Lecture 22B • 03/13/12

Nucleophilic aromatic substitution

I'll start out first with an observation about the reactivity – or the lack thereof – between something like chlorobenzene and sodium methoxide. Based on the reagent, what kind of reaction, ignoring the substrate that's being attacked, what kind of reaction might we imagine that's possible here? Sn2. What kind of nucleophile do we have? A strong, basic nucleophile. But is this compound able to undergo Sn2 reactions? No. Why not? Because vinyl positions in general don't really like to because the electron clouds of the pi bond help repel the nucleophile. Aside from that, we have the fact that the nucleophile would have to travel exactly through the benzene ring in order to come around and attack from the back, which is exactly the way that these Sn2 reactions occur. Both because of sterics and an electronic consideration, no Sn2 is possible.

What about Sn1? This is not the right nucleophile for Sn1, but why would Sn1 not want to occur? If it had good hyperconjugation, you'd think it would want to react with Sn1, but it doesn't react with Sn1. In fact, it doesn't have hyperconjugation; why not? If you put a positive charge on there, there's a geometric problem with this. Technically, in theory, if we had sp hybridization, which is what we would have if we have a positive charged, it'd have to be linear at that point. Can we make a six-membered ring that has three atoms that are in a row? No. Aside from that, it's the opposite of the favorable that we had when we change hybridization. This discussion came up in the terms of the acidity of an alkane, alkene, and alkyne, that therefore resulted in an sp3 anion versus an sp2 anion versus an sp anion. In that case, when we had sp-hybridization, that meant the electrons were effectively held closer to the nucleus, which is a favorable thing. That's why an alkyne was more acidic, more able to lose a proton. Effectively – there's a chlorine there but imagine that we were taking hydride off, we're taking a lone pair with it – that's a positive charge we're forming, and on an sp-orbital that positive charge would be more exposed, because [of] the lack of electrons would be closer to the nucleus. So, a carbocation on what was initially an sp3-hybridized center is much more favorable than a carbocation formed form something that was sp2-hybridized or something that was sp-hybridized.

Sn2 is not possible due to steric hinderance – in this case, the nucleophile would have to pass through the ring – and due to repulsion form the pi system. Sn1 is not possible because the resulting change in hybridization – going from sp2 to sp – would be unfavorable geometrically, and would form a carbocation that is at a vinyl position, which is unfavorable due to the large[r] s-character of the orbital.

Why is it, then, if we take chlorobenzene and just add a nitro group, but at the ortho or para positions, that substitution does occur, but not really for the meta position. What's going on here? Would a positive charge form? If stabilization of positive charge is the reason this reaction occurs, where does the positive charge originally come from? Imagine that you've got the beznene ring, you've got all these p orbitals of the beznene ring, and the chlorine, therefore, would be perpendicular to that benzene ring. If chlorine came off, the p orbital that was part of benzene is still part of benzene, so that doesn't have an effect on the aromatic system. That also means that whatever positive charge forms, whatever orbital corresponds to it, would not have any form of conjugation with anything else.

So if it's not a positive charge, how could a negative charge be stabilized? What if we more fully wrote out the structure of the starting material. Remember, the reason that the nitro group is a meta director, is a deactivator, is because it pulls electron density from the ring – which is bad if you're trying to use the ring in electrophilic addition. But we now have a negative charge that's trying to attack the ring. The nitro group is pulling electron density off of the ring, making the ring, therefore, more attractive to a negative charge. We could write this series of arrows: when methoxide comes in to attack, it does not kick the chlorine out directly. If we attack and we pretend that there really is a double bond there, we could imagine that it's pushed around the ring, which can then be pushed off of the ring by delocalization onto the nitrogen, by the nitrogen-oxygen double bond opening up. This is a different mechanism; it would occur from the front side. This Sn2; Sn2 requires that the nucleophile comes from a certain direction. This is not trying to replace the chlorine at the same time, so there's not the same constraint on the direction that this approaches. Once this happens, we have this intermediate – this is in theory reversible. This intermediate is not isolatable, and it will collapse again, so one of the two oxygens on the nitrogen will try to reform its double bond. That'll cause the carbon-nitrogen double bond to open up, because nitrogen can't have more than four bonds at the same time. The molecule's symmetric, but I'll go ahead and crawl back up the lefthand side, since that's the way I did the reaction the first time. We attack that double bond; that double bond can collapse. It's got a choice: it can kick out the methoxide, or it could kick out the chloride. Which is the better leaving group? Chloride by far. Methoxide's a base; it's not a leaving group. Chloride's neutral, so it'd be the one to leave. Once that happens, the reaction's not reversible any more, because it's so unfavorable for chlorine to come back and try to come back to kick out methoxide.

