Lab 7A • 02/06/12

Let's cover the answer for exam one.

First theory problem first; it was a two-parter. You were told that both aldehydes and ketones and react with either lithium aluminum hydride or sodium borohydride in a reduction reaction. You're told that, generally, aldehydes are more reactive than ketones, and regardless of which one you're reducing, lithium aluminum hydride is more reactive than the sodium borohydride. The two questions are: why is it that aldehydes are more reactive than ketones, and why is it that the lithium aluminum hydride's more reactive than sodium borohyride. Let me address those in reverse order. In the case of which of the two reagents is more reactive, that would have to do with electronegativity. Boron is less electronegative than hydrogen, but aluminum is even less electronegative than that, because aluminum is below boron on the periodic table. Whatever electronegativity difference you have between boron and hydrogen is not as great as the electronegativity difference between aluminum and hydrogen. Given the larger electronegativity difference, that's why the hydrogen in lithium aluminum hydride has a greater activity, because it's as if it was more of an ionic compound. Why is it that the aldehyde is more reactive than a ketone? That has to do with hyperconjugation; hyperconjugation is the one-word answer to that part of the question. You were asked to draw some sort of appropriate diagram in connection with that question. A SMOG – structural molecular orbital graph – is s a depiction of the different types of orbitals present. It is not a drawing trying to show phase of the orbitals. For this question, you need to show that there's some form of orbital interaction, and these SMOGs are where you show what things are sp2, what things are sp3, what's p, what's sigma bond, and what's pi bond. You didn't even need to draw a full diagram, you just needed to show one of two key types of interactions that do – or don't – happen. What we could do is look at a molecule like ethanal.

Ethanal has a pi bond in it. Notice that I'm color coding as to type of orbital, not the sign of the wavefunciton. We've got a methyl group and we've got a hydrogen attached to the carbonyl. That methyl group's going to have sp3 hybridization. One of those sp3 hybrids is actually going to be part of the sigma bond that I have being drawn back towards the carbonyl. Then, we'll have three more of these sp3-hybrids; each one in this case has a hydrogen. I'm going to show you the two types of comments you could make; one or the other you needed to make. If you focus on the fact that this is an aldehyde, the fact that you have a hydrogen there, that hydrogen is at a 90° angle to the pi bond. If you're at a 90° angle, you've got no orbital overlap, so there's the lap of donation of electron density from that side of the molecule into the carbonyl. That's versus what we have on the other side. On the side that does have an alkyl group – it doesn't really matter that it's hydrogens attached to that carbon, it's the fact that you have sigma bonds there, and that those sigma bonds can overlap with the pi bond, providing some electron density to the pi bond, lowering the energy – but if you're lowering the energy, you make it less reactive, you're stabilizing it, so it wouldn't need to, as much, react. When you have hydrogens, less of that hyperconjugation overlap, less stabilization, more reactivity. When you have the alkyl groups – there is another argument you can make as well, which is sterics. Put two alkyl groups on either side, you've got a bit more steric hinderance, although recall that the carbonyl is a planar system. Besides sterics, though, we have this electronic effect, that each of the alkyl groups can, if you have a ketone, on either side to those alkyl groups has the potential to have hyperconjugation, which stabilizes and makes less reactive the carbonyl bond.

Let's jump to the second of the theoretical problems, which had to do with PCC. You had two different alcohols that were discussed in that problem, one of which was butan-1-ol – which you're told that if it react with PCC under anhydrous conditions that you'll end up with an aldehyde, butanal, but if water was present that that oxidation would continue until you end up with the carboxylic acid. If you did the same type of process with butan-2-ol, instead, here you have PCC with or without water, then it doesn't matter which condition that you have, you're only going to end up with the secondary alcohol. The question was, why is there, then, this difference in reactivity with a primary alcohol – whether or not you have water – versus for the secondary alcohol there is no difference if you have water or not. You did not have to write a full mechanism; in fact, very little of the mechanism you need to show. There's only one key point where this difference in reactivity stems from, and that's what you needed to focus on. So for a primary alcohol, the reason that you have overoxidation is because, in the presence of water, you can form a hydrate. But even beyond the fact that you have a hydrate, is the fact that you have a removable hydrogen that's attached to the same position as the two alcohol groups. A little further into the mechanism, we'll have the chromate ester, which is going to get eliminated, by water or some other base in solution. If we didn't have that removable hydrogen, that elimination would not be possible, we wouldn't be able to oxidize further. I could say simply that oxidation is possible due to the removal of a hydrogen. In the case of a secondary alcohol, once we oxidize to the ketone, we can also form a hydrate. But, there's no hydrogen there. And, on top of that, there's already four bonds to carbon, so we can't make another one. The key mechanistic intermediate that if refer to in the problem is this removal of hydrogen – if that can't happen, oxidation can't occur. With primary alcohols, it happens because, one, you form the hydrate, but two, elimination can occur. For secondary alcohols, even if you form the hydrate, nothing else can happen.

