

Lecture 3A • 01/13/12

Today we're going to be starting chemistry of carbonyl compounds. We're going to be talking about aldehydes and ketones. What is the main difference between an aldehyde and a ketone? In both cases, it's a carbonyl that only has alkyl groups or hydrogens. For an aldehyde, we have to have a hydrogen attached to the carbonyl; for a ketone, it can only be alkyl groups that are attached. The fact that in terms of functional group priority for nomenclature aldehydes are more important than ketones is related to the fact that aldehydes are more reactive than ketones. Why is an aldehyde more reactive functional group than a ketone? It has to do with the difference in charge on the carbon and the oxygen of the carbonyl. If we did look at something like an aldehyde, oxygen is a more electronegative element so it's going to be partially negatively. Carbon is therefore going to be partially positively charged.

There are two flavors of reactions, and we're going to see one example of each today: cationic reactions, which involve the attack on oxygen first, since oxygen is partially negatively charged, that's why it would interact with something cationic in nature; the other way to have a carbonyl react, though, is to just charge and attack the carbon, so carbon is partially-positively charged, so if we had something that was anionic, it would gravitate towards that carbon center. Whether we're doing a cationic reaction or an anionic reaction, the more of a dipole that we have there, the more likely that that functional group's going to be reactive. Just thinking about electron withdrawing capability, let's think of our old friend hyperconjugation. There is a p orbital on both the carbon and the oxygen. This case we have a hydrogen there that would be perpendicular to the p orbital. Why don't we write a partial structural molecular orbital graph (SMOG). This diagram represents the types of orbitals that exist on each atom, usually in order to show the types of overlaps that we have between orbitals on different atoms. I'm going to draw a reduced version where I'm focused just on the pi bond of the carbonyl and then on the orbitals of what's neighboring the carbonyl; not a full SMOG.

Here's our single bond that exists, but in any kind of pi bond, you would normally have a set of p orbitals as well. SMOGs do not indicate the phase of the wavefunction but just the type of orbital we have present. We then have what kind of orbital coming off of the carbon to join with the hydrogen? What would be the hybridization of the carbon at that point? Sp². I'll show one of the three sp² orbitals that comes off the carbon. Hybrid orbitals technically have a nodal plane through them, meaning they have a plus and a minus half just like a p orbital, it's just that hybrid orbitals are lopsided in terms of the size of the two lobes. But for simplicity sake, I don't draw the two lobes on the diagram, cause then we start getting a clutter of bubbles. So this is just showing the major lobe of the sp² hybrid. The whole point of this diagram is to show that the hydrogen and the p orbital from the carbon form a 90° angle with each other. Since there's a 90° angle, there's no overlap, so the hydrogen provides no form of stabilization to the p orbital. In an aldehyde, the hydrogen attached to the carbonyl is unable to hyperconjugate with the carbonyl itself since the bond to hydrogen is perpendicular to the pi bond. But if we had a ketone, where there was no hydrogen, where on both sides of the carbonyl we would have an alkyl group, different situation exists.

Let me do a full SMOG this time. We'll look at this molecule, acetone. You need to know this common name because this molecule is almost never called by its proper name propan-2-one. In acetone, we have three carbons. What's the hybridization of the central carbon? Sp². How do we know what the hybridization is? What's the rule for determining hybridization? Double bond only counts as one type of bond, because the sigma bond counts in VSEPR theory but the pi bond does not. In fact, to figure out hybridization, you count the number of sigma bonds and the number of lone pairs. For the carbon that's in the carbonyl, it has a total of three sigma bonds, so it needs three hybrid orbitals, which is why it's sp²-hybridized. The methyl groups all have four [sigma] bonds, those require four hybrids, that's why it's sp³-hybridized. The central carbon being sp²-hybridized, it's going to have three orbitals on it. The oxygen, if we're following this method, is going to have an sp²-hybridization as well. There's then the p orbitals, and then on either end of the carbon, there's then an sp³-hybridized carbon. Of course, each of these end orbitals on the sp³s has a hydrogen. Let's not forget to show the fact we have a pi bond there. Let me fill in the sp²s. [colors] Point here is that we have hyperconjugation possible. One of the carbon-hydrogen bonds, a sigma bond, is able to provide some extra electron density into that carbonyl. The carbon of the carbonyl is already delta positive because of the electronegativity of oxygen, so this is offsetting that delta positive a little bit. Well, if you offset that delta positive, effectively making it less delta positive, you're making the carbonyl bond less polar, and therefore less reactive. That's why carbonyls in ketones are less reactive than aldehydes. In a ketone, both groups attached to the carbonyl are able to undergo hyperconjugation with the carbonyl. Hyperconjugation effectively reduces the partial positive charge on the carbon, which therefore makes the carbonyl less polar and less reactive. Later on, we're going to learn about conjugation, where instead of this partial overlap that we have from a neighbor's sigma bond, instead if we had a pi bond next door, where you could have complete overlap. We're going to see that has an even more profound effect on structure and reactivity.

