Lecture 8B • 01/31/12

[Review for exam]
[topics: alcohols – turning into chloride/bromides/iodides/sulfates, dehydration, oxidation and overoxidation of 1° alcohols, oxidation of 2° alcohols, WIlliamson ether synthesis, alkoxides; POAD; hydrates; reduction of aldehydes and ketones; reactivity of aldehydes versus ketones; LiAlH4 versus NaBH4; epoxides – formation, cationic and anionic opening; pinacol rearrangement; formal charge versus oxidation state]

Cationic and anionic reactions of carbonyl compounds
Hemiacetals, hemiketals, acetals, and ketals

I'm going to show you the formation of a hemiacetal and an acetal. That 'a' that's in there for hemiacetal or acetal is related to aldehyde. You might guess, then, that hemiketals and ketals are related to ketones. The ketal term [has come to represent both classes of compounds], but I [prefer using] these terms. [MCAT example] The reason we learn these at all is because sugars form these different functional groups.

Let's start with the aldehyde first. This is a cationic mechanism, so you'd have an alcohol plus some kind of acid source, a source of H+ in solution. I'll choose ethanol, a nice, common alcohol. The first step would be protonate. This is a fully-reversible reaction. Realize that the open step at this point is nothing more than resonance. Two resonance structures really aren't in some sense; the true molecule is somewhere between those two structure. [Thus,] you can condense down the reaction mechanism a little bit, save a little bit of writing time. If you recognize that that opening of that carbonyl is just resonance, then to some extent it doesn't matter whether you show that opening separately or whether you show it occurring simultaneously with the incoming attack of the alcohol; this is the open and attack steps combined. We'll have a deprotonation occur after than, and we end up with this intermediate that looks kinda like a hydrate, except notice that it has one –OH group on it and it's also got one –OH group on it. Since it's half and half, that's why it's referred to as a hemiacetal. The hemi part of it comes from the fact that it's got half and half these different functionalities, and the acetal comes from the fact that it came from an aldehyde. You've got a hydrogen that's there on that common carbon between two oxygen. These hemiacetals are normally not isolatable; they tend to either fall apart back to the aldehyde they came from, or they further react to make a full acetal. When it further reacts, it's another cycle of protonate, open, attack, deprotonate. The –OH group gets protonated, you make water which can then leave; after it leaves, you still have alcohol in solution, so you have attack of another alcohol; and a deprotonation. This is a full acetal.

Instead of just showing the reverse reaction, I'm going to switch to a different example. The example molecule that I'd like to use [to show the reverse reaction] is a full ketal. The way that we know it's a ketal is that there's no hydrogen at that carbon that's common to the two oxygens. That same central place which is kinda like a disguised carbonyl, this is effectively a way of hiding the fact that you have a carbonyl there, temporarily. There's no hydrogen there, that's how we know it's not an acetal. The way we know it's a full ketal is we have two –OH groups attached and no alcohol attached. If we had the alcohol, then it would be a hemiketal. How does this mechanism work in reverse? It's still rounds of protonate, open, attack, deprotonate. The first thing that happens is one of the two oxygens gets protonated. Since both of those oxygens will eventually come off the carbon, it doesn't matter which one we start with. Then, something's going to open up. You can imagine a couple of different possibilities. This central oxygen is the thing that's positively charged, so technically the top part of the molecule here could disconnect, you can break that oxygen-carbon bond; but if you did so, you'd be making a primary carbocation that's not all that favorable. If instead this lower carbon-oxygen bond broke, the one that's connected to a carbon that's connected to another oxygen, if you broke that bond, you're going to form a carbocation right next door to an oxygen with lone pair. That lone pair helps stabilize the carbocation, so even if it were a primary (which in this case it's not), it'd be a lot more stable than normal. So the ring's going to open this way. The carbocation is stabilized by the neighboring lone pair.

