

Lecture 23A • 03/23/12

Synthesis problems

First one was a halogenated ketone reacting with an aldehyde to form an unsaturated ketone. The hint you were given was note: no magnesium may be used. What that meant is that you had to do a Wittig reaction, because this is a carbon-carbon bond-forming reaction, and we only have a very few ways to do that: there's Grignard; there's using acetylides; and there's doing a Wittig. In order to do the Wittig, we need to make a Wittig reagent. If we notice the structure of the two starting materials, we've got a three-carbon compound. Notice that we have the carbonyl, and we have some kind of functionality at the end of the molecule. Notice in the product, we could still identify a carbonyl, and we could still, if we wanted to isolate these three carbons of it, see that there's still some kind of functional group at the end of those three carbons. It'd be reasonable to assume, since there's already a halide there, that we could make the Wittig reagent out of that starting material. Once it reacts with the aldehyde, that would form the double bond exactly the way that you want anyways, so it seems like a very logical approach.

There's only one small problem with it: the carbonyl is already there, so if you tried to make a Wittig reagent out of it, it's going to react with itself – maybe not within the same molecule, but before you could throw another molecule to react, the solution would react with itself. That means: protecting group. For example, you could even use just plain old ethanol. Now that we've protected the carbonyl, we could react that with the triphenylphosphine. That does mean we form a salt, so you have to show the positive charge on the phosphorus, and, technically, you need to show a counterion. You can't have a bottle of something that's just a carbocation. At this point, we deprotonate; you do really have to deprotonate before it turns into the Wittig. I'm writing it as the octet violation form; you could also write it as a zwitterion. That, once it reacts with the aldehyde, directly makes the alkene. We still have the protecting group. Now, if you're careful about it, I know there's an alkene there, but as long as you don't have a strongly acidic solution, it is possible for alkenes to survive mildly acidic environments. I'm sure there's cases where it doesn't work, but in theory, you should be able to knock off that protecting group. If you were worried about the possibility of acid reacting with it, you could show this pathway: it could get hydrated, which you can then either heat with acid and do a thermo dehydration, or, you could react it with something like PBr_3 to make a bromide and then eliminate using something like *t*-butoxide, because there's only one way that elimination can occur.

For our next synthesis, we have a halogenated alcohol that reacts with an epoxide to make a diol. We're going to try to identify some structural elements. We have the three-carbon fragment here that has functional groups at either end, and then we have the ring that has two functional groups on it. In the product, aside from that ring, here are those three carbons, so there's a new carbon-carbon bond. The alcohol doesn't change, so it's still in that position. The unbelievable hint, as it says it, is silicon. Why does it say silicon? Because we do form a new carbon-carbon bond, and since it's a single bond, that means it's more likely we're going to do a Grignard. But, if we have an alcohol here, if we tried to make a Grignard reagent out of that, it again would react with itself, it would just self-neutralize. So, first we have to protect. TMS, trimethylsilyl chloride, works; the one I had more recommended was TBDMS – in real life it's more capable of staying stuck on. Once you protect it, you can react it with magnesium in ether; that makes the Grignard. Throw the Grignard at the epoxide, the epoxide's symmetric, so it doesn't really matter which side it attacks on. Then, if you used acid and water, you would both reprotonate the alkoxide and knocked off the protecting group in one step. [Or,] you could use a gentle acid to first reprotonate the alkoxide, and then you use TBAF. Both routes are correct; the second route is just the more careful one. [need TBAF mechanism]

[two protecting group problem] Imagine we had DHP and TBDMS on the same molecule. If you used acid, you would knock both groups off at the same time. If you use TBAF, you can keep the THP without affecting the TBDMS. In other words, the following is possible: imagine that you had a diol. There are methods for being able to protect a secondary versus a primary or a primary versus a secondary alcohol. You would be able to end up with a molecule like this: two different protecting groups. TBAF, because it's not acidic, it's just a salt, it affects the silicon, not the THP, I could knock just one protecting group off, which means now I can do some further reaction of just the one alcohol before I deprotect and do something with the other alcohol.

