Introductory Organic Chemistry-II
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Lecture 6
Electrophilic Aromatic Substitution Part – 2

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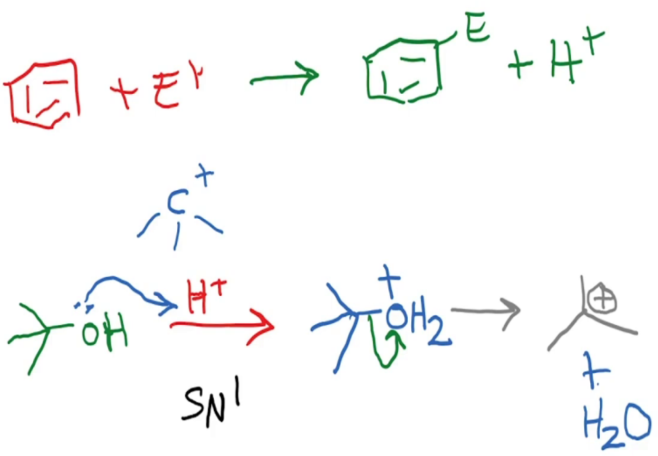

So, now let us get back to the Electrophilic Aromatic Substitution with other electrophiles. So, so far, we have been looking at, for example, Bromination. So, the basic reaction just to recall is basically reaction of an electrophile with Benzene to give you the electrophilic aromatic substituted product which is this. Now, the electrophile can actually be a variety of compounds and for example, the electrophile that we can think about is one of the most important reactions that organic chemists are interested in which is the formation of a Carbon- Carbon bond.

So, how do we generate carbon-based electrophile? So, this is something that we have looked at previously. So, for example carbon-based electrophiles can be produced as intermediates during S_N1 reactions. So, for example here if you have an alcohol such as this and if you expose this to H^+, and based on the S_N1 mechanism that we have previously looked at, our E_1 for that matter, we are familiar with the formation of protonation of this center.

So, it is going to form OH_2^+ and if you were to draw the arrow pushing mechanism, it would look like this. This is a lone pair on Oxygen, it attacks here and gives you the OH_2^+ and now you can propose this Carbon-Oxygen bond being broken because water is an excellent leaving group. So, you would end up producing tertiary carbocation over here as well as water.

So, this is something that we already know from our previous courses. So, therefore, the formation of the carbocation is something that we have some prior exposure to. So, now, the question is can we put both of these in the same bottle and that is what we want to do, if we want to do Friedel Crafts Alkylation reaction.

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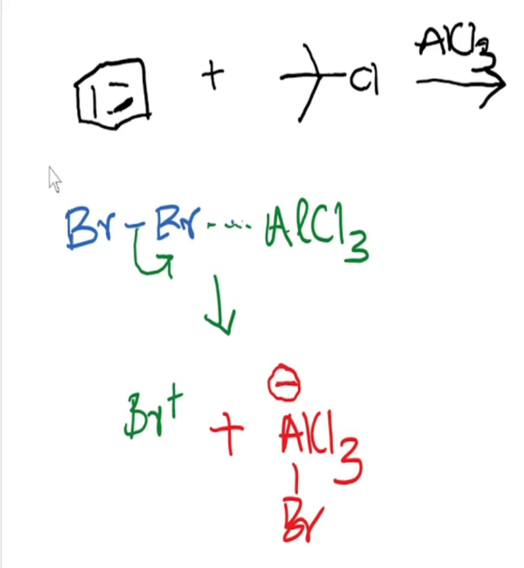

