Mechanisms in Organic Chemistry
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Lecture – 38
Electrophilic Catalysis

So welcome. In the last class we had looked at two different types of catalysis which are sort of related to each other. We had looked at catalysis due to binding.

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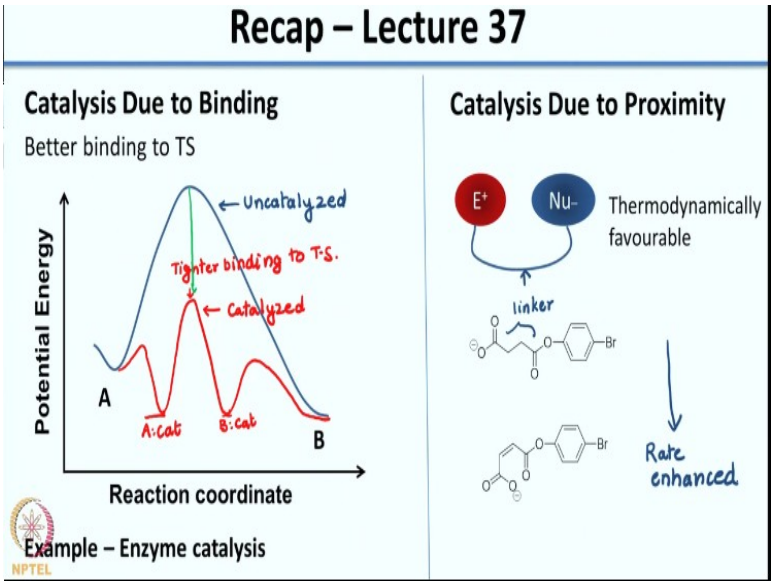

So when you have a reaction co-ordinate shown in red on your screen that would be a good representation of a catalysis due to binding where you have the reactant-catalyst complex which is highly stable so lower in energy and the catalyst also forms a tight coordination with the transition state. So it form the tight complex with the transition state. So you see a lowering in energy this leads to the rate enhancement. So this leads to the rate enhancement.

So it is very important that it needs to have better binding to the transition state and then you have the product which is again bound to the catalyst and finally you have your product and the catalyst is released. So we had looked at the example of enzyme catalysis where you see a pathway like this; typically you have the enzyme, you have a substrate. The enzyme and substrate form a complex which is highly stable and the enzyme-substrate complex because the substrate is close to the enzyme the reaction takes place.

You have a transition state which is further stabilize more by the enzyme and then you have the product being formed. So we had also derive the rate law which is commonly called as a Michaelis-Menten kinetics for enzymes. Then towards the last part we had looked at catalysis due to proximity. So what happens is when you have a reaction in a reaction flask, you have the molecules far away from each other,

so to improve the probability of collision it makes more sense to have them tied together or bound together. So in a way it is similar to the binding effect earlier, here you binding the 2 reactants. Another advantage of binding is that at it is thermodynamically more favorable because initially what you see is, if the reactants are unbound, there is a greater disorder in the system and so once you form the transition state where they are bound, the

it is not entropically favorable whereas if you have the reactants already bound, the degree of disorder is lesser in the system to start with. So then thermodynamically it becomes more favorable. So we had looked at a few examples and I have shown you only one representative example here. So what is seen is even among the intramolecular reactions, so these reactions are call intramolecular because both the components are part of the same molecule. So among intramolecular reactions what you see is if you have a linker,

so this is the linker here, also shown by the blue thing joining the electrophile and nucleophile, so here you have a linker and now if you change the linker such that the linker forces the 2 reactants to come closer to each other you see a greater enhancement of rate. So essentially what that tells you is you can play around with this proximity effect by designing suitable linkers which actually help you do the reaction. So in todays class we will mainly focus on what is called as electrophilic catalysis.

