Introductory Organic Chemistry - II
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Lecture 13
Nucleophilic Aromatic Substitution Part - 1

So, the next topic is Nucleophilic Aromatic Substitution. We have thus far discussed several aspects of the Electrophilic Aromatic Substitution, where the electron-rich Benzene ring donates its electrons or it reacts with species such as electrophiles, which have a positive charge on it, to undergo an addition elimination reaction which finally amounts to substitution.

So, now, in this lecture what we will try and understand is whether a benzene ring can undergo a Nucleophilic Aromatic Substitution, that is whether a benzene ring can be activated in an electronic sense to undergo Nucleophilic Aromatic Substitution. So, in order to understand this first let us understand why benzene rings are not very good at undergoing Nucleophilic Substitution.

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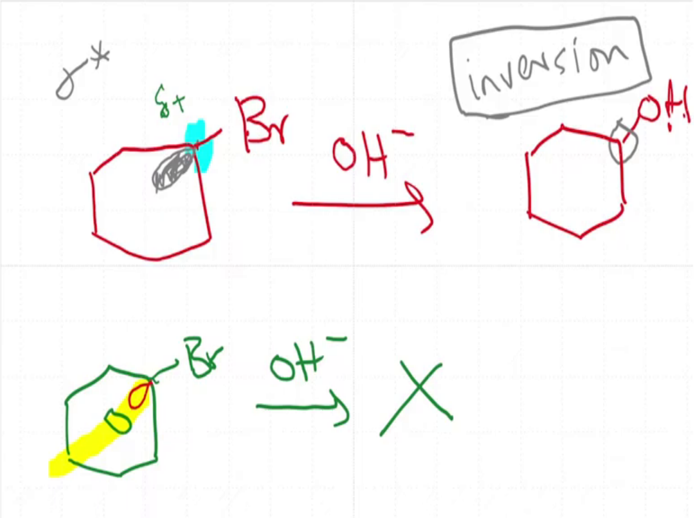

So, when we consider an example of, S_N2 reaction for example, where, you have a cyclohexyl bromide or equivalent here, which then reacts with hydroxide ion, which is the nucleophile to give you the S_N2 substituted product. Now, this reaction occurs for several reasons, one of them is that the carbon is delta plus, and therefore it is a site for attack.

Also, the other important aspect of the S_N2 reaction is that the attack happens from the backside where the sigma star orbital is located. And the third aspect of S_N2 reactions is the inversion in stereochemistry, so that means that you have an inversion going on here. So, now when we look at S_N2 reactions, at least, they are not very conducive to occur in Bromobenzene. First of all, I mean, there is a delta plus charge on the carbon next to the bromine. So, therefore, that is not a problem.

The second issue, which is the backside attack might be problematic because you see that there is quite a bit of hindrance from this part of the benzene ring. And the third criteria, which we looked at, is an inversion in stereochemistry. So, even if the attack happens from here, this SP^2 carbon will have to undergo an inversion, which is going to give you an extremely strained molecule, which is just not possible or it does not happen.

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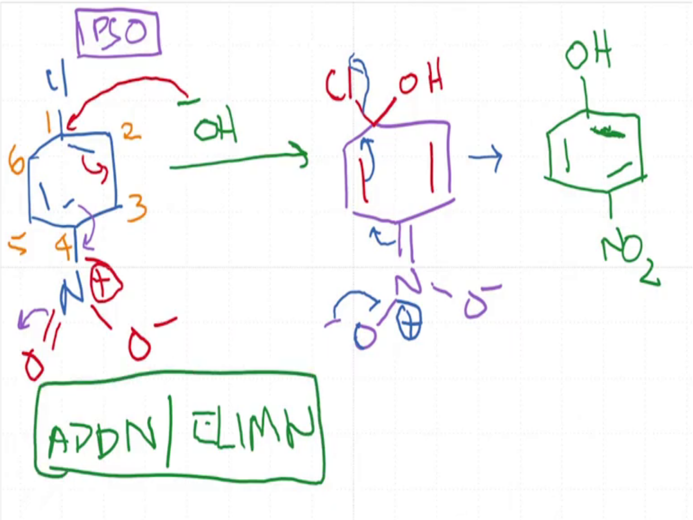

So, therefore, the S_N2 reaction is quite difficult, or if not impossible, but benzene rings can undergo Nucleophilic Substitution. And just like Electrophilic Substitution, they go through an addition and elimination mechanism. So, here is the example, so let us start with 4-Nitrochlorobenzene. So, you have N double bond O, O minus there is a positive charge here.

