Lecture 2A • 04/13/12

Fischer de-esterification

I want to show that it's exactly the same mechanism, but in reverse.

Let's talk about nomenclature. In an ester, you have the alkyl group, and you have the main carboxylic acid itself. The way that an ester name is made is that alkyl group by itself and then you have the carboxylic acid name that you add an -ate ending to. You might remember that something like nitric acid that the anion you [make from it is] called nitrate; sulfuric, sulfate, that's irregular, but still; acetic, acetate; same thing here. We could use the common name and call this propyl acetate. But, that is the common name. The systematic name for this is ethanoate, which comes from ethanoic acid. Notice that you take the number part of the term, methane without the 'e', ethan, protan, butan, and you add -oic acid. Methanoic, ethanoic, propanoic, butanoic. I'm going to generally use the systematic terms, but so many carboxylic acids have common names. If you look at the back of your shampoo bottle, all these different laurates and laureths, long names, many of those are actually the common names for carboxylic acids. [memorization – acetic acid, formic acid]

De-esterification. I'm going to use ethyl acetate. Very, very common lab solvent; it's going to be my default compound to use, just cause it's a small compound to write. The formation of the ester was a fully reversible reaction. We'll talk about what is normally done to favor the formation of the ester, because energy-wise, carboxylic acids and esters, they're very very close to each other in energy, so there's no huge driving force to convert one to the other. In this case, we would have acid and water, and we'd reflux it.

Why is it that it's the carbonyl oxygen and not this oxygen that gets protonated? There is delocalization possible if you protonate on the carbonyl oxygen; if you protonate on the other oxygen, that's all that happens. We already saw that protonate, open, attack, so on and so forth happens by protonating on the carbonyl. If you protonate here, it can and will get protonated, but nothing useful happens, cause there isn't even a lone pair next door to do any resonance with. This oxygen, with its remaining lone pair, could delocalize with the carbonyl, but that would make a doubly positively-charged oxygen, which is totally unfavorable.

In the forward direction, making the ester, it's protonate, open, attack, deprotonate. It turns out that's the same sequence of events that happens in reverse, cause if you look back at that forward mechanism, the very last step is the deprotonation of the carbonyl, which means, going in reverse, it is going to be the carbonyl that gets protonated first. That's our principle of microscopic reversibility coming back. Whatever the most energetically favorable pathway of a reaction in the forward direction is automatically, step-by-step, the same pathway that would be the most energetically-favorable in the reverse direction. I am going to again say that, for this particular reaction, you do need to use reversible arrows, because it's entirely important that the reaction is fully reversible. We now have a open step, in this case the carbonyl opening. It is water that we're using now, and so water will be the thing that attacks, which will make an oxonium ion, which will then deprotonate. This is called a tetrahedral intermediate because you've got four things attached to the central carbon, but functional group-wise [ortho ester?]. This is only half way there.

We have three oxygens that could potentially react; the question often comes up: which one is it that's going to be the one that reacts. The answer is all three of them. If it is one of the oxygens from the -OH groups that reacts, that is going to take us back where we came from, so the reaction will keep on going back and forth and back and forth until, eventually, the portion that looks like an ether, until that gets protonated. That will move us, from our current perspective, in the forward direction. That'll get protonated, it'll leave. In this case, just to be able to use that same acronym from POAD, I called it attack, but it's really just the drawing of a resonance structure – if you wanted to put it that way, an intramolecular attack, followed by a deprotonation.

