

Lecture 3B • 01/13/12

Today we are going to begin our discussion of the carbonyl bond and the reactivity of aldehydes and ketones.

The pinacol rearrangement involves this symmetric diol. It's a double tertiary alcohol. Let's see what happens when we react this with H^+ under dehydrative conditions. The alcohol initially gets protonated in a reversible reaction; we form water, which is a leaving group, which can therefore leave; and we have a tertiary carbocation, which we might think would be the most favorable carbocation that we could have. What is it that makes a tertiary carbocation so stable? Hyperconjugation. What if we had true conjugation to stabilize the carbocation instead? Is there a way we could achieve that? Turns out the answer is yes: if one of these alkyl groups from next door migrates over to the carbocation, which is a similar process to a hydride shift. If that were to occur, it means that we technically end up with just a secondary carbocation, but it's not a normal carbocation, because we do have the lone pair on oxygen right next door, which can now undergo resonance. What we end up with as a result is a carbonyl, which after deprotonation gives us a neutral molecule. The original compound is called 'pinacol' and the product is called 'pinacolone'. This is not its own special reaction, in a sense; it's just an example of rearrangement. The purpose of [this reaction] is to convert a vicinal diol into a ketone; the reagents are just acid and heat; there are no special conditions other than you don't want water since you're trying to remove water. You've seen the mechanism for this reaction. Stereochemistry, there's none to be worried about in this case because we don't end up with stereocenters, but the main feature of this reaction is that, in terms of regiochemistry, here is an alkyl shift that is occurring.

Reaction of aldehydes and ketones

What is the difference between an aldehyde and a ketone? An aldehyde you have to have at least one hydrogen on the carbonyl itself. It turns out, in fact, that by having a hydrogen there instead of an alkyl group, it makes a more reactive functional group. That's part of the reason why in terms of naming aldehydes are more important than ketones; aldehydes happen to be more reactive than ketones. It is true that aldehydes have less steric hindrance; there's yet one more factor, though. What was the factor in what determined that a tertiary carbocation was more stable than a secondary than a primary? Hyperconjugation; why was that true? Because hyperconjugation provides more electron density to stabilize that positive charge on the carbocation; in that case, that's what made it easier to form. But we're talking about the reactivity of the carbonyl. What if it turns out that hyperconjugation is also the reason why there's a difference in reactivity.

To better explore that, let's example two different molecules. Let's look at ethanal. To understand how this thing reacts, let's draw a structural molecular orbital graph (SMOG), which is a diagram, the intent of which is to show what kind of orbitals are in a molecule and, more importantly, how do those orbitals interact with each other. In a SMOG, I do not worry about the shading of orbitals in terms of their wavefunction. If we're worrying about the sign of a wavefunction, an s orbital is all shaded the same way, a p orbital has one half shaded different than the other half; a d orbital has every other lobe, every other color, but that's not what this diagram is going to show. The coloring, when I do these diagrams, is just to show the kind of orbital that we have. If we're going to show kind of orbitals, though, we need a reminder about how to determine the hybridization.

What is the hybridization of the carbon in the carbonyl? sp^2 . How did you determine that? The number of domains, meaning the number of directions that there's bonding occurring. The way that I normally express that is to say the number of sigma bonds, because remember that because pi bonds have their electron density above and below the direction of the bond, they don't effectively count for VSEPR theory. Another reason that we can rationalize that is in a double bond, that's the same as having one electron extra on each atom, and single electrons don't count towards VSEPR, don't count towards hybridization. So it's the number of single bonds or, if you had a lone pair, that would also count towards hybridization. We only have three sigma bonds in this case. Three sigma bonds requires three hybrids, which is why we end up with sp^2 hybridization? What about the methyl group? sp^3 , because there's four bonds total – there's the bond that's explicitly written to the carbon, plus there's the other three hydrogens that are surrounding it. In terms of hybridization, we've got sp^3 , sp^2 ; I could the oxygen as sp^2 ; and hydrogen is never anything except s. Let's draw this picture out. If I say that it's got sp^2 hybridization that automatically means there's three hybrids that come from it. I know I'm going to be writing a pi bond, so from practical experience I know I want to write my sp^2 in such a way that I don't overlap with the p orbitals, making a clearer structure to read; I keep that in mind as I start writing these out. If we is sp^2 hybridization, there is that one p orbital automatically left over; any time there's sp^2 there's automatically a p orbital. That p orbital is going to form a pi bond. sp^3 automatically means there's four orbitals there, one of which comes back to the carbon it's connected to, the others of which are connected to hydrogens which are just s hybridized. [color code]