Now, imagine that this carbon is a site for attack. So, now you add a nucleophile. And the nucleophile we are looking at is a Hydroxide ion. So, among the various positions in the benzene ring, so I am going to just number these carbons so that it is easy for us to follow. So, when the attack happens at the 2-position, for example, to a substituent, the attack is called the ortho, meta, and para.

But what if it attacks at exactly the position at which the substituent is, so for example here if the attack happens, this is called an IPSO attack. So, an IPSO substitution can happen if the attack happens here. So, that is exactly what happens in this case. So, the hydroxide ion attacks here. And these electrons can then go towards the nitro group. And the intermediate that is obtained is the following intermediate. So, you have N and you have, the rest of the molecule is the same, there is OH, and then there is Cl.

So, this is what we would expect as the intermediate that is formed. And Nitrogen of course, as a full positive charge. Now, if you think about it, is this intermediate extremely unstable? Not really, very, very unstable, but it can be formed, the species are all right, so there is nothing really wrong with this kind of structure. Now, if you look at it, this is set up in a nice way to actually kick out or to do an elimination reaction.

So, when this pair of electrons comes in here, then you have this going up here, and this coming up back here. And now there is a choice between Hydroxide as a leaving group and Chloride as a leaving group. And you are already familiar that Chloride is a much better-leaving group compared to Hydroxide ion. So, therefore, the product that is formed is basically the substituted product. So, you have NO_2 back, here, here, here, and 4-Hydroxynitrophenol, this is the product that is formed. So, this is an Addition/Elimination reaction, which amounts to substitution.

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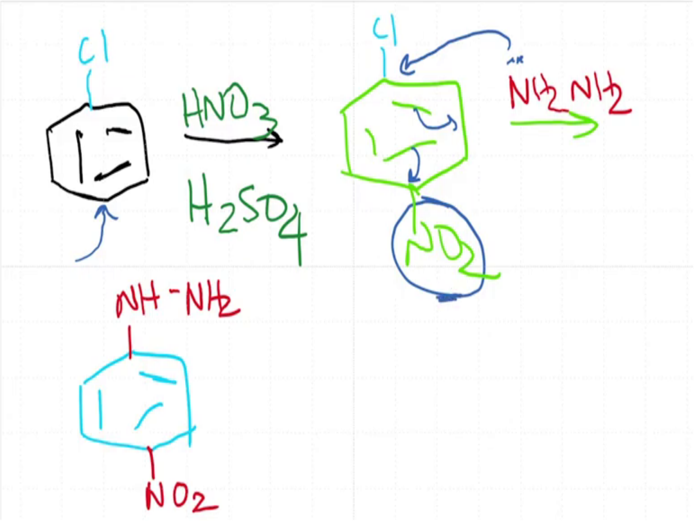

Now, let us look at an example of how to use this electrophilic aromatic substitution in synthesis. So, if you want to make 4-Nitrophenylhydrazine, whose structure is shown here, then we could start from chlorobenzene. If we do nitration, HNO_3, H_2SO_4, the nitration occurs at the para position and you get 4-nitrochlorobenzene and then subsequently react with hydrazine, this is going to give you the desired product.

So, now the mechanism of this reaction is likely to go through Nucleophilic Aromatic Substitution. So, I let you guys work on the mechanism at some point. And this is going to give you the following product. So, it is a fairly straightforward reaction.

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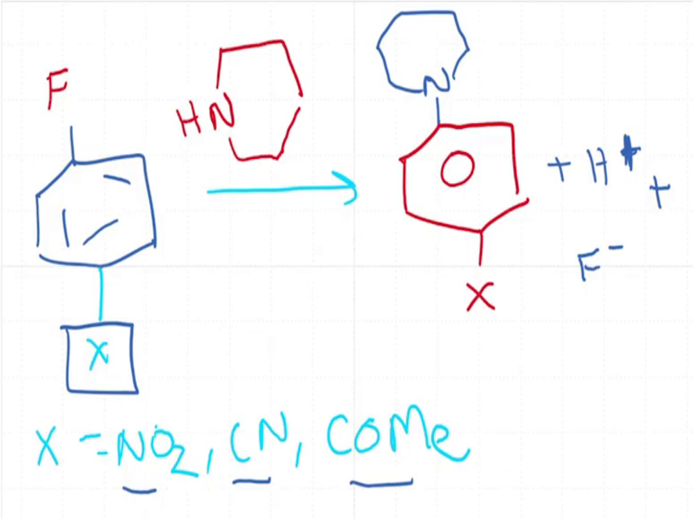