To help make this reaction happen, to force it back to the ketone (or aldehyde), you're going to have water around as a reagent. If you looked at the forward mechanism, water is removed at some point, so in the reverse, water comes back; then, we'll have a deprotonation, which will get us to the hemi ketal. It's hemi because you have half of it being –OH functionality, half of it being an ether functionality, and it's a ketal because there's no hydrogen at that common. This is just half way there, though; you're going to have the other round of protonate, open, attack, and deprotonate. You might look at this and say: wow, we have three different oxygens. Which one of them is going to get protonated? The answer's yes; they're all three at some point or another might get protonated, but only the protonation of one of them's actually going to get us in the forward direction. How do we know that one's going to happen? It has to happen eventually; all of them will get protonated at some point. In one case, if this –OH group that just got put on got protonated, we'd be going back towards the ketal. If the –OH that's at the end of the chain gets protonated, it's unlikely much is going to happen, since it would just form a primary carbocation even if it came off. But if the ether oxygen gets protonated, then something else can happen. Carbon-oxygen bond can open, which is made more favorable by the fact that we have a carbocation that forms with a lone pair next to it. To show that stabilization, I'll show that lone pair attacking and closing up to make the carbonyl. The last step there is just deprotonation.

I could talk about how making the ketal from the ketone is an equilibrium process, where you're having to add water in. If an equilibrium can occur, it will occur. You might look at this and say – water was needed to get to this point, that means water is still around. A ketone can react with water to make a hydrate, and so since equilibrium happens, that means this going to make a hydrate. Yes it is, but a hydrate's not normally a thermodynamically stable product. Even though in solution you might get the hydrate, if you try to remove your solvent, isolate the product, you're only going to get the ketone. Although technically, because water's still present, a hydrate will form; since it's not thermodynamically stable, it won't actually be isolated.

To summarize, you have hemiacetals which form from an aldehyde by adding one molecule of an alcohol to it; adding a second molecule of an alcohol makes it into a full acetal. Exactly the same mechanism, we take a ketone and add a molecule of alcohol, that get's a hemiketal. Add two molecules of [alcohol] that gets a full ketal.

Grignard reaction

This is going to be the first time that you see the use of an organometallic reagent. The way that a Grignard reaction generally starts is you have an alkyl halide, usually a chloride or bromide, that you react with magnesium metal, along with diethyl or THF, tetrahydrofuran. Here's the molecule furan. If you add four hydrogens to it .... Just like [O] can be a general term to represent oxidation, [H] is sometimes used as a general term for reduction. Add four hydrogens, that's where the tetrahydro comes from. Very common lab solvent. Why is ether or THF used in this case? Because the reagent that's going to be formed can only form due to complexation between the oxygen and the magnesium. If you don't have the ether or THF, the reaction won't be successful. What you end up with is an organometallic reagent, which means it's got carbon, but it's got a metal incorporated into the structure as well. More specifically, these are generally referred to as Grignard reagents. This is not the only example – there are other metals that can get involved sometimes – but this is one of the most common ones.

Essentially, the Grignard acts as if it is a carbanion; it therefore attack a carbonyl center. If I had a ketone, for example, and I used one of these Grignard reagents, because the carbonyl gets attacked, gets pushed open, you'll end up with an alcohol. Most importantly, we end up with a new carbon-carbon bond. A general term often used is alkylaton – where we're adding an alkyl group to something. Grignard reagents, because they act like carbanions, are really basic reagents. That's why we end up with an alkoxide first, because you push open the carbonyl, there's no acid for anything else to happen. As a second step, you add H+, the alkoxide gets neutralized, and you end up with the product alcohol.

I want to show you some of the synthetic use of ketals and acetals, anticipating [what are known as] protecting groups. I want you to consider the following factoid: another way to introduce deuterium into organic compounds is to use a Grignard reagent. If we took something like isopropyl bromide, react it with magnesium in ether, we make a Grignard reagent. Because it acts like a base, if you throw water at it, water is a relative acid, you throw D2O at it, heavy water, you could add a deuterium to something. This is considered an advantageous reaction, but normally this would be considered a bad thing; normally, if we wanted to do a reaction with a Grignard reaction, we want to throw it at a carbonyl containing compound.