Let's talk about favoring equilibrium. If I felt like it, we could have a long discussion about delta G right now, and reaction progress diagrams, and draw a bunch of graphs, but let's just keep this simple. What are the definitions of equilibrium? The rate of the forward and reverse reactions are equal; no observable energy change because you're at the lowest point in energy; and, no observable change in the concentrations of reactants and products – it's not that the reactants and products have the same concentration, it's that it's static. Le Châtelier's principle says that you mess with the reaction somehow. Let's say, for example, that we pull out products. If we pulled out products, then the forward reaction's still going at whatever rate it was going, but all of a sudden, the reverse reaction rate has dropped. Overall, you're going to make more products, because you removed products. Energetically, if you removed products, you're changing the energy balance, and automatically makes it such that you push the reactants higher in energy again, which means they'll react to make more products, until again you've made more products. In other words, whatever way that you've stressed the system, in this case by pulling products out, the system responds to regenerate that balance, to make more products in this case, to make more of a reverse reaction, to again balance the forward reaciton that was not affected by removing the products. But if we're trying to affect the balance of a reaction, then what if we kept removing the products, continuously?

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The the reaction position is constantly chasing the end, constantly trying to make more products, trying to establish that reverse reaction that never comes because you keep on removing the products. [Dean-stark apparatus]

A classic type of esterification you might do is such: whatever carboxylic acid you might choose – what would be the systematic name of this one? Butanoic acid, also called butyric acid, from butter, smells like bad butter. If we wanted to esterify it, we usually use a large excess of the alcohol involved, because one way to favor products is by throwing a whole bunch of some kind of reactant, so we flood the reaction. During esterification, water is going to come off, and water can compete to do the reverse reaction. Of course, the Dean-Stark apparatus takes care of water and helps pull the reaction forward. Flooding it with the alcohol doesn't hurt. We have our acid catalyst [tosic acid]. Then, toluene. Why? Because toluene makes an azeoptrope with water – it's two things that normally would not soluble in each other, but they end up forming a mixture in the vapor phase. What that does is it helps remove water from the system. The end product here is going to be your ester.

Let me draw that Dean-Stark apparatus. You're heating your reaction mixture at the bottom here. If you're heating to reflux, it means you're heating enough till it evaporates, till it boils. That condenses on the sides of that channel and flows back down. But, some of it will automatically flow to the side in this Dean-Stark trap. What happens there is that, inside, the water is heavier; the toluene and ethanol and everything else mixed together is lighter, and so it's on top. Over time, the more water that collects, it pushes that organic layer back up, until the point where, depending on the quantities involved, that organic layer spills back over into the reaction mixture, which means if there was any incomplete reaction that occurred, it's being pushed back over, while the water's being removed. You can drain the water out a little bit over time, and that prevents the water from re-entering the system. Therefore, it does not allow equilibrium, cause water can't participate in the reverse reaction, and so the reaction only has the ability to go forward. This is assisted because toluene is helping pull the water out, cause it makes that azeotrope. Even though water's boiling point is much higher than the boiling point of this reaction, it's still pulled out of solution.

Toluene forms an azeotrope with water, which is a vapor mixture of two or more [substances] that would be mutually insoluble – you could say immiscible – in the liquid phase. It is used in Fischer esterifications to help pull water out while a reaction is refluxing.

Usually, what you'll have is some kind of value, so you can control the flow of water that comes out of it, and fancier ones also have marking like you'd have on a graduated cylinder, so you can measure the amount of water and calculate how much the reaction's been completed.

Two questions I'll ask: what would happen in this case; separate, what would happen in this case. Similar questions, first is a carboxylic acids that's being treated with water, but a special kind of water, isotopically-labeled water, 18O, which means a version of oxygen that has more neutrons on it. Very, very, very expensive stuff, but this is a good theoretical question. This other one, I'm taking one ester and reacting it with an alcohol that's not the same alcohol that was already part of that ester. The question is: what would happen in this case?

