Principles of Organic Synthesis
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Lecture 13
Electrophilic Aromatic Substitution

Welcome you all to Principles of Organic synthesis. So far, we had 12 lectures. In lectures 1-9, we studied the C-C formation, while the lectures 10-12 focused on the C-N bond formation. Today, we will start the electrophilic aromatic substitution. In this topic, we will have 3 lectures. In this lecture, we will study the principles of the electrophilic aromatic substitution and Friedel-Crafts reactions.

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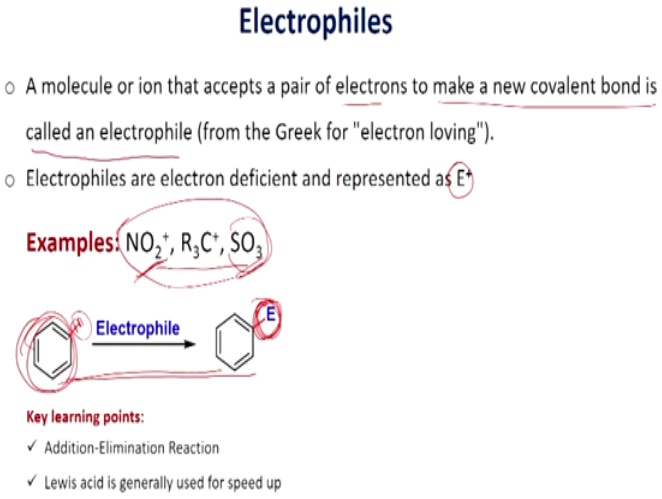

Electrophiles are electron deficient and represented as E^+. A molecule or ion that accepts a pair of electrons to make a new covalent bond is known as an electrophile. For examples, nitronium ion, carbocation and sulfur trioxide.

For the common representation of the electrophilic aromatic substitution, look at here, you have benzene ring, in which, the C-H bond is converted to C-E bond. First, the benzene ring undergoes addition with the electrophile that loses a proton to give the substitution product. So it involves addition-elimination reaction. This reaction is performed in the presence of acid as a catalyst. For example, we use Lewis acid to speed up the reaction as benzene is a poor nucleophile.

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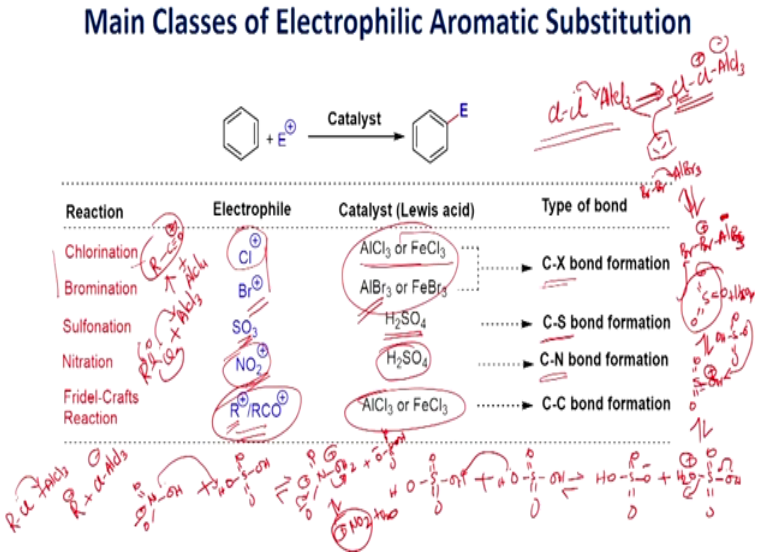

Now let us look at the main classes of the electrophilic aromatic substitution. For example, chlorination, in which, Cl^+ acts as an electrophile. This reaction is usually carried out in the presence of Lewis acid like $AlCl_3$ and $FeCl_3$.

$AlCl_3$ activates Cl_2 by chelation, which reacts with benzene ring to give the carbocation intermediate that loses a proton to give the substitution product. Similarly, $AlBr_3$ activates Br_2 that reacts with benzene to give bromobenzene. Likewise, sulfuric acid activates sulfur trioxide via protonation that reacts with benzene to give carbocation intermediates, which loses a proton to give benzenesulfonic acid.

HNO_3 in the presence of sulfuric acid produces NO_2^+ that reacts as the electrophile with aromatic system. In this reaction, sulfuric acid protonates nitric acid that loses water molecule to produce the nitronium ion.