Let's do the last synthesis problem. We have this: which functional group is this? Imine. Which functional group do you have to have in order to do a Wolff-Kishner reduction? Hydrazone, which means there's another nitrogen on there. Some of you tried to do this; it doesn't work. You have to have a hydrazone in order to do the trick of knocking off the nitrogen. What you could do instead is hydrolyze, use acid and water, because that will get you an aldehyde. The overall synthesis you were supposed to do is to take that imine, take two equivalents of it, and somehow make hexane. There's many approaches we could take once we get to the aldehyde; I'll show you a couple of different ones. First, let me continue from that aldehyde, because a couple of the approaches need an alcohol, so I'm going to reduce. Reduction is a two-step process: the reduction itself, but then there's the post-reduction acidification. You can't put H^+ at the same time that you put the reducing agent. That gets us an alcohol. Two of the methods, we need to have a leaving group, so I'll use PBr_3 . One approach is to take that, turn it into a Grignard reagent, and then react that with the original aldehyde. That will initially get us an alkoxide. There's a couple of different ways to deal with the alkoxide.

You could first neutralize it to get the alcohol, and then the alcohol, you could eliminate by first turning it into a leaving group, and then, after elimination, regardless of which kind of alkene forms, we don't care, because just hydrogenate and you get rid of it, wherever it happens to form. Elimination will give you four products: cis and trans hex-2-ene and cis and trans hex-3-ene, but it doesn't matter which one forms because once you hydrogenate, it's the product you want. Right there at that same halide step, though, we could turn that into a Grignard reagent. You might think: why? Because if you just use water, you kill off the Grignard reagent, which normally is bad, but it's exactly what you want in this case. It's a sneaky way to do it.

What else could we have done besides this route? The other one I remember seeing was to do a Wittig. It would be possible to take the aldehyde, take the alkyl halide, make a Wittig [reagent] out of the alkyl halide and just combine it with the aldehyde. Triphenylphosphine; make the triphenylphosphonium bromide. React that with butyllithium to make the Wittig reagent; react that with the aldehyde to make the alkene; and then reduce to make the alkane.

Let's go to exam 3.

The first real question. How could you figure something out physically that shows that benzene is unusual, and how could we do something chemically. Question 3 said that although benzene is written with three double bonds, it doesn't react like something with double bonds. This can be explained by its being cyclicly conjugated. You were asked to describe the physical property of benzene that demonstrates how the true structure doesn't match what you write; that's the fact that all of the bonds are the same length. If you draw something with a single bond, double bond, single bond, double bond, that should be long, short, long, short. That's not the way that the compound exists. All the bonds are the same length; that's something physical, something measurable. That's what the first part of the question was trying to get at.

The second part that says how can the unusual stability be demonstrated chemically through some form of experiment. The question tells you it doesn't react like other alkenes, so the question is how could you demonstrate that? That's the graph where you had cyclohexene, cyclohexa-1,3-diene, and then this mythical molecule cyclohexa-1,3,5-triene, which means benzene. What we're doing is we're comparing what benzene does compared to what this triene would do if those three alkenes actually were separate from each other. You get one energy value, -360, for what the triene would do, versus what benzene really does, which is -208. The difference between the two (152), that's the stabilization energy due to benzene being cyclicly conjugated. There's a much smaller, an 8 kJ difference, that you get between a diene that is conjugated versus a theoretical diene that's not conjugated. Then there's the hydrogenation of cyclohexene itself, which is the [-]120 that you use to make the comparison for a double bond and a triple bond case. [In your graph,] did you make sure to show what you're comparing. You had the three starting compounds: cyclohexene, cyclohexa-1,3-diene, and cyclohexa-1,3,5-triene, but then you have to show they all make cyclohexane. There is no x-axis, it's just a comparison; the y-axis is energy.