Now, let us spend a little bit of time and try to understand the various aspects of this mechanism of this reaction. So, in order to do this, the following experiment was conducted. So, you have substituent over here, and you want to see if you can vary the, so let us say we will start with the fluoro compound. And we have this substituent X. And now when you vary X, let us say NO_2, CN, and COMe, and you measure the rate of the reaction with an amine-based nucleophile.

So, the amine-based nucleophile that you are looking at is piperidine. So, what happens here is, the product that is formed is basically the benzene ring continues to be here. And the product, of course, H^+ plus F^-, so this is the product that is formed. So, if the group here, X is hydrogen, this reaction does not happen.

So, this we have already looked at in the past, so the ring is not activated enough for it to undergo Nucleophilic Aromatic Substitution, but when X is nitro, cyano, or a ketone, the reaction does go forward. And what we can do is we can actually measure the rate of the reaction. And we can measure the loss of the starting material, and also the formation of the product. And once you have measured the rate of this reaction, then you can derive a rate constant.

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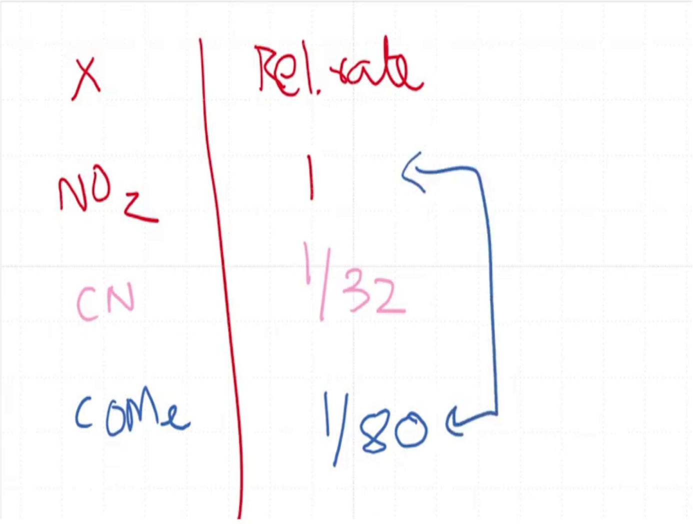

X	Rel. rate
NO_2	1
CN	1/32
COMe	1/80

And once the rate constant is there, then you can do what is known as a relative rate. So, when you change X, and then you look at the relative rate of the reaction. So, when X is nitro, the relative rate can be designated as 1. And then, when you move to a cyano group, the relative rate is 1 divided by 32. That means it is 32 times slower than that of benzene. The last example we are looking at in the series is the COMe Group, which is 1 by 80. So, therefore, the difference in the rate of Nucleophilic Aromatic Substitution between these two compounds is quite significant. So, what does this mean in terms of the reaction.

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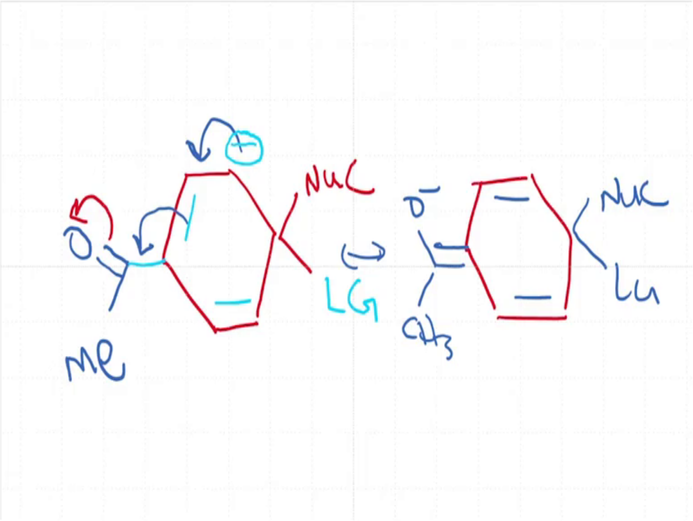

So, let us look again at the key intermediate that is formed. So, when you have a nucleophile, that is attacking, and you have a leaving group that is leaving, let us imagine that the first sort of species that is produced is shown here, which is the negative charge here. So, now when it delocalizes, it delocalizes, in such a way that it can go here.

