Lab 6B • 02/07/12

First theory question on reduction. You're told that aldehydes and ketones can react with either sodium borohydride or lithium aluminum hydride to be reduced. You're told that aldehydes are generally more reactive than ketones, and, regardless of whether it's an aldehyde or ketone that you're reducing, lithium aluminum hydride tends to be a more reactive reducing agent than sodium borohydride. You're asked why is it that aldehydes are more active that ketones, and you're asked why is it that lithium aluminum hydride is more reactive than sodium borohydride. I'll answer those in reverse order.

For the reducing agents, it has to do with electronegativity. Boron is less electronegative than hydrogen, and aluminum is even less electronegative than that. Aluminum is less electronegative than boron is less electronegative than hydrogen. The electronegativity difference between hydrogen and boron is not as great as that between hydrogen an aluminum. That hydrogen aluminum bond acts more ionically, or you could say that the hydride is more reactive. So it's on the basis of the difference of electronegativity.

Why is it that aldehydes are more reactive than ketones. The one-word answer is hyperconjugation. You were asked to draw some kind of appropriate diagram, [which is a] SMOG, structural molecular orbital graph, which means a picture of the different types of orbitals that make up that molecule. We [don't] shade in plus and minus, the sign of the wavefunction; instead, we just show what things are sp2, sp3, pi bonds, sigma bonds, that type of thing. You needed to show one of two possibilities: either that there is hyperconjugation, or that there's not. To show both of those possibilities, I'm going to do a partial SMOG diagram for ethanal. Ethanal has a pi bond in it, which we represent with a pair of p orbitals. Attached to the carbon, you've got two things – a hydrogen, or you've got a methyl group, which that methyl group is sp3 hybridized. Notice I'm leaving out portions of the molecule – specifically the sp2 hybrids that would be on the carbon and oxygen of the carbonyl – but they don't really matter for this diagram, which is why I'm choosing to leave them out, cause here are the two things you could focus in on: if you have an alkyl group attached to that carbonyl, then you have the possibility of hyperconjugation, which means electron density comes from the sigma bond, regardless of whether there was a hydrogen attached to that carbon or not. This happens to be a methyl group I'm using to show, but even if you had other alkyl groups there, there still would be the sigma bond coming from that carbon. That sigma bond provides electron density into the pi bond, which stabilizes the pi bond. If you make something more stable, you make it less reactive. That's versus what we have on the other side here with just plain hydrogen, because that hydrogen is at a 90° angle to what the p orbital, so there's absolutely no orbital overlap there, so there's the lack of stabilization, which means that it's more reactive. There is the potential to make a kinetic argument, because if you have two alkyl groups, that would somewhat block the approach to the carbonyl, but do realize that the carbonyl is planar. Maybe that has an effect, but a large proportion of this effect is due to hyperconjugation. Between the pi bond and the hydrogen, there's a 90° angle, so there's no overlap. An aldehyde has at least one of these hydrogens that's at a 90° angle, so it has less hypeconjugation, automatically, than a ketone would.

The second theoretical problem was related to mechanism. It was about the oxidation of two different alcohols. You were told that if you had butan-1-ol, a primary alcohol, that you oxidized in PCC, but in anhydrous conditions, that you ended up with an aldehyde. Turns out, though, that if you did allow water in the system, that the compound would continue to oxidized and instead form butanoic acid, a carboxylic acid. You're shown that if you did the same type of procedure with butan-2-ol, where you oxidized it with PCC, turned out that whether you used water or not, the result is exactly the same – you end up with a ketone, which you won't oxidized past. You were asked why is it that there's a difference in behavior between a primary and a secondary alcohol when water is present or not. There's one key point that shows why you can have overoxidation for a primary alcohol but can't for a secondary. Part if it is, yes, you're going to form a hydrate. That formation of a hydrate, if it happens with the primary alcohol, when you continue on to make the chromate ester – main intermediate before the actual oxidation occurs – the super important thing is that there is a hydrogen, which means if a base – water or something like that – comes along, pulls that hydrogen off, kicks off the chromium group, you will have oxidation. But if you look at the case of the secondary alcohol, the key part of that mechanism, the removal of that hydrogen which forms the double bond with the oxygen, that hydrogen doesn't exist here, so no elimination is possible. That and, since you can't remove the hydrogen, you'd be creating yet another bond to carbon so you would end up with five bonds to carbon. This is the main difference right here: that on a primary alcohol, after the first oxidation, there's one more removable hydrogen, while the secondary, there is none – only the first oxidation, the first removal of hydrogen, is possible. If I put a tertiary alcohol up, there's no removable hydrogens to start with, and so you can't do elimination, which means no oxidation at all.