Here's the situation: let's say I had this combination ketone/alcohol. What I'd like to do is to be able to add an alkyl group to the carbonyl, but I have an alcohol there. Even if I threw a Grignard reagent at this, then the only thing that would happen at first is to deprotonate. Grignard reagents are destroyed by O2, CO2, water, or protic molecules. Anything that's even a little bit acidic, because of how basic these Grignard reagents are. What could we do if we wanted to do a reaction where we did something so that the alcohol doesn't react? We could use what's called a protecting group. There are such things as incompatible chemical reactions. What if, instead of doing this example, what if I want to make a Grignard reagent out of this molecule? It won't work, because if you did get it to form, it would instantly react with itself. The first example, the alcohol's a problem, because the Grignard reagent's gonna attack it. In the second example, the Grignard reagent, if you formed it, would attack itself. But what if we did this? What if we took the carbonyl and added an alcohol to it? This specific alcohol has the systematic name of ethane-1,2-diol; it has the common name ethylene glycol (antifreeze). Why is it used? Because it makes that cyclic acetal or ketal, it rapidly forms a five-membered ring, protects or masks the fact that you have a carbonyl. But you still have the bromide, which could still now do a reaction. Grignard reactions are basic reactions; acetals and ketal form and decompose in acid. If we're doing a bunch of basic reactions, this ketal that we just made won't do anything, so I could react it with Magnesium to form a Grignard reagent; this is base-stable. If I then added some other molecule – let's say I just wanted to make the chain one step larger, a type of reaction know as homologation, homologue that's something that's the same but just a little different size. Homologation means to make a new molecule that's very similar but usually just one carbon bigger. This Grignard reagent would attack. Later on when you're working up the alkoxide, you have a little water around as well, then at the same time that the alcohol forms from that alkoxide, you'll decompose the protecting group.

Up here, when we made the ketal, that was a protection step – you're masking the carbonyl. At the end, we deprotected, we get rid of that masked functionality. There's entire systems of protecting and deprotecting conditions and reagents, because in advanced synthesis you might have four or five different types of protecting group on a molecule that you pop on and off at will, selectively, at just the right points of different syntheses so you could make really complicated connections between molecules.
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Hemiacetals, hemiketals, acetals, ketals

Although a hydrate could potentially form from the product ketone since water is present, hydrates are normally thermodynamically unstable, so only the ketone will be isolated from solution
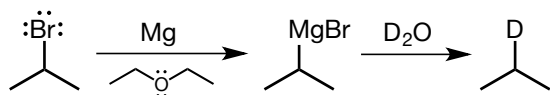
Grignard (grin-yard) reaction
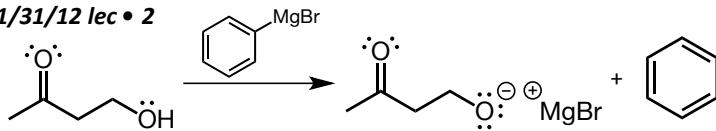
alkylation – to add an alkyl group

Grignard reagents will be destroyed by O2, CO2, H2O, or protic molecules

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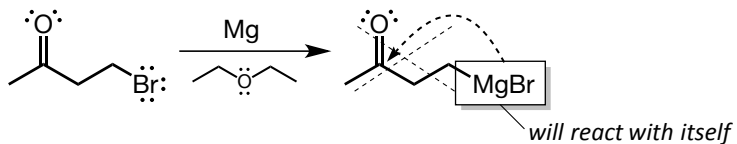**Structures** *(remaining structures identical to lecture 6A)*

01/31/12 lec • 1

01/31/12 lec • 2

01/31/12 lec • 3

will react with itself

01/31/12 lec • 4

ethane-1,2-diol
ethylene glycol

protect

masked or
"protected"
carbonyl

base-stable

new C–C bond   *deprotect*