And now, if let me take the example of the ketone, just to understand this, so you have C=OMe, then you can push electrons into the O^-. So, one of the important resonance forms that we are looking at would have the enolate as the major or the most important resonance form that we are looking at because that helps us understand the stability of the intermediate. So here is the leaving group.

Now, when I compare this versus a nitro group being an electron-withdrawing group, so clearly, the nitro group is a better stabilizer of the excess negative charge. So, the interpretation from this experiment is that the electron-withdrawing ability stabilizes the transition state leading to the formation of this intermediate. So, therefore, the more stable the intermediate, the lesser is the energy barrier towards its formation.

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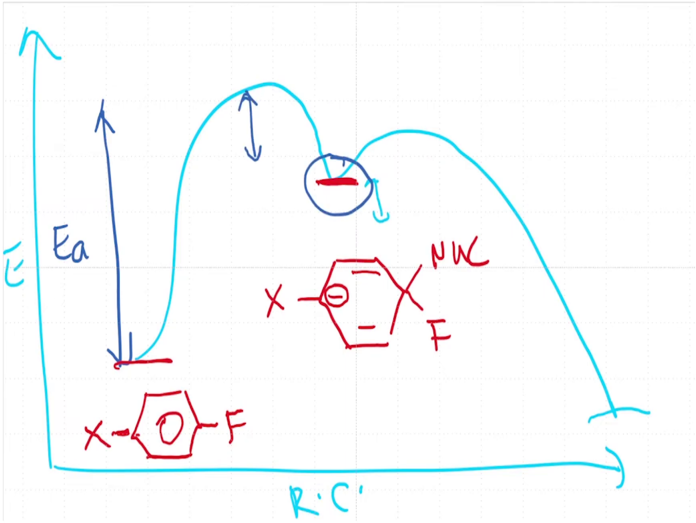

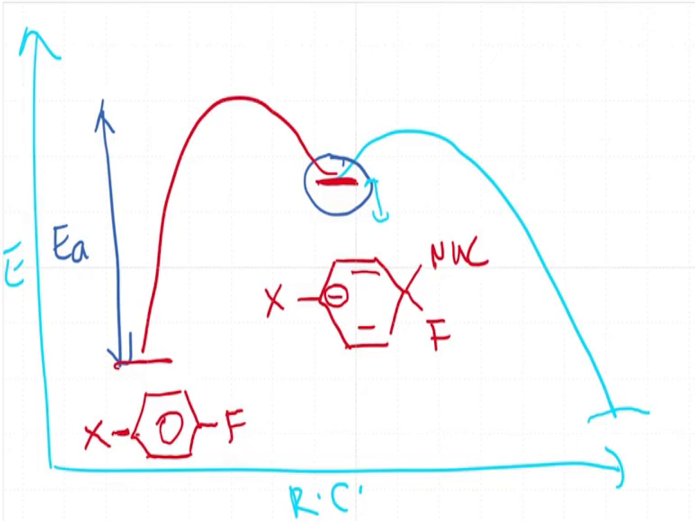

So, let me just draw this out in the form of an energy profile. So here is the energy and here is the reaction coordinate. So, when we start with the reactants, which is let us say fluoro, and then X. And now, here is the intermediate that is formed nucleophile, fluoro. And then here is your X. So, let us assume that the negative charges over here, and then the rest of the molecule is the same.

So, therefore, the more stable this intermediate is, the greater the effect on the transition state leading to the intermediate. So, the next step, which is the loss of the negative charge, and formation of the product might be considered as the second step, which is not the rate-determining step.

So, therefore, this is the activation energy or the barrier to the important reaction, and therefore anything that stabilizes this, is going to have an impact on the rate of the reaction. So, therefore, this becomes an important piece of information for us to understand, in that the stabilization of the negative charge here has an impact on the rate of the reaction. Now, what about the leaving group.