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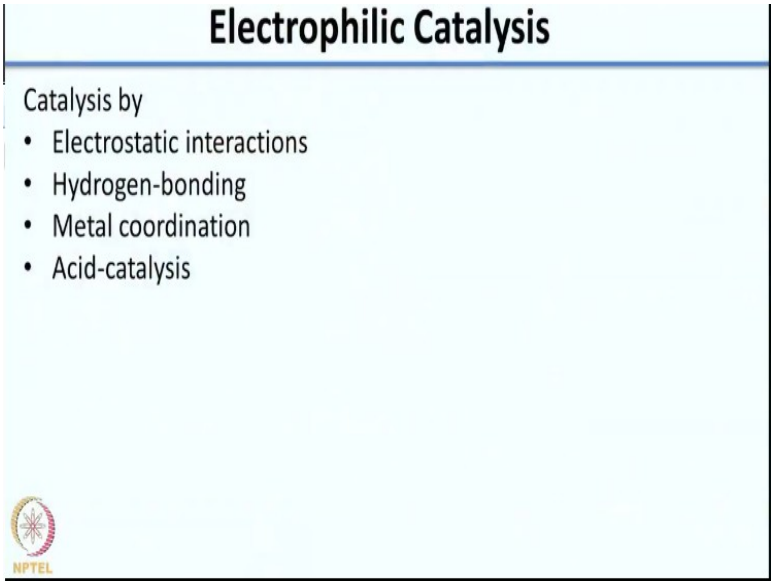

So in electrophilic catalysis, you have catalysis by electrostatic interaction, hydrogen bonding, metal coordination or acid catalysis. So acid catalysis we already saw. The electrostatic interactions can be simple electrostatic interactions where you have may be charges coming together. So your catalyst has some charge and you reactant has a charge; so it comes together to help you catalyzed reaction it can be a hydrogen bonding interaction. So, hydrogen bonding meaning you have hydrogen bonds formed between the catalyst and your reactant

which helps in stabilizing it. You can have metal coordination. So, this is seen a lot. So metal coordination also helps in the reactivity. Now again remember in all these cases the stabilization has to be more in the transition state otherwise you will not get much of catalysis because if the reactant is also stabilized, the transition state is also stabilized there is in it much difference in energy. But if you have the transition state more stabilized than the reactant that is when catalysis takes place. So again, I will give you an example from biology.

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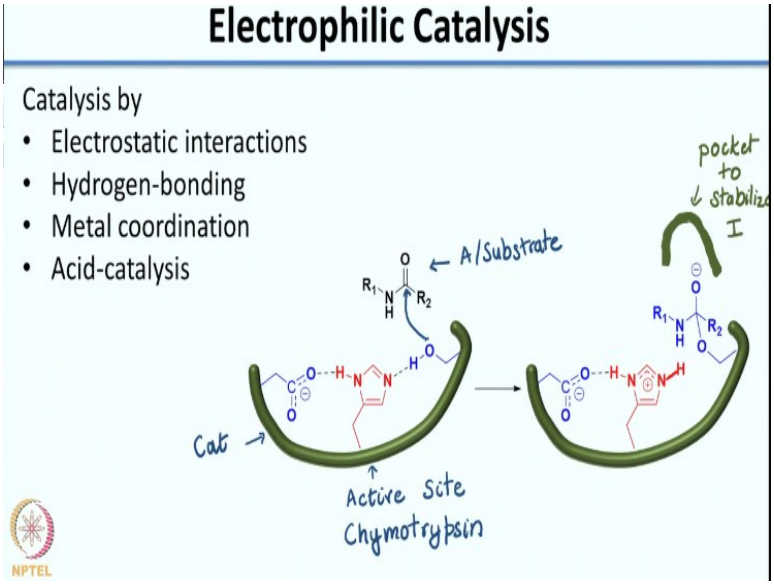

So this is an example form an enzyme. So to simplify things for you the entire enzyme is not shown. Shown in green is what is called as the active site of the enzyme. So shown in green is the active site, I will label it for you. So what happens in enzymes is you have the entire protein structure and there is a pocket within the enzyme called as the active site where the catalysis actually takes place. And if you see closely you would see a lot of these effects that we are talking about within these enzymes. So what you would see here is in the active site you have different functional groups.

