibility of making mixed anhydrides. If you had two different carboxylic acids, how could you reproducibly dehydrate one versus the other.

You can synthesize a mixed anhydride; how? If I gave you this synthesis problem, how would you accomplish it? What's more reactive than an anhydride? Acyl halide. What if we took one of the carboxylic acids [and] made it into the acyl halide. Separately, we took the other carboxylic acid and deprotonated it – [this is a] carboxylate salt, the conjugate base of an acid. [carboxylic/-ate] Salt is basic is a nucleophile; put it together with the acyl halide, you get a mixed anhydride. But, since it takes effort to make the anhydride, and we have the more easily-formable acyl halide, generally if we wanted to do something with an anhydride, we'd try to do it with an acyl halide instead. Anhydrides function like acyl halides, so if we took acetic anhydride, react it with an alcohol, it's still reactive enough to react with a neutral alcohol, so it'd be an anionic-style mechanism, in order to make an ester.

The next functional group I would like to talk about is esters. On top of basic saponification, you could use water, acid, and heat to cause an ester to decompose again.

Let's talk about amides. Amides are the least reactive of the carboxylic acid functional groups [with a carbonyl]; that's because the nitrogen's so heavily delocalized with the carbonyl next door. [good because proteins are made up of these kinds of linkages] There is a way to totally blast an amide apart, which is to either do hydrolysis or saponification; we have both an acid and a base method available. Amides are less reactive than any of those higher derivatives, so we're never going to take an amide and go directly an acyl halide, for example.

[reduction and alkylation]

Will there be a significant difference in reaction mechanism if I do a reduction of a linear amide or a cyclic one, better known as a lactam?

Let me wrap up with saponification of an amide. You do have to use harsher conditions to get amides to react. When you do saponification, it takes a good, concentrated solution of hydroxide and a good amount of heat and time. The acid version of this also requires a strong acid, a lot of time, and a lot of heat. This is the same saponification mechanism we saw with an ester; everything is identical. Carbonyl opens up, it collapses back down to kick one of two groups off: O minus, or N minus. Which one's more favorable? Which one's more electronegative, nitrogen or oxygen? Oxygen, so it better likes the negative charge. Nitrogen, being less electronegative, does not tolerate the negative charge as well as a much more basic compound. We have hydroxide, which is the conjugate of something with a pKa of about 16, versus this amine that's got a conjugate of 36. In other words, that nitrogen doesn't want to get kicked out at all. But what happens if it is? It's same thing that we saw in the saponification reaction: we just made something that's hella basic, which means instant acid-base neutralization. It's not favorable to saponify an amide, that's why it's less reactive. Besides the nitrogen being delocalized, our other excuse for it's reactivity was leaving group ability – nitrogen negative doesn't want to leave. But, although nitrogen negative is a very poor leaving group, if and when it comes off, it instantly neutralizes the product, preventing the reverse reaction.

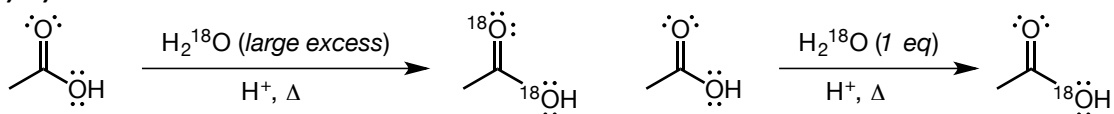
Results of 18O experiment indicate carboxylates do go through tetrahedral intermediates → the above step during saponification must be shown separately

hydrolysis – rxn w/ H₂O; solvolysis – rxn w/ ROH; aminolysis – rxn w/ amine

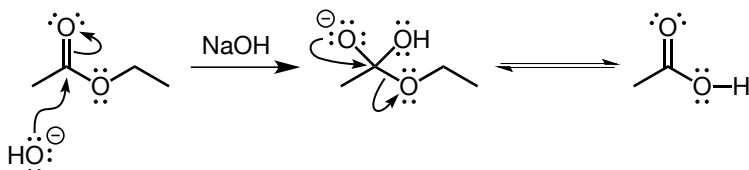
Although N⁻ is a very poor leaving group, if & when it comes off, it instantly neutralizes the product, preventing reverse rxn.

Structures

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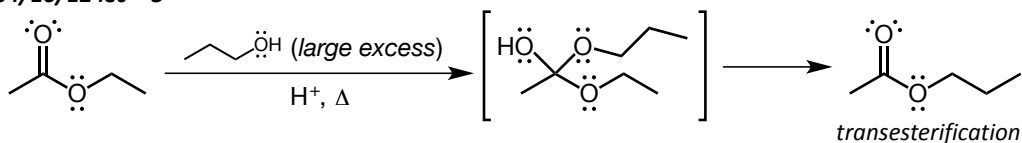


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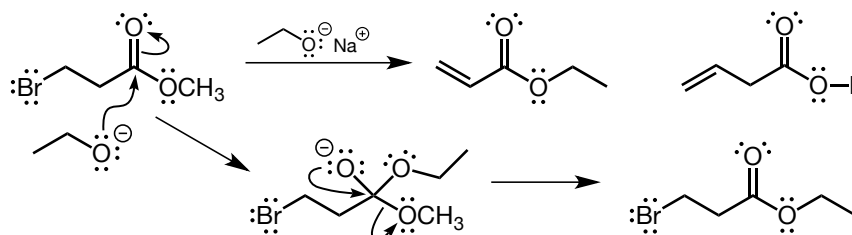