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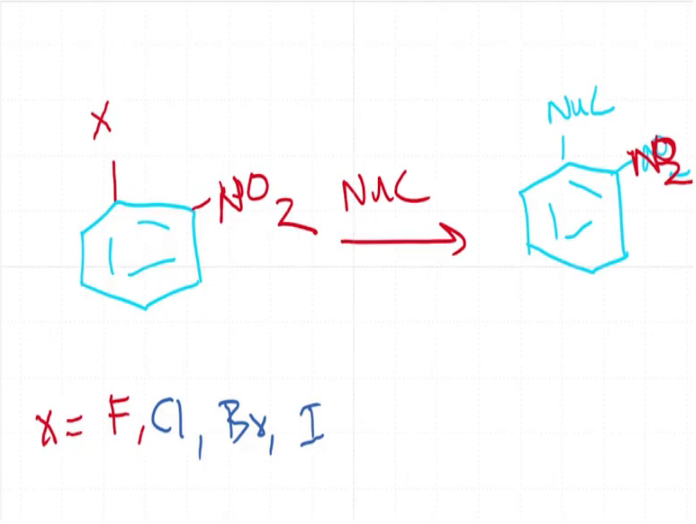

So, the next experiment that we do is to change the leaving group. So, we have X here, and then we can keep nitro as the electron-withdrawing group, and then we carry out the reaction in the following manner. Let me just redraw this, so that we can better understand this. So here is the X, and here is the nitro group.

So, the reaction that we are doing here is just the same reaction with a nucleophile. And the product that is formed is NO_2, Nuc, and what we do here is X equals fluoro, chloro, bromo, and then iodo. So, we just vary the halogens in the series that we are by now quite well acquainted with. And then again, we measure the relative rate of this reaction.

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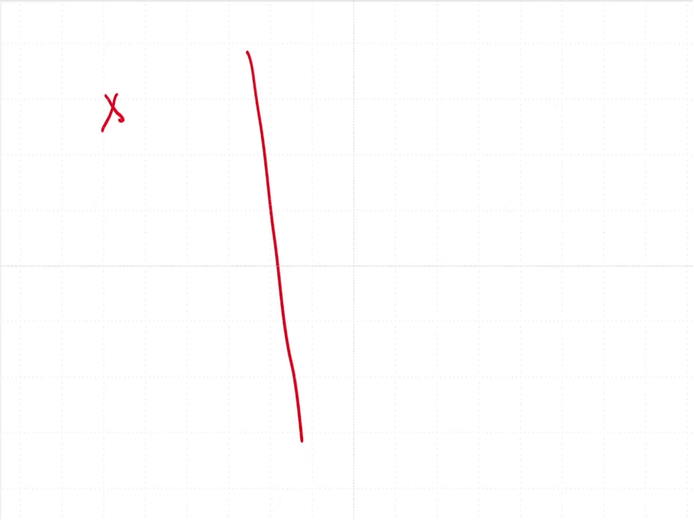

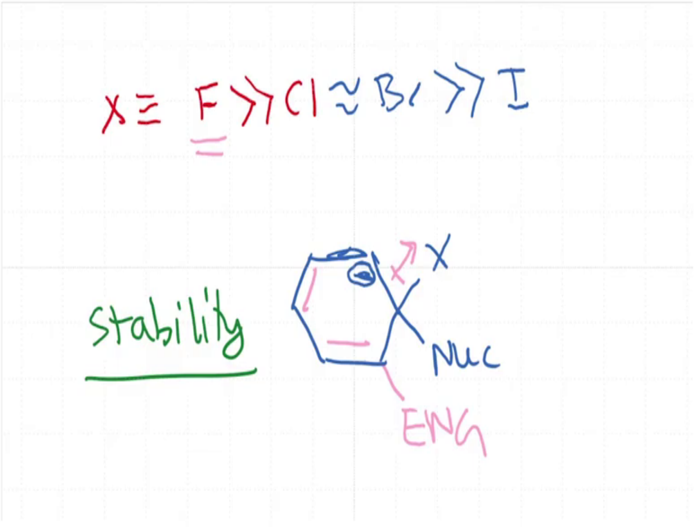

So, when I change X, and I measure the rate of the reaction, what we find is the fluoro is much greater than chloro which is almost equal to bromo and which together is greater than iodo. So again, if we look at the intermediate that is formed, we have already determined that the rate-determining step is the addition to the group here. Now, what we can infer from this experiment is that, so here in this case your electron-withdrawing group is right next to it.