What would be the instructional point of drawing a diagram like this? Notice that the hydrogen that's connected to the carbonyl is on a bond that is perpendicular to the pi bond, so there is absolutely no way that that hydrogen can overlap with the pi bond. In aldehydes, there's no overlap between the bond connecting the hydrogen to the carbonyl and the pi bond from the carbonyl, since they are orthogonal to each other. Slightly different molecule, slightly different situation, but same story if we looked a methyl group, and why a methyl carbocation is not stabilized at all. That is the same situation, hydrogens would end up being perpendicular to the p orbital, just the same way here. How's this different from in a ketone?

Let's fill a SMOG for a ketone, and let's acetone as our example. You do need to know this common name. There is another aldehyde that you do need to know the common name of – formaldehyde, which is related to formic acid, which that name comes from formica, which is Latin for ant, which is related to the fact that formic acid is often found in some of those stinging components of ant bites. On acetone, we have very similar hybridization as we did in ethanal: the central carbon, the one on the carbonyl, is sp^2 -hybridized, the two different methyl groups are sp^3 hybridized. Let's draw a SMOG for this. Going to look very similar; going to have the sp^2 -hybridized carbon and oxygen, which means we're still going to have a pi bond. The only main difference, in fact, is that on either side of the carbonyl, we have an sp^3 -hybridized carbon.

What's the instructional point of a diagram like this? The fact we can show that the neighboring sigma bonds on the carbon one away from the carbonyl, are now in the correct geometry – or close enough – that there is overlap between the sigma bond and the pi bond, which means there is hyperconjugation that can occur. Why does this matter? There is a duality in the way that carbonyls tend to react. It has to do with the fact that a carbonyl is a polar bond. We look at the structure of acetone, oxygen is the more electronegative atom, so it has a partial negative charge on it; the carbon in response has a partial positive to it. These opposing charges are what lead to opposing types of reactivity. The two reactions that we're going to learn today, one of them is a cation reaction, which since oxygen is partially negatively charged, it would be attracted to reacting with things that are cations, things that would be electrophiles. One of the reactions we're going to see is protonation of oxygen, a cationic reaction. We're going to find out, in fact, that many of these cationic reactions of aldehyde and ketones are reversible reactions. The opposite would be the fact that we have this delta positive carbon that could be attacked by some form of nucleophile. We're going to see that there are reagents that will force this carbonyl bond open, and because of the fact that they force their way open, many of those reactions are irreversible. The carbonyl has two main flavors of reactivity, due to the fact that it has a plus end and minus end.

The stronger the plus and minus are, you might imagine, the stronger reactivity the carbonyl is going to have, the enhanced reactivity. If you have a ketone like there, where you have a neighboring alkyl group that is providing electron density into that carbonyl bond, you're reducing the polarity of that carbonyl bond. If I just made this link between polarity and reactivity, if you lowered the polarity of that carbonyl bond by squeezing so electron density into it, you've now made it less reactive. This is one of the prime reasons that ketones are less reactive than aldehydes, because of the hyperconjugation that occurs between the neighboring groups of the carbonyl on a ketone that you only have, at most, one of for an aldehyde; for formaldehyde, you don't even have that, just hydrogens. In a ketone, both of the groups attached to the carbon are able to undergo hyperconjugation with the carbonyl. Hyperconjugation effectively reduces the polarity of the carbonyl bond, because hyperconjugation is providing electron density to that delta positive carbon, which therefore reduces the reactivity of the carbonyl. Aldehyde, lacking some of that hyperconjugation and being sterically less crowded, are more reactive than ketones.

Let's look at our first of two prototype example mechanisms. We're going to examine a cationic mechanism involving aldehydes and ketones, and we're going to look at an anionic mechanism. Let's look at the cationic one first. This is the formation of a hydrate. The way this would look synthetically is an aldehyde or a ketone can reversibly react with water and an acid catalyst – much in the same way that an alkene can be hydrated to form an alcohol. Because there's already one oxygen on this double bond, then when we added water we end up with a second –OH group. Another term for a hydrate is a geminal diol geminal like gemini, being twins, so geminal diol means a twin diol, twin meaning that both of the –OH groups are on the same carbon. This is a fully reversible mechanism.