Let's learn one of the two main reactions I wanted to cover today. There's this duality to the way that carbonyls react, that you can have cationic reactions and anionic reactions. Both aldehydes and ketones can form a compound called a hydrate. If I just wrote it out in terms of synthesis, the reaction would be taking an aldehyde or ketone, reacting it with water, and some kind of acid catalyst. The end product is that we lose the carbonyl bond, and we've added, effectively, another alcohol. Another term for a hydrate would be a geminal diol. Geminal – that's like Gemini, the Twins, the constellation. Geminal means twin diol, meaning both of the –OH groups are located on the same carbon.

This is, in fact, a reversible reaction, so let me change the arrow that I'm using here. This is very similar to hydration of an alkene. The reactivity's a little different here because this hydrate is normally not thermodynamically favorable. Very small aldehydes, forming a hydrate is actually a favorable reaction. In fact, as a side note, the common name of this aldehyde is formaldehyde, which comes from formica, which is Latin for ant. Formic acid is, in fact, one of the compound in some forms of ants' sting, the stinging component of an ant's sting. Formaldehyde will react with water favorably to form a hydrate, because it forms something which has -OH groups which are very similar to the structure of water. Once you put an R group on, and the larger the R group is, the less polar the molecule is and the less likely it will be water-compatible and, it turns out, the less likely it would want to form a hydrate.

Let's see the mechanism for this reaction. This general style of mechanism I'm about to show you, you're going to do over and over and over again. First step of the reaction is much like what we had when we tried to throw acid in water at an alcohol. Really, there's nothing likely to happen with this molecule, except for oxygen to be protonated. Later on, we'll learn situations where that's not quite true. This is a cationic mechanism that I'm showing you, which is why the oxygen gets involved first. Later on, when we have a strong base, it will be the carbon that reacts first. Focusing on this particular reaction, acetone gets protonated. This is now a delocalized ion; the carbonyl, we can show on paper as opening up. Remember that resonance structures are fake, because there isn't really resonance, it's just the fact that we can't write a delocalized system properly using standard line drawings. I'll show this as its own individual step where you have a bond open. We have formed a carbocation now, which if we're in a solution where there's a lot of water, water can now attack. When we form an oxonium ion in this manner, it's then going to lose a hydrogen to deprotonate. So protonate, open, attack, deprotonate - I'll sometimes abbreviate that sequence with this acronym POAD.

Let's draw the reverse reaction mechanism from taking a hydrate and going backwards to an aldehyde or a ketone. This example was a ketone going to a hydrate; let me start with a hydrate of an aldehyde, just to have done an aldehyde, and see it going backwards. The way that you can tell that we started with an aldehyde versus a ketone is, at the point where the two -OH groups meet, that has to be where the carbonyl carbon was. You can see that I've got a hydrogen attached, next door to what must have been the carbonyl carbon, so I know, I can predict this is an aldehyde. Principle of microscopic reversibility; it's the idea that if you have any process, whatever the easiest way to go forward through that process will, in the reverse direction, automatically be the same pathway that you would take in the reverse direction. The example that I often give is: imagine that you're climbing over a mountain. If you find the easiest path over, there's not going to be another easier pathway back, because if there is, that's the one you would have taken the first time to get over in the first place. Every step that happens in the forward reaction is exactly the same step that's going to happen in reverse in the reverse reaction. Last step here is a proton coming off; first step in the reverse is going to be that proton hopping back on. We make water, which is now a leaving group. We now have a carbocation that is adjacent to an oxygen, therefore we can write formally the fact that it's delocalizing, and then show that hydrogen coming off the positive-charged oxygen to make the neutral carbonyl. Notice that it just so happens we can label these steps as protonate, open, attack, deprotonate. Slightly different actions are happening this time, but the same acronym applies - partly the reason for making this acronym. So if you can remember that sequence - protonate, open, attack, deprotonate - you can remember both the forward and reverse reactions.