So you have a carboxylate, you have an imidazole and you have a OH and all these come from amino acids that make up the protein. So this is an enzyme, this enzyme is called chymotrypsin, if you are interested, you can look at it. So now this is your substrate. So this is your catalyst and the amide bond here is your substrate so A or substrate. Now what you see here is the reaction that needs to take place is, you need to have this oxygen attack the electrophilic position of your carbonyl of the amide

and the transition state structure is also shown here. So this is what needs to take place. Now what is seen is that you have this relay here shown by the dotted lines. So you have this carboxylate O hydrogen bonded with this imidazole NH and then you have this imidazole nitrogen hydrogen bonding with this OH. And what this does is, as this because of this hydrogen

bonding your O becomes more nucleophilic. Right? Because its acidity improves. It would like to give away its proton

so that you have O^- which is more nucleophilic right? So what you see is in the transition state again you have now this NH, so now it has formed a bond here. So NH has formed the bond here. So that is why you have this positive charge and you have again the hydrogen bonding between the carboxylate and the NH. Essentially also have an electrostatic interaction. So this kind of a relay catalysis, so here you see electrostatics as well as hydrogen bonding helping the reaction.

How is the hydrogen bonding helping? The hydrogen bonding is helping improve the nucleophilicity of this O and I have not shown you here, but what is seen further here is that in the same catalyst there is another pocket here. So this is your catalyst structure. So there is another pocket here and what that pocket does is, it stabilizes this tetrahedral intermediate further. Alright? So you have an additional pocket here.

So this is an example of electrophilic catalysis where you can see electrostatic interactions as well as hydrogen bonding and this is seen in a lot of enzymes. You would also see metal coordination, acid catalysis all of this coming together when you look at enzymes. So now let us look at an example slightly away from biology. So people have tried to mimic the activity of enzymes.

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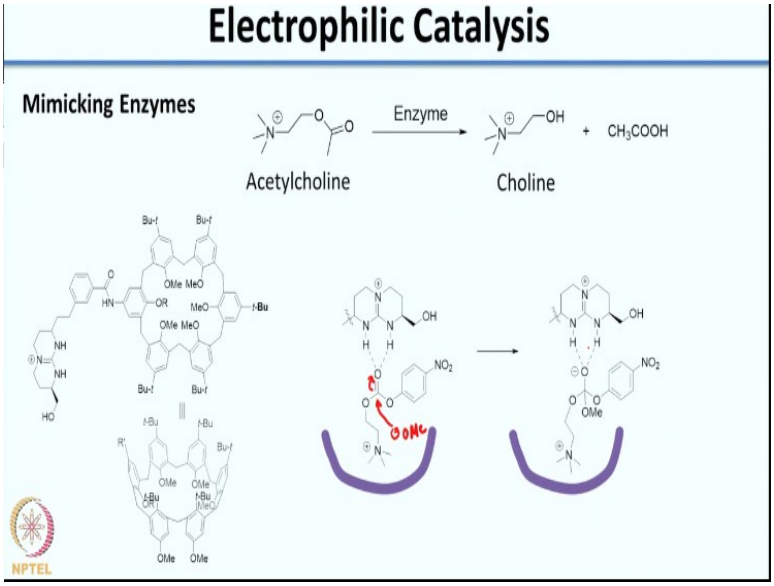

So here you have a reaction. So, we are not immediately going away from biology. We are trying to mimic what this enzyme does. So the reactions shown on your screen; you have acetylcholine this is a structure of acetylcholine. This is hydrolised to give you choline and acetic acid. Now the enzyme that does this is called acetylcholinesterase. So acetylcholine de-esterase. So what it is doing is it is hydrolyzing the acetylcholine.

