

## Lecture 3B • 04/17/12

What would happen if we did have an excess of isotopically-labeled water and acid and heat? [The acid oxygen could be replaced.] Could the carbonyl oxygen also get replaced with  $^{18}\text{O}$  if there was a massive excess of the water? Yes it will. Here's the point of this. [You could start with] an  $^{18}\text{O}$  at the carbonyl position, and then it has a reaction that involves water, hydroxide. Here's the point: if there was never that tetrahedral intermediate that I pointed out – if at some point we imagined water attacking the carbonyl (since this is an acid mechanism, yes the carbonyl will be protonated first), the carbonyl gets attacked and pushed open – if the carbonyl never got involved in that process, then if you had an  $^{18}\text{O}$  on the carbonyl, it would never get substituted.

Let's say you had a carboxylic acid that you reacted with water somehow. The other form of the question is: can you get rid of the  $^{18}\text{O}$  by prolonged exposure to water? If water were to attack and kick off hydroxide, suppose that whatever carboxylic acid derivative is reacting, if you somehow attacked and pushed off the leaving group without the carbonyl ever being involved, there would be no way to remove  $^{18}\text{O}$  from that starting molecule. The point of the experiment is that if you got rid of it, that means you went through that tetrahedral intermediate. That means when we're writing a reaction mechanism like saponification, there's two ways, in theory, that we could write it: one is if we did this, we ignore the opening of the carbonyl and show it kinda like you're doing  $\text{S}_\text{N}2$ . This is just the first step; of course afterwards we have that neutralization that instantly occurs. But in principle, then, if I put  $^{18}\text{O}$  here for the carbonyl oxygen, if this were the mechanism, you would always end up with the  $^{18}\text{O}$  up top in the product as well, because by this mechanism, the carbonyl never is involved; it really is like an  $\text{S}_\text{N}2$  reaction.

The answer is, yes, the  $^{18}\text{O}$  will disappear, and the fact that  $^{18}\text{O}$  can be added to or removed from the carbonyl position means the reaction goes through a tetrahedral intermediate. This means that saponification, for example, cannot be written as if it was an  $\text{S}_\text{N}2$  reaction.  $^{18}\text{O}$  can be detected separately from regular  $^{16}\text{O}$ , so there's a way to trace that this really is happening.

There's another question I asked: if I have – what is the name of that molecule? It's an ester. What kind of alkyl group is attached to the oxygen there? Ethyl. If I put an O minus instead of that ethyl group, what would we call this ion that's there? Acetate. This is ethyl acetate. If ethyl acetate reacts with an excess of propan-1-ol, acid, and heat, what's going to happen? This is a process known as transesterification. Transesterification doesn't mean cis/trans; it means like transferred, a change. You're taking one ester and creating another. Think about what the reaction mechanism is: it's a whole bunch of protonate, open, attack, and deprotonate. After the first round of protonate, open, attack, deprotonate, you'd have both of these alcohols – the one you start with, the ethanol, and propanol potentially connected together. [admonition to study] How would I write out the intermediate after one cycle of protonate, open, attack, and deprotonate, what would I have that that point in this case? A two carbon-compound with an alcohol, ether, propyl. So, you have three different oxygens, all three of which, if they were to dissociate, if they came off all of a sudden, they'd be all about the same strength as each other, in terms of bases. That means that once you do go through protonate and open, that all three of these are just as likely as each other to come off the molecule. If the -OH came off, you'd get something you can't isolate. If the propoxide came off, you'd come back to the starting material. But since you're flooding this with the propanol, you're gonna end up with that product. This is the acid version of it, but the base version is just as important.

