Lecture 17A • 03/05/12

Let's talk about some of the other electrophilic aromatic substitution reactions that you need to know. We covered nitration [as a] simple example of the way that a mechanism works for one of these electrophilic aromatic substitutions. The other reactions we're going to see, they have different ways in which the electrophile is made, but they all react in the same way once you have the electrophile. Benzene opens up an attacks that electrophile, and then a hydrogen gets eliminated right afterwards in order to reform the benzene ring.

Let's go to sulfonation next. If we have sulfur trioxide and sulfuric acid, which is quite a potent combination ... sulfur trioxide has this formula – really, it is just dehydrated sulfuric acid. If you think about how reactive sulfuric acid is, and then we put energy into it to dehydrate it, you must imagine that sulfur trioxide's pretty hot stuff. In sulfuric acid, what happens is you protonate the compound to even further activate it. Once you protonate it, then it can open up. Now benzene can attack. Whenever benzene reacts, wherever the electrophile ends up attached to, there is already a hydrogen there, if we're starting with plain benzene. The positive charge goes on the position that the electrophile does not. Something floating around in solution, best candidate might be the bisulfate ion, that'll pull a hydrogen off, reform the benzene ring, and we get a sulfonic acid. Notice this is just a methyl group short of being p-toluenesulfonic acid. We're going to learn how to make tosic acid.

Let's move on to Friedel-Crafts acylation. There are two Friedel-Crafts reactions we're going to learn, very similar in nature – one's acylation, which means to put an acyl group on; and then there's alkylation, which means to add an alkyl group to something. In general, when you have an alkyl group attached to a carbonyl, that fragment of it is known as an acyl group. Acylation means to put an R group with a carbonyl on some other molecule. If you have attached to the carbonyl on the other side a halogen, then this is known as an acyl halide. Acylation involves the reaction of an acyl halide with a strong Lewis acid. One of the most common ones used is aluminum trichloride. Can you rationalize why aluminum trichloride would make a good Lewis acid? What does it mean to be a Lewis acid? It accepts a lone pair; it wants to get electrons. What makes something want to get electrons? If it lacks electronegativity, if something else is pulling on it to create a positive charge, if we drew out the molecular structure, the Lewis structure for aluminum trichloride, what are you going to find out about aluminum? It doesn't have an octect, it's only got six electrons in it; that's similar to boron, except that since electronegativity differences between aluminum and chlorine are not so stark, and also since aluminum is a large atom, it's not as reactive as borane. This is a solid that you can measure out in open atmosphere – with the understanding, though, that it is reactive, in open atmosphere it would decompose to make hydrochloric acid – but, safe enough that you could at least quickly measure it out.

The way that the aluminum trichloride works is you could start with an acyl halide; this particular compound has the common name acetyl chloride. Acetyl chloride with aluminum trichloride will make a complex where one of the lone pairs from chlorine donates into that electron-starved aluminum. What can happen next is the chlorine can dissociate from the carbonyl; that's only because of the strong Lewis acid nature of that aluminum. That makes an intermediate known in general as an acylium ion. -ium is an ending very commonly added to mean positive charge; acyl, that's that carbonyl with an R group; so, acylium means a positively-charged acyl group. Very, very, very strong electrophile – strong enough to cause benzene to break apart. Benzene will attack. This time I won't go on autopilot, I'll only draw two of those double bonds in; show the carbocation. Chloride can disassociate from that complex at some point and therefore can act as our base to eliminate that hydrogen and end up with this compound.

Let's look at its close cousin. Friedel-Crafts alkylation, which means to use an alkyl group. Acylation is a fairly predictable reaction, as far as what kind of structure you're going to end up with. Alkylation, you've got to be a little bit more careful what you use as a starting material. To show what can happen, I'll use an example starting material that's going to have some sort of issue with it. Friedel-Crafts alkylations starts with an alkyl halide instead of an acyl halide. Next couple of steps are very similar, though. The chlorine donates a pair of electrons into the aluminum, and then, at some point, that chloride dissociates. There's gotta be some evidence for that to be possible, because this is not what ends up reacting, because what did I just make? A primary carbocation, which if it really is its own, unique, isolated primary carbocation, that's not favorable. You're gonna have a carbocation rearrangement occur, hydride shift. Since the secondary carbocation is as good as we can do in this case, then that's what's now going to react with benzene. Then, we eliminate to reform the benzene ring. Carbocation rearrangement is possible in Friedel-Crafts alkylation. It can be bad enough, in fact, that if you have an 18-carbon compound with a halogen somewhere in the middle, in theory, that carbocation can crawl up and down the chain and you can get a dozen products, let's say. Sometimes, that might not actually be a bad thing, depending on your application; but, something you need to be aware of.