There is a slight technicality in terms of the way we could write this mechanism. You can write the mechanism just as I have, or you can realize that the carbonyl, once it's protonated, that is a delocalized ion. It is perfectly valid, in the forward reaction, where we're showing the carbonyl being protonated and then opening, there's no reason we can't write that as simply one step. Because, once the carbonyl is protonated it's delocalized, there's some legitimacy in writing the mechanism combined in this way, where you show the opening simultaneous with protonation. You can do either method that you prefer. This is an example of a cationic reaction. Cationic reactions, especially involving acid catalysts, are normally reversible. Why? Whatever protonated oxygen intermediate we make, they're all pretty much equally as bad as each other, so if you could get it to happen in the forward direction, it's no harder for it to happen in the reverse reaction. No one intermediate is so much more unstable than the other, in other words, that we get stuck at some point in the reaction. That is not many times in the case of anionic reactions. Let's now see the opposite type of situation.

Our example is going to be reduction. There are two very common major reducing agents that you need to be familiar with. One of them is NaBH₄, sodium borohydride; the other one, LiAlH₄, lithium aluminum hydride. Both very common, but when possible, sodium borohydride is generally used instead of lithium aluminum hydride. Let's see if we can come up with a rationalization as to why. Which element is in the same column as boron? Aluminum is in the same column as boron. Because aluminum, though, is below boron, which element is more electronegative? Boron is more electronegative, but between hydrogen and boron, which element is more electronegative? Hydrogen. That's why in the hydroboration reaction, boron ends up acting as the electrophile, making hydrogen act like H⁻, backwards of most other electrophilic reactions which is why hydroboration is an anti-Markovnikov addition. So if boron is already less electronegative than hydrogen, and aluminum is less electronegative than boron, then that means there's an even greater electronegativity difference between aluminum and hydrogen than there is in boron and hydrogen - which is the explanation for why the hydride in lithium aluminum hydride is so much more reactive than in sodium borohydride.

Sodium borohydride, in fact, can be dissolved in alcohols, things that will react in a side reaction with the reagent itself. But, the reagent will decompose at a slow enough rate that, if you had an aldehyde or a ketone present, it will still get reduced, the reaction will still happen, even though it's in a very bad choice of solvent. We take advantage of that in real life because sodium borohydride is relatively inexpensive, so if we use a little excess, no problem. Through a little excess in some methanol, through in whatever ketone or aldehyde, shake it around, and 90-something percent yield; it's a fantastic reaction. Lithium aluminum hydride will also work, but the dry powder itself, if you let it sit around in air, will eventually ignite, because it that violently reacts with the water in the air. [story of fire in Berkeley lab]

What we're going to see in the future is, because there is a big difference in the reactivity of these two reagents, we're going to find other carbonyl groups that one reagent will touch, while the other won't.

The electronegativity difference between aluminum and hydrogen is greater than between boron and hydrogen. Lithium aluminum hydride is therefore a more powerful reducing agent. Sodium borohydride can be safely used in the presence of products. Decomposition will occur, but slowly enough that reduction can still occur. The side reaction will be just like what we saw with sodium hydride, cause sodium borohydride is effectively a source of hydride. The side reaction would be that the sodium borohydride would neutralize the alcohol, forming an alkoxide and hydrogen gas. What's really the reaction we want to see happen? The simplified way of showing it is the following: if we had something, for example, like an aldehyde. We simply show the aldehyde being attacked by hydride. Notice that, simultaneously, we push open that carbonyl, because that carbon otherwise would have already had four bonds to it. Notice that I'm not using a reversible arrow, because the pKa of hydrogen gas is much, much greater than the pKa of an alcohol. If the pKa of hydrogen gas is greater than the pKa of this alcohol, what does that mean in terms of the strength of H⁻ versus the alkoxide I just formed? Which is the stronger base? H₂ has the greater pKa and the alcohol has the smaller pKa. Which of those two compounds, H₂ or an alcohol, is the stronger acid. pKa is the negative log of the Ka. Acid dissociation constants for most organic acids are less than 1, so most pKa values are big values. The bigger the value, the weaker the acid, so H₂ is the weaker acid; the alcohol is therefore the stronger acid. Whichever is the stronger acid makes the weaker base conjugate, because a strong acid means the hydrogen wants to come off, which means the base doesn't want it back. So the alkoxide is the weaker conjugate base; H⁻ is the stronger conjugate base. Hydrogen has a pKa of [36]; the alcohol is going to have a pKa of roughly 16, since it's a primary alcohol. That's [20] orders of magnitude difference; that's a huge difference in basicity. So this reaction I've written with a forward arrow because the reagent is so much more basic than the product, it is highly unlikely the product would try to react in reverse. Reduction is essentially an irreversible reaction, because the reducing agent is far more basic than the product formed. Anionic reactions are often irreversible, especially when there is a large difference in the basicity of the reactants versus products.