The next example involves Friedel-Crafts reaction. If you have alkyl halide or acid chloride, it can be activated by Lewis acid, which undergoes reaction with aromatic ring to make alkyl or acylbenzene. We will study them in detail later.

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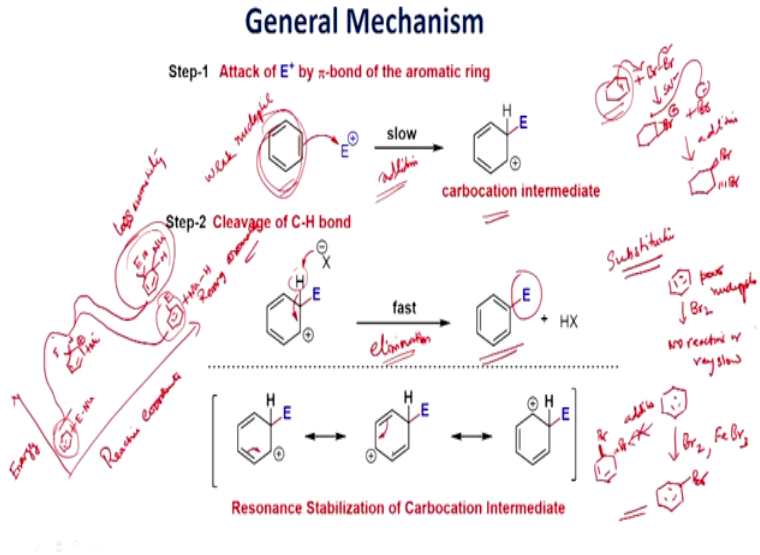

Here the general mechanism for the electrophilic aromatic substitution is shown. As you can see here, first step is slow, in which aromatic ring as a weak nucleophile undergoes addition reaction with electrophile to give the carbocation intermediate. This is the rate determining step. The second step is fast, where the base deprotonates to give the substituted aromatic compound. In place of hydrogen, you have now introduced "E" and overall this is a substitution reaction.

Now let us compare the electrophile aromatic substitution with the addition reaction of alkene. Let us see the reaction of cyclohexene with bromine. The double bond of cyclohexene acts as a nucleophile, which is stronger compared to benzene nucleophilicity. This is because of the aromaticity in benzene ring, which is more stabilized. The double bond of cyclohexene reacts with bromine to form the cyclic brominium ion intermediate, which is reacted by Br^- via S_N2 pathway to give the addition product. In this reaction, the double bond undergoes addition with bromine readily to give the addition product. While benzene with Br_2 shows no reaction or very slow due to poor nucleophilicity. Thus, when we use Lewis acid, which activates bromine that reacts with benzene.

If you see the energy level of these reactions, the addition reaction is not favored in the case of aromatic system due to loss of aromaticity but when you carry out the reaction by substitution you are able to recover the aromaticity.

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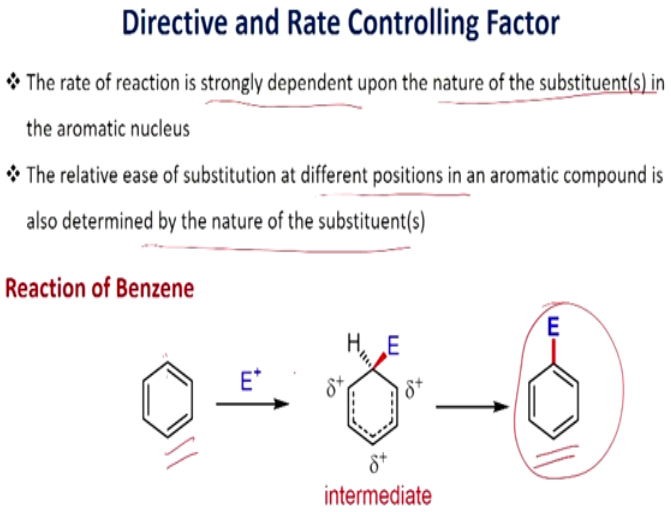

If simple benzene, you will be able to introduce electrophile. On the other hand, if the aryl ring has already substituent, it can affect the nucleophilicity of the aryl ring. Thus, the rate of the reaction depends on the nature of the substituent present in the aryl ring.