First the hydration. The first time I show this mechanism, I've show it with four distinct steps. First step is much like what we would have if we were trying to react with an alcohol: the only logical thing that could happen is that carbonyl gets protonated. Water can't attack the carbonyl direction, which is why the acid catalyst is there to help pull the carbonyl along into being reactive. So that proton can reversibly add. Once it does add, we have to realize, there's effectively a bond opening that can occur, at least on paper – I say on paper because it's really delocalized, so it's not really bouncing back and forth between these two structures, but it is the way that we write it down. First step, we have something protonated; then, the bond in the second step opens. We now have this carbocation that something can come in and attack; there's going to be a deprotonate step that happens next. This sequence of steps I give the odd acronym name POAD to, only because you're going to see this sequence – protonate, open, attack, deprotonate – [countless times]. If you can remember this sequence of steps, it's going to get you through lots of mechanism problems in the future.

This is the forward mechanism; I did say I wanted to show you a reverse mechanism just so we had done it. I showed a ketone being made into a hydrate; let me take the hydride of an aldehyde to go in the reverse direction, just to have something different. This would be dehydration. How could I recognize that I had a hydrate that came from an aldehyde versus a ketone? Because, wherever the two –OH groups do meet, that common carbon, that's where the carbonyl carbon had to be. Notice that, attached to that carbon, I have a hydrogen there. That's how I know this wouldn't have, in the past, been an aldehyde. The principle of microscopic reversibility is exactly this: that in some of process, whatever the energetically most likely pathway is in the forward direction through that process must automatically be the energetically most favored pathway coming in the reverse direction. The example I often give for that is: if you going from here over the hill to Santa Cruz, if you found the easiest way to get over, it's automatically the easiest way to get back, because if you found an easier way to get back, that's what you would have originally taken to get there. Chemically, the same thing is true.

What that means is every single step of the reaction in the forward direction, you take exactly the same steps in the reverse reaction, which we've seen with the hydration and dehydration of alkenes; works the same way here with aldehydes and ketones.

The last step in forming the hydrate is for a proton to come off, so the first step in decomposing a hydrate is for a proton to come back on, which is reversible, but it does make water as a leaving group, which can then leave. The bond opens up, forming a carbocation, which is right next door to an alcohol, so we have a resonance structure that can occur, or, it is delocalized – a better way to say it. That carbonyl, once formed, can then lose its hydrogen, become deprotonated. I follow that habit of writing my hydrogens in on the carbonyl to show an aldehyde, even though, technically, according to the way we write line structures, we wouldn't need to show that aldehyde; it would be understood. [But I prefer to] show the hydrogen to show it's an aldehyde. I could leave the hydrogen off in all of these structures and it would be correctly written, but I'm writing it to help emphasize it's an aldehyde. Recognize that, in this reverse direction, I could still show that this first event is something getting protonated, and then afterwards water, its bond opens up, and then the lone pair on oxygen attacks the carbocation, and then you have the carbonyl deprotonate afterwards – so the same mnemonic device, the same acronym can be used in either direction. Deprotonation is a very specific form of bond [breaking or opening].

Comments on this hydration. It turns out that small aldehydes, they favorably hydrate. In other words, if we took formaldehyde and threw it in water, almost spontaneously it's going to make the hydrate like this. When we have larger compounds, particularly when we get to ketones, they're less polar compounds, they're less water-compound, they end up less-favorably forming a hydrate. Whereas something like 99% of formaldehyde would form a hydrate naturally, only something like 0.1% of acetone would. Hydrate formation is not necessarily spontaneous, but whether it is or not, it's an equilibrium process, and if equilibrium can happen, it will happen. Even if it's not favorable to hydrate, if it's a reversible reaction, a little bit of it will happen. In fact, as we see in this case, cationic reactions of aldehydes and ketones – especially involving acid catalysts – are normally reversible reactions. Why? Because each one of the protonated intermediates is got about the same acidity level as any other of the protonated intermediates. In other words, there's no one really hugely bad intermediate that we make anywhere along the way. So, whether we're starting from reactants or products, the activation barriers are not that much different in the forward and reverse reactions. That's why this reaction is reversible.

