Lecture 19B • 03/06/12

[Quiz 3 review]

Let's start with ortho/para directors. Name some example molecules that would contain ortho/para directors: phenol. Why is electrophilic aromatic substitution difficult? Why does benzene not want to react? Because it's aromatic. What does aromatic mean? The unusual stability that comes about by the fact that it's got cyclic conjugation. We weren't try to say, which one of the following is most stable; we weren't trying to compare cyclohexene, cyclohexadiene, and benzene and way which one of these is most stable. What we're trying to do is say: what is the heat of reaction we predict from this molecule versus how much heat did we really get. If there's a lower release of energy than we expected, that means that the molecule was lower in energy to begin with, so, compared to what we expect, it's more stable. in benzene, we saw that huge difference, so there's a huge stability coming from it being cyclic. The first step of the reaction, that's the tough step of the reaction. Let's draw a reaction coordinate diagram. Let's do a generalized reaction coordinate diagram, where we're not worried about the specific reaction going on; we have some electrophile that's reacting somehow. In the case of phenol, there'll be two products that will result; we'll stick with one [to make a less confusing reaction coordinate diagram]. If these reactions tend to be spontaneous, and let's say that entropy doesn't have an effect, if this is a spontaneous reaction, do you guess that it's overall endothermic or exothermic? Exothermic, cause if entropy doesn't matter, there's gotta be some reason why the reaction wants to happen – that would be if energy's being released. The point is: phenol plus the electrophile versus the product, we're going to go downhill in energy. In between, there's going to be an intermediate, and it's a definite uphill step in energy. This diagram may not accurately reflect the energy differences, because I bet you in real life, to get up to the intermediate is probably way more energy than the reaction releases.

Let's say that we were comparing two different reactions. Let's say we were looking at just plain benzene reacting with the electrophile, and compare that back to phenol plus an electrophile. Let's say we were looking at just the first step of the reaction. Looking at I how I drew these, one compared to the other, it's not terribly obvious. But, it is true that energy energy of the products, it's a higher step-up if we come from benzene than if we come from phenol. Why? What was the point of showing all of those different resonance structures? To show where the electrons could or could not be delocalized. What did we discover was true for phenol, but only if we substituted at the ortho and para positions? Oxygen can become involved in that delocalization. The more you delocalize the ion, the more stable it is – lower energy to get up to that intermedate. You might remember the Hammod postulate; what is says is that the structure of the transition state most matches whatever energetically the transition state is closest to. If you look at this, the transition state is going to be closer to the intermediate in each case. It's like you've mostly formed the carbocation. If the reaction with benzene, making that carbocation, requires a lot more energy than the same process for phenol, then the activation energy to do it for benzene is greater than the activation energy for phenol, and smaller activation energy means faster reaction. That's why these ortho/para directors tend to be activators, because the same thing – resonance – that allows the substituent to direct where the next substituent's going to come in, the same thing that's causing that is also causing the reaction to speed up. The formation of an arenium ion – which means a cation made from benzene – is the rate-limiting step in electrophilic aromatic substitution. As such, any factor that can stabilize the intermediate will also lower the activation energy. If you stabilize the intermediate, you lower the activation energy, that means you speed up the rate of reaction. So, most ortho/para directors donate more electron density in through resonance than they might happen to withdraw due to induction. Oxygen, even though it's electronegative, has a really good orbital overlap with carbon. Most ortho/para directors donate electron density in, therefore stabilizing the arenium, therefore making the reaction easier to occur, which means that it's faster. Since ortho/para directors help stabilize an arenium ion by providing electron density by resonance, they undergo faster electrophilic aromatic substitution.

Let's return to the question again: what are some good ortho/para directors? We have phenol; what about some others? Toluene, which doesn't have resonance, but what does it have? If resonance can't stabilize something, what if something else could? What if you didn't have a lone pair, but you did have electron density? Hyperconjugation. How about some others? Styrene. That's conjugation, resonance. Anisole. What about this one? Aniline, one of the strongest activators, because that lone pair so easily delocalizes because nitrogen does not mind having a positive charge. We have alcohols, ethers, alkenes, alkanes, and amines.

Let's get into this question between directing and activating abilities. In the case of oxygen, oxygen's the second-most electronegative element on the periodic table, so how is it that oxygen stabilizes a carbocation if it's pulling electron density away from it? It is because of resonance, it is because of delocalization. Oxygen and carbon are very similar in size, so they have good orbital overlap, so the delocalization that occurs is beneficial, then oxygen can share electron density through resonance, yet pull some of that back back by induction. It turns out, in the case of oxygen, more donation occurs than withdrawal. If you have an oxygen, sulfur, nitrogen – things with lone pairs, in general, most of those will be ortho/para directors, and because you're putting electron density in, they'll normally be activators, which means speeding up the rate of reaction. Although oxygen is very electronegative, and can withdraw electron density by induction. It also has very good orbital overlap with carbon. The ability to share electron density through resonance with carbon is greater than its ability to withdraw electron density through induction. Oxygen is, overall, an activator.