So now in order to mimic the activity of this, scientists have made this molecule. So I do not want you to get confused looking at the large structure. So shown here is a cyclic molecule alright? So you have 6; 1, 2, 3, 4, 5, 6. You have 6 aromatic rings which are tied together by CH_2 groups. Alright? So you have 6 aromatic rings tied together by methylene groups. Now look at the substitution pattern on the aromatic ring. On one side you have OMe and on another side

you have a large t-butyl group. So you have the t-butyl group on 1, 2, 3, 4, 5 of the rings you have t-butyl groups and you have OMe again on 5 of the rings. On one of the rings you have OR where R is cyclohexane it is not shown here. On the other side you have this interesting amide. The amide has a linker here and it has this guanidinium. So it has this guanidinium group here. So you have NH, NH. So this can hydrogen bond alright?

So that is the reason for having this guanidinium group. Now shown here you have these 6 aromatic rings tied up. But how actually it looks is, it looks like a bucket. Or you can think of it

as a cone. So that is the structure shown below. So it looks like this bucket and because you have bulky t-butyl groups the bucket is such that the bulky groups want to be far away from each other. So the top side would be spread out. Alright? So the top side would be spread out and you will have all these oxygens, OMe, OMe, OMe, OMe coming inside.

So you have this bucket where you can think of inside the bucket it being lined with all these oxygen atoms alright? And on the top of the bucket you have this linker. I have just shown this is R′ so that it does not look that crowded for you. So this R′ is this whole group here which can hydrogen bond. Alright? So this is your structure of the catalyst which is made to mimic and enzyme. As I told you enzymes also have this pocket called as an active side.

So in this case your compound here has this bucket like shape which is similar to the active side of the catalyst. Now what is so interesting about this enzymes is that when you add, so in this case your substrate is this molecule shown here. So instead of acetylcholine, so you do not have the acetyl group, you have this p-nitrophenol group alright? So you have this p-nitrophenol group attached here. So what you get here is that you will have this ammonium ion, so it is positively charged.

So it has a liking for all these oxygen atoms which are lining inside your catalyst bucket. So what happens is this positively charged ion likes to sit inside your bucket. So now you also see binding happening here due to electrostatic interactions. So due to electrostatic interactions you have binding taking place. Now once you have this sitting inside the bucket, you have this guanidinium group proximal to it because it is hanging towards the top of the bucket. So like a handle of the bucket you have this group sitting on top. Now this group can hydrogen bond with your substrate.

So when it hydrogen bonds with your substrate it increases the electrophilocity at this centre. So when you have a methoxide it can add to this. Now as I told you the electrophilicity at the centre is improved to form this tetrahedral intermediate and you would see the tetrahedral intermediate would be hydrogen bonding even better than the reactant because now you have a partial negative charge on the oxygen. So it would be interacting even better than the reactant which is why you see catalysis.

So shown here is an example of how using elegant design scientists have created an enzyme like catalyst which could catalyze hydrolysis. So now we will move on and we will look at metal coordination and we will start with the simplest possible example for metal coordination. So what in general metal coordination does is it polarizers the bonds improving reactivity. We already saw that in terms of hydrogen bonding as well. The hydrogen bonding was polarizing the bonds further which was improving the electrophilicity. So here also what you see is

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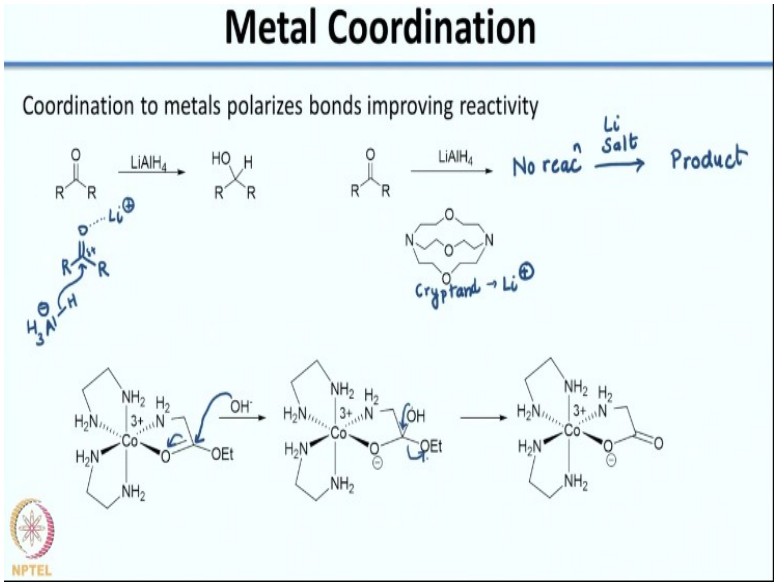