Next question: phenol, benzene, and nitrobenzene are all reacted in separate beakers. You observe that phenol reacts more quickly; nitrobenzene, less quickly. Explain this observation using at least one appropriate reaction coordinate diagram. You do not need to include any completed mechanisms, but you should label your reaction coordinate diagram with appropriate structures. Hint: is it necessary to write a diagram from the entire reaction? No, because it's only the rate-limiting step of this reaction that controls anything, and the rate-limiting step of the reaction is when the benzene ring, with whatever might be on it, attacks an electrophile. That is as much of the mechanism that you even need to discuss in that part of the problem. Why? Because depending on whether electron density is given to or taken from the benzene ring, that determines how easily it is able to provide electron density to an electrophile. If you have phenol there's one diagram. Here's the ideal way to do it. [rare metal rings] Three different activation energies: smaller for phenol, because the oxygen provides electron density. Benzene's the vanilla flavor; it's the unsubstituted one; phenol[s] is smaller than that. Then nitrobenzene, because the nitro withdraws electron density, it's got a larger activation barrier. Lower activation energy, higher rate of reaction, that's why phenol is faster. Higher activation energy, lower rate of reaction, that's why nitrobenzene's slower; that's the answer. You had to at least say something about activation energy.

The next part of the question: in analyzing the products, you discover that the substitution pattern resulting from phenol differs from that of nitrobenzene. Explain this difference using one or more judiciously-selected reaction mechanisms or portions of mechanisms. You don't even have to show that much; you could just show that if you had something that had substituted at the ortho position relative to phenol that you could then show that positive charge next to the oxygen, because there you could have resonance. That's all that you need to show, this much of it; this is the core point right here that that resonance can happen. Versus in the nitro case, where no matter what you do, if you tried to move the charge around, no matter how far you move it, it never gets onto the nitro, which means you avoid the bad resonance structure that could occur [if you substitute at the meta position]. I'm answering the question in the favorable; this is favorable because you can delocalize on the oxygen. What I'm about to finish drawing here is favorable because it at least does avoid putting the positive charge next to the nitro. You could have also explained it the flip side, the glass half empty version, where, if you tried to do meta substitution with phenol, you can't put the charge next to the oxygen, so you never get that beneficial stabilization. And, if you did end up with ortho substitution [with] a nitro, you would put the positive charge next to the nitro, which is bad. Something you had to say about oxygen, something you had to say about the nitro. Whether you did it the positive or the negative doesn't matter. If you only showed this much of the mechanism, that'd be fine.

The next question was the mechanism problem where I did want to see if you did know how to write a complete mechanism. Write a complete, detailed mechanism for the following reaction. Be sure to clearly indicate all mechanistic arrows, charges, lone electrons, and intermediates. Do not show transition states. You will get two [products]. Toluene. Aluminum trichloride and the alkyl halide will react first. Lone pair.... We make a complex, which can dissociate; makes a carbocation, which is not favorable, so you get a hydride shift. Then, toluene opens up and attacks it. Toluene is an ortho-para director. I've substituted at the ortho position, but whenever ortho is possible, para is possible; that's why you get two products. You have chloride still floating around in solution; I could use that to show the halogen being removed. We end up with this plus the para product. It is possible for the carbocation to be attacked by chloride, but that's not a stable product compared to making the benzene ring; that would immediately dissociate again because once this happens, so much energy is released. [need to find out how to, or if you can, predict ortho/para ratio]

Question 1. That was the one about butadiene versus cyclobutadiene. You were told that butadiene is a gas that has a boiling point that is near the freezing point of ice, a little bit below 0 °C. In contrast, cyclobutadiene is very unstable, can only be isolated below -238 °C. In the butadiene case, you're told that the single bond there was unusual because it's shorter than what you'd predict, and in the cyclobutadiene case, the single bond there is longer and it's not equal to the carbon-carbon double bonds. First part of the question: draw an MO diagram that graphically shows representations for each molecular orbital in the pi systems for A and B. For A, we've got four orbitals; we've also got four orbitals in this case. In both cases, the lower energy orbital is when you have zero nodes, so you have equal phase across all p orbitals. The next orbital up in both cases is where you have exactly one node. Remember, for the cyclic case there's two ways to do it to have the node go: between the bonds; the other way is to have it go through the bonds. One more level up, you have one more node.