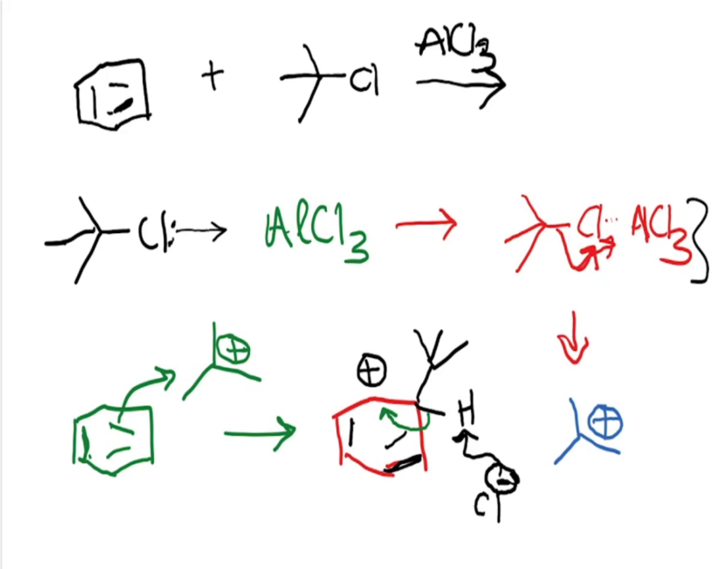

So, the reaction is as follows. So, you need to be able to generate a carbocation in the presence of benzene and one of the ways in which you could do this is, to react it with an alkyl chloride in the presence of a Lewis acid, such as $AlCl_3$. So, we already seen prior that when you have Br_2 in the presence of a $AlCl_3$, you have a weak bond that is being formed with Aluminum and this Aluminum is then, gives rise to complex such as this, where you have this being kicked off and giving you Br^+, which is the active electrophile and $AlCl_3$ Br minus. And so, this is the role of Aluminum Chloride.

So, if you were to think about a similar role for this group over here, then you can imagine that, instead of the Bromine, the Fluoride can be lost by using this sort of chemistry. So, now let us look at this. So, instead of Bromine, we now have tertiary butyl chloride, this compound, and you have a lone pair on Cl, and that is again going to coordinate with aluminum chloride. And this is going to result in the formation of a complex such as this Cl, where it is going to be bound to $AlCl_3$, and then you can push electrons in the following manner and give you the formation of this bond.

And it is going to give you the tertiary butyl carbocation as one of the products and now you know the rest of the chemistry, it is fairly straightforward. So, when Benzene reacts with a carbocation, you are going to have a formation of the intermediate that we discussed earlier which is going to give you this kind of intermediate and the Hydrogen over here, and you have a positive charge being formed.

And the rest of the bonds are essentially the same. So now, this is the intermediate that we are looking at. And as we discussed earlier, they could be some base, maybe there is some more of chloride that is floating around as a dissociation of this complex, and it attacks, and you have a loss of a proton, essentially, to give you the product, which is nothing but the Alkyl Benzene. So, which we shall look at in the next slide.

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Friedel Crafts alkylation
RXN

So, you have this kind of a compound and if you lose a proton, maybe there is some mild base, such as chloride ion being present. And it is going to give you the desired product, which is this. So, this is something that you know, we could straightforwardly, maybe propose and this is essentially called the Friedel Crafts Alkylation reaction. So again, as I said, the name is not really important here, but you need to understand the mechanism. Now, let us go back to the example of S_N^1 reaction.

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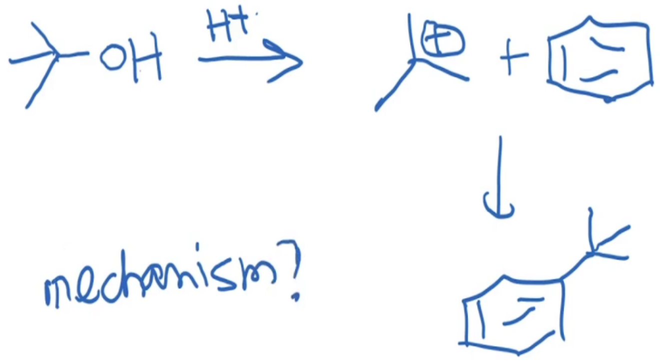

So here, if you imagine that the carbocation is indeed being produced when you take a tertiary butyl alcohol and add H^+, so under these conditions as well, you would get Friedel Crafts type of reaction. And if you add Benzene here to this, then the product that you want to get is this; I would urge you to go back and solve this problem. Work out the mechanism of this reaction. So, this is an assignment for all of you, go back and do this.

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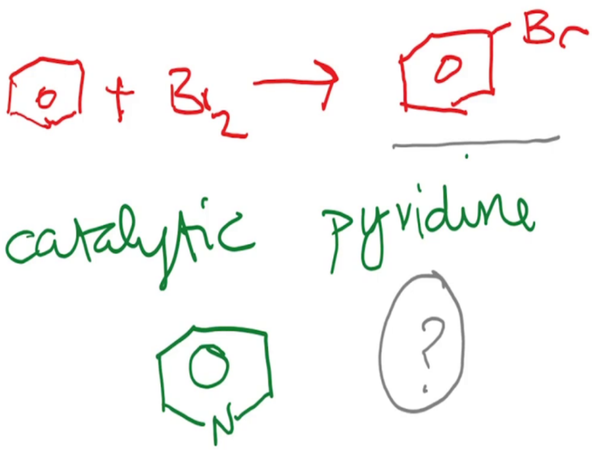

So, let us start this part of the lecture with a problem. So, the problem that we are looking at is a nice mechanistic question. So, we all know that when you react Benzene with Bromine, there is basically no reaction if you do it in the dark and you need a Lewis acid such as $AlCl_3$. But this reaction to give you the product Bromo benzene is possible if you add a small amount of catalytic Pyridine.