Let's move to mechanism next. The first mechanism problem was the pinacol rearrangement. You had a symmetric starting material, so it didn't matter which one of the alcohols you showed react first, but one or the other will get protonated. [comments on reversibility arrows]

Technically, any protonation or deprotonation is an equilibrium process, so every time you show H+ hopping on or coming off, technically, you should be using reversible arrows – but I'm not, because if the overall process is not reversible, I'm choosing not to show each individual step as reversible. If you did show it a reversible, you're right. We end up with water, which is a leaving group, so it comes off. We already have a tertiary carbocation, which rearranges to form a secondary. But you may think: wait, tertiaries are more stable than secondaries. Yes they are, but this is not a normal secondary carbocation – it's a secondary carbocation that has an oxygen right next door to it. That oxygen allows for instant delocalization of the lone pair, one the carbocation ends up next to it. So, even though it's secondary, it's far more favorable, which is the only reason that it would happen in the first place. Once we have that delocalization, we show deprotonation occurring to make the ketone, which that is the product.

The next mechanism; three-parter. We had a chiral alkyl halide reacting first with sodium hydroxide, second with a chiral epoxide, and third, sodium hydride. First step, reaction of the alkyl halide with sodium hydroxide; that's classic Sn2. Simultaneous attack of the nucleophile and loss of the leaving group, with inversion of stereochemistry; you've gotta make sure that you've inverted that deuterium. The second step involves a sort of side reaction first, because in acid the epoxide is going to get protonated, so I'm going to need to show the epoxide being protonated before I show this alcohol reacting with it. I'm going to break the flow of this mechanism for a moment because I need to show that preliminary step. Separately, we have the epoxide; protonation occurs; we form the cyclooxonium ion, which is just like the cyclobromonium and cyclcomercurinium ions, in that one of the two bonds is longer and weaker. It's the bond to the tertiary positon that's that longer, weaker bond. The alcohol is now able to attack, because by protonating the epoxide, we activated it. It's going to attack at the less substituted position, which is consistent with this being cationic ring opening. This has unintentionally complicated product to draw. One, we're going to have inversion of configuration where that epoxide ring opens; that you've got to show. Notice how we effectively lose stereochemistry at the other position, but here's the thing – if you draw the two carbons of that alcohol the way I have, yes, you're going to write the deuterium with a dash the way I just did. But if you weren't paying attention, and, just in your haste, you accidentally wrote the opposite way, then you'd have to write a wedge for it, because it would have been as if you had flipped it on paper 180° around. It's not that we got two different compounds, but there are two different ways to represent it. Just to make sure, let's look at this, is this R or S? Oxygen more important than carbon more important than deuterium; it looks like it's clockwise, but which way's the hydrogen pointing? It's pointing at us so we reverse whatever we see so it's really counterclockwise, so it's really S. What about down here, did I draw this one correctly? Oxygen, carbon, deuterium, going to the right, but the hydrogen's pointed towards us, so that really is still S. What about over here, where I'm using the wedge? Oxygen, carbon, deuterium, it's counterclockwise, and the hydrogen is pointing the back the way it's supposed to be, so yes, that's also correctly drawn. When you've got multiple stereocenters, you've gotta be careful. I'm going to continue just with the first one, deprotonate it. The step, sodium hydride deprotonates. After the deprotonation, nothing happens. There are no leaving groups, so there's no reason that alkoxide's going to react. This is just the reagent to make an alkoxide, so nothing else is going to happen. That's, with the sodium there, the product.

Let's do the fill-in-the-blank problems next. First one is another epoxide problem. This one is anionic ring opening conditions, since we have an alkoxide. Alkoxides attack at the less substituted position. We're going to lose stereochemistry, so I'll write it with a plain bond. The side that did not get attacked does not change stereochemistry, so the oxygen is still written with a dash, and because there's no H+ shown, again nothing further happens, so the product is an alkoxide. If you put an H+ on there, you created reagents that weren't shown; you can't write –OH cause there's no acid in this case.