Label each orbital as bonding, non-bonding, or antibonding, and show how many electrons fill each orbital. On the first diagram, you only have bonding and antibonding. If you labeled something with non-bonding on this part of the diagram, there is no such thing. Yes, there's a zero energy level, but there's nothing there, so non-bonding would be an incorrect label to put at all on the first diagram. On the second diagram, though, we have the top orbital which is anti[bonding]; we have the bottom one which is bonding; and then, we have two non-bonding orbitals. As far as putting the electrons is, four electrons go only into the bonding orbitals for the linear case, whereas two electrons go into the bonding orbital and then one each into each of the non-bonding orbitals for this case. Briefly explain what causes a molecular orbital to be bonding, nonbonding, or antibonding. Bonding would mean that you have more favorable than unfavorable interactions between orbitals, p orbitals. Antibonding, where we have more unfavorable versus favorable, and non-bonding would be if you have equal favorable and unfavorable. If you said bonding is lower in energy, antibonding is higher energy, and non-bonding is the same ... [question open as to what way to answer is acceptable]

The last part of that question: using the MO diagrams, explain why there's such a difference in stability of A and B, and why the single bond is short for the first and long for the second one. In the first case, notice that we have this one molecular orbital that's going to cross the molecule. That helps to pull the entire molecule together. Due to conjugation, those two pi bonds are closer together, which is why the single bond is shorter. The reason this molecule's stable is because there's only electrons in bonding orbitals, so there's no reason for it not to be stable. Versus in the cyclobutadiene case, even though you have the same number of electrons, only two of them are bonding, and you're supposed to be holding four atoms together somehow. That's not favorable. Two electrons that otherwise could have been bonding were forced to be non-bonding, if the double bonds end up a certain distance from each other. If you let those electrons pull again, then they avoid this antiaromaticity, which means the pi electrons would turn back into being bonding electrons again; that's why the bond stretches: to try to avoid antiaromaticity.

Quiz 3 – two questions

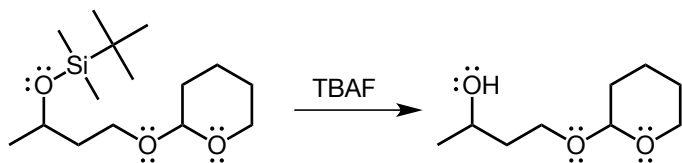
The first question was about imidazole. You were given this kind of set up: that wow, it sure looks like it should be antiaromatic, because there's eight electrons: two lone pairs and two pi bonds. But it's not antiaromatic, it is aromatic. It appears to have eight electrons for delocalization, however the compound is quite definitely aromatic and is readily synthesized an isolatable. Explain why the compound is aromatic using an appropriate SMOG. What's the hybridization of every atom in the ring? sp² – including the nitrogen with just single bonds. Remember that nitrogen auto inverts, so that lone pair is actually effectively in something that looks like a p orbital in practice. If it ends up that way, which means it can then delocalize with the rest of the ring, that means it's going to end up being aromatic. The [nitrogen] with the lone pair goes to the side. We have a nitrogen with a hydrogen, which means that lone pair has to be part of the pi system. The nitrogen that already has a double bond, the lone pair can't be where the double bond is, so it can't be part of the pi system; that is why it's off to the side here. In the other case, this other nitrogen, since we have a hydrogen, the hydrogen can't be in the way of the pi system, so the lone pair ends up there. So, two of the pi bonds and only one of the lone pairs are there, so it's cyclic, conjugated, planar, the right number of electrons – all the electrons in bonding orbitals – it's aromatic.