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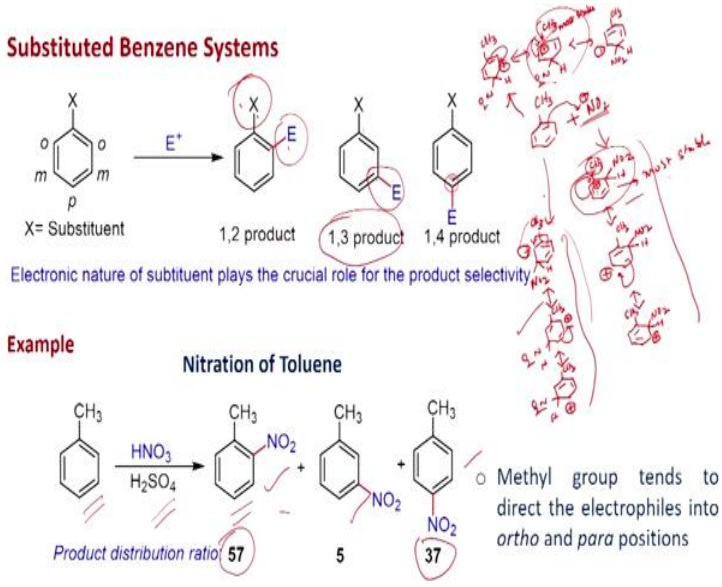

For example, the "X" substituted benzene can react with electrophile to give three types of products: 1,2- 1,3- and 1,4-disubstituted compounds. The selectivity depends on the nature of X. For example, let us look at toluene. When you do the nitration, you will end up with a mixture of compounds. If you look at the ratio of these compounds, the *ortho* nitration is the major product then you get the *para*, compared to *meta* compound.

This can be easily understood if you draw the resonance structures. If the reaction occurs at *ortho* position, you will be able to form these 3 resonance structures. On the other hand, if the reaction takes place at *meta* position, you will form the following 3 resonance structures. Similarly, the reaction at *para* position will generate the following 3 resonance structures. If you compare the resonance structures of the *ortho* and *para* substitution, in one of the resonance structures, the carbocation is bonded with methyl group, which is more stabilized due to electron donating nature of methyl group. On the other hand, the resonance structures of the *meta* substitution does not have the similar stabilization. Thus, whenever the aromatic ring has electron donating, electrophilic substitution is favored at *ortho* and *para* positions, compared to *meta* position.

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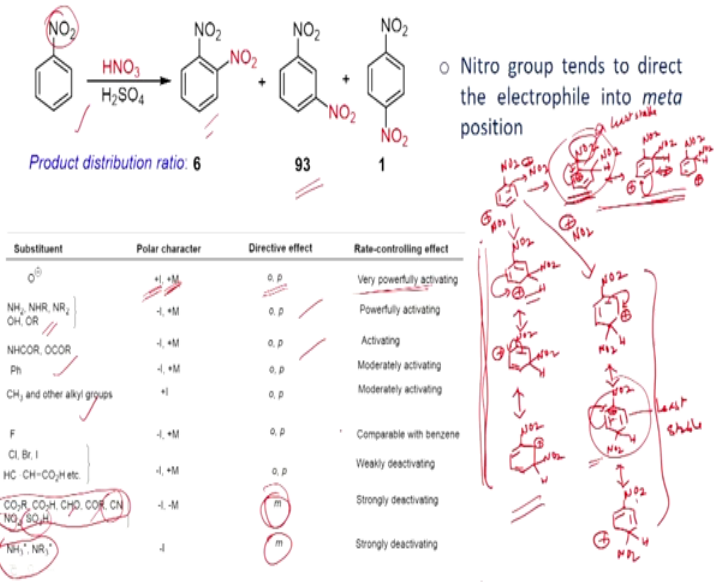

Now let us go for the nitration with nitrobenzene. Just we have seen the nitration with toluene. In this case if you look at here the ratio of the compounds, 1,3-dinito compound is major compared to 1,2- and 1,4-dinitro compounds. The selectivity can be easily understood drawing the resonance structures.

If you look at the 3 resonance structures of *meta* reaction, the carbocation is not bonded with nitro group. On the other hand, if you look at the resonance structures of *ortho* and *para* reactions, on the of the resonance structures has carbocation which is bonded with nitro group. Since nitro group is electron withdrawing, the carbocation is less stabilized. Thus, the *meta*-nitration is favored compared to *ortho* and *para* nitration.