Mechanism

First mechanism problem. You've got a secondary alcohol which reacted with heat and tosic acid. I could have just said H+, but I wanted to show tosic acid to make sure that you know that tosic acid is just an acid catalyst. It is that same acid that I've described as an inexpensive, organic-soluble, strong catalyst. Part of the reason it's a good catalyst, though, is that once it dissociates, the tosylate ion that you get is not nucleophilic. If you had tosylate participating anywhere in the reaction, then you got off track, cause the only thing that this compound is going to do is act as an acid catalyst. What's going to happen, then? The only logical first step of the reaction is for the –OH group to get protonated.

Technically, every single protonation or deprotonation step is a reversible process, cause acid-base systems are equilibrium systems. But, if we're making a product that I'm showing forming irreversibly, then even though individual portions of the mechanism may be reversible, I've been ignoring that. This gets protonated, we make water, which is a leaving group; it leaves; we form a secondary carbocation, which would like to become a tertiary carbocation. That's not impossible, but another thing that might happen is that the little bit of ring strain that's there gets relieved. That forms a carbocation, which is still secondary, so there's a couple of options here. You should show directly the product that would form in this case, or, if you wanted to, you could show one last hydride shift. One way or another, eventually you would show water removing a hydrogen, which means overall this was a dehydration. Portions of this mechanism are certainly reversible, but it would be unfavorable to move from a tertiary carbocation back to a secondary, and it would be unfavorable for the ring to contract. Maybe on paper, this is all reversible, but in practice, no. Seven-membered rings do have an energetic penalty to them; that's because there's enough of a twist that you get not exactly staggered conformations, and so that raises the energy up a little bit. So you'll go from a four- to a five- [membered ring] or a five- to a six-, but you won't go to a seven-. Six-membered ring, thermodynamically, is the most favorable; five-membered is also really darn close to perfectly favorable, so five-membered rings, they can form, but the can open like this.

The second mechanism was a three-parter: started out with a chiral alkyl halide that you first reacted with sodium hydroxide, followed by a chiral epoxide, followed by tosyl chloride. First part of the mechanism's pretty straightforward: this is a primary alkyl halide that we have a small, basic, strong nucleophile, so this is going to be Sn2. Point of that (besides the fact that we make an alcohol) is that you'll have inversion of configuration of that stereocenter. I'm going to have to interrupt the flow of this mechanism a little bit because the next part is going to be cationic epoxide ring-opening that occurs. There's a protonation step that occurs before the ring itself opens. I'm going to show this protonation first and then show this alcohol attack the protonated epoxide ring. Once we have that protonated ring, this cyclooxonium ion is very much like the cyclobromonium and cyclomercurinium ions I had referenced when we covered this topic. The commonality between all of those is the fact that that ring is unstable more towards one direction than the other. The bond towards the tertiary position is longer and weaker than to the primary. So it'll be the tertiary position that gets attacked, but this a concerted mechanism, so stereochemistry is going to be inverted at the point of attack. An unintended consequence of this problem was an issue with writing the product correct. We push this ring open. The righthand carbon is no longer a stereocenter (it wasn't really to begin with either); I'll drop the wedge we were using there. We had inversion of stereochemistry at where the attack had occurred. We have an oxonium ion initially, and then we still have that stereocenter. Here's the trick: if you weren't careful about how you wrote that substituent, if you were in a hurry and you wrote that ethyl group with the point pointing the other direction, you had to make sure to use a wedge when you're writing that deuterium. Why? The alcohol that we have – R or S? S? Oxygen, more important that carbon, more important than deuterium; it looks like it's R, but there's a hydrogen pointing at us; whatever we see, we have to reverse. Yes it really is S. Did I do it correctly down here? Oxygen-carbon-deuterium; still looking clockwise, but the hydrogen's pointing at us, so it's still reversed, so yes it's still S. Did I do this one with the wedge corrected. Oxygen-carbon-deuterium couterclockwise but the hydrogens point away from us the way it's supposed to be, so it is also still S. Continuing on with the mechanism, we have deprotonation; we have an alcohol, but we also have tosyl chloride. There's different ways that you could write that mechanism. The most compact way is do to the simultaneous wrap-around mechanism that I'd shown you, where at the same time the alcohol attacks, sulfonyl opens and closes, kicks out a chlorine. Since I wrote the structure out once, I'll abbreviate now; there is one last deprotonation step.