So, just to give you the structure of Pyridine is this. So, if you had a small amount of Pyridine, the reaction goes forward and gives you the product Bromobenzene. So, the question is, what is the mechanism of this reaction? So, all of you work on this and we will take this up sometime in the next few lectures.

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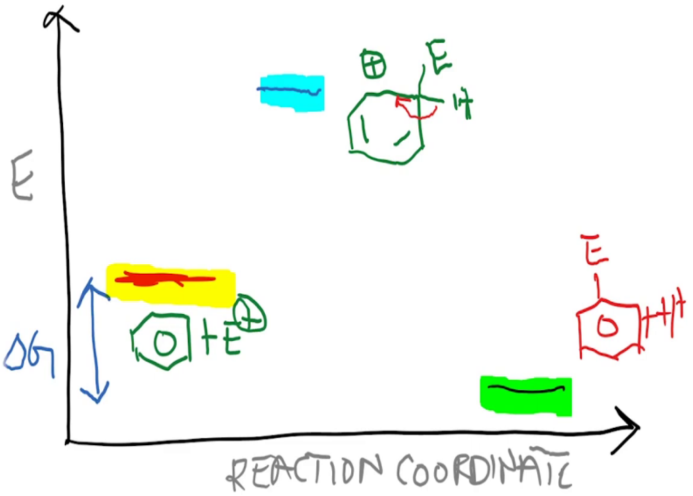

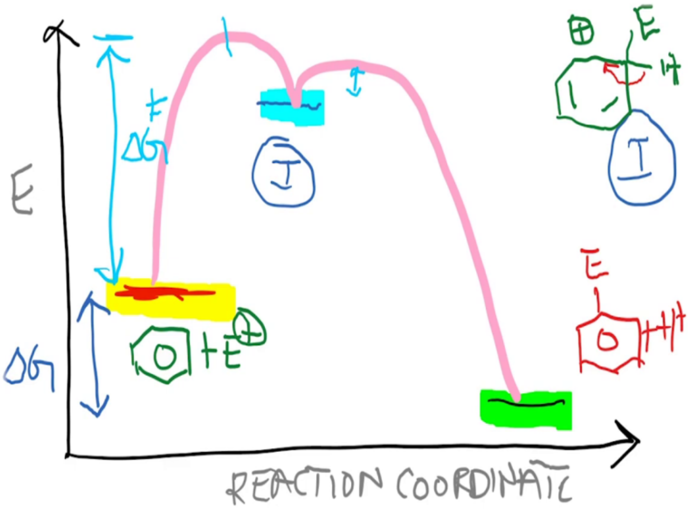

So now, I want to discuss in this lecture, the part of the energy profile associated with the electrophilic aromatic substitution. So, just to be clear, we normally represent the energy profile in the following manner. We have our x-axis and the y-axis and so the x-axis is basically a reaction coordinate. Some people also call it progress of reaction, and this is energy.

So, when we want to start, we would start with the starting compound basically Benzene and I am just going to draw Benzene and a generic electrophile. So, let us call it E^+. And so let us say this is the energy level that you are starting. So, here is the energy of the starting material. Now, we know that the first step of the reaction is actually to form the intermediate.

The intermediate is basically the complex where the aromaticity has broken and that structure is as follows. So, you have E, then you have H and then there is a positive charge over here. And so, this is going to be the structure of the complex and now based on what we sort of know about this, it is quite likely that the energy of this complex is substantially higher than that of the individual starting compounds, because the intermediate actually has lost aromaticity in its structure.

So therefore, if you want to look at it, you can consider that the product or the intermediate that is formed is going to be quite highly energetic. So, what I am doing is I am just trying to get this intermediate out of the way so that we can draw the remaining structure clearly, nevertheless. So now, the product that is going to be formed is basically the electrophilic aromatic substituted product, which is basically E and you are going to get a byproduct of H^+. So, which is going to be basically the loss of proton.

Now, if you want to look at this, many of the electrophilic aromatic substitution reactions are actually Exothermic in nature. And so, you would imagine that the product is going to be more stable than the starting material. So, this is going to be my ΔH or ΔG and now coming to the sort of intermediate over here, we are going to try again, to see if this intermediate can be moved. And yes, this time, I am able to select all of the structures, and I am just going to move over here, so that it is easy for us to draw out the energy profile.