The next one. It looked complicated cause you have this cyclic alkyl [mesylate] that reacts with something in order to make an ether. What kind of substrate did we start with? A primary [mesylate]. So what kind of reaction probably occurred here? Primaries can't do Sn1, so the only thing it could have done is Sn2, which means we need a strong, basic nucleophile. So the answer is going to be that. Because if you had an alcohol, an alcohol is not a strong enough reagent to do an Sn2 reaction; you need an alkoxide in order to do an Sn2. This is nothing more, in fact, than the Williamson ether synthesis. It might look a little strange, since I've only shown you half of it; I only showed you the substrate. But I was expecting or hoping that you'd notice that something making the ether, that's the Williamson ether synthesis.

Let me move to the next one. On of the easier reactions. An alcohol reacting with something in order to make an alkoxide, in this case the sodium alkoxide. There are two right answers there: either sodium metal itself, or sodium hydride; either one would have been acceptable.

Next one, probably the toughest of them. Something reacting with lithium aluminum deuteride, followed by deuterated sulfuric acid, to create this doubly deuterated alcohol. The reason this was the trickiest one is you had to recognize that the deuterium that's attached to a carbon is a different carbon that the one that the alcohol's attached to. The reason that's important is because if you had an aldehyde or ketone that you reduced, then wherever that attack occurs, that's the same carbon that the alcohol ends up at. For an aldehyde or a ketone, if the reduction occurs, the deuterium is going to end up at the alcohol, this is obviously not the same place, and so the answer is an epoxide – because if you have an epoxide and you're opening under basic conditions, the attack occurs at the less substituted position. If we drew this ring – the less substituted position, that's where the deuterium would go. Whichever part of the ring gets pushed open, or which part does not, does no undergo inversion; that stereocenter does not invert. That is, in fact, the answer, that particular epoxide.

The next one. [riff on multiple choice exams] You have this molecule with three different molecules that reacts with excess PCC and without water. You also have pyridine present. What happens? With a primary alcohol under anhydrous conditions, you oxidize up to the aldehyde. For a secondary, it doesn't matter what it is, it oxidizes to the ketone. And for a tertiary, nothing happens; although what if we made the chromate ester with that tertiary alcohol but did not show the elimination? Technically correct, it could make the chromate ester – as long as you didn't show the elimination.

Next one. Aldehyde reacting with something in order to make an alcohol, were it's not the alcohol that's deuterated, it's right where the alcohol is. This is one of those cases where we have a carbonyl; we know that because we can't have an epoxide because there's only one carbon off the ring. What's going to be the reducing agent? It's a deuterium that ended up where the carbonyl used to be; that means that it's sodium borodeuteride or lithium aluminum deuteride, followed by non-deuterium acid work-up. If the D was on the oxygen, then the D would be on step two; cause the D is on the carbon, it's part of step one.

Then the last one, another one of the easier problems. Something reacting with PBr_3 in order to make the alkyl halide. It's a alcohol that does it; it happens with inversion. So we started with that alcohol.

I've accidentally skipped one of the problems, so let me come back to that. That was kinda going the opposite direction, where you're given the alcohol and the reagent and you have to show what you make. It's a chiral alcohol that's shown reacting with thionyl chloride, that makes a chloride with inversion of configuration.

Let's do the two synthesis problems. You needed to make a new carbon-carbon bond with an alkyl. If you carefully looked at the products versus reactants, you'll notice that there's the same total number of carbons between the products and reactants, so it is alkylation of an alkyne. I was hoping you might be able to remember that technique, where we're going to deprotonate the alkyne. Of course, in order to do this reaction, you need to have a leaving group, so you needed to turn the aldehyde into something that could be attacked by the alkyne. Hopefully one of the other things that you remember is that alcohols usually make a good intermediate for synthesis reactions. We need a leaving group; do we know how to turn an alcohol into a leaving group? Sure. Do we know how to turn this aldehyde into an alcohol? Yes we do. That's what we could start with. Since sodium borohydride works with aldehydes and it's easier to handle than lithium aluminum hydride, although it would have been correct if you had showed lithium aluminum hydride. That'll get us the alcohol. Because it's a primary alcohol, we could have used whatever reagent we wanted to to convert it into a leaving group – tosylates are good, bromides are good; I haven't used tosyl chloride yet, so I'll use it here. We're ready to do an Sn2 reaction. Notice, by the way, the choice of substrate that I made. Next to the primary carbon, next to the leaving group, is a quaternary carbon, one that has four carbons attached, no hydrogens. Elimination is not possible; the only thing that can happen in this case is an Sn2 reaction. We need the nucleophile, which comes from protonating the alkyne. It was sodium amide that I had shown as being used for deprotonation. [question of whether sodium hydride acceptable] One way or another if you get to that acetylide salt, then there's an Sn2 reaction that occurs, and you get the product.

