

## Lecture 6A • 01/30/12

There is no formal functional group ending for an ether, so it is less important than an aldehyde or a ketone. So as far as establishing which direction we're going to number the chain from, it's a six-carbon parent; don't forget that that methyl group is part of the main chain. If we numbered from the left-hand side, the first number would be 2; if we numbered from the right-hand side, the first number would be 3, so we're going to number from the left. We do have this substituent here which is ethoxy, and it is a stereocenter. In terms of functional group priority, we have an oxygen, which is more important than either of these two carbons, a carbon that's connected to oxygen is more important than a carbon with just hydrogen on it. This stereocenter is S. No numbers needed, since there's only one stereocenter. We get (S)-5-ethoxy. It's a six-carbon compound, so it's hex-; it's saturated so it's ane. Every name that you're gonna have is going to have -ane, -ene-, or -yne in it: -ane if it's all single bonds for the carbons; -ene if there's a double bonded carbon somewhere, and -yne if there's a triple bond somewhere. It's never hexone; hexanone. But it's not hexanone because there's two of them, so throw the 'e' back in, the 2 & 4 position is where they're located, so it's (S)-5-ethoxyhexane-2,4-dione. There's no need for methyl because it's part of the main chain; it looks like a substituent, but it's a trick.

Next problem. This one had an aldehyde and an alcohol. We have an aldehyde; this time we really do have a methyl group. [There is one stereocenter that] you can't determine whether it's R or S because I drew it with a plain line. [commenting on quiz directions] There only one stereocenter you could name, which you technically would have needed phantom atoms to do, because if we look at that carbon-oxygen double bond, we treat it as if there were two oxygens connected to that position; we double whatever is written to it. That's going to automatically win out over the only one oxygen that's at this other position, so the lefthand branch is more important than the righthand branch, and both of those are more important than the methyl group, because a methyl group's only got hydrogen attached. So the priorities are going clockwise, so that stereocenter is R. We do have two substituents; substituents are always named just in plain alphabetical order. We have an alcohol that's going to be named hydroxy, because it's not the most important functional group. We also have the methyl group. The 'h' in hydroxy comes before the 'm' in methyl, so this will be (R)-3-hydroxy-2-methylbutanal.

Next one. We had an aldehyde, a ketone, and an alcohol, for three different types of functional groups, four functionalities total – one aldehyde, two ketones, and the alcohol. Again, we're just going to list in alphabetical order for substituents. The point of this problem was to see if you recognized that a ketone, when it's part of an aldehyde, is the less important functional group, that aldehydes are more important. The two ketones are both going to be called -oxo. The 'o' in oxo comes after the 'h' in hydroxy. Yes, there's two oxos, but the di that you're going to put there doesn't get alphabetized, so you don't look at the 'd' in 'di', you just look at the 'o' in oxo. It's going to be hydroxy first, then oxo; there's no stereocenters, so we just start naming. The aldehyde is automatically given 1, because it is the more important substituent. This is 4-hydroxy-2,3-dioxobutanal.

[comment on topic for exam]

Synthesis problem. You have not learned how to make epoxides directly from alkynes. Even if you could and even if you tried, you'd make a double epoxide because you have two pi bonds. To make this product, you needed to start with an alkene. We have learned a couple different ways to make an alkene. [comments on reactions from previous quarter] You notice that the benzene ring is pointed the opposite direction of the methyl group, which is perfectly fine, cause the epoxide ring itself, both of those bonds are pointed the same direction, which is what we have when we have an epoxide. If, for example, we had started with a cis alkene, an I tried to use either MCPBA or MMPP or make a bromohydrin and do intramolecular Sn2 – whichever route I wanted to use to make an epoxide – I would have gotten enantiomers because the double bond can be attacked from either side. But that's not what's really important; what's really important is that both the methyl group and the benzene ring would be either pushed to being wedges or dashes when that epoxide ring is made. In other words, a cis double bond wouldn't give you the right product stereochemistry. That means we need a trans double bond, so the answer to this last problem was, you start with the alkyne and you reduce using sodium in ammonia. Then, if you take this and react it with MCPBA, you get the product. It is only a two-step synthesis, but it did require you recognizing you need an alkene, and, more specifically, it required you know that it had to be a trans alkene.