But in general, I mean, it is also possible that the electron-withdrawing group is at the para position. Now, when you have this kind of an intermediate that is produced fluorine being highly electronegative atom clearly pulls electrons from this negative charge and then, therefore this leads to some stability. So, the leaving group ability, which comes in the next step, that is, after the rate-determining step is done, does not play an important role. But here, the electronegativity of the group would be very important in determining the rate of the reaction. Therefore, this reinforces the concept that the first step is the rate-determining step.

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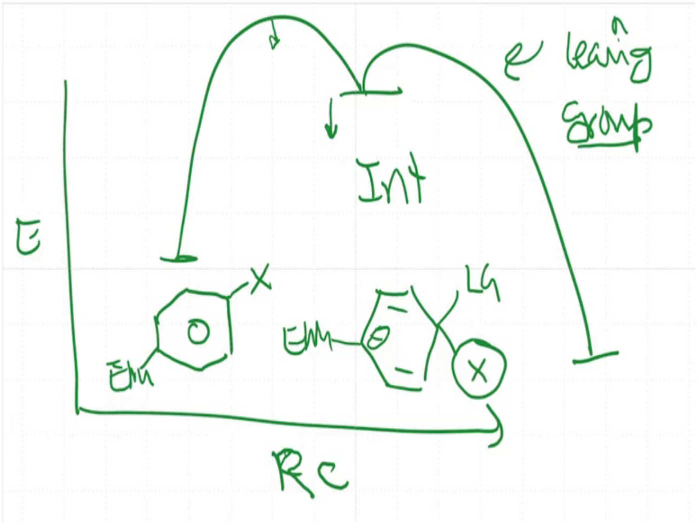

So, our energy profile, if you remember, was telling us that the first step wherein the intermediate was formed was the rate determining step and not the second step wherein the leaving group, would have an effect. So, therefore, it is really important that we understand this. So, here is the leaving group, here is X, and here is the electron withdrawing group.

In this case, it is in the para position. So, the second step is not very important and therefore, the reason or the way we understand the fluoro is being faster in this reaction is that, it seems to be stabilizing the negative charge that is formed or this intermediate that is formed. And therefore, the intermediate gets a little more stable. And the energy of this reaction or the rate determining step of the reaction, the transition state leading to that is actually going to be more stabilized.

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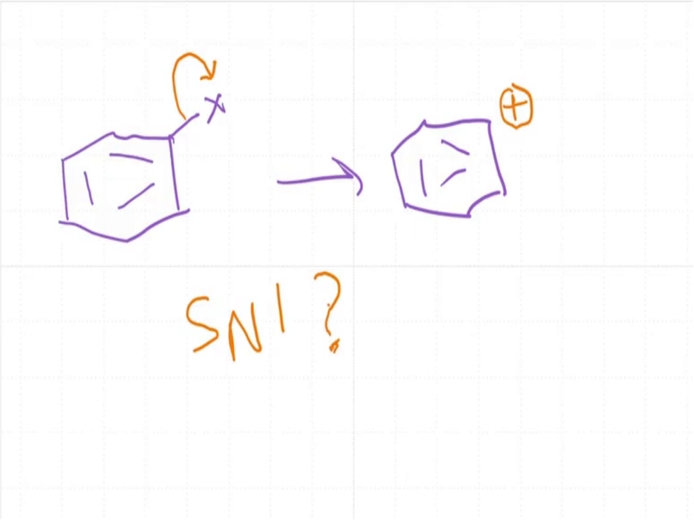

So, the next question that we could ask is, what about S_N1 reaction? So, we just looked at electrophilic aromatic substitution, which is an addition elimination reaction, but S_N1 involves the loss of the leaving room to produce a carbocation. So, the question that we could ask is what about this situation? So, the phenyl carbocation is not really a very stable system and therefore, it is unlikely that it will be formed.

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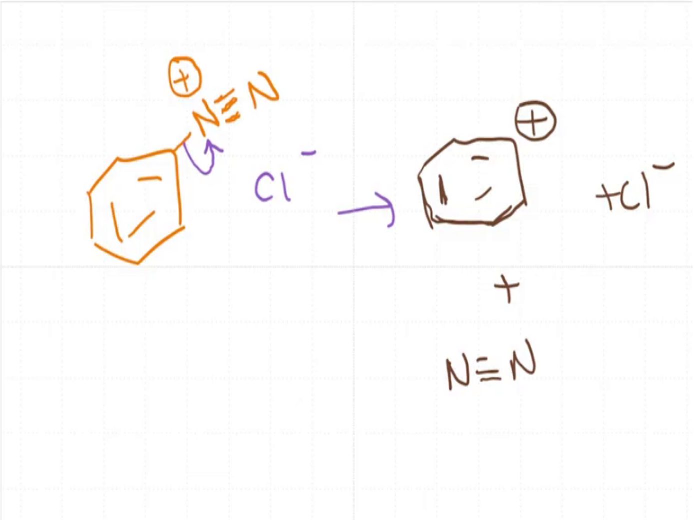