This is nucleophilic aromatic substitution. Notice that, because the nitro group was at the para position, that's why this particular favorable resonance structure resulted. You gotta make an observation here about opposites: plus versus minus. I [had] talked about cationic versus anion reactions of carbonyls.

We could characterize carbonyl reactions as either pushing electrons onto the carbon to force oxygen to open up, or pulling electrons from oxygen using an acid, again to make the carbonyl open up. They're opposite events, therefore. In one case, you're attack with something to push the bond open; the other case, you're protonating an atom, so to induce a bond to break. That difference in reactivity right there is why, for example, forming a hydrate is a very different reaction from a Grignard reaction. In a Grignard reaction, you use this extraordinary base that slams in to the carbonyl, whereas, for example, in making something like a hydrate, you'd have to wait for an oxygen to be protonated and then, hopefully, a leaving group falls off and more steps occur, but every little bit of it's reversible.

There's an opposition in behavior that occurs here. When we use the electrophile to react with the benzene ring, the benzene ring is opening up to attack. We did these resonance structures already to show that, at the ortho and para positions, when we have an electron donor, it causes preferential substitution at the ortho and para positions. This is the reverse situation. Now we're trying to push electrons on to benzene. If we had that nitro group at the ortho-para position, you can't delocalize the negative charge that forms onto nitrogen. Even though nitro group at the meta position in the electrophilic reaction is a deactivator, a nitro group in the para position, when you're doing a nucleophilic reaction, is now an activator. You can push the negative charge onto the nitrogen in this case. If I did the same thing with the meta group, this reaction might be faster than just plain chlorobenzene, because regardless of resonance effects, there'd still be an inductive effect. Since nitrogen is pulling electron density off the ring, even in a slight way it's going to make it more susceptible to nucleophilic attack. But, if you do attack while you have the nitro group at the meta position, the best you can do is to get the negative charge to one side or another of that nitro group. In the meta position, there's no way to move the negative charge off of the ring. In the ortho or para – I only did the para, but ortho's going to come out the same, just as in electrophilic reactions, the results of ortho was the same as the result of para in that case. To summarize, here the negative charge is delocalized off the ring, which is favorable; but, [here] we have no delocalization of the negative charge off the ring, so it's not really that much more favorable than plain old chlorobenzene. Opposite behavior.

Phenol is an ortho-para activating director in electrophilic reactions. Phenol would be a deactivator in this kind of reaction. This is a nucleophilic reaction; that means that something's trying to attack the benzene ring. If you have phenol, which is pushing electron density onto the ring, then a ring that already has excess density, why would it want to react with yet another negative charge, something else with electrons? It wouldn't, so whatever helps an electrophilic reaction hurts a nucleophilic one. Nitro, that's an ortho-para director in electrophilic reactions, but here, when it's placed in the para position ... this is another different. We have electrophilic addition; this is substitution. You already have another functional group there. In the electrophilic addition case you have one thing on the molecule which is controlling where the next one is. Here, you have two things on the molecule, one that's helping substitution at the other, so a very different reaction. Whatever trends occur for electrophilic addition are reversed for nucleophilic. There's a negative charge that you're attacking with, and instead of just ending up on the ring, we could push it all the way off so it effectively comes over to the oxygen. On this other one, the negative charge never goes anywhere except the ring, and so [the] nitro group is not, in terms of resonance, involved in this second reaction at all. In real life, it may be that this reaction happens very, very, very slowly, because nitro is an electron withdrawer. If you're pulling electron density away, that makes it easier for electron density to come in, but it's nowhere near as easy as this top case, cause this top case, the negative charge goes to an oxygen, in the bottom case, it goes to a carbon. Oxygen's more electronegative than carbon, and you're delocalizing off the ring, so this is more favorable.