if you have a carbonyl group you can imagine when you add lithium aluminum hydride to the carbonyl group of a ketone here; so what you can imagine is you have coordination of the carbonyl group. So here what you can imagine is you have the coordination of the carbonyl group with the lithium alright? And then this would increase the electrophilicity at this center. So δ^+ increases.

Now you have, so now you can have the hydride attacked here and this would work better because you have coordination of the lithium. So now remember in the very first or second class in the course I told you okay you can propose a mechanism but how do you prove that this lithium is actually so important? Right? One can say it is just a counter iron for your salt and that is why it is there in the reaction. It has no role to play as shown here. So to prove the hypothesis what researchers have done is they have done the same reaction with lithium aluminum hydride.

So now they have done the reaction in the presence of this molecule. This molecule is called a cryptand and the cryptand really likes lithium alright? So if you have lithium aluminum hydride in the solution the cryptand really likes the lithium and it will take it away alright? So if lithium were not important, the cryptand would actually improve solvation of the lithium aluminum hydride and one would assume that the reactivity would improve and the reaction would take place. But what is seen is that when you add the cryptand you have no reaction.

So that indicates clearly that lithium is actually playing a very important role as shown earlier where it is coordinating with the carbonyl. Then what is shown is if you add the lithium salt again you would get your product. So this is a very simple and nice experiment to show the effect of the metal on enhancement of reaction or rate alright? So this is a very simple example but there are many examples where metal coordination is used. If you are interested you can try to look up this whole area called as CH functionalization of CH activation. It is seen that in the presence of a metal,

you can even activate CH bond which are considered to be not much polarized right? It is not like your CO bond of CX bond. So your CH bond is not that polarized and it is very difficult to do reactions but in the presence of metals they are shown to activate of polarized these CH bond. So that you can look at yourself. I will show you some other examples of how metal coordination polarizers a bond. So shown here you have a complex of cobalt with ethylenediamine.

So this is something you have studied in 12th standard also; the complexes of ethylenediamine with cobalt. Now here this is an octahedral complex but when you add a substrate here, so this is your substrate hear this glycine ester; Now when you add the substrate the oxygen and nitrogen coordinate with the cobalt alright? And what this coordination does is it increases the electrophilicity at this carbon centre.

So what happens is now if you were to do hydrolysis of the ester, so you add the OH^- and what you end up getting is this intermediate here and now remember the very ground rule I told you. What you see is the transition state would be bound better than the reactant because in your transition state you have a delta - on your oxygen. So it would be coordinating better with the cobalt center here. So you get the tetrahedral intermediate and once you get this tetrahedral intermediate you will have these lone pairs come in.

And then you will have leaving group go to give you the product. So this is another example of how metal coordination can be used for polarizing this CO bond even further to improve the reaction rate and in all these cases were seen that the stabilization of the transition state is more

than stabilization of the reactant. So again, we will look at how you can mimic biology. In biology as I said lot of this metal coordination takes place.