Fill-in-the-blank

First one, we have a chiral epoxide that reacts with a basic nucleophile. Since that's basic – you know that because of the potassium, it's anionic – we're going to have anionic ring opening of an epoxide, which means that it attacks at the less-substituted position. There's the ethoxy group attached to the less-substituted position, which isn't and never was a stereocenter so I'm using a plain line. The tertiary carbon, where the oxygen ends up at, that one never gets attacked, so the stereocenter doesn't invert there. I didn't show H+ following up this attack, so you can't write –OH there, you have to leave it as the alkoxide. If I don't show H+, it isn't there, and you can't create a reagent out of nothing. It's not possible to have a compound that's just a cation or just an anion, so you normally should show a counterion, whichever's appropriate.

The next one. This is a mesylate, which hopefully you recognized as being structurally identical to a tosylate. We have some unknown compound that reacts with this mesylate and we end up with this symmetric ether. This is not exactly the Williamson ether synthesis. You did take something with a leaving group to form an ether, but the one big difference here is what kind of mesylate is this? Primary, secondary, or tertiary? Tertiary. The Williamson ether synthesis is technically an Sn2 reaction; we take a strong nucleophile and displace a leaving group. But if you have a tertiary substrate and you try to use a strong nucleophile on it, what's going to happen? You're going to have elimination instead. You do need something to attack in, but it must be non-basic; it's 1-methylcyclopentanol. It'll do an Sn1 reaction.

Next one. You've got a chiral alcohol reacting with thionyl chloride. It's exactly the reagents that we use to make an alkyl chloride. The one gotcha is that it is inversion of configuration; you needed to make sure that you inverted that stereocenter.

Next one. Small variation of what we did in class. You react an alcohol with something in order to make the postassium alkoxide. If sodium hydride and sodium work to make a sodium alkoxide, and since potassium and sodium are in the same column of the periodic table, hopefully it makes sense that the answer here would either be potassium or potassium hydride.

Next one. Something reacts with first lithium aluminum deuterated followed by deuterated sulfuric acid in order to make a double-deuterated alcohol. The challenge here was to recognized that the deuterium that's added is not at the same position where the alcohol is. If you think about a carbonyl, whenever you reduce a carbonyl, you're attacking the carbon where the carbonyl's going to open up and therefore the alcohol forms. Well this, the deuterium's next door to that, so what's the only functional group that we learned we can reduce in this way? It's an epoxide, because reductions of epoxides happen at the less substituted position, which would explain how the deuterium ended up on that part of the molecule. It also would explain why you end up with –OD, because after the epoxide ring gets opened, normally we'd say protonation occurs, but that's D2SO4, so that's why deuteration occurs.

Next one. This one had three different alcohols on it – primary, secondary, and tertiary. This reacted with excess chromium trioxide in sulfuric acid and water, the conditions of the Jones' reagent, which means overoxidation is going to occur. For the primary alcohol, that means it turns into a carboxylic acid. For the secondary, that means it turns into a ketone. For the tertiary, nothing happens.