This example is not to show you something about synthesis, not about substitution or elimination; the example is to show you what else you must consider in terms of compatibility of reagents with the molecule you're trying to do a reaction on. Here's the example. Let's say we had an excess of sodium hydroxide. Let's say that I want an elimination reaction to occur. Why would it make sense that an elimination reaction could be happening? We have a secondary alkyl halide, and we have a base, which secondaries with basic nucleophiles tend to eliminate, especially if we've got heat like this. But that's not going to be the product of this reaction. If we wanted to do elimination, fine, but we needed to choose a different base, because hydroxide, with heat and time, is not just going to cause elimination, it's also going to cause saponification. Even if we did use an [alkoxide], because it's a strong base, we're going to get elimination, but because it's not the same as what was already part of the ester, we're going to change the ester also. Whenever you use bases if esters are present, care must be taken that you choose the correct base, based on the structure of the ester. The above example demonstrates that the base used to perform a reaction with an ester present must be chosen carefully, so as to avoid saponification or transesterification of that ester. If you have a longer chain in the alcohol, the alcohol itself [is possibly marginally less acidic, but if it is more branched, it will be somewhat less acidic].

Fischer de-esterification is also called hydrolysis, which essentially just means reaction with water. But you can take an ester and do an acid-catalyzed reaction with water and get a carboxylic acid; that would be called hydrolysis. We could do saponification, which is the base version. There is both an acid and base version of going from an ester to a carboxylic acid; there's not both a way to go in an acid version and a base version from a carboxylic acid back to an ester. That's because of carboxylic acids themselves being unusual in that they're acidic; so it doesn't have just to do with the fact that they have a carbonyl, it's the fact that they're an acidic functional group.

[Now we need to approach the other carboxylic acid derivative, such as acyl halide, anhydrides, nitriles, amides] We're going to be studying a set of reactions with those functional groups, one of which hydrolysis, another one of which is similar but it's called solvolysis. It's usually used as a shorthand way of saying a reaction with an alcohol. Transesterification could also be called solvolysis; you're reacting with a different alcohol. Then they're aminolysis, which means a reaction with an amine, which we'll see is one of the ways that we can produce an amine.

Acyl halides. Remember that acyl halides are the most reactive of the carboxylic acid derivatives, one because they have a chloride which is a good leaving group, and two, because the carbonyl has got a larger than average delta positive on it; both of those reasons together make the acyl halide more likely to react. What reactions can an acyl halide do? The three right here: hydrolysis, solvolysis, and aminolysis – along with two other reactions. The two other reactions that we'll more carefully discuss are reduction and Grignard reactions, alkylation. Each functional group has its own special gotcha that occurs when we're doing mechanism with lithium aluminum hydride or with a Grignard reagent. For these reaction, hydrolysis, solvolysis, aminolysis, the mechanisms are all very, very similar. We're starting with these because these are the simpler ones.

Let me show you two more functional groups. We take an ester and we twist it around in a circle. What is this kind of creature called? Lactone, which makes it sound like it has something to do with milk [from soured milk]. It's on the basis of this that we get the name for its nitrogen equivalent, lactam. [Lactam is a portmanteau of lactone and amide.] Besides the fact that you need to know what these functional groups are, there is a difference for one of these two groups between its reactivity and its non-cyclic counterpart.

Let's start with acyl halides. Acyl halides are reactive enough that you don't need a strong base to force the carbonyl open; you don't need an acid catalyst to cajole the carbonyl into reacting. If we use neutral, acid, or basic reagents, all of them will work. If you use a basic reagent like sodium hydroxide, that's going to be a massively favorable reaction, because you're using a strong nucleophile with this thing that's got a good leaving group, so very rapid and likely extremely exothermic reaction. This is going to occur by an anionic mechanism. Hydroxide's a reagent; you're making an acid as a product. Before the carbonyl can get attacked by more hydroxide, doesn't that mean that the acid can get deprotonated? Yes; that means we [have to] follow it up with an acid work-up step. If we use neutral water, the acyl halide is still reactive enough to react with water. If you used this particular acyl halide, acetyl chloride, and you open a bottle up and just sat there with it, you would have known that water was reactive enough, because you would have gotten that cloud of hydrochloric acid vapor coming your way. It forms the same product. It is still effectively the anionic mechanism, cause water is not acidic enough to cause protonation to start the process, but you also don't end up with hydroxide in solution; you end up with HCl in solution, so there's no need for a follow-up H+. In theory, you could use water in acidic conditions to get the same product, but if water's reactive enough, why throw another chemical at this, especially if you're acid catalyst is wet. If we wanted to react with an alcohol, but we use an acid catalyst that was wet, then that means we're going to end up with multiple products. This is all hydrolysis.