This table gives the summary of the effect various substituents. For example, if you have the O^- that has +I and +M effects, which facilitates the electrophilic substitution at *ortho* and *para* positions. Thus, the electron withdrawing group like ester, carboxylic acid, aldehyde, ketone, cyano, nitro and sulfonic acid, usually favor the *meta* substitution, while the electron donating group like methyl, amide and methoxy group favors *ortho* and *para* substitution reactions

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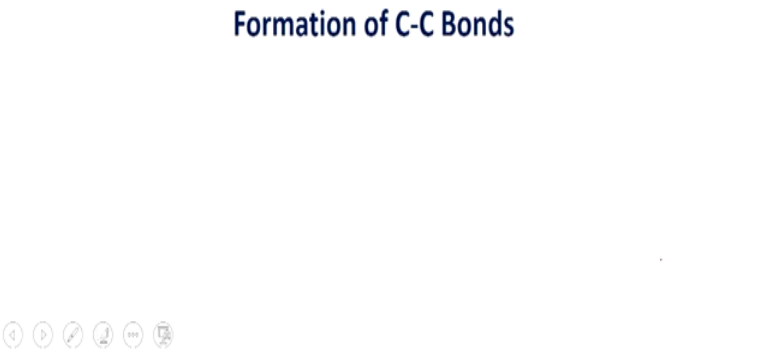

Now let us see some example for the carbon-carbon bond formation.

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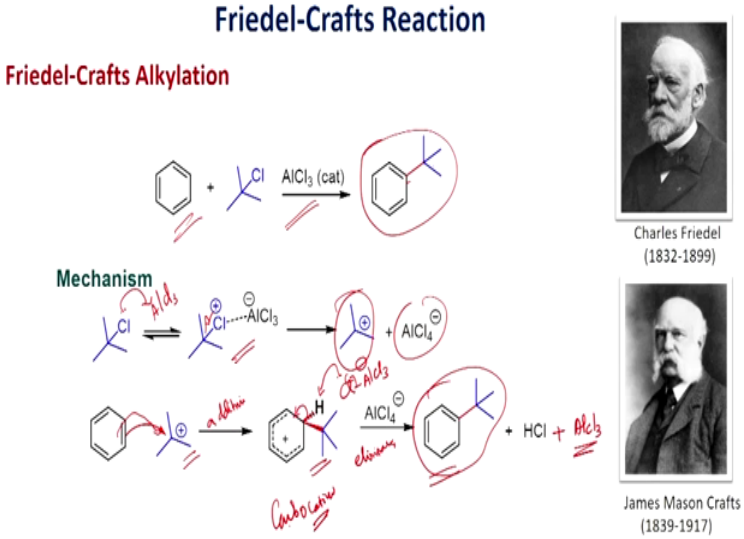

Here alkylation is shown. t-Butyl chloride reacts with benzene in the presence of $AlCl_3$ to give t-butylbenzene. The mechanism starts with the activation of t-butyl chloride with $AlCl_3$, which leads to the formation of t-butyl carbocation and $AlCl_4^-$. Benzene reacts with t-butyl carbocation to give carbocation, which undergoes deprotonation using Cl^- to produce t-butylbenzene. You need a catalytic amount of $AlCl_3$ to carry out the reaction as it is regenerated after completion of the electrophilic aromatic substitution.

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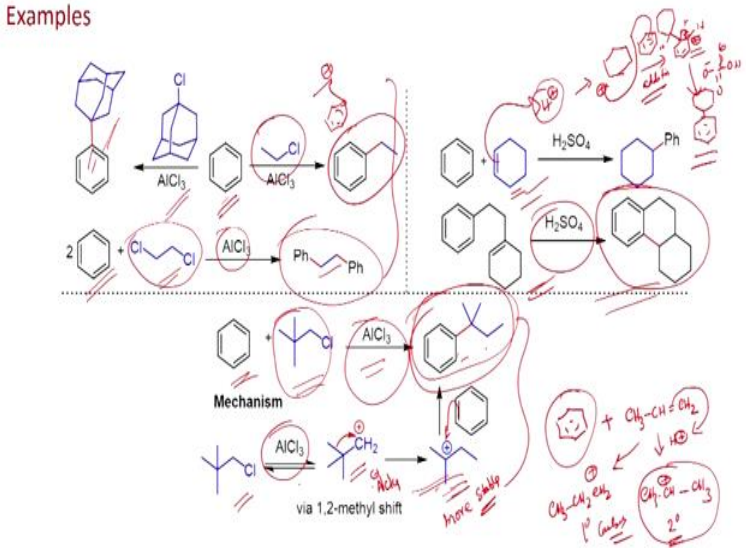

Here are some more examples for the Freidel-Crafts alkylation. The first example involves the reaction of benzene with adamantyl chloride in the presence of $AlCl_3$. We will be able to form the corresponding tertiary carbocation, which can undergo substitution reaction with benzene to give phenyladamantane. Similarly, ethyl chloride reacts with benzene to give ethylbenzene. 1,2-Dichloroethane reacts with benzene to give 1,2-diphenylethane. These reactions involve $AlCl_3$, which activates the alkyl halide to form the carbocation that reacts with aromatic system.