The only way in which or one of the important ways in which it can be formed is if you had an excellent leaving group. So, the kind of leaving group that we are looking at is, for example, the loss of molecular nitrogen for example. So, if you imagine that this can be kicked out like this, then the product that you have is the phenyl carbocation and the formation of N≡N which is an extremely stable species.

And of course, Chloride remains here. So therefore, the S_N1 type of reaction wherein a carbocation can be formed is in principle possible, only when you have an excellent leaving group, such as Nitrogen. Otherwise, we would not normally encounter the formation of a phenyl carbocation.

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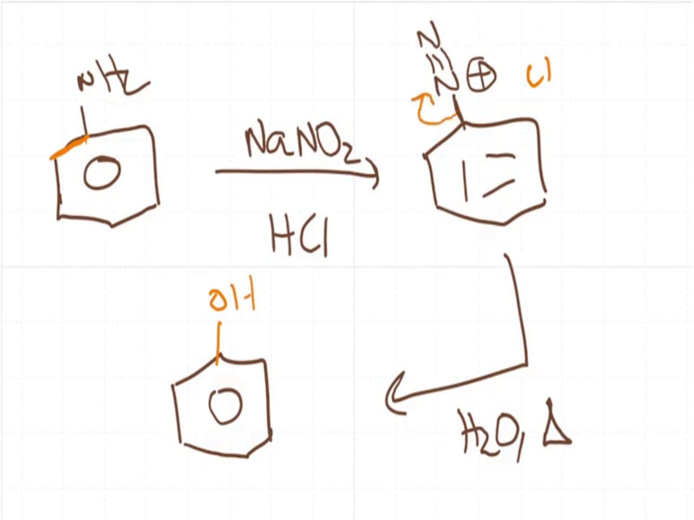

Now, how does one generate this kind of an intermediate. The way it is done is we start from amines and amines are reacted with the $NaNO_2$ in the presence of HCl and they generate the diazonium species in $N≡N^+$ and then what you do is you react this with, under suitable conditions. For example, if you just add water and heat, you end up with the phenol as the product.

So, actually converting Benzene to Phenol is quite challenging. So, you could do it through a somewhat longer route. We will look at it shortly. But nevertheless, so the mechanism for this reaction is that there is a loss of Nitrogen gas and then addition of water and loss of H^+ to give you the Phenol.

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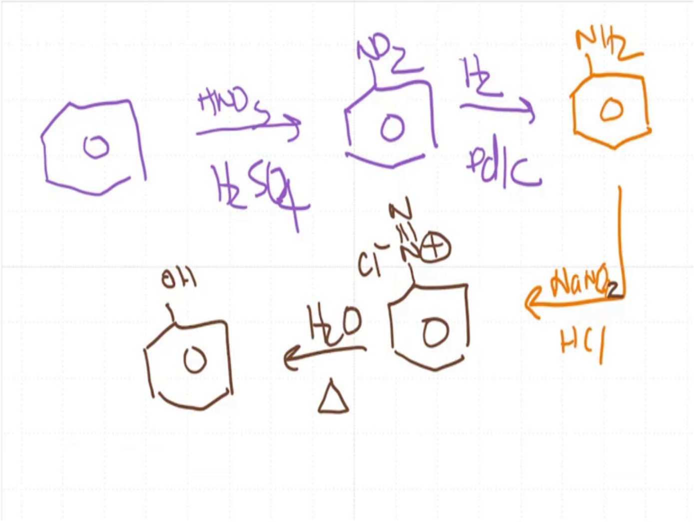

So, now coming to the question that I just mentioned is how do we convert Benzene to phenol? One of the ways in which you could do it is you start with Benzene; you nitrate it HNO_3, H_2SO_4 and that gives you Nitrobenzene.