What about solvolysis? Let me show you an example of a short synthesis to demonstrate why acyl halides can be useful. Let's start not even with an acyl halide, let's start with this unsaturated carboxylic acid. Let's say we wanted to make an ethyl ester out of it. That's fine. These are the conditions to make an ethyl ester – they're also the conditions to add to the double bond. If you have excess alcohol sitting around, you're not just going to get an ester, you'll get an ether as well. In this case, esterification will occur, but a side reaction will occur as well, since the reaction conditions are incompatible with alkenes. What can we do? Make an acyl halide. [The thionyl chloride mechanism with a carboxylic acid] is nearly identical the mechanism that you would have if you did it with an alcohol. The most missed aspect when writing this mechanism is the fact that sulfur has a lone pair on it. Sulfur, really delta positive because it's got these chlorines and oxygens around it. Very likely to be attacked by even the alcohol portion of a carboxylic acid. After we pushed open that sulfur-oxygen double bond, it will reform. When it does so, one of the two chlorines gets kicked off. Deprotonation of the oxonium can then occur. Last step – even though chloride's not all that basic, this functional group starting from the oxygen with the sulfur and the oxygen and chlorine that are all attached, that thing really is a good leaving group, so normally it wouldn't be favorable for a carbonyl to be attacked by chloride, but in this case, if it does, then when the carbonyl reforms, instead of chloride being kicked out, it's this whole sulfur group that gets kicked out instead. The carbonyl reforms; it kicks off the leaving group, which decomposes because of it – that's part of the driving force for why this is a good leaving group, because we form sulfur dioxide as a byproduct. Then, we have our acyl halide. Even though H+ comes off here, we have acidic conditions, often we can use a base scavenger like pyridine to help mop up some of that extra acid that's around so we can do this while still preserving the alkene. We can then take that first step of creating a leaving group from a carboxylic acid – convert the carboxylic acid, in other words to the acyl halide – react that with a neutral alcohol. It will have an anionic-style mechanism [that] lets us form that ester without the alkene being affected. [amides?]

[From acyl halides,] we can revert back to carboxylic acids just by reacting with water, we could make esters if we use an alcohol, we can make amides if we use amines. Another mini-synthesis: we make the leaving group, now react it with an amine. It's also an anionic-style mechanism, since the amine is a base. The base attacks the carbonyl without the need for pre-protonation. Once the carbonyl's open, it collapses again, kicking out the alcohol.

One last reaction: if we take an acyl halide, we could react it with a carboxylic acid salt. That salt's a base; this is a weak base, though, because it's stabilized by the carbonyl, but it could still attack an acyl halide. Look what you would make as a result: if the R groups were the same, you'd make what's called a symmetric anhydride; or, you have the potential, if the R groups are different, to make an asymmetric anhydride.

Let's move into talking about anhydrides. You should understand why it is that they're not usually as useful. It's exactly because of this asymmetric anhydride. An anhydride reacts much like an acyl halide will, meaning that if we had a symmetric anhydride, when it reacts with water, we get two of the same product, the same carboxylic acid back again. But if we took a mixed anhydride, an asymmetric anhydride, then you get two products. By extension, if you wanted to try to make one specific ester, then, if you use a mixed anhydride, half of your product is garbage; only one half or the other is usable, so usually only symmetric anhydrides are useful synthetically. Another reason why anhydrides aren't as commonly used is if an acyl halide is a more reactive group and it's an easier group to form, why would you use an anhydride? [DEA issues] It's not that anhydrides are never used, and there may be some applications where they may be the only choice – maybe they're less reactive enough that they prevent some other bizarre sort of side reaction.

Let me show you two tricks with anhydrides that you should know. One is how to form them. That's often done using a dehydrating reagent, specifically diphosphorus pentoxide. That diphosphorus pentoxide will absorb water because it's trying to form phosphoric acid. It ends up being incredibly hygroscopic – enough so that, with time and maybe some heat – it will call the removal of water from two carboxylic acids to make the anhydride. There is also this trick that can be done: to form an anhydride from a larger carboxylic acid, you'll often react that carboxylic acid with an anhydride. Initially, you might end up with a mixed anhydride, but over time and with some heat, you're going to end up with this larger anhydride. Why? Because acetic acid can be distilled at a relatively low temperature; a larger anhydride would be much more difficult to distill, the boiling points go shooting way up. In a mixture of all of this put together, it's going to be the acetic acid that bubbles out first, so you keep removing acetic acid, which keeps driving the reaction further to the right, so it's not solubility, per se, but it is an equilibrium trick that is done.