We've seen a prototypic example of a cationic reaction, showing that a carbonyl can be induced to open, to react by first protonating the oxygen of that carbonyl. We've now also seen a prototypical example of an anionic reaction, where the carbonyl is forced open, in a reaction that's effectively not reversible because of the huge difference in the basicities of the reagent you start with versus the product you get from that carbonyl.

Multistep synthesis

Here we have a primary alcohol that's being converted into a primary alkyl azide. N₃⁻ can be provided by the reagent NaN₃. [Here is] one possible resonance structure for the N₃⁻ ion. An alcohol is not a leaving group, so this is not a one-step reaction. Design a multistep synthesis, using only that alcohol as your original source of carbon. On a quiz or an exam, this is exactly how the problem might be presented: you see the starting compound, you see the end compound, and you've got to figure out how many steps there are between, and what should be used in each of those steps. Assume azide is a strong nucleophile and not very basic. What if we start with using tosyl chloride versus thionyl chloride? Let's approach this retrosynthetically. Retrosynthesis means start with the product and imagine what might have been there before the product formed. If we step back one step, in order for the azide to have reacted, we need some leaving group there instead. I could even just leave this in the general form LG for leaving group. The point of doing the retrosynthesis is we have to analyze both regiochemistry and stereochemistry. What must be the stereochemistry of the deuterium in this one previous step? It has to be a wedge, because when N₃⁻ attacked, it would have happened by S_N2 substitution. Notice that is the same stereochemistry that we have for the original starting material. Do we know a way of converting the original starting material to a leaving group while retaining stereochemistry? The answer is yes. So if sodium azide is the reagent that would have been used [in this last step], then tosyl chloride would have been the reaction to get us from this alcohol. The way you should write the answer is show one reagent at a time, and the result of that reagent. No mechanism is necessary on this type of problem, because it's a synthesis problem. Then I would show sodium azide making the desired product with the desired stereochemistry.

Shall we do another? I suggest this may be a four-step reaction. Let's try a retrosynthetic approach on this. We end up with an alkyl chloride, which is different from the alcohol, and it's regiochemically in a different position. Before we even start worrying about functional groups we want to think about the carbon backbone. If we have a reaction like this, in which you have two different positions of the molecule involved, there's only a handful of ways that you can make a position move like that. One might be carbocation rearrangement. Is it likely that carbocation rearrangement happened in this problem? Not at all, because what kind of rearrangement would have had to have happened?

You would have gone from tertiary to primary, the chloride ends up at a primary carbon. That's not favorable thermodynamically, so it can't be carbocation rearrangement. What other ways could you have two different positions on a molecule somehow being involved with each other? If we had an alkene or an alkyne, or, an epoxide, because an epoxide has two carbons bridged by a single oxygen. We're going to learn how to take an alcohol – if it has the right functionality around it – turn it into an epoxide to then move the oxygen to the other carbon.

Let's say that this is going to involve an alkene, because it does have two carbons involved. We're going to think retrosynthetically, at some point I want to have ended up with an alkene. Do we, as far as what this class has learned, know a way that we could have gotten this chloride from an alkene? The answer to that question is no – although there are reactions of alkene involving radicals, we only talked about reactions of alkanes involving radicals. So, is there some other functional group we might have been able to get this chloride from? What reactions do you know that form chlorides? Thionyl chloride, or, in theory, we might have been able to do some sort of S_N2 reaction, and alcohols are an incredibly common intermediate in synthesis. Let's see whether the thought that it came from an alcohol is on the right track. Do we know a way that we could have produced this alcohol from an alkene that would have involved these two carbons, because it's not at the most substituted position, is it? But that's exactly the point of [using] borane and then oxidiz[ing] it, it could have come from this alkene, because the primary position would have been the least substituted position. Is there a way we could have made that alkene from the starting alcohol? Is that the thermodynamically most stable alkene? No, so we could not have done a direct dehydration, but couldn't we have done a kinetic elimination with potassium t-butoxide, where even though you might have had the leaving group at the more substituted position, because we use a big bulky base, it makes the less stable alkene. Do we know a way of getting from the original alcohol to an alkyl halide? You do, but you don't know it, because you might be thrown off by the fact that it's tertiary, but it turns out that both thionyl chloride and PBr_3 have alternate S_N1 -like mechanisms when you have tertiary substrates. So yes, you could have taken PBr_3 , reacted the alcohol to make a leaving group, eliminated to the less-favorable position to make the alkene, hydroborated and oxidized it to make the anti-Markovnikov alcohol, which then you could have used thionyl chloride to make the alkyl chloride.

Structural Molecular Orbital Graph (SMOG)

In an aldehyde, the hydrogen attached to the carbonyl is unable to hyperconjugate with the $C=O$ itself since the bond to hydrogen is perpendicular to the pi bond.