Let's start our discussion of the Diels-Alder reaction. The Diels-Alder reaction is known as a [4+2] cycloaddition. What does that mean? Why don't we look at an example Diels-Alder reaction, a very classic one. Maleic anhydride, a very common molecule. The Diels-Alder reaction involves what is known as a diene and a dienophile. It is a form of pericyclic reaction, cause it's going to be a cyclic mechanism, but across a molecule that is not connected in all ways around that circle. [Previously] we saw a reaction where you could go around the ring and then there was on hop across the ring that occurred; this is going to be two hops across that ring. With these carbonyls here, we could imagine, possibly, that the double bond is having a lot of electron density withdrawn from it, so compared to other double bonds, it'll be slightly positively charge. This diene and reach out and attack it, which would cause the double bond to have to react, which it could come back to the other side of that diene and push that double bond around. We end up with this product. To help identify what went on here, I have circled what used to be cyclopentadiene in the product. There's a lot of detail in this reaction we need to get to, because even though this mechanism looks pretty simple, there are several factors that can affect both the speed – or whether the reaction can happen in the first place – and since this is another example of frontier orbital theory, we need to get into an orbital description of this reaction.

Let's start with a few of the essentials. Diels-Alder reaction can only occur if the pi bonds are in a pseudo-cis configuration. If you're not familiar with this word pseudo, a very loose translation is fake, so fake-cis. What do I mean by that? I know pseudo starts with a 'p', but for whatever reason, it tends to be abbreviated 's'. Is this compound locked into this configuration? Is this the only possible configuration of this butadiene? Is this the only rotomer possible? No. There's nothing preventing rotation around this single bond. Now we have the two double pi in what otherwise would look like a trans configuration, if we were two swap what we wrote as a double versus a single bond, then we could easily identify it as cis versus trans. The reason that pseudo-trans can't react is imagine this: I've got two atoms here on an alkene that I want to react with. I can get one of those atoms up against the diene, and they could be overlapped with each other reacting. That means that that other position at the other end is way away from the alkene that's trying to react with it.

It'd just be too far in order for bond formation to start to occur, and you can't twist it around in the right way so you could get the right overlap on both atoms at the same time. That's the key part: this reaction does happen all at the same, so even if it'd start one bond and go back and finish the other, doesn't work in this kind of mechanism.

If a compound is locked – cause this one's not, this one can flip around – but because it's flipped around, that means some of the time it's in its pseudo-cis configuration, which means it can't react. If it's locked into a pseudo-cis configuration, it makes it a much more reactive diene. One of the classic examples of a locked diene is cyclopentadiene, which reacts with itself. In fact, when you buy this stuff, it normally comes as a dimer – di meaning two, di two forms, means two of the same molecule stuck together. Oligomer, a few forms, a few molecules stuck together; polymer, a bunch of them stuck together. Cyclopentadiene does this reaction. One of the double bonds on one molecule reacts with both double bonds on the other. When you buy a bottle of cyclopentadiene, you often have to undergo what's called cracking – you heat it up to thermally cause the reaction to go in reverse.

If we can lock a compound into a pseudo-cis reaction and that makes it unusually reactive, what do you think would happen if we lock a molecule into a pseudo-trans configuration? Won't react at all [in] a Diels-Alder reaction. I should qualify all of these statements I'm making. The word diene does just mean having two alkenes in it, but in all of these examples, and in any cases where we're doing a Diels-Alder reaction, it must be a conjugated diene. Here, we do have a conjugated diene, but it can never change the relative position of those double bonds, so you can never get an alkene to straddle the diene just the right way for there to be a cyclic reaction, and so it doesn't react.