Let's now do our prototype example of an anionic reaction, reduction. There are two main reagents that we tend to use for reductions of aldehydes and ketones. One of them is the compound NaBH_4 , sodium borohydride – the same sodium borohydride in oxymercuration-demercuration. The other reagent is lithium aluminum hydride. [commentary on aluminium] What's the difference in reactivity of these two compounds? Which is more electronegative, boron or hydrogen? Hydrogen; that's why in hydroboration-oxidation, boron ends up at the less-substituted position because it ends up acting as the electrophile. Where is aluminum versus boron on the periodic table? It's below it; it's in the same column as boron, aluminum below it. If boron was already less electronegative than hydrogen, if aluminum's even lower [on the periodic table], what can we say about the electronegativity difference between aluminum and hydrogen? It's even larger, because aluminum is below boron, so it's a less electronegative atom than boron is, and boron is already less electronegative than hydrogen. So the electronegativity difference between boron and hydrogen is small that aluminum and hydrogen, then the aluminum hydrogen system is going to be more reactive, because it's more polarized. That shows up in the following way: sodium borohydride is a source of hydride, so just like sodium hydride, it will react with alcohol. But we can get away with using an alcohol as a solvent, because the reaction is slow enough that if you have an aldehyde or ketone dissolved in that alcohol solvent, in a protic solvent, the solvent would decompose but not as rapidly as the reduction would occur. Lithium aluminum hydride, you would never, ever, ever attempt that, not if you didn't want to burn up the room. [story of LiAlH_4 fire at Berkeley] Lithium aluminum hydride is a much nastier compound. So much difference is the reactivity between these two compounds that later on we'll do tricks, where we'll have multiple functional groups in a molecule and we'll be able to reduce one without touching the other.

The electronegativity difference between aluminum and hydrogen is much greater than between boron and hydrogen. Lithium aluminum hydride is therefore a more powerful reducing agent than sodium borohydride. Sodium borohydride can safely be used in protic solvents. You can't let them sit around all day, because it will decompose, but the reduction is a favorable enough reaction, even under those conditions, that'll happen to be over with before all of the reagent completely decomposes. That means you have to add a little extra, but sodium borohydride, comparatively, is not so expensive. Sodium borohydride can be safely used in many protic solvents. Decomposition will occur, but slowly enough that reduction can still occur. Let me show you what the side reaction is: if we treat sodium borohydride as just a source of hydride, an alcohol can be deprotonated, which will form an alkoxide and spit off hydrogen gas as a by-product. Let's see the real reduction itself. If we've got something like butanal, the simple way of writing the mechanism is just to show that hydride attacking that carbonyl, and, because there were already four bonds to that carbon, therefore you show simultaneously the carbonyl opening to form an alkoxide.

We start out with hydride, which is a strong base. Hydride is much, much more basic than the alkoxide that we form. In this example, reduction is virtually an irreversible reaction. Reduction – like many anionic reactions – is normally irreversible, because of the large difference in basicities of the reactants and products.

Structural Molecular Orbital Graph (SMOG)

In an aldehydes, there is no overlap between the bond connecting the hydrogen to the carbonyl and the pi bond from the carbonyl, since they are orthogonal to each other.

In a ketone, both groups attached to the carbonyl are able to undergo hyperconjugation with the C=O. Hyperconjugation reduces the polarity on the carbonyl carbon (by providing electron density to the delta+ carbon), which therefore reduces the reactivity of the C=O.

Hydrate (geminal diol)

hydration
dehydration

cationic reactions – especially involving acid catalysts – are normally reversible

reduction (of aldehydes & ketones)

NaBH₄ sodium borohydride
LiAlH₄ lithium aluminum hydride

The electronegativity difference between aluminum & hydrogen is much greater than the difference between boron and hydrogen. Lithium aluminum hydride is therefore a much more powerful reducing agent than sodium borohydride. NaBH₄ can be safely used in many protic solvents; decomposition will occur, but slowly enough reduction can still occur.

side rxn

Reduction, like many anionic reactions, is normally irreversible because of the large difference in the basicity of the reactants and products.

Structures (remaining structures identical to lecture 3A)

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