Let me show you that an anhydride could react [by] aminolysis as a brief example.

[In the saponification of an amide], the hydrogen on the nitrogen is not acidic, so it's really going to be the carbonyl that tends to get attacked here. This is exactly the same as the saponification that you've seen before – the only difference is that usually has to be a much more vigorous reaction, because yes, at this point, the carbonyl's going to try to reform, but look at the two choices of what's going to get kicked out – hydroxide, or O minus, or N minus? Which one is the stronger base in general: something that's O minus or something that's N minus? N minus, because N is less electronegative, so it is less favorable to try to tolerate the negative charge, so nitrogen positive is not that unusual; nitrogen negative is extraordinarily basic, generally. There's a mismatch in base strengths, but if equilibrium can happen, it will happen. If there's a small chance that at some point this oxygen minus will get kicked out even though it's unfavorable, when it does happen, the reaction becomes irreversible: we've just made a base – a really strong one – and an acid, so you'd get instant neutralization, which means after acid work-up, we can get the carboxylic acid back again.

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The fact that 18O can be added to or removed from the C=O position means the rxn goes through a tetrahedral intermediate. This means that saponification, for example, cannot be written as a  $S_N2$  rxn.

The above example demonstrates that the base used to perform a rxn with an ester present must be chosen carefully so as to avoid saponification or transesterification of that ester.

hydrolysis – rxn w/ H<sub>2</sub>O; solvolysis – rxn w/ alcohol; aminolysis – rxn w/ amine

In this case, esterification will occur, but a side rxn will occur as well since the rxn conditions are incompatible with alkenes.

Anhydrides

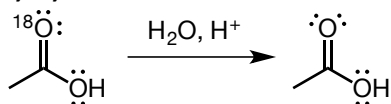
Since rxn with an asymmetric anhydride could form two products, only symmetric anhydrides are (normally) used synthetically.

Amides

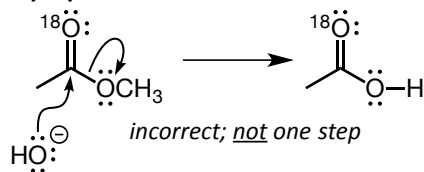
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Structures (remaining structures identical to lecture 3A)

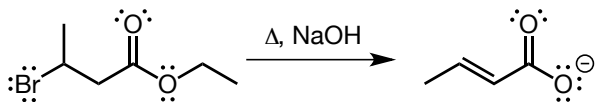
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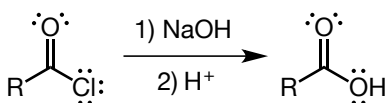
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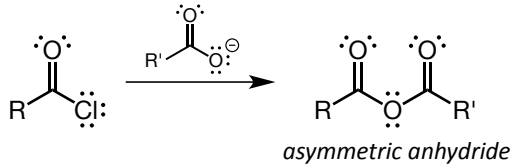
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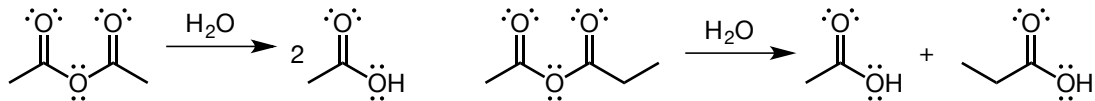
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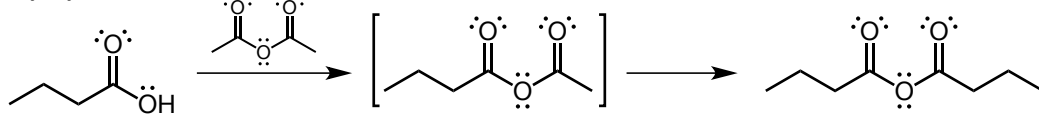
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