Two more problems. An aldehyde being reduced to an alcohol. But not just any alcohol, an alcohol with a deuterium on it. How did this occur? First, it was lithium aluminum hydride or sodium borohydride. Why? Because a hydrogen ends up at the position where the carbonyl was; there's no deuterium in the middle of the molecule there, so that means hydride was used originally. When working up the reaction, in order to get the alcohol with the deuterium on it, it needed to react with D+ afterwards. Reducing with deuterium and then protonating or reducing with hydride and then deuterating puts the deuterium in alternate positions.

Last problem. A two stepper. Something reacting first with PBr3, followed by sodium iodide in acetone to form an alkyl iodide. Hopefully you recognize that as the process of the Finkelstein reaction, where you start with an alkyl halide then you do this solubility trick to convert it into an iodide. That second step, because this is a secondary position, is an Sn2 reaction, which means it's inversion, and PB3 reacts by inversion as well. Two inversions means nothing happens overall in terms of stereochemistry. The reactant is this alcohol. It must be an alcohol because that's what PB3 reacts with.
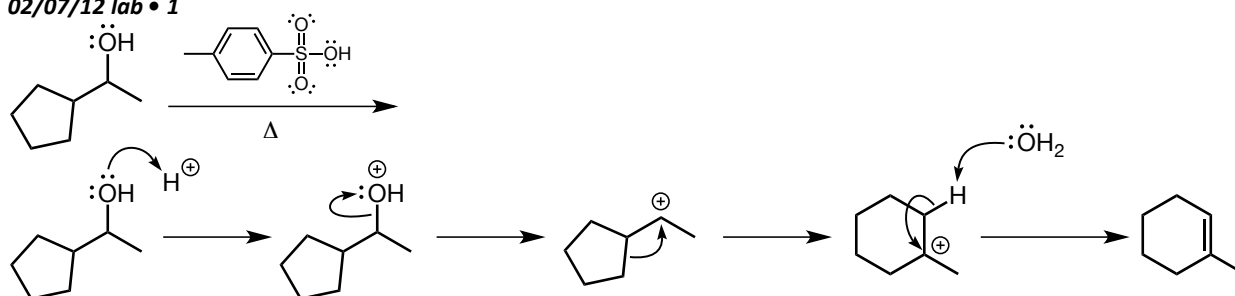
Synthesis problems

First one involved alkylation with an alkyne. If you notice the reactants and products, we maintain the same total number of carbons. Notice that where the aldehyde is, there's a new bond between that position and the alkyl; that should have clued you into the fact that this is an alkylation reaction. In order to do alkylation, we need to have an alkyne salt, one of those acetylide ions, that we can easily get from one of the starting materials; one of the starting materials we do very little with. The other one, though, we need to convert into a leaving group, because you need a leaving group in order to do alkylation. Alcohols are often a synthetic intermediate; do we know of a way of going from an alcohol to a leaving group? Several ways. Do we know how to go from an aldehyde to an alcohol? Yes. That's the sequence of steps you want to have taken. Take the aldehyde, reduce it; in real life it's much easier to do a sodium borohydride reduction. Once you get the alcohol, turn it into a leaving group; why not make a tosylate, a really good leaving group. Next door to the leaving group is a quaternary carbon, meaning there's no hydrogens on it, meaning no E2 or E1 is possible in this system; you're only going to get substitution. To do that substitution, we need the acetylide ion; the reagent we saw last quarter was sodium amide. [does sodium borohydride or lithium aluminum hydride or sodium hydride work as well?] Once you get to the acetylide, you simply combine those two together, and Sn2 occurs, and you end up with the product.