only product if carbonyl not involved and only "S_N2" occurred

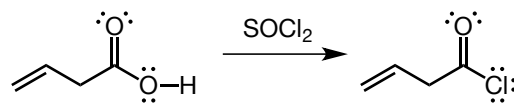
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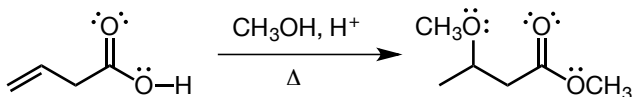
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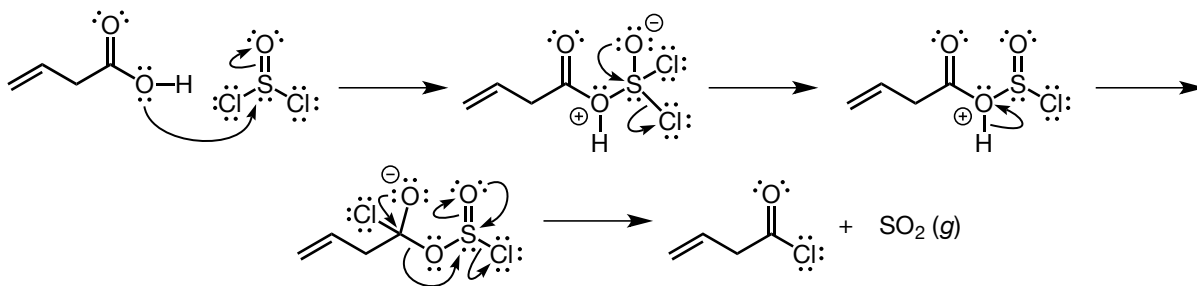


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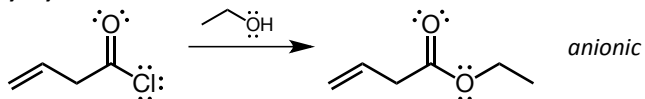


poor way to make this ester due to other acid-sensitive functional group

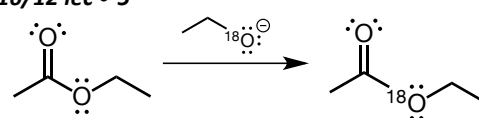
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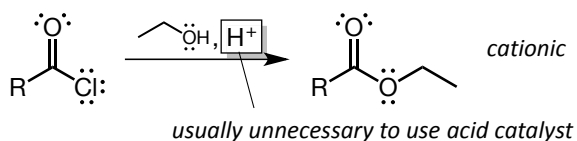
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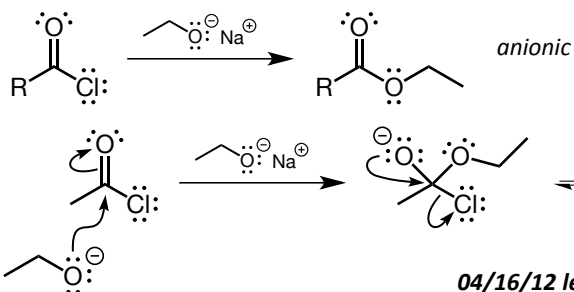
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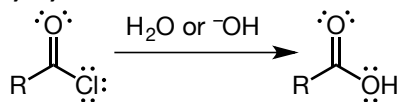
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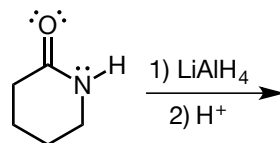
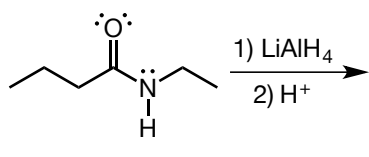
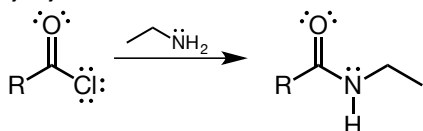


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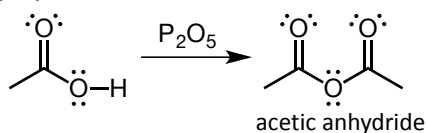


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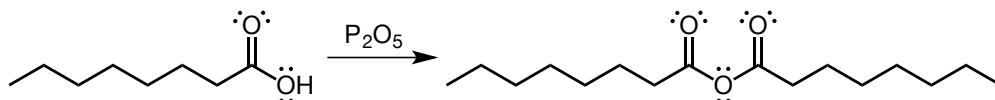
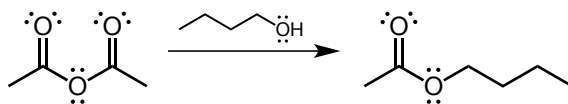
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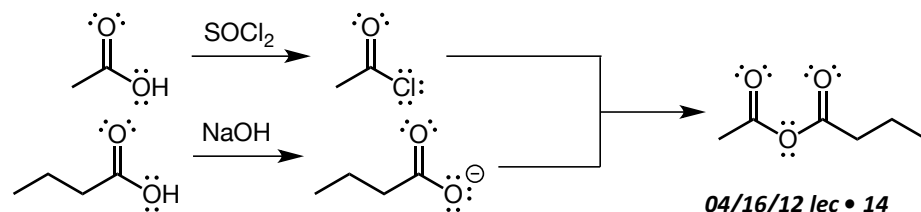
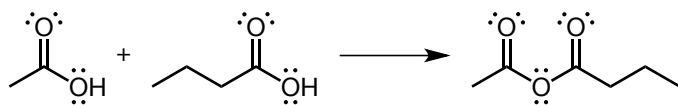
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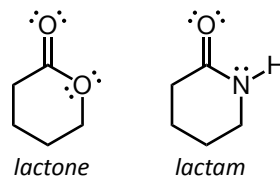
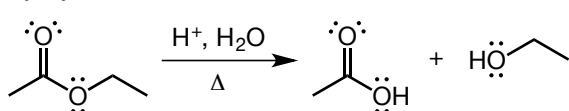


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