What about fluorobenzene? It's in the same row of the periodic table as carbon. Still good orbital overlap, but now it's the most electronegative element there is, so even though fluorine will delocalize, it's at the same time pulling electron density away from the ring, which causes two contrasting effects: it's going to be an ortho/para directors, but because of induction, it's a deactivator. Although fluorine can participate in delocalization, it withdraws more electron density by induction than it provides through resonance, which means it's a deactivator. Why? Because if it's pulling electron density away, it's destabilizing the arenium ion that forms. If you destabilize it, it means it takes a higher activation energy to get there, which means it's a slower rate of reaction.

Just to show again why it's an ortho/para director, let's do the same process we did the other day. [don't just memorize resonance structures] Let's have any random reaction, keeping a generalized electrophile. Notice that I put it in the ortho position, because I'm predicting this is an ortho/para director. Let's draw the resonance structures that would put the carbocation in a place where we could see fluorine participating in resonance. Fluorine is still an ortho/para director, since it can delocalize the positive charge formed.

For chlorine, it's the opposite problem. For chorine, it's a bigger atom; it does not have as good an orbital overlap with carbon. It's less electronegative than fluorine is, but the fact that it's less electronegative matters less than the fact than it provides less electron density by resonance. In other words, it stil takes more than it gives. It's still electronegative enough that it counteracts whatever donation might occur by resonance. Chlorine, also bromine and iodine, has poorer orbital overlap with carbon, so it cannot provide as much electron density through delocalization. More importantly, it can't provide as much electron density by delocalization as it withdraws due to induction. The other halogens are ortho/para deactivators. An ortho/para director is potentially an activator or deactivator. A meta director is always a deactivator. An activator is always an ortho/para director. The reason that ortho/para directors are ortho/para directors is because, in one way or another, they provide electron density. Most ortho/para directors are therefore activators, because most of them cause that energy gap to get up to the carbocation to shrink. But, halogens are the one exception; they give less than they receive, but the fact that they give at all through resonance is why they're ortho/para directors, but then they take that electron density right back again, so they cause that energy gap to increase, because you're destabilizing the positive charge, so they are ortho/para deactivators.

Meta directors are always deactivators, cause what causes it to be a meta director is exactly the same thing that causes it to deactivate – the fact that you're pulling electron density off the ring – another way of saying it is, if you've got a positive center that you've attached to the benzene, you don't want to put another positive charge right next door. Let's see if we can come up with a list of meta directors. One of the strongest is the nitro group. An aldehyde, maybe benzaldehyde. What else? Benzoic acid. If benzoic acid, why not an ester? Are all esters deactivators? What causes something to be a deactivator? If it pulls electron density off of the ring. What causes something to be an activator? It gives electron density. Why does it matter if something gives or takes electron density to or from that benzene ring? Cause the first step in a reaction is for the benzene ring to open; if it actually has some electron density to work with, it makes it easier. Meta directors are anything that pull electron density away. Nitro, there's a positive charge; carbonyl, delta positive. That's an ester, it's got a delta positive right next to the benzene ring. Are all esters going to be deactivators, then? What functional group is that? It's an ester, but look at the position of the oxygen compared to the example up above. Here, the oxygen is directly connected to the ring. The carbonyl is going to pull a little bit of electron density away from that oxygen, so it won't be as good as something like phenol, or something like anisole. But, it still has lone pairs on the oxygen that can delocalize. So, this is an ester, but it's an ortho/para director because you've got a lone pair right next to the benzene ring. It is an ortho/para activator; the only [ortho/para] deactivators are halogens. If you look at the other ester, though, there's a delta positive center there instead, which means it's going to be deactivating. All carboxylic acid derivatives that have a carbonyl on the ring, deactivators, meta directors.

We have these three categories: ortho/para directors that are also activators – they include things like alkyl groups, alkenes, alkynes, alcohols, ethers, thiols, amines, reverse esters; we then have a small clump of ortho/para deactivators – those include the halogens; we then have the meta directors, which include nitro compounds, anything with a carbonyl – aldehydes, ketones, and carboxylic acid derivatives. [benzene also ortho/para]

[synthesis problem]

Let's say I want to make this molecule from benzene. Let's say that I have a more liberal policy on synthesis – what if I say you can use any materials you want to to synthesize, but you have to start from benzene: how would you do it? Let's see if we can name the electrophilic aromatic substitution reactions we've learned so far. Halogenation, alkylaton, acylation, sulfonation, nitration. Point of this synthesis problem is: one way you'll get there, one way absolutely you won't. What happens if you put the nitro group on first? Put the nitro group on first, whatever your next electrophilic aromatic substitution is, it's going to go in the meta position. We want a product that's para, so this can't work. We have to do it last; an alkyl group is an ortho/para director. We will not worry about how do I avoid ortho. Ortho comes with para, para comes with ortho, nothing we can do about it. But, at least if we put the alkyl group on first, we won't get meta. What kind of reaction would I do first? Halogenation? Put a halogen on a benzene ring, and then make a Grignard reagent out of it and then do some form of Grignard reaction. You'd have to do some follow-up steps, because a Grignard reaction make an alcohol, but we have ways of oxidizing and removing alcohols. [What about] alkylation? [Is there] a particular reason [to be worried about using the reaction]?