The second synthesis was inspired by another type of problem that involved two carbons, each of which had or has a functional group on it. I've moved functional group positions. In problems that involved two different positions like that I had suggested that an intermediate in those kinds of reactions is usually an alkene, an alkyne, or an epoxide. Again, there's this idea that an alcohol's maybe a useful intermediate. Do we know how to turn an alcohol into a ketone? Of course. Do we know how to get an alcohol to move positions like that? Not directly, but we know how to make an alcohol from an alkene, and we could make an alkene out of the starting material, can't we? In fact yes, because there's only one type of elimination possible with that starting material, only one way the double bond can form. If I use a bulky, hindered base like that, I'm going to ensure elimination versus substitution. From there, I can make the alcohol; this is the only part of the syntheis that's kinda a gotcha. If you tried to do just plain old hydration, you're going to end up with carbocation rearrangement, so you can't do plain hydration; it's gonna be oxymercuration-demercuration. Oxymercuration-demercuration gets us to the alcohol. No matter how you oxidize it, PCC or chromium trioxide, the only thing you can make is the ketone.

[lab directions]

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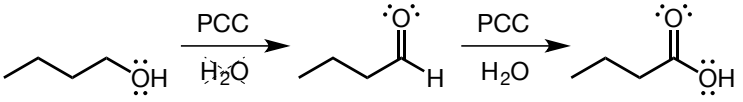

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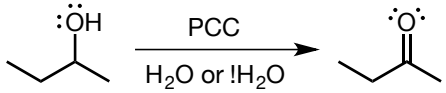

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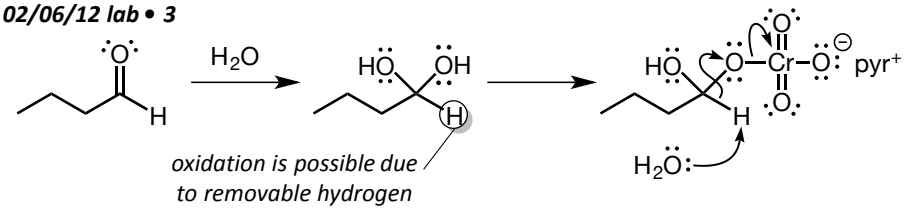

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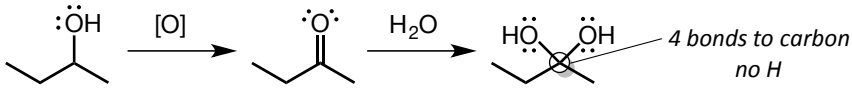

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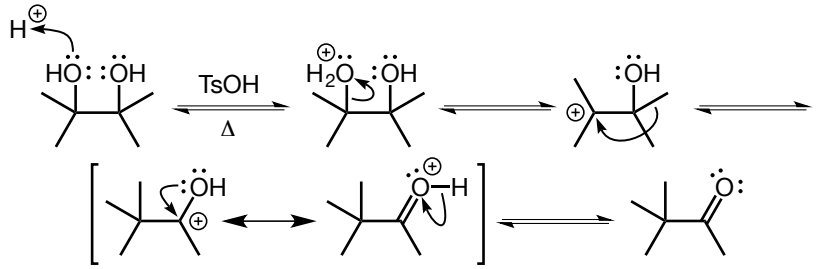

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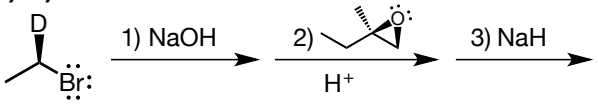

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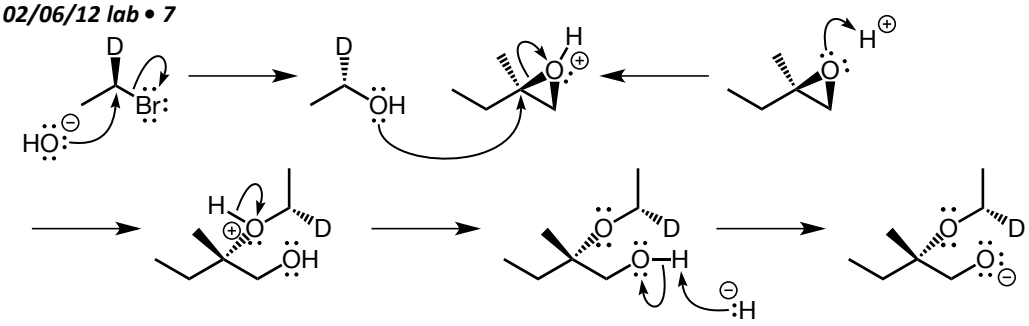