Let's switch to an anionic [mechanism], saponification. What is the word 'saponification' related to? Soap. Saponify, savon, sabon, related to soap. It's related to the old-style way in which soap was made where you'd take lye, which is just this really basic, caustic stuff, mix it together with animal fat; that gives you carboxylate salts. Why is it that a carboxylate salt would be a soap in the first place? 16-carbon carboxylic acid – palmitic acid. Why do these things work for cleaning up greasy stuff? They're good at cleaning up greasy organic-compatible things, why? You have an ionic headgroup; to use biological terminology, we would say it's hydrophilic or lipophobic, meaning water-loving or fat-hating. Why is it both of those? Because it is ionic; it is fully charged. The other end, we have the organic tail which we would say is hydrophobic – it doesn't like water – but it is lipophilic – fat-compatible. If you get above a certain concentration which is called the CMC, the critical micelle concentration, if you're above that, then you form the micelles, which are the structures in which the organic tails end up forming the interior of that body, and then you have the polar headgroups that form the surface. It's spherical in nature. That sphere dissolves in water macroscopically cause the surface of it's ionic, but on the interior of it it dissolves fats because the interior is lipophilic. When you've got a nice, greasy meal that you cook and you drop soap onto it, you'll notice on the surface – because surface effects often do these interesting things – drop the soap on it, and it's like this ring radiates out very quickly – it's because it's forming these types of micelles. That's why soap works. Soaps are often called surfactants as well, because they're surface-active – they do strange things at the boundaries of phase layers like this.

Getting back to the real story of the sapoinification reaction itself, it would look like this. You'd start out with an ester; again I'm going to default to my example of ethyl acetate. You'd use a concentrated solution of sodium hydroxide; often you need to heat these reactions. Part of this reaction is reversible; part of this reaction is irreversible. You need to understand why for both of those – why part of it is reversible, and what the significance of that is, and why part of it is irreversible. The behavior we're modeling here we're going to apply to other anionic reactions. For example, what would happen if we did a Grignard reaction with an ester? Let's talk about going back to carboxylic acids. Notice, our first reaction was take a carboxylic acid, make an ester, then we're taking the ester back to a carboxylic acid.

We'll then rapidly expand and talk about transforming between all of the different functional groups. What are the different carboxylic acid derivatives in descending order of reactivity? What's the most reactive? Acyl halide, followed by anhydride, then acids and esters, then amides.

What's going to be the main reaction? What's going to be the only logical thing that occurs? Sn2, which brings up that question of the tetrahedral intermediate. Let's say that it's not directly Sn2, because remember that vinyl positions generally don't like to undergo Sn2 because of repulsion of the electron cloud on the nucleophile by the double bond. But the carbonyl could be attacked, couldn't it? Why? Because hydroxide, that's a nucleophile, and you have a delta positively-charged carbonyl, so you could push that open. Three compounds that we want to compare. What is the pKa of water? 15.7. An aldehyde has a pKa of about 16, and a ketone has a pKa of about 19. More related to today's lecture: ethanol, roughly, has what pKa? 16. Primary alcohols in general tend to have a [lower] pKa in solution than tertiaries. If you deprotonate hydroxide versus ethanol versus t-butanol, the relative basicities of those ions are very similar to each other, cause their parent acids are very similar in acid strength. Notice that we start with hydroxide, we end up with an alkoxide, but that alkoxide is probably not too different in basicity from the hydroxide that you started with, so that is a technically reversible step.

We're not used to that when we attack carbonyls cause in the past, we attacked carbonyls with things like alkyl groups that are so darn basic that it's almost a completely forward reaction; even if on paper we write a reversible arrow, it's so lopsided we [don't really need to]. Now it comes up, especially when we're using carbonyl groups that have what could be called leaving groups, because if that oxygen negative is not that much more basic than what we started with, yes it could collapse and kick hydroxide back off, but by the same logic, it could also collapse and kick ethoxide off – again, it not being much different in basicity than the other two things we've already played with here. That step of the reaction is also, technically, reversible. But look at what we just made – a carboxylic acid. Here's the important part: you also spit out ethoxide, which is a base, which means there's an instantaneous neutralization that goes on. That is, on paper, I guess we could write this as reversible, because all acid-base reaction are [technically] reversible, but recognize the pKa of ethanol is 16, whereas the pKa of acetic acid is, rounded up, 5; it's actually 4.76. That's more than 10 orders of magnitude difference with ethanol, meaning it's so lopsided that we don't call it reversible any more; it neutralizes.