Last thing I want to show you is a comment on mechanism. PCC you use when you're trying to be selective. With a secondary alcohol, no matter what you use, you can only oxidize to the ketone. So it would make more sense if you use chromium trioxide. We have the Jones' reagents, which is a combination of aqueous chromium trioxide with a little bit of sulfuric acid thrown in as an acid catalyst. How does this react differently from PCC? Just a small bit different. You start with the chromium trioxide, which in the presence of an acid source can get protonated. Protonation is a reversible step; [the overall] oxidation isn't. I now have a positively charged oxygen which activates that chromium-oxygen bond. There's two ways you can show the next step; the only difference between them is how we handle resonance; technically, that oxygen plus, that's a delocalized ion, cause we could write that pi bond as being over here instead. Whether we show that happening by itself of the way I'm about to show it, where you have something simultaneously attack and push it open, it doesn't matter which way you do it. I've showed this as two steps: oxygen-chromium bond opening first, and then the attacked. They're the same thing. The point is, after this attack, it looks almost exactly like what we would have with PCC.

We made that positive charge on the oxygen that was part of the alcohol; that hydrogen falls off, and then a hydrogen that would need to be on the alcohol then gets eliminated. The rest of this mechanism works exactly the same way as PCC does; the only difference is instead of an O-, with a pyridinium hanging off as a counterion, we have -OH instead.

[list of reactions: converting alcohol to leaving groups, chloride, bromine, iodide, sulfonate; dehydration of alcohols; oxidation, which includes selective oxidation of primary alcohols, overoxidation of primary alcohols; POAD; Williamson ether synthesis; reduction of aldehydes and ketones; lithium aluminum hydride versus sodium borohydride; formation and opening of epoxides; forming an alkoxide; pinacol rearrangement; ring expansion; reactivity of aldehydes versus ketones; formal charge versus oxidation state]

[types of problems]

Anionic versus cationic additions to aldehydes and ketones

Acetals, ketals, hemiacetal, and hemiketals. The reason these functional groups come up is twofold. In terms of biology, that's what sugars are; sugars form these different functional groups, so if you're going to know something about sugar chemistry, you need to know these functional groups. From a chemists' perspective, acetals and ketals are often intermediates used as what's known as a protecting group. Let's say that we have a ketone. We want to do a reaction on some other functional group that might unfortunately cause the ketone to react as well. What if we could hide the ketone, change it temporarily into another functional group, do whatever it is we needed to do, and then get the ketone back. Sometimes in more modern texts they'll call acetals and ketals just by the word ketal, and they'll talk about hemiacetals and hemiketals being the same functional group. I like making the distinction. Aldehydes 'a' make acetals and hemiacetals; ketones 'k' make ketals and hemiketals; otherwise, the chemistry is the same.

Let's make an acetal. It's two cycles of POAD, two cycles of protonate, open, attack, and deprotonate. Let's write that mechanism out. P for protonate – this is a fully reversible reaction, so everything I'm drawing is going to have reversible or resonance arrows. I make my protonated carbonyl. I'm going to show the opening and attack as part of the same step. It's the same as if I had written it individually, because recognize that if all I do is open that carbonyl bond, that's a resonance step anyways, and a resonance step isn't a resonance step, it's just something we write on paper. Instead of water coming in, now we use an alcohol; this is otherwise the same mechanism I had with water, but I'm using an alcohol as a reagent instead. Then, I have my deprotonate step to get rid of the oxonium ion. Look at this product I get. Notice how it looks like it's half hydrate, half ether. That's why this is called a hemiacetal; hemi means half, like hemisphere. It's called hemi because you have one -OH, one -OR. This is an unstable intermediate, usually not isolatable, because it'll either collapse back to the ketone or aldehyde that we start with, or this will get pushed forward. This is a [hemi]acetal because there is a hydrogen that connected at that same position as where the two oxygens are.

This is the halfway point. What can happen next is the -OH group that we just formed can react, reminiscent of the overoxidation step. It can get protonated, we form water, which leaves, we form a carbocation that's a more stabilized than normal carbocation because we've got an oxygen next door here that could be in resonance with it. That looks like a primary carbocation, but it's much more stable than a regular primary carbocation, so it forms more easily than you'd expect. You'd still have alcohol in solution, an alcohol could again attack. We again have this final deprotonation step. The product still has a hydrogen attached to the carbon common to both oxygens, but notice now that we have just -OR groups. This is an acetal.