So, I am just going to call this as 'I', which is basically the intermediate. And so, the 'I' structure is over here. And now if I have to draw the energy profile, it is going to look something like this. So, there is going to be a fairly high barrier to get to the intermediate and then the intermediate is going to collapse and give you the product.

So, now what we know based on Hammond postulate is that the transition state, which is approximately here, the transition state is going to resemble the product, which means that you know, essentially the Hammond postulate says that in a highly Endothermic reaction, the transition state, sort of resembles the product. And as a corollary, in a highly Exothermic reaction the transition state resembles the starting material.

So, therefore in Electrophilic Aromatic Substitution, you can imagine that the intermediate that is formed is going to be of high energy and therefore, the transition state leading to that intermediate is going to resemble the product. So, a lot of this is going to be important, when we want to understand the course of a reaction, for example, from a regioselectivity standpoint.

So, you know from your prior courses, that you know, there is distinct ortho, para selectivity versus meta selectivity and so on. So, all of this can be explained using this concept. So, just to complete this diagram, this sort of measure here is going to be your activation energy or $\Delta G^{\neq}$. So, that pretty much takes care of the Electrophilic Aromatic substitution.

And now, you will notice that the barrier for the second reaction or the reaction of the intermediate is not very, very high, because you would assume that the intermediate is going to collapse fairly rapidly and give you the product. There are examples in the literature of extremely stable intermediates, that is, they hang around for a fairly large amount of time, but most of these intermediates are actually quite unstable.

So, that sort of brings us to the conclusion of this energy profile. And to summarize, the reactions of Electrophilic Aromatic substitutions are usually Exothermic and not necessarily so, but many of them are Exothermic. And the formation of the intermediate which is the first step is the rate determining step. And, you know that the transition state leading to the formation of the intermediate actually resembles the intermediate and therefore, a lot of the stability issues can be taken care of by understanding this concept.

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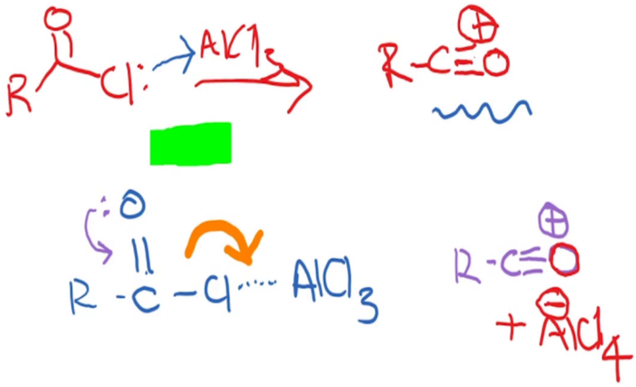

So now, let us move on to the next topic, which is basically Friedel Crafts Acylation reactions and so Friedel Crafts Acylation reaction basically depends on a very important sort of reaction that some of you are already quite familiar with, which is basically when an acid chloride reacts with a Lewis acid such as $AlCl_3$.

So, you can apply the same principles that we looked at previously, which is that the Aluminum is going to start coordinating with the Chlorine and starts pulling electrons in this direction and so once that happens, you are going to generate $RC=OCl$, and then there is going to be a complex with $AlCl_3$, and this is going to eventually produce, the electrons are going to be pulled from here.

And while those electrons are being pulled, it is also likely that the lone pair of Oxygen is in play and it moves over here. So, if you write out the product that is formed, you will get $RC\equiv O^+$, and you would get $AlCl_4^-$. So, this is the kind of intermediate that you start producing.

And so therefore, $RC=OCl$ in the presence of aluminum chloride is going to generate highly reactive electrophilic species, which is $RC\equiv O^+$. Normally, if you have, you know, water or something, then this is going to get hydrolyzed and give you carboxylic acid.

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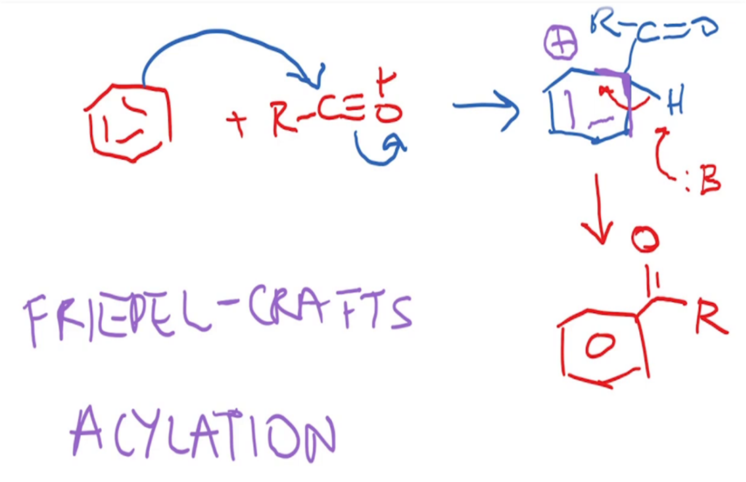