The initial portion of this saponification mechanism is technically reversible, since the base used and the intermediate formed at similar enough to each other in terms of basicity. A Grignard reaction, the mechanism will look very similar, but it won't be reversible, because one base is so much more powerful than the other. Where this mechanism formally becomes irreversible is, again, at that neutralization. At the end of the mechanism, both an acid and the base are produced, which instantly neutralize each other and prevent the reaction from reversing – which brings up an important point – for many of the reactions we're going to learn with carboxylic acid derivatives, there might be both an acid (cationic) version of that reaction and a basic (anionic) version of that reaction. But when carboxylic acids themselves are involved, sometimes that can't be true, because the carboxylic acid is an acid – this is exactly one of those cases. We could take an ester and use a base to get back to a carboxylic acid, but, with only one exception, we can't take a carboxylic acid and try to make an ester out of it. The following is possible: that we an do Fischer esterification. It is the several common ways to make an ester; I'm about to show you another common way to make esters that avoids the need for prolonged heating and acid catalysts, cause what if we're trying to do something where you already have some kind of sensitive functional group. We can take ethanol and a carboxylic acid, heat them up with an acid catalyst, and successfully produce an ester. If we took a carboxylic acid and tried to do the basic equivalent, use sodium ethoxide, all that will happen is you'll neutralize, so esterification is not possible under basic conditions.

There is one exception to this, which is the reaction with the molecule diazomethane. The azo prefix has to do with nitrogen. Rather reactive molecule. Particularly reactive molecule. Explosively reactive molecule – so much so that you have to use special glassware; you have to use plastic or plastic coated glassware cause normal glass glassware has these little crevices that this gets into and somehow that initiates the very explosion that you want to try to avoid. You might think: why in the world would you use such a compound? Because it's a beautifully clean reaction when it doesn't blow up that reproducibly and almost quantitatively – which means one mole in, one mole out – 100% yield; it's a wonderful way of making a methyl ester. Here's the mechanism. Starting with a carboxylic acid, diazomethane is basic, as you might guess from the carbanion that we start with. If you react it with a carboxylic acid, that means we get this instant neutralization that I told you about. But, then we have an unusual situation, where we have nitrogen as a leaving group. [The] formation of nitrogen [diatomic] is an extraordinarily thermodynamically favorable process, which is why this compound's explosive to begin with; it just decomposes into nitrogen almost spontaneously. But, once this protonation's happened, you have an excellent leaving group on a methyl position, and so even though a carboxylate's not a strong base, you get an "instant" Sn2 reaction, which gives you the methyl ester.

Let me summarize what we've done the first two days in this unit of material. We've seen different carboxylic acid derivatives, and we've talked about why both in terms of induction and leaving group ability there's a difference in the reactivity of those different derivatives. We've seen one the prototypical examples of a cationic mechanism, Fischer esterification. We've talked about how it is reversible and how we an influence that product distribution by using tricks of removing one of the products – in this case water – from that reaction.

We've also now seen an anionic reaction where we've talked about how base strength of what you start with an end with can influence the reversibility of that reaction, and we've now seen all the ways possible to convert an acid and ester back and forth to each other.

[plan for the future – hydrolysis; solvolysis; reduction – LiAlH4 versus NaBH4; alkylation]

Let me show you a couple of examples. Why are acyl halides useful? Because if you take an acyl halide and react it directly with an alcohol – this is an example of solvolysis. [An] acyl halide's reactive enough you don't need an acid catalyst to get this reaction to occur; you'll very rapidly get the ester. In principle, if you had something on the molecule that was an acid-sensitive functional group, HCl is spit off as a by-product of this reaction, so we want some kind of base scavenger in – maybe something like pyridine – but it does avoid having to do the Fischer esterification. What would happen if we took an ester and did a Grignard reaction? You [can take] methyl or ethyl benzoate and react[] it with phenylmagnesium bromide. Keeping this generalized, after one Grignard reagent reacts, there'd be this opening of the carbonyl and collapsing, but that would generate a ketone, which means if you have any more Grignard reagent around, you're going to get a second addition, a double overall addition by Grignard reaction.