Last one – halogenation, which works for chlorine or bromine. Very similar to the alkylation and acylation, in that we're going to use a Lewis acid. If we want to add a chloride, we're going to use something that's got a chloride as the counterion; if we want bromide, we're going to use something with a bromide as the counterion. For example, if we had Br2, we could throw iron tribromide at it. It'll form the same kind of complex, forming, yet again, a strong electrophile. Notice that this effectively makes Br+.

We know bromine wants to be negatively charged, it doesn't want to become positively charged, so if you make it positively-charged, seems reasonable that it's quite reactive. Then, same closing steps: benzene attacks, and then the benzene ring reforms.

What is the name of this molecule that I just wrote? Phenol. This, when you react it with nitric acid and sulfuric acid, will have what added to it? A nitro group; those are the conditions for nitration. It turns out that the vast majority of the mixture that's produced is a combination of ortho-nitrophenol and para-nitrophenol; turns out there's hardly any – it's non-zero, but hardly any – of the meta forms. Almost exclusively, ortho and para substitution occurs. It turns out the reaction, compared to just plain benzene, is fast. What if we had something like nitrobenzene that we reacted under the same conditions? It turns out only one major product forms: the meta product; and, this reaction is quite slow, it requires lots of heat. What's going on? Why is it that one substituent causes many just ortho and para substitution to occur, and it also causes the reaction to speed up; whereas another substituent slows the reaction down and guides the next one to substitute at the meta position instead. [sabbatical]

Let's see what happens when we take phenol and we substitute it with any general electrophile. It doesn't matter the reaction that we do; whatever's already on the benzene ring is what's going to determine the result. Let's say I have some electrophile E that I allow to react with this, and let's say that I first allow it to react through the ortho position. Remember that wherever the electrophile adds, that's where there is a hydrogen; wherever it doesn't add, that's where the positive charge ends up. Instead of completing the reaction, let's notice that that positive charge can be delocalized, can be be scooted on over to the oxygen. It's not favorable for a positive charge to be on oxygen, but it's delocalized, and delocalization is a favorable thing. Let's see what would happen if we did it at the meta position instead. Yes, I'm writing it through a particular carbon; it's not my typical style, but it is allowable. The electrophile I want at the meta position, that's gonna put the carbocation at the para position. Let's make a resonance structure, move the positive charge around and see what I get. I move the positive charge once; I'll move it again. But no matter how I move it, do I ever get it to where the positive charge itself is right next to the –OH group? No. When I say delocalization, I should point out it's the delocalization with oxygen.

Another way to put it is that oxygen's putting electron density into the benzene ring. One way that we're going to talk about this reaction is to point out that the formation of the arenium ion – the positively-charged benzene – that's unfavorable cause you break aromaticity. If you notice, once we add the electrophile, that electrophile's at an sp3-hybridized position, so it's breaking the stabilization. We talked about how we could observed that stabilization by hydrogenating different compounds. [review of hydrogenation examples] If that first step of making the positive charge is rough, but if you put some electron density into the benzene ring to help it attack the electrophile, shouldn't that make the reaction even easier? The answer ends up being yes. By the oxygen getting involved, that's favorable.

Here, in the second one, no matter what we had as a substituent, any form of benzene ring that we add an electrophile to is initially going to have a positive charge that can go back and forth across most of the ring. But there's really no extra stabilization going on here, so it's not unfavorable, but it's not favorable; there's no delocalization with the oxygen. What would happen if we now looked at the para case? You might predict from the observation that I started with – the fact that phenol only produces the ortho and para – I bet you we're going to find out that the para is favorable; let's demonstrate that. The meta position, if you substituted there, it generates a carbocation that is not able to receive, through resonance, the electron density from oxygen. That electron density from oxygen helps stabilize the positive charge. Anything that helps stabilize the positive charge makes it easier to form. The first step of this reaction's rough, so if here's my reactant and here's my intermediate, the carbocation, if I can stabilize the carbocation by letting other electrons interact with it, that makes my energy gap smaller, which lowers my activation energy, which makes the reaction faster. This is not the end of the reaction; this is not the full reaction mechanism. At the end of each of these, a hydrogen has to be eliminated and benzene has to reform. What I'm showing you is that these different intermediates – because you start from the same reactant but go three different directions – if you have these three possibilities that we're working on – the ortho, the meta, and the para – what I'm showing you is that ortho and para are favorable, meta's not. Meta's not unfavorable, but it's not favorable. Since ortho and para are actively favorable, they're the ones that form. That's why this type of molecule, phenol, is known as an ortho-para director.