I'm going to change compounds. I'm doing the forward reaction with one set of reagents; I don't want to do the reverse reaction of this. I want to show you another example. I went from an aldehyde to an acetal; I'm now going to go from a ketal back to a ketone. The reverse mechanism, mechanism-wise, identical, I'm just changing reagents. This is a ketal, how do I know that? Because there's two -OR tied to one carbon. If you see two oxygens connected to one carbon, it's either a hemiacetal, a hemiketal, an acetal, or a ketal, one of those four things. We know it's an acetal, not a ketal, because there's no H on the carbon that's common to both, so it came from a ketone. This is a very common reagent used to make this kind of cyclic intermediate; the formation of five-member rings is usually favorable, so very common trick.

What is the reverse mechanism? Everything that happened, just exactly backwards. Notice that we get rid of water when we're making an acetal or ketal; water comes off. In order to get rid of an acetal or ketal, you have to add water back in. It's the same sequence of protonate, open, attack, deprotonate. Protonate first. How do we know which oxygen is going to get protonated first? It doesn't matter – they're both going to go eventually. Open: which way does it make sense that the opening occurs? I could disconnect this carbon-oxygen bond, but that's a primary carbocation that would form. What if this opened up? Then you'd have another position that would be in resonance, so much, much more likely for that to happen; it also is the reverse of the forward mechanism. You have that carbocation, which, because water's around, it can now attack. It will now deprotonate, and we're halfway there, because instead two -OR groups attached to carbon, one of them is an -OH group. This is a hemiketal. It's hemi because we have one -OH and one -OR; it's a ketal because there's no hydrogen on that common carbon.

The rest of the mechanism is just another cycle of protonate, open, attack, deprotonate. Which one of the three –OH groups is going to get protonated at this point? The answer is yes – all three of them will. It's a fully reversible mechanism. All kind of side reactions could occur, but the one that we care about, the one that's most likely if we're adding water to this, is for this one to react overall. Protonation; that whole darn thing leaves, that's the open; now, intramolecular reactions are often quicker than intermolecular reactions. This is not a reaction, it's resonance; rapidly, we have this resonance occur, which means that deprotonation can occur, so we end up with a ketone. This alcohol, this diol, it has the formal name of ethane-1,2-diol, but it has a name you might recognize – ethylene glycol, antifreeze.

You put water in this reaction to help go from the ketal to the ketone; what's to say the ketone won't just react with water and make a hydrate at this point? It will, but you won't isolate it, because the hydrate is not thermodynamically stable. Although the same conditions that convert a ketal to a ketone will also convert the ketone to a hydrate, most hydrates are not thermodynamically favorable, and it will therefore not be isolatable; it will be the ketone that we get as a result. In general, a hydrate means to add water to something, so a ketone hydrate is when you have two –OH groups on it.

Introduction to Grignard reaction

I'll show you a simplified mechanism. A Grignard reaction is a reaction of alkyl halides, where you react it with magnesium metal in the presence of either ether or THF, tetrahydrofuran. Furan is this aromatic molecule. Just like you can write [O] to mean oxidation without worrying about the reagent, [H] means hydrogenation without worrying about the mechanism. If I fully hydrogenate this, reduce it, there's a total of four hydrogens I've put on there, that's where tetrahydro comes from. Tetrahydrofuran or ether, they are both necessary – one or the other – in this reaction with magnesium. There is a complexation that occurs that assists the formation of this organometallic reagent. Organometallic means that you've got some form of metal-carbon bond. It is that bond that makes this particular react[?]. This acts as if it is just R-, at least when you're using it towards an aldehyde or a ketone. If you take a ketone and you react it with methylmagnesium bromide, follow that up with H+, what you end up doing is putting a new carbon on, and, at the same time, forming an alcohol. Let me highlight that this is a new carbon-carbon bond, super duper important if we're suppose to be doing synthesis.