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Favoring equilibrium – Dean-Stark trap

Toluene forms an azeotrope w/ H2O (a vapor mixture of two or more compounds that would be immiscible in the liquid phase). It is used in Fischer esterifications to help pull water out of sol'n while refluxing.

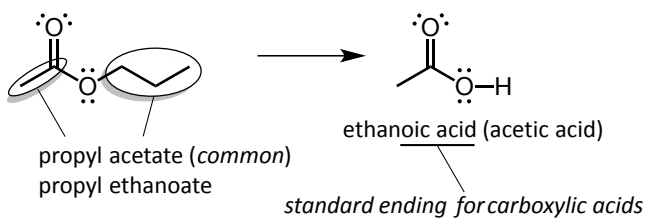Saponification – Formation of carboxylic acid salts

CMC – critical micelle concentration

* The initial portion of this saponification rxn 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 and prevent the rxn from reversing.
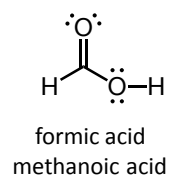
– hydrolysis (H2O, delta, time); solvolysis (ROH, delta, time); reduction (LiAlH4 vs NaBH4); alkylation (Grignard)
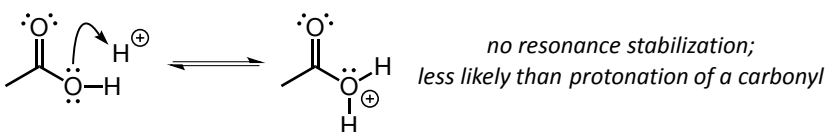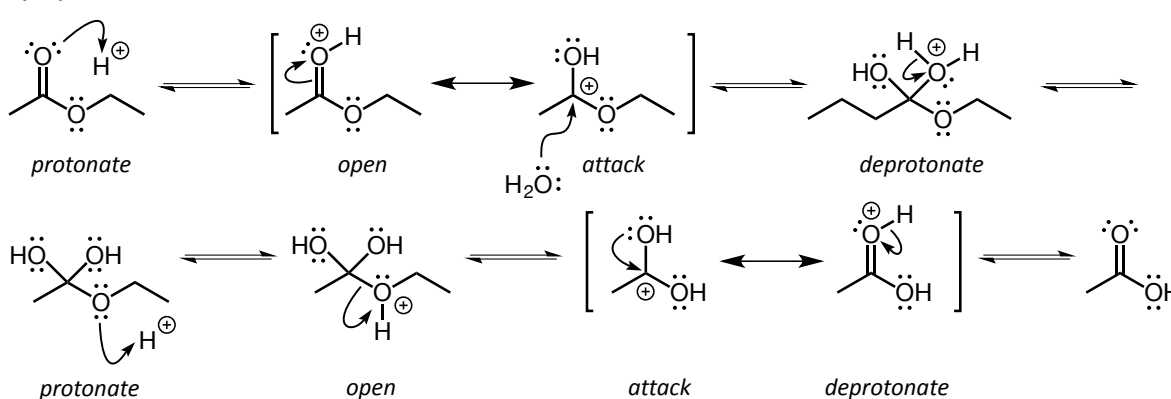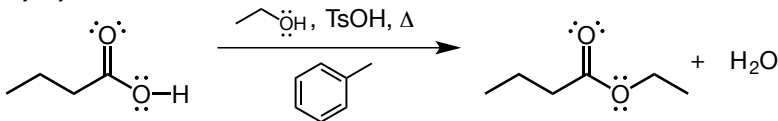
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Structures