Now I'm going to have reaction through the para position. I'm going to delocalize that carbocation. Notice that just moving it over one, I've already got the carbocation drawn in such a way it's again right next to the lone pair of oxygen; that means it can delocalize with the oxygen, which ends up being favorable. Because the positive charge can be delocalized with oxygen in the ortho and para cases, phenol and other similar molecules are known as ortho-para directors. Why is it skipping one carbon? What's the allyl system look like, that skips one carbon, too, doesn't it? Can you think of a way to get the positive charge into the middle carbon on a molecule like this? Same thing with a benzene ring; that's why the positive charges skips a position each time it moves around the ring. There are some other molecules that are ortho-para directors: [pyrrole, furan, thiophene] aniline, an extraordinarily reactive ortho-para director; we have phenol; if we had an ether attached to that position, if you put –OCH3, what's the common name for that molecule? Anisole; also has a lone pair that can delocalize so also an ortho-para director. Any time electrons can delocalize off the substituent, then they're ortho-para directors.

I have just enough time to show you the other case, the meta director. Any time you can take a lone pair off a substituent and delocalize it onto benzene – in other words, when you add electrons to benzene – that makes it go to the ortho-para position. You can if you have aniline; but what if you had a nitro group? Let's look at the other case now. To do this, but to not make this too tough to read, let's remind ourselves that if we had something like nitrobenzene and we wanted to write the Lewis dot structure out, here's what it would look like. I want to remind you that nitrogen can't have five bonds to it, so formally, when we write the structure, there is a positive charge on that nitrogen. In reality, this is a delocalized ion, but still, the nitrogen is delta positive, at the very least. Keeping that in mind, let's look at what would happen if we took nitrobenzene and tried to do electrophilic aromatic substitution.

I'll again start with the ortho position. Hidden in this structure is the fact that there's a plus charge on the nitrogen. I just made a carbocation that has a plus charge right next to the nitrogen. Do you think it's favorable for those two plus charges to be right next to each other? Uh uh. It's quite unfavorable for two positive centers to be right next door to each other. What about the meta case, then? I could move the charge around the ring once, which will get that positive charge closer to the nitro group, but I could move it around again, which keeps it just as close to the nitro group, but notice that we never end up with the positive charge at the position where the nitro group is. This turns out not to be favorable compared to benzene, because the first step of any electrophilic aromatic substitution reaction is to make the carbocation. Having the electron density thrown at the benzene ring provides the electron density to help start the reaction; that's why phenol's more reactive. Here, we have a nitro group that is pulling electrons off the benzene ring – the same benzene ring we're trying to have take those electrons and attack something else. If you're pulling electron density off of the benzene ring, that means it doesn't want to attack something else. At least this is not as bad as the thing I drew up above; at least I don't end up with two positive charges right next to each other. So, comparatively, this is the ok case. What would the para case look like? Turns out it's going to be just like the ortho.

This is related to a theme of opposites of reactions: if one reaction does one thing in the cationic form, then it's going to do another in the anionic form. Notice that whole previous page, we were looking at a substituent that was adding electron density to the benzene ring; that made ortho-para better. Notice that we're writing all the same structures, but now the opposite is true: we want to avoid the substituent, so now the ortho-paras are worse. Changing the type of substituent made exactly the opposite kind of behavior. I move the charge just once, and you see we end in a case where I have positive charge right next to the nitro group. Because the intermediate formed by adding to the ortho and para positions causes and unfavorable charge interaction, substitution occurs at the meta position instead. We call a molecule that has this kind of behavior a meta director.

I've conflated two issues here in this initial presentation: the fact that we have ortho-para versus meta substitution; but there's also the fact that I said that, in the phenol case, the ortho-para case, it sped up the reaction, in the meta case, it slowed it down. Those are not always true. The meta case doesn't have an exception – any time you have something that causes meta, it also causes a slower reaction. But halogens end up causing ortho-para substitution, but also end up slowing the reaction down. Think about this: is oxygen electronegative? Then how is it that I'm saying that oxygen – even though it's an electronegative element – is adding electron density to the benzene ring? Oxygen does pull electrons away, but, because it has a lone pair that can delocalize, it ends up adding more electron density by delocalizaiton than what it steals by induction. When you have a halogen, the opposite is true: its inductive effects end up being stronger than the resonance effects. It's partially due to the size of the atoms involved: chlorine, bromine, iodine, they don't overlap as well with carbon, so delocalization doesn't provide as much electron density. Fluorine's in the same row as carbon on the periodic table, so the overlap's good, but fluorine's the most electronegative element. So, even if you have resonance, fluorine still steals it back away by induction.

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*Carbocation rearrangement is possible in Friedel-Crafts alkylation.

Because the intermediates formed by adding to the ortho & para positions allows for delocalization of the + off of the ring substitution @ the ortho & para positions is more favorable –> ortho/para directors

Common o/p directions : aniline

Because the intermediate formed by adding to the ortho & para positions causes an unfavorable charge interaction, substitution occurs & the meta position instead –> meta directors

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Structures *(remaining structures identical to lecture 18B)*

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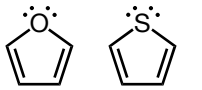

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