Lecture 4B • 04/19/12

[schedule for the quarter]

Alkylation and reduction

Let's start with reduction first. Let's talk about sodium borohydride versus lithium aluminum hydride, cause it matters that there's a difference in the reactivity between the two. Very briefly, why is it that one of these reagents is so much more reactive than the other? There's a difference in electronegativity. In the case of the borohydride, it's boron and hydrogen that we're looking at, in the aluminum hydride, it's aluminum and hydrogen. Aluminum is less electronegative than boron; both of them are less electronegative that hydrogen. Since aluminum is less electronegative than boron and less than hydrogen, the difference between aluminum and hydrogen is greater than the difference between boron and hydrogen. Because of that, that means that the hydride in aluminum hydride acts more like hydride, acts more like H-, so it is the more reactive reagent. Lithium aluminum hydride is a much more reactive reducing agent due to the greater electronegativity difference between aluminum and hydrogen, versus boron and hydrogen.

Here's where this difference comes up. If we were to take an ester, [which is less reactive than a ketone?]. If we throw sodium borohydride at it, effectively, there's no reaction. Maybe over long periods of time, then maybe there might be a reaction. We could imagine why this might be less reactive than a ketone, for the same reasons we said the alpha proton of an ester is less acidic than that of a ketone, because of the stabilization of the carbonyl, cause you've got resonance with that methoxy group there. If you make the carbonyl less attractive to H-, it doesn't react. If we had lithium aluminum hydride instead, we're going to see that that leads to a reduction all the way down to an alcohol.

Here's the neat trick that can occur. Because of this difference [in the difference] in electronegativity, because [of] the difference in reactivity of these reagents, if we had a difunctional molecule, such as an oxoester (combination ketone/ester), if we used sodium borohydride, it still would not affect the ester portion, it would react with the ketone, so it allows us to do selective reduction. Of course, if we flop the reagent again, we don't get selectivity. If we had an oxo[ester] that reacted with lithium aluminum hydride – let me say that we throw an excess of the lithium aluminum hydride in – if we did, both the ketone and the ester would be reduced down to alcohols. That's just our starting point: the difference in reactivity of sodium borohydride and lithium aluminum hydride.

Let's look at the mechanism for the reduction of an ester using lithium aluminum hydride. It's going to be very similar to the mechanism, at first, to the mechanism for the reduction of a ketone, but there'll be one big diverging point. I'll write out the structure of lithium aluminum hydride. Recognize that, because aluminum starts with four bonds to it, it starts with a negative charge on it as well. One of these hydride will disassociate. The notation [here] simply show[s] the bond itself attacking; a chemist would recognize that hydrogen, being the more electronegative element and the one more likely to carry the negative charge, is gonna be the thing that ends up connected to the carbonyl, not the aluminum. That will kick the carbonyl open. This reaction I've written with a forward arrow. It is appropriate to write it with a forward arrow. [When we discussed aldol condensations,] we had a situation where an intermediate versus the reactant had similar basicity; they're conjugates were similar in pKa. But hydrogen [diatomic has a pKa of 33?], whereas an alkoxide is more between 16 and 18 for its parent acid. So, hydride is much more basic than the alkoxide is, so this reaction is effectively irreversible.

But, it is also not over, like it would have been if we had a plain ketone [or aldehyde], because that's what's going to form right here [– an aldehyde]. Previously, when we did these reductions, we pushed a carbonyl open, there was an alkoxide, and there was no leaving group. But now, because methoxide, in fact, might be a weaker base than this particular alkoxide, it is possible for the carbonyl to reform and kick that group off. If you can make an aldehyde, that's more reactive that a ketone, even[, and much more reactive than an ester]. The conditions that allow us to reduce the ester will automatically cause the aldehyde to be reduced as well. So, we show another hydride being transfered over. Now, we'll be stuck at the alkoxide, cause here's why nothing further [can happen]: we have either a methyl group that the alkoxide could try to kick back out, or we have a hydrogen – both of which are far more basic than the alkoxide, so no way is any kind of elimination going to occur. The reaction stops here, until we switch conditions and use H+. [Do not mix acids and bases]. If you look at the way that I wrote this reaction synthetically, I start with the lithium aluminum hydride and, step two, I switch to H+, so it's fine for me to suddenly use H+ at the end of the mechanism, cause that's the point that we would switch conditions. [esters react twice]

It is the identical mechanism that an acyl halide would follow. The reaction of esters and acyl halides with either reducing agents – or alkylating agents – occur twice. In both cases, with both functional groups, you'd first produce either an aldehyde or a ketone, depending on whether you're doing reduction or alkylation. That carbonyl compound reacts a second time; unless you use a special set of reagents, there's no way to prevent it, so you get two reactions. Let me show you the acyl halide mechanism. The acyl halide reacts with lithium aluminum hydride to make an alkoxide, which would easily collapse because you'd have chloride that could be kicked out.