Because if we do alkylation, we're going to get carbocation migration. What if we did acylation first? We take a three-carbon acyl halide and add it to the benzene ring, which is no problem, cause we could just do a Wolff-Kishner reduction and knock off the carbonyl. There's one more way to do it, which is if we have an alkyl halide, we could so what's called a coupling reaction. Once we're here, it's just nitric acid with sulfuric acid to put the nitro group on. Yes, we get the ortho product as well; we don't care, we just know in real life we're going to have to separate the two products we get.

_____

o,p-directors

The formation of an arenium [ion] is the rate-limiting step in electrophilic aromatic substitution. Any factor that would stabilize the intermediate (the arenium ion) would also cause a lower Ea to reach that intermediate, which increases the rate of rxn.
Since o,p-directors help stabilize an arenium ion by providing electron density by resonance, they undergo faster electrophilic aromatic substitution.

directing vs. activating
Although oxygen is very electronegative and can withdraw electron density by induction, it also has very good orbital overlap with carbon. The ability of oxygen to share e- density via conjugation/resonance is greater than its tendency to remove e- density by induction, so oxygen is an activator.
Although fluorine can participate in delocalization it withdraws more e- density by induction than it provides through resonance –> deactivator.
(withdrawing e- density raises the energy of the arenium ion, which means forming the ion requires greater Ea, so the rate is lower)

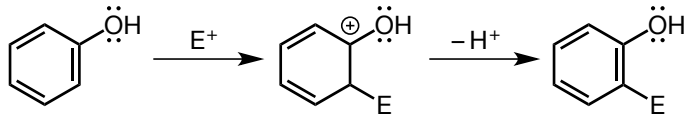
Fluorine is still an o,p-director since it can delocalize the + charge formed.
Chlorine (and bromine & iodine) has poorer orbital overlap with carbon, so it cannot provide as much e- density through delocalization as it withdraw due to induction –> o,p-deactivators.

meta directors

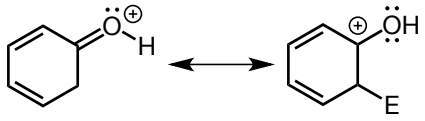
synthesis
Must perform nitration last!

_____

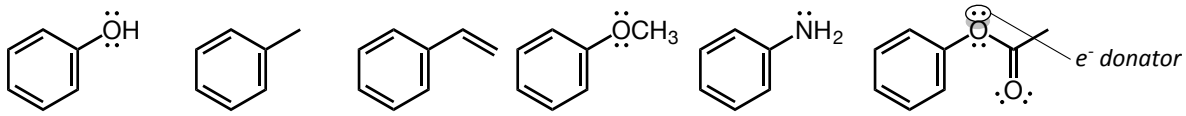
03/06/12 lec • 1



03/06/12 lec • 2

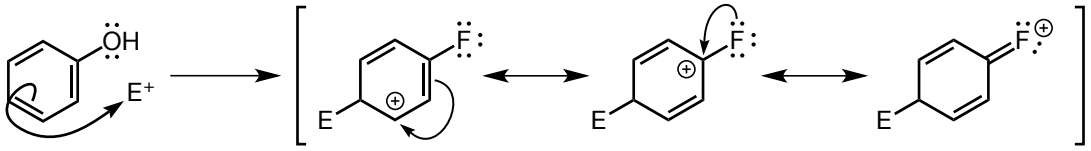


03/06/12 lec • 3

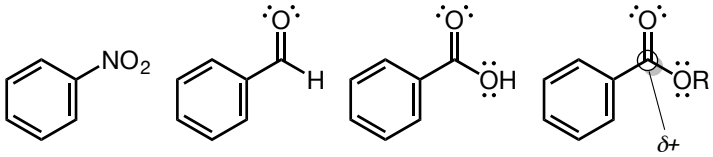


due to hyperconjugation

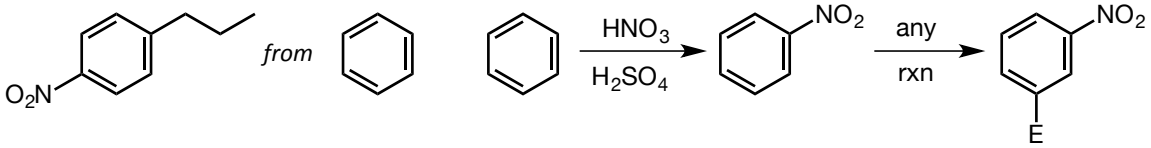
03/06/12 lec • 4



03/06/12 lec • 5



03/06/12 lec • 6



03/06/12 lec • 7