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Jones reagent – CrO<sub>3</sub>, H<sub>2</sub>O, H<sub>2</sub>SO<sub>4</sub>

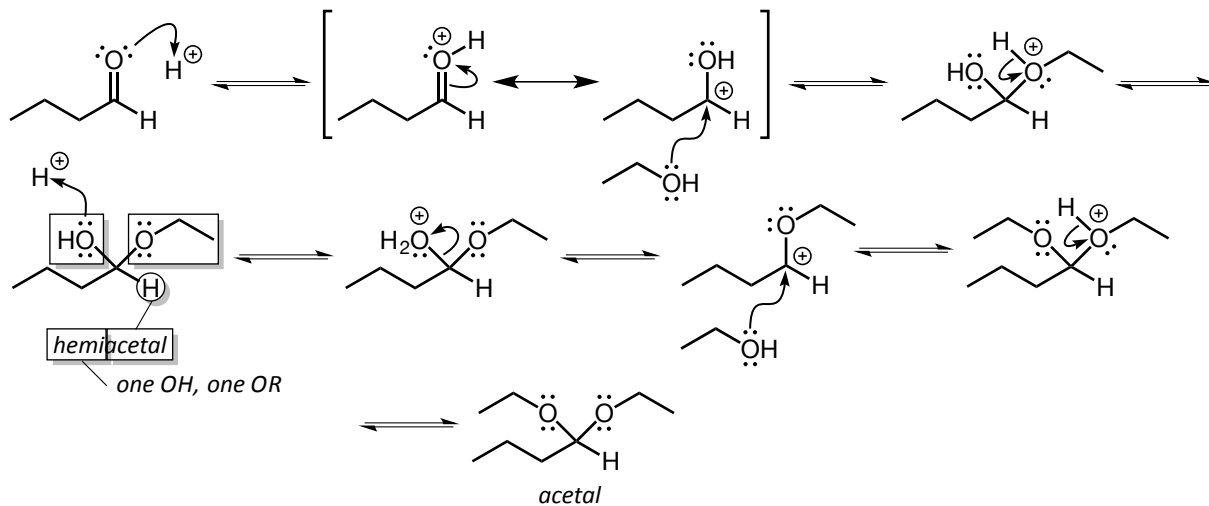
acetals, ketals, hemiacetals, hemiketals

Although the same conditions that convert a ketal to a ketone will also convert the ketone to a hydrate, most hydrates are not thermodynamically favorable and will therefore not be isolatable.

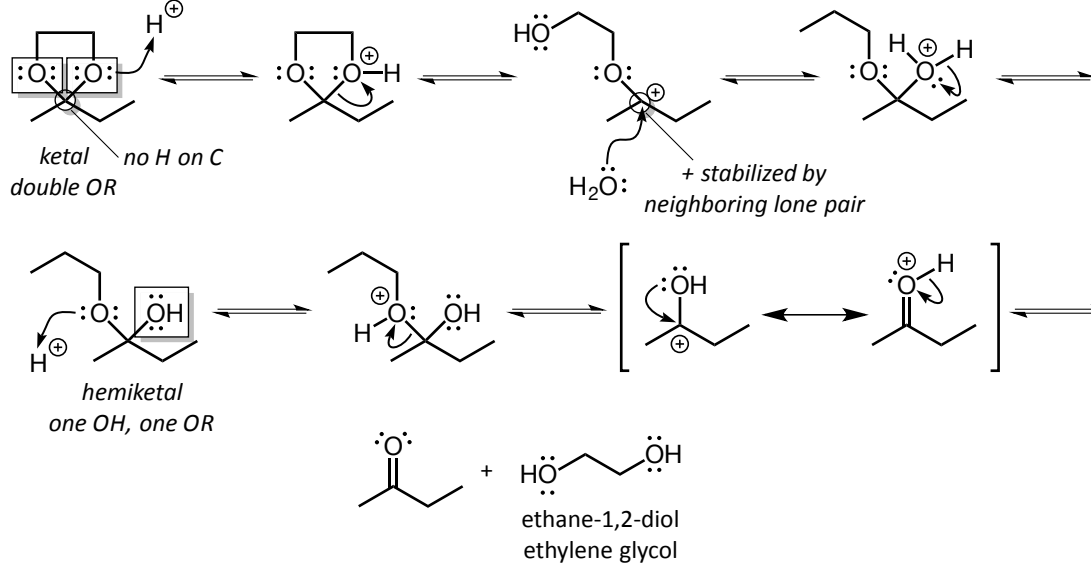
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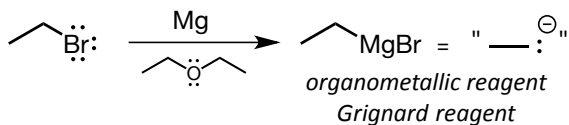
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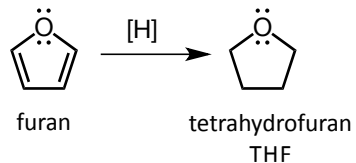
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