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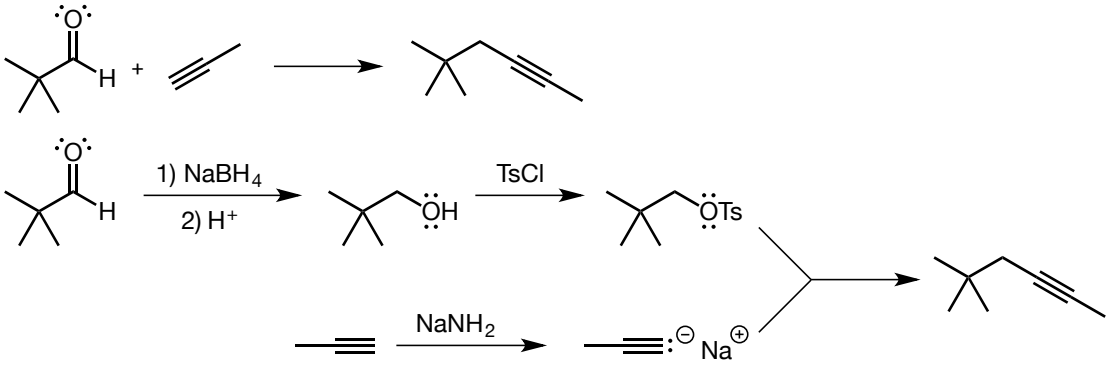

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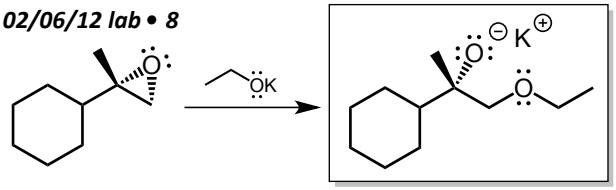

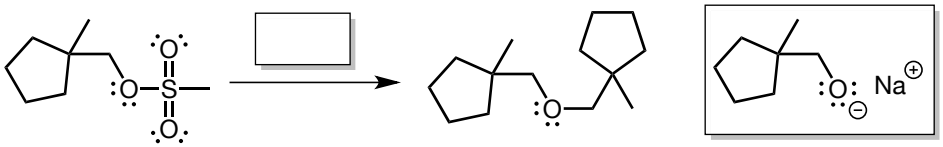

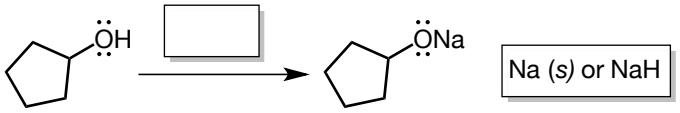

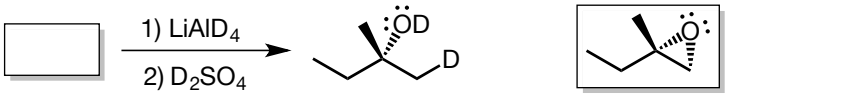

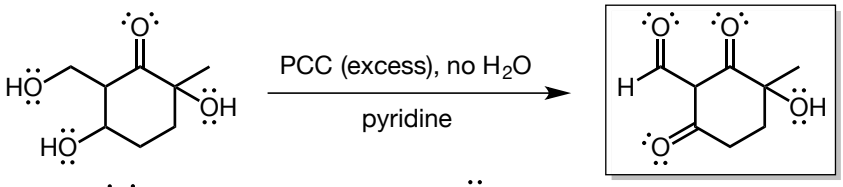

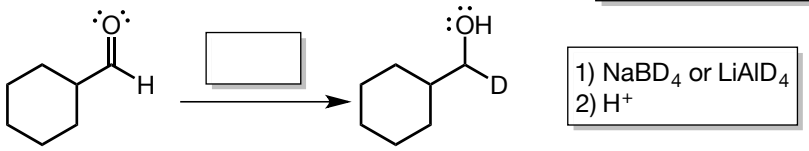

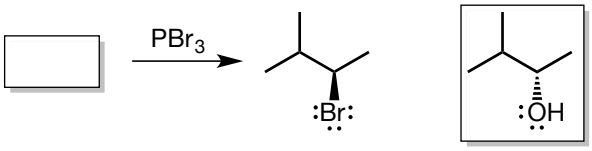

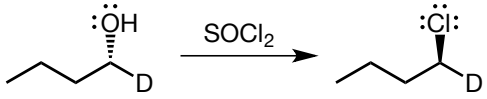

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