04/13/12A lec • 1

propyl acetate (*common*)
propyl ethanoate

ethanoic acid (acetic acid)

standard ending for carboxylic acids

04/13/12A lec • 2

formic acid
methanoic acid

04/13/12A lec • 3

no resonance stabilization;
less likely than protonation of a carbonyl

04/13/12A lec • 4

protonate   open   attack   deprotonate

$H_2\ddot{O}:$

protonate   open   attack   deprotonate

04/13/12A lec • 5

$\overset{..}{O}H$, TsOH, Δ

$+ H_2O$

04/13/12A lec • 8

pKa = 16   pKa = 19

04/13/12A lec • 6

$H_2^{18}O$ (*large excess*)

$H^+, Δ$

$\overset{..}{O}H$ (*large excess*)

$H^+, Δ$

04/13/12A lec • 7

$Na^{\oplus}$

organic tail
hydrophobic/lipohilic

ionic head group
hydrophilic/lipophobic

04/13/12A lec • 9

pKa = 15.7   pKa = 16   pKa = 18   pKa = 4.76

04/13/12A lec • 10

NaOH

Δ

$+ H\overset{..}{O}$
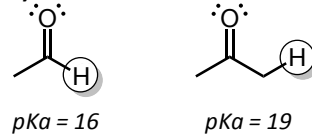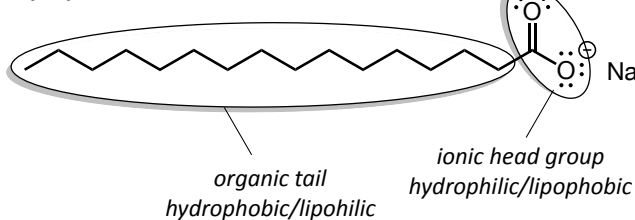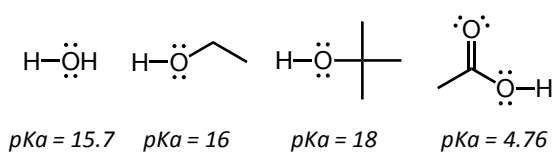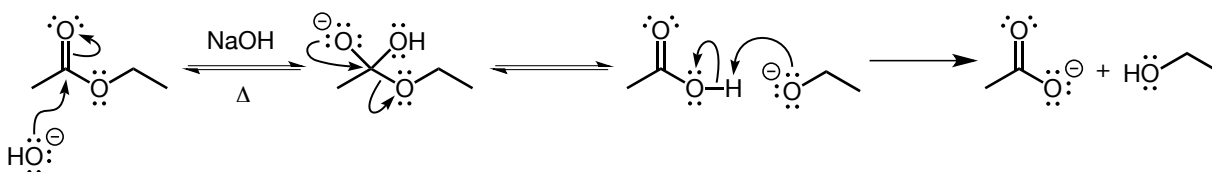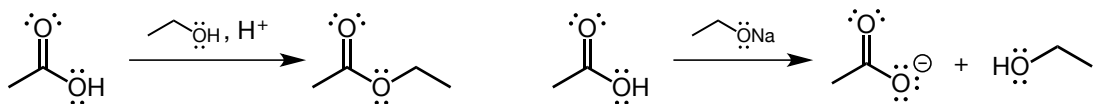
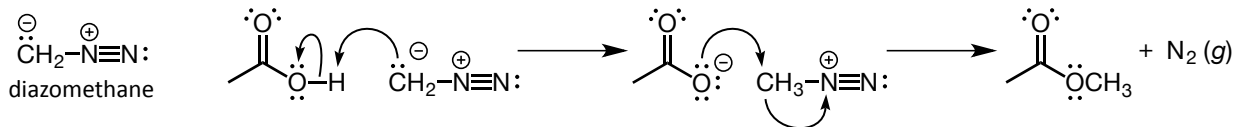*04/13/12A lec • 11*

esterification not possible under
basic conditions due to neutralization

04/13/12A lec • 12   *04/13/12A lec • 13*

diazomethane

$+ N_2 (g)$

04/13/12A lec • 14

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