But since we are dealing with Electrophilic aromatic substitution reactions, this intermediate that is produced is going to react with Benzene and $RC\equiv O^+$, this is going to react with Benzene. And you are going to end up with an intermediate such as this, C double bond O, R and then this Hydrogen will remain the way it is. And the other double bonds that are shown here will continue and there is going to be a positive charge.

So, now when you do this, you end up with a situation where you are going to have possibly a loss of proton which is going to occur in the presence of a base, attacks, and regenerates aromaticity and it gives you the product which is the acylated benzene. So, if R is basically CH_3, then you will start with acetyl chloride and you will get acetophenone, and so on and so forth.

So, this reaction is called the Friedel Crafts. So, the Friedel and Crafts were actually two different people who got together and discovered this Acylation reaction first. And then subsequently, they also found the Alkylation reaction. So, this is known as the Friedel Crafts Acylation reaction. And as we looked at previously, you know, it is not important for us to know the name of the reaction. But it is important for us to understand the mechanism and also the implication of this reaction.

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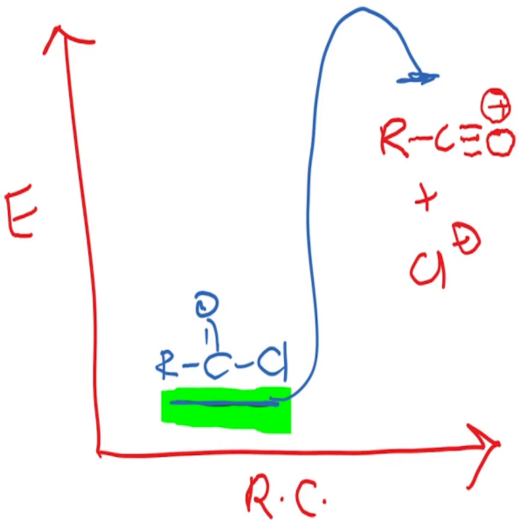

So, just to understand the energetics of this process, we have a very similar energy profile to what we looked at, in the previous case, so you have RC=OCl, it is going to, sort of, that is the energy that we are looking at. And now, the product that is going to be formed is $RC\equiv O^+$ and Cl^-, and if you are doing it in the presence of Aluminum Chloride, it is going to give you, that is going to catalyze the reaction.

So, this is going to give you an intermediate here, which is this. So, this is going to be the first step of the reaction. I am just going to redraw this so that it is a little clearer over here, so basically, this is R-C≡O, and then there is a positive charge. So, this positive charge is going to be mainly located on the Oxygen.

So, we will get back to the concept a little bit later during the problem-solving session and the rest of the energy profile would be identical to the reaction of Benzene with an electrophile. So, this is going to be an important step in Friedel Crafts Acylation, is the generation of the electrophile. The next important steps are described in the previous section which is basically the Electrophilic Aromatic substitution, the general mechanism for that. Now, if you can do this, if you understand this reaction.

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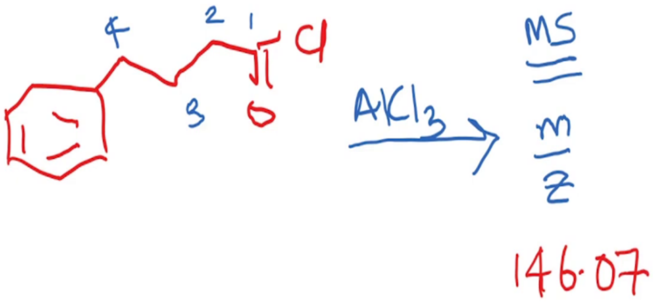

Now, let us look at a problem that will help us put a little bit of perspective into this reaction. So, the problem is as follows. So, you start with this very interesting compound and if you want to number the carbons, it is 4 carbons and then expose this to Aluminum Chloride.

I get a product which essentially has m/z, which is, m/z is basically Mass Spec. When we record the mass spectrometry, then we get a mass by charge ratio and we get a peak at m/z = 146.07. So, the question here is, what is the product that is formed? So, you can take some time and work on this problem. We will take this up again in a subsequent lecture.