Another common discussion point in this reaction is the geometry of what results. If you look at this condensation of cyclopentadiene, I'm not very carefully showing whether these attached groups are pointed in an equatorial fashion or an axial fashion. I know that this not a chair cyclohexane, but on this side of ring, we could look at it that way, so there could be a substituent that should be written pointed straight down, or a substituent that's pointing up, and I've written it somewhere in between. That's on purpose, because when we finish talking about this reaction, I'm going to show you another orbital interaction diagram that explain why one form of addition is preferable to another. I'll just tell you that the two forms, whether they're pointed up or down, are referred to as endo or exo, whether it's pointed a little bit more into the ring – that, in our terminology, would be like the axial substituent – or whether it's pointed more away – that would be the exo case.

What I want to show you today is the primary orbital overlap that can occur. I'm going to do that with just a slightly more complicated than normal case, only because we did the work [already] to draw molecular orbitals for a six p-orbital system. We're going to revisit the first reaction I showed you with Diels-Alder, this one with the anhydride. This is a slightly more complicate than normal Diels-Alder reaction because we do have conjugation between the carbonyls and the carbon-carbon double bond. Why is it that the carbonyls don't interact? That's a good question. [why?] This reaction that I'm going to show you with a diene occurs due to heat [although it can also occur at room temperature], not due to light. What is going to mean, in the context of the discussion we had [previously]. We're going to explain what happens using frontier orbitals, but the fact that we're using heat and not light means both of the molecules, we're going to presume that they're in their ground state.

If we are in the ground state, then it is the third and fourth orbitals that we care about in the six-orbital system, and it is the second and third orbitals that we care about in the four-[orbital] system. How do we know which one's going to react with which? It doesn't really matter, because however which way we model it, both end up giving us the same result. The point is that I've shown you the equivalent of the valence electrons from both of these molecules, the highest-occupied molecular orbital. For the diene, there are only four orbitals to begin with that have 0, 1, 2, and 3 nodes. 0 and 1 would be the bonding orbitals; 1 node is the bottom orbital that I've drawn there. For the six-orbital system, we have 0, 1, 2, 3, 4, and 5 nodes; 0, 1, and 2 nodes would correspond to bonding orbitals; two nodes would be the highest energy of those bonding orbitals.

Let's declare that it's going to be electrons from the six pi orbital system that are going to interact with the LUMO of the four p-orbital system. Let's see if we can draw out a superposition of that six-orbital and four-orbital diagram. Realize something: whether I draw this, the orbital where I'm pointing at, the lowest antibonding orbital of the diene, I drew it [with one particular pattern of shading]. That's the exact same thing as if [I had shaded it the other way]. Which we call negative and which we call positive is arbitrary. In order to make this match, I [may] have to flip the apparent sign, and what I'm telling you is that that doesn't have any consequence for this reaction. If you look at the mechanism, the alkene is effectively attacking one of these outside positions, so here's the orbital interaction that we worry about. Notice that those interactions match in terms of sign; that's why this reaction does occur [under] thermal conditions, because the phase[s] of the orbitals match each other.

One of these molecules is going to react with the other. Electrons have to be involved. Which ones? From one or the other molecule, it's going to be the highest-energy electrons that are available. So, I didn't draw all of the orbitals [out]; I just took the ones that had those highest-energy electrons. Whether this molecule reacts with that one, that one reacts with this one, in either case, the electrons have to go somewhere, and they can only go into the lowest-energy orbital available on the other molecule. I said that let's imagine that the six-orbital system reacts with the four, so the highest-energy electrons from the six system, which is in the third orbital, are going to go into the lowest-energy orbital, which happens coincidentally to also be the third orbital, so it's valence electrons going into the lowest-energy orbital available.