The next example involves the reaction of benzene with neopentyl chloride in the presence of $AlCl_3$. Neopentyl chloride with $AlCl_3$ generates the primary carbocation, which rearranges to tertiary carbocation via 1,3-methyl shift. The tertiary carbocation reacts with benzene to give the alkylbenzene.

The alkylation can also be carried out using alkene in the presence acid. For example, cyclohexene with acid produces the secondary carbocation, which reacts with benzene ring to give cyclohexylbenzene. The next example involves an intramolecular electrophilic aromatic alkylation. There are two possibilities to form the secondary as well as tertiary carbocation. The secondary carbocation is involved in the reaction to give tricyclic compound.

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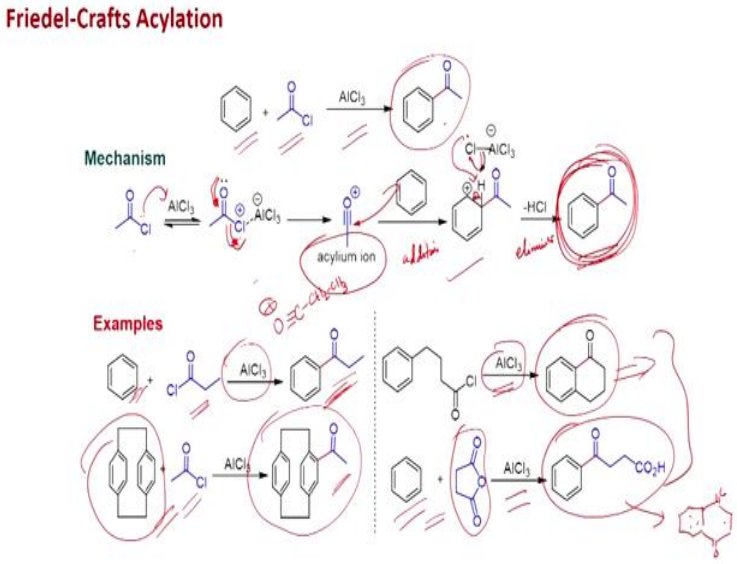

Now let us look at the acylation. As you can see here, the reaction of acetyl chloride with benzene in the presence of $AlCl_3$ gives acetophenone. This is very common method for the acylation of aromatic system. Acetyl chloride with $AlCl_3$ produces acylium ion, which reacts with benzene to produce acetophenone.

The next example involves the reaction of propionyl chloride with benzene in the presence of $AlCl_3$ to produce the corresponding ketone. Similarly, cyclophene can be reacted with acetyl chloride in the presence of $AlCl_3$. So far we have seen intermolecular acylation using acid chloride as the acylating agent. Here an example is shown for an intramolecular acylation using $AlCl_3$ to produce the bicyclic ketone.

The acylation reaction can also be carried out using acid anhydride as an acylating agent. For example, succinic anhydride reacts with benzene in the presence of $AlCl_3$ to give the carbonyl derivative. In the presence of phosphoric acid, the carboxyl group can be converted to acylium ion, which undergoes intramolecular acylation to give the diketone as the product.

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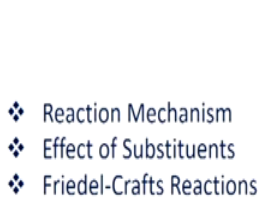

In summary, we have seen the principles of electrophilic aromatic substitution. These reactions involve the addition electrophile followed deprotonation to give the substituted compound. Overall, it involves addition-elimination reaction.

If you look at the alkene, which undergoes addition reaction. On the other hand, aromatic system leads to substitution, which is because to recover the aromaticity.

We have seen effect of substituent. For example, electron donating group favors *ortho* and *para* substitution, while electron-withdrawing group facilitates *meta* substitution.

Finally, we have seen Friedel-Crafts reactions. We have seen examples for the alkylation as well as acylation reactions. With this we conclude this lecture. Thank you very much.