And now, you can do reduction reaction; you can use Hydrogen in the presence of Palladium/ Carbon and you get Aniline, and then Aniline is reacted with $NaNO_2$ and HCL and the product that is formed is this diazonium salt which then is reacted with water, by heat, to give you Phenol. So, there are possibly other methods that one could use to do this transformation, but this is one of the ways that one could use using Nucleophilic Aromatic Substitution as one of the key steps in the reaction.

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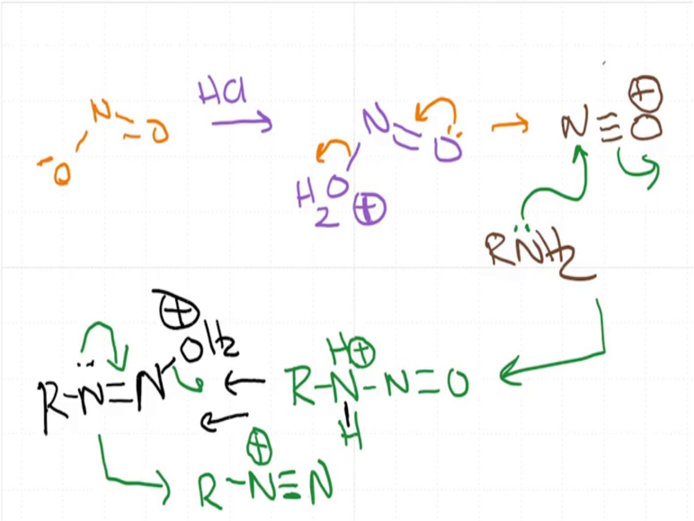

Now, moving forward, let us try and understand how this diazonium salt is actually formed. So, the mechanism by which diazonium salt is formed is that when you have nitrite anion in the presence of H^+ which is basically it is going to get N=O, OH and if you imagine that another proton is added to this you get OH_2^+ and then you have a loss of water.

So, this lone pair can come in here and you can imagine that the water is eliminated and you get $N \equiv O^+$ and here the oxygen has a full positive charge, Nitrogen is neutral. And this nitrosonium ion here is the key intermediate, that is used in this reaction. Now, RNH_2 which is basically the amine can react with nitrosonium ion, so in the following manner and the product that is formed here is R NH_2 N=O.

So, this is a N-Nitroso compound which can then, there is still a full positive charge over here. And what can next happen is that you have a loss of proton and then you have, which can subsequently get converted to $RN{=}NOH_2^+$. So, this undergoes a series of steps, there is going to be a proton transfer followed by the movement of this lone pair on the Nitrogen, which is then restored.

Now, you can, this is the key step here for us to work through. So, this is going to move here and there is a loss of water and you get the $N \equiv N^+$. So, if you look at any standard textbook in organic chemistry, you will be able to look through the mechanism of this diazotization reaction.

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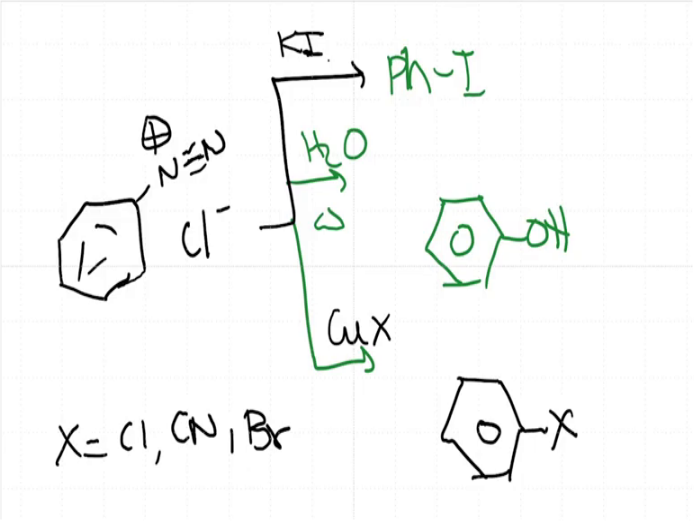

And the important part about diazonium ions is that, you can use this for a variety of reactions. So, once you generate these diazonium salts then you could react it with the Potassium Iodide and the product that you get is Iodobenzene.

You could react it with H_2O, we just discussed this and heat and you get Phenol. You could react it with the copper nucleophiles and you get the corresponding X substituted Benzene rings. So, X here can be chloro, cyano, bromo, and so on. So therefore, the diazonium salt becomes a very important intermediate in synthesis and a variety of products can be formed using this as an intermediate.