The second synthesis involved make a deuterated compound. Notice, first of all, that we end up with an alcohol at the same position as the bromide, which means it's unlikely that it involves an alkene, an alkyne, or an alkoxide, because those are functional groups that normally I've been exploiting to move the position of a functional group. You might this that this could a plain old Sn2 reaction, except for the fact that you do have a deuterium there. The point of this is could you remember another way of introducing deuterium into this system, which is: reduce an aldehyde using lithium aluminum deuteride. We want to reduce an aldehde, we have to make one first. We can't make one directly from the bromide, but we can make one from an alcohol intermediate. We could us sodium hydroxide – in real life there is the possibility that we'd have a little bit of by-product, maybe a little elimination could occur. There's enough distance from this alkyl group and the point where substitution's occurring that it shouldn't be much of a real problem. And sodium hydroxide's a small base, so out of all the possible bases to use, this might have the least change of elimination. From here, we do PCC in pyridine; it would be understood that those are anhydrous conditions; that would get us to the aldehyde. Then, sodium borodeuteride to reduce, followed by H+ to get the product.
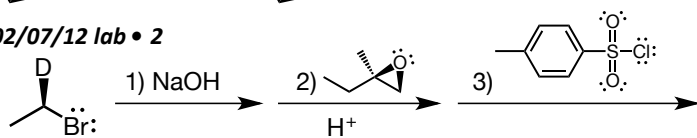
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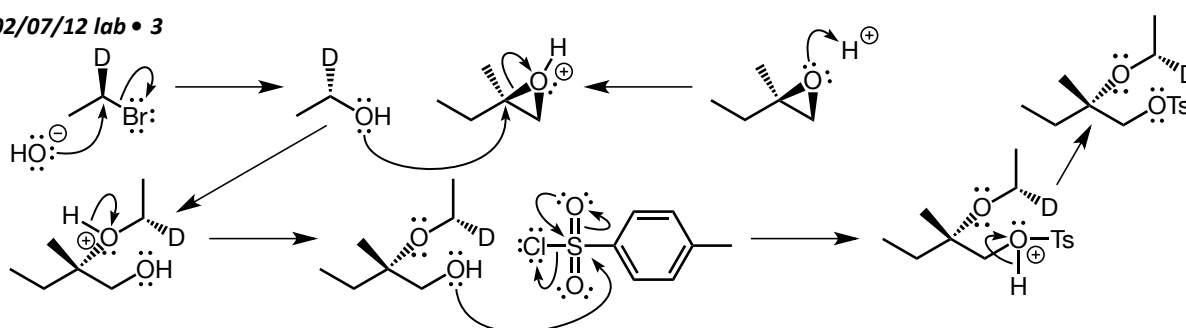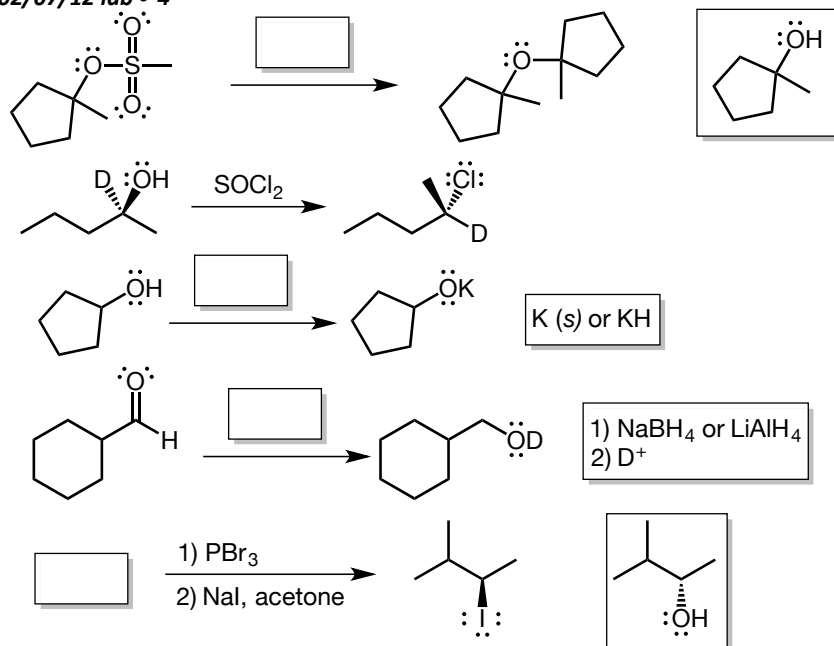**Structures** *(remaining structures identical to lab 7A)*

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1) NaBH$_4$ or LiAlH$_4$
2) D$^+$

1) PBr$_3$
2) NaI, acetone

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NaOH

PCC
pyridine

1) NaBD$_4$
2) H$^+$