As soon as we form the resulting aldehyde, another hydride is transfered, which means we get to the alkoxide, which does nothing further until acidification. Notice the acyl halide with the same number of carbons as the ester, they form the exact same product.

What would happen if we tried to reduce a lactone: would the ring open, or not open? First, [what is] a lactone? A lactone's a cyclic ester, so it's got a carbonyl in it; a lactone looks like this. Do you think that ring is going to be intact or opened by the time reduction's over with? Let's see if we can figure that out. What's going to be the first step of the reaction? Hydride attacks the carbonyl. Now what? Now the carbonyl reforms; this is going to be an identical mechanism [to the reaction up above]. The only thing that's different is the fact we've got a ring; it doesn't really matter. When the carbonyl reforms, it's going to kick out the other oxygen. Because it kicks out the other oxygen and it's part of the same compound, it does mean the ring opens. When we do the same thing with lactams, they won't open. [story about 2008 quiz] Lactones, when reduced, open their rings, that is. We end up with a carbonyl; this compound has five carbons total; and there's an alkoxide, now, at the end – which sticks around, because we're not going to have protic solvents if we have lithium aluminum hydride. But, that doesn't prevent the carbonyl from reacting again. Hydride gets transfered, the carbonyl opens up – now we end up with a dialkoxide, which sticks around until we protonate, and we end up with a diol.

Let's go [to] reduction of carboxylic acids. The mechanism for the reduction of carboxylic acids is virtually identical to that of an amide. Carboxylic acids require lithium aluminum hydride; the acyl halide is reactive enough you can use sodium borohydride. If I have a carboxylic acid an lithium aluminum hydride, what would be the first thing that happens? Lithium aluminum hydride is an extraordinarily basic compound, so before the carbonyl even has a chance to react, we get an acid/base neutralization first. We then get something that you might not expect: the oxygen that just got deprotonated in turn attacks aluminum. Why? Because aluminum's electron deficient; if it's lost a hydride, it's back to only having six electrons in its valence shell. Oxygen's got a negative charge there, [so it can] easily act as a Lewis base, and it does. Once it does, we have a transfer of hydride possible, which now causes a result very different than the ester reduction, because this oxygen connected to aluminum, that now becomes a good leaving group. We are able to kick it out, which makes an aldehyde. That aldehyde will react; that makes an alkoxide. Since the follow-up step is acidification, [that] gets us an alcohol. Here are some of the key aspects of this reaction. First, we start with neutralization. Then, we have the complexation between oxygen and the aluminum, which causes that oxygen to be eliminated.

Let's see how this plays out when we have an amide. If you throw a base at an amide, it is the hydrogen on the nitrogen that's more acidic; it's going to be lower in pKa than the alpha proton here [what is the pKa]. That means that when we throw lithium aluminum hydride at it, it's going to react with that nitrogenous alpha proton. We deprotonate; I'm going to combine delocalization [with] the deprotonation [fine to combine resonance]. What do we end up with? We're on our way to something that looks kinda like an imine, but we also have that negative charge on oxygen, even though we have aluminum hydride in solution, so we'll get complexation of that oxygen with the aluminum. As with the carboxylic acid, we're going to get a transfer of a second hydride that will push the carbon-nitrogen double bond open. That produces a negatively-charged nitrogen, which is extraordinarily basic – the pKa of the conjugate acid would be 40, which is a really basic ion. Just as above, we're going to kick this oxygen group off. Why is it that that oxygen group becomes a leaving group? Because aluminum is electron-deficient, so if you kicked oxygen off this molecule, it's able to allow its lone pairs to interact more with that electron-deficient aluminum. When this occurs, what functional group have we made? An imine. Imines can be reduced just like aldehydes and ketones can, so one more hydride now attacks the imine. Nothing further happens until acidification, at which point we're able to get the neutral amine.

Notice something about this mechanism: I started out with an amide that had an R group on the amide. That R group never got kicked off. If you think about an ester the way an ester reacted, after the initial attack of a hydride, an alkoxy group did get kicked off; it didn't in this case because nitrogen, if it's negative, is more basic. Does oxygen minus or nitrogen minus get kicked out? It's so much easier for oxygen minus to get kicked out, so the nitrogen persists. What's the big deal? What would happen if we reduce a lactam?