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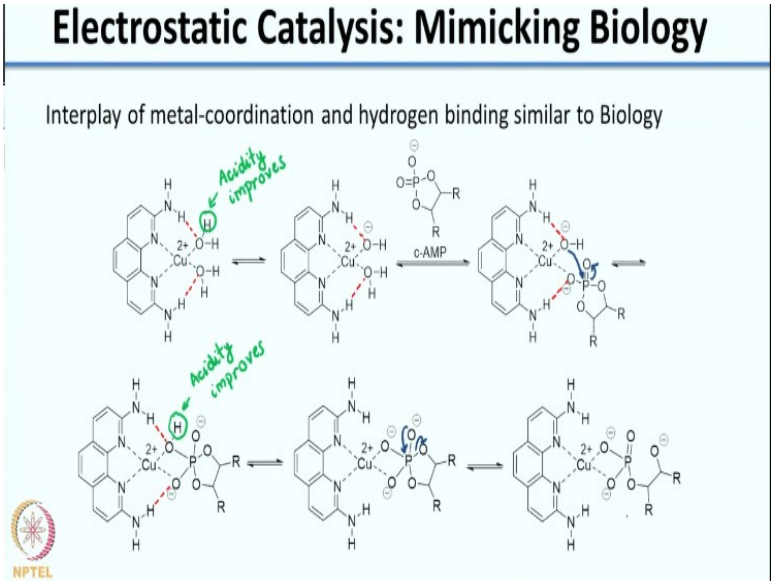

But scientists have created this enzyme. So this is a phenanthroline moiety. So you have two nitrogen here which can co-ordinate with Cu^{2+} and the rest of the coordination of copper is satisfied by water molecules. Now what is very nice about this complex is that this catalyst is that you have these additional NH_2 groups here at the 2-position compared to the nitrogen. So what happens is what these do is they can hydrogen bond with the oxygen.

So this further stabilizes the structure of this molecule of the complex; this additional hydrogen bonding. So here again you are seeing metal coordination as well as hydrogen bonding. Now a very important role of metals especially when you see them binding with water is that, because of this metal oxygen interactions what is seen is that the acidity of this hydrogen, the acidity improves. So what you would see is if you just take a metal complexing with water the pKa of water will change just because of complexation with this metal centre.

So now because its acidity improves, this bond can cleave more easily as compared to just the dissociation of water to give you OH^- to hear you generate the OH^-. So here again you have the O^- coordinating with the copper alright? So now let us look at the actual reactant and what is the reaction that is being catalyzed. The reactant here is called c-AMP and this is a cyclic compound.

This is called cyclic adenosine mono phosphate alright? So this is your cyclic compound. Now what you see is when you add your reactant it binds to the Cu^{2+}.

So it displaces a water molecule and you have it binding to the Cu^{2+} and obviously between the O^- and the double bond O, the O^- would prefer binding to the copper. So now what you have is you have OH^-, you have O^- both of these binding to the copper. As before all these complexes are stabilized by hydrogen bonding. So now that you have your c-AMP bound to your catalyst and you also have your nucleophile in close proximity,

so here again you see proximity also playing a role in enhancing the catalysis and the metal ion is helping polarize this bond so that it can add to this phosphorus centre. So what you have is, you have the OH^- adding to this phosphorus centre. So what you get is this intermediate shown right here. Alright? Now in the intermediate and as before you have the hydrogen bonding interactions. So now intermediate is also stabilized by the complex due to hydrogen bonding interactions as well as metal coordination.

And what you see is once you have this intermediate, again the pKa of this phosphorane, this hydrogen here its acidity improves because of complexation to the metal. So what you have is, you can have it easily deprotonated to give you this deprotonated intermediate. So once you have this deprotonated intermediate. So you will have this free O^- come in and kick out this leaving group to give you the product which is your hydrolyzed product.

So shown here is a very nice interplay of metal coordination and hydrogen bonding similar to what is seen in biology in design of the catalyst and what is beautiful in this catalyst design is, it has the phenanthroline nitrogens which bind to copper. Additionally, it has two amine groups flanking the phenanthroline unit on both sides which help in hydrogen bonding with the solvent as well as with the substrate. So what this does is it not only helps in stabilizing the catalyst complex with the substrate,

but it also helps in improving acidity of the hydrogens that it is coordinating with. So we will stop here today and in the last class on catalysis what we will look at is we will look at the

remaining 3 types of catalysis which is nucleophilic catalysis and covalent catalysis, we will club those together and phase transfer catalysis and strain catalysis due to strain. So thank you and see you in the next class.