In a ketone, both groups attached to the carbonyl are able to undergo hyperconjugation with the carbonyl. Hyperconjugation effectively reduces the δ^+ on the carbonyl carbon, which therefore makes the $C=O$ less polar and less reactive.

Hydrate (geminal diol)

reverse rxn

alternate notation:

cationic reactions – especially involving acid catalysts – are normally reversible

reduction

$NaBH_4$ sodium borohydride

$LiAlH_4$ lithium aluminum hydride

The electronegativity difference between aluminum and hydrogen is greater than between boron and hydrogen. $LiAlH_4$ is therefore a far more powerful reducing agent. $NaBH_4$ can be safely used in the presence of protic solvents; decomposition will occur, but slowly enough reduction can still occur.

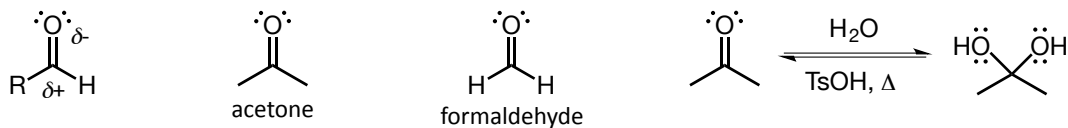
side rxn

Reduction is essentially an irreversible reaction because the reducing agent is far more basic than the product formed.

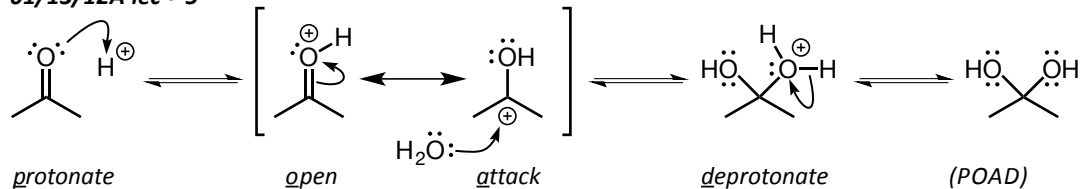
Anionic reactions are often irreversible, especially when there is a large difference in the basicity of the reactants vs. products.

Structures

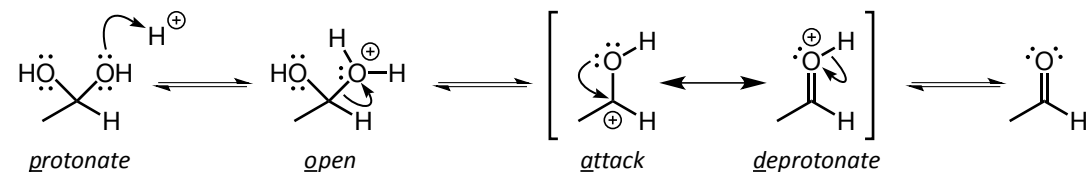
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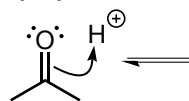
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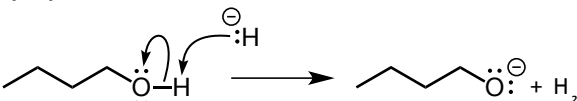
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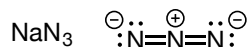
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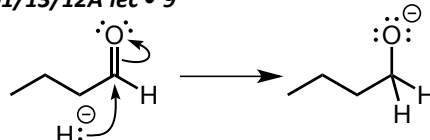
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01/13/12A lec • 10



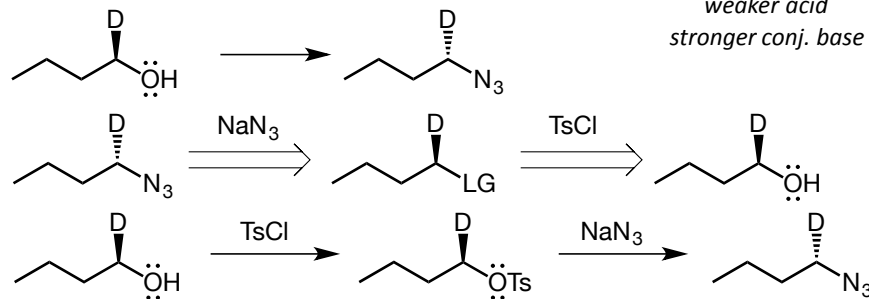
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H2 larger pKa
weaker acid
stronger conj. base

ROH smaller pKa
stronger acid
weaker conj. base

01/13/12A lec • 11



01/13/12A lec • 12