The terms lactone [and] lactam have nothing to do with the number of carbons; it has to do with the fact that it's cyclic.

Let's do this same mechanism of reduction that we did with a linear amine. The first step is going be attack of a hydride on the [nitrogen's] hydrogen. We deprotonate nitrogen; to be efficient with writing the mechanism, I'm also showing delocalization afterwards. We have the negatively-charged oxygen which complexes with the aluminum. We have the transfer of a hydride over, which makes a negatively-charged nitrogen, which now kicks out the oxygen. Notice, since the nitrogen is itself part of the ring, we end up kicking the [oxygen] off of the ring, but the ring does not open – that's the big difference between the reduction of a lactone and a lactam. There's one last hydride that reacts. We end up with an ion that, upon acidification, we get our product: an amine, a cyclic amine. The reduction of lactams results in no ring opening, versus for a lactone, reduction of lactones does cause ring opening.

Let me show you two specialized reagents. [trisalkoxy only works on esters if they're phenolic esters] For esters, you use something [abbreviated] DIBAL-H; it stands for diisobutylaluminum hydride, which looks like this. Isobutyl is a four-carbon compound where you connect through one what would otherwise be equivalent methyl groups. You do this reaction at far sub-ambient temperatures, way below [20]° C. This -78 [°C] is not a random number; with the appropriate combination of dry ice and acetone, which are both commonly available in [fully-equipped] research labs, put the two of them together, you can make that temperature reproducibly. Part of the reason to cool this down is to prevent over-reaction. Steric hinderance [plays a role here], as well as the fact that each aluminum only has one hydrogen. If you're careful with this reaction, you can stop at the aldehyde. That's the special reagent for esters.

For acyl halides, it is lithium aluminumtris(t-butoxy) hydride, also at the same reduced temperature. The [t-butoxy groups] are both providing electron density to the aluminum and sterically crowding around that aluminum; this reduces its activity [and] lets us come up with an aldehyde as well.

Let's look at alkylation. [If we take] an ester, for example, and use some generic Grignard reagent, the reaction mechanism is identical to that of reduction, because similar things happen: extremely basic reagent attacks the carbonyl; because the reagent itself was extremely basic, but the alkoxide that forms is just basic, the reaction up to this point is not reversible. It continues, because we can kick an alkoxy group off because it is similar in basicity to the alkoxy just formed. With reduction, since all we were adding was a hydrogen, we would have ended up with an aldehyde. Since we're doing an alkylation reaction, now we end up with a ketone, but similarly, that ketone is going to react a second time with a Grignard reagent. We show another attack; we have a second R group. In this case, since we didn't start with any kind of methanoate, no kind of formate, no kind of single-carbon carboxylic acid, all we have is R groups now. If we did start with methyl formate, methyl methanoate, a one-carbon carboxylic acid, we'd have a hydrogen at that joint carbon, which still would not want to be eliminated by the alkoxide, so nothing further happens until acid workup. We get an alcohol formed by double reaction of the Gringard reagent with the carbonyl compound.

[In the alkylation of a carboxylic acid, the] first step would be neutralization. We end up with a carboxylate that could complex with the magnesium, but magnesium does not turn that oxygen into a leaving group. We have a carboxylate that Grignard reagents can be strong enough to attack. But, look what we've made: a dialkoxide. An alkoxide's certainly not going to kick an R group off, and no way is one oxygen going to kick the other oxygen off to form oxide, so at this point, nothing happens. What if you added acid? if you weren't thinking, I'd say: I'd protonate the two oxygens and end up with a diol. If you were thinking, you'd say: hydrate, which means you get a ketone, which doesn't react because we've already added the acid. So, we deprotonate a carboxylic acid; you could attack it by one more Grignard reagent. Because of what you end up with in that tetrahedral intermediate, you can't use yet one more Grignard reagent. Because nothing happens until you add the acid, once you add the acid, the reaction's over, and you get a ketone.

If I know the pKas of these different functional groups, will I have the ability to predict where the attack's going to occur? Yes.

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NaBH4 vs LiAlH4 – LiAlH4 is a much more reactive reducing agent due to the greater EN difference between Al & H vs B & H.

Reaction of esters and acyl halides with reducing agents or alkylating agents occur twice.

– Reduction of lactones does cause ring opening.
– Reduction of lactams results in no ring opening.

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Structures *(remaining structures identical to lecture 4A)*

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