The second question on the quiz was about 2-ethylcyclopenta-1,3-diene. You were told it's not aromatic, but it's very acidic – about pK_a of 15, which is unusual. First, explain in no more than two sentences why B is not aromatic.

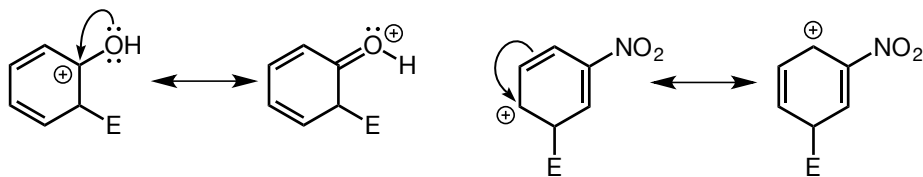
Because you have an sp^3 -hybridized center, because there's actually two hydrogens there; there's no lone pair there to be able to delocalize at all, so it blocks cyclic conjugation, so it's not aromatic. Next, list the rules for constructing a Frost circle. The first rule is the number of points in that polygon are equal to the number of atoms in the ring. Since there's five atoms in the ring, you're going to have a five-sided figure. The next rule is that one of those points is put at the bottom, and you have a regular polygon that's otherwise inscribed. The dividing line at the center: above that that's antibonding, below that it's bonding, on it is non-bonding. We end up with this kind of set of molecular orbitals. It says be sure to mention how to determine how many orbitals are generated – that's the number of atoms in the ring. Which orbitals are bonding, non-bonding, and antibonding – that's relative to the zero position here. How many electrons are placed in those orbitals? You have to draw a Frost circle not for this molecule, actually, but what you're drawing it for is the anion that forms, because if the anion forms easily, that's why the original compound is acidic. That lone pair delocalizes, so we have six electrons. Notice they all only go into bonding orbitals. This explains why it's acidic, because it turns aromatic once it loses the hydrogen.

Structures (remaining structures identical to lecture 24B)

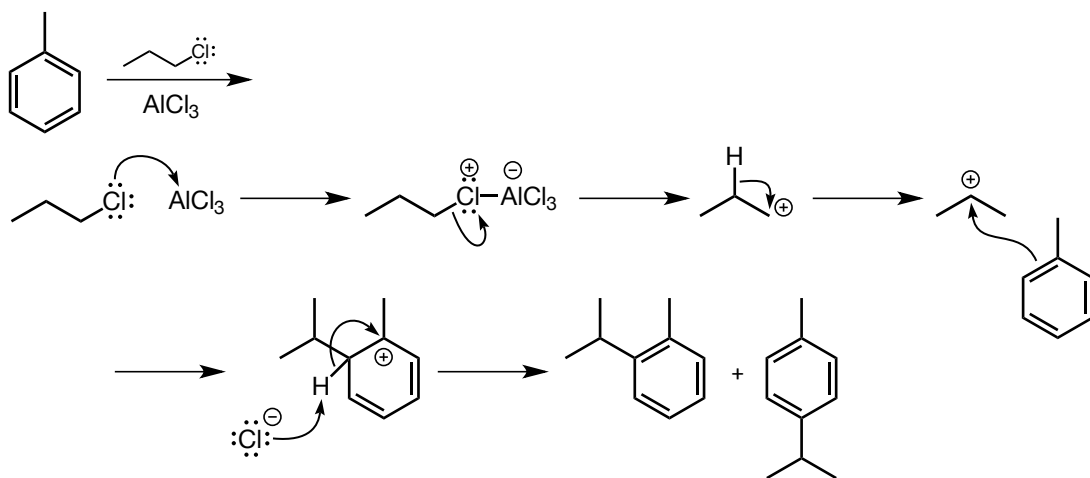
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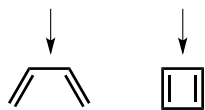
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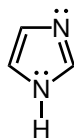
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