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Sn2 is not possible due to steric hinderance (the nucleophile would have to pass through the ring) and due to repulsion from the pi system.

Sn1 is not possible because the resulting change in hybridization (sp2 –> sp) would be unfavorable geometrically and would form a carbocation at a vinyl position, which is unfavorable due to the large s-character of the orbital.

Nucleophilic Aromatic Substitution – What helps an electrophilic addition hurts a nucleophilic addition.

Diels–Alder rxn: [4 + 2] cycloaddition – Diels-Alder rxns can only occur if the pi bonds are in a pseudo-cis (pseudo = "fake") configuration.

If a diene is "locked" into a s-ci configuration, it would be a lot more reactive than a comparable diene. Cyclopendatiene is reactive enough that it naturally occurs as a dimer (two of the same atom/molecule bound together).
If a diene is locked into a s-trans configuration, it will be unreactive.
*In Diels-Alder rxns, the diene must be conjugated.

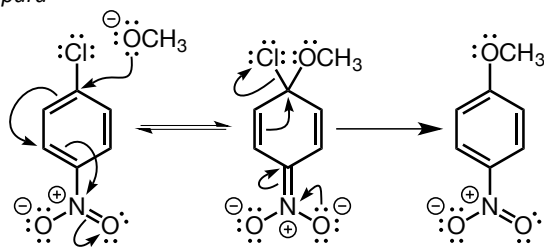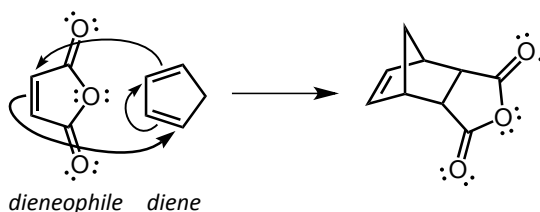————

Structures

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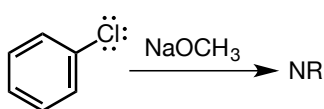
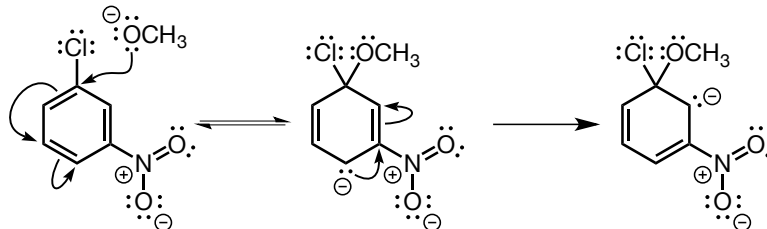*03/13/12 lec • 2*
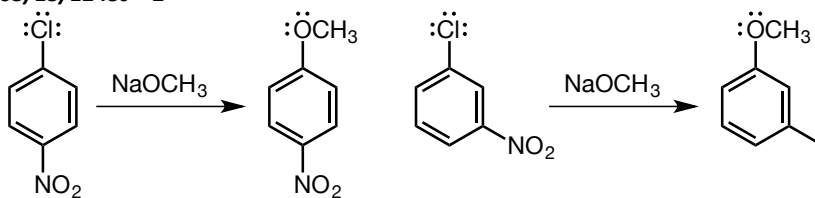
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para

- is delocalized off the ring

meta

no delocalization of - off ring

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dieneophile   diene

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rotation around

single bond not restricted

s-cis
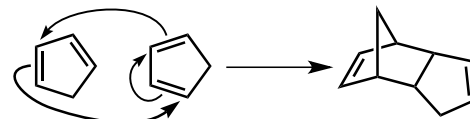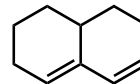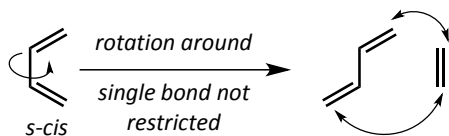
If the top carbons on either molecule were close enough to react, the bottom carbons would not be.

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ground state