**Mechanisms in Organic Chemistry**
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**Lecture – 39**
**Other Types of Catalysis**

Welcome back. In the last class we had looked at electrophilic catalysis. So we had looked at multiple interactions that lead to electrophilic catalysis.

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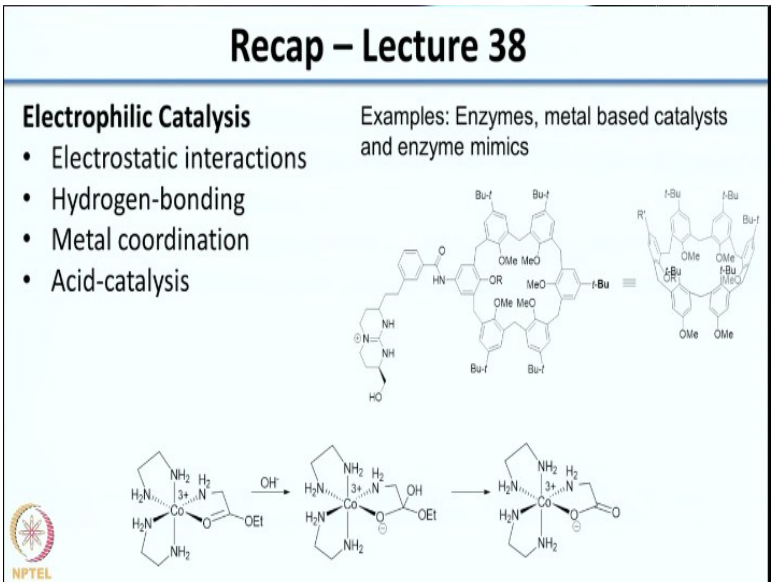


So you have electrostatic interactions, hydrogen bonding, metal coordination and acid catalysis. So acid catalysis we had already done quite a bit in detail. So we had focused on the first three and you would see that in biology or in nature enzymes used all of these together to catalyze reactions. So we had looked at examples of enzymes and we had also looked at some metal based catalysts and mimics of enzymes that are shown here like this bowl shaped molecule.

And what is shown here is you have all this oxygens here in the lower rim of the molecule. A positively charged species can interact with all these oxygens via electrostatic interactions and you have this hydrogen bonding donor here which can again interact with the reactant which had a carbonyl group to catalyze the reaction. So this is an enzyme mimic we had also looked at several examples of metal based catalysis. So in this class what we are going to look at is first nucleophilic catalysis.

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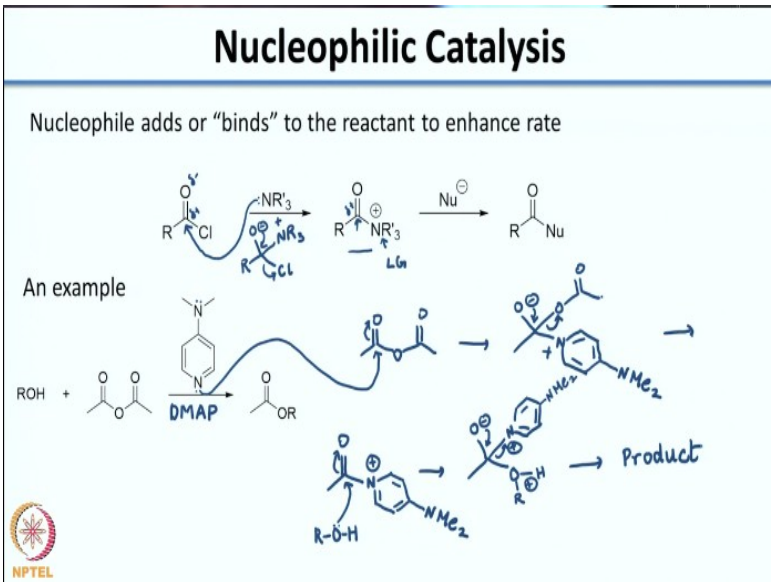


So in nucleophilic catalysis a nucleophile adds or binds to the reactant to enhance the rate. So shown here is an example. So what you can see here is you have a tertiary amine and this tertiary amine can attack the electrophilic centre to give you a tetrahedral intermediate and then you have this coming in and kicking out the Cl to give you this intermediate. Now what you see here is if you compare your amine, this is a good nucleophile.

So this adds into the electrophilic centre and once you form this intermediate you have a very good leaving group here. So this is a very good leaving group. So then when you have a nucleophile add in there are two ways in which this helps it is a good leaving group and it also improves the electrophilicity at the centre. So it catalyses the reaction in 2 ways. One is by improving the electrophilicity and 2 is by becoming a very good leaving group. So typically you see a lot of tertiary amines being used for nucleophilic catalysis. So I am showing you an example here.

So if you have an alcohol and you are reacting it with an anhydride to form an ester, what is seen as in the absence of the catalyst the reaction takes quite some time. So now you have a catalyst here. This is called as the DMAP. So the DMAP helps in catalyzing the reaction. So I have shown you the generic mechanism on the top. So what I want you to do is press the pause button

and then go ahead and write the mechanism for catalysis by DMAP. So let us see if you were able to get the mechanism correct. So you start with your anhydride.
Now you have 2 lone pairs here. The pyridine lone pair is not conjugated with the aromatic ring. The lone pair on the other nitrogen but is conjugated with the aromatic ring. So you will have the pyridine actually attack the anhydride. So if you attack the pyridine the lone pair you again form this tetrahedral intermediate. And now you have a positive charge here. So once you generate this intermediate as I showed in the mechanism above, this will leave and now what you get is; so now you have a more electrophilic carbonyl centre here.

So now your nucleophile can add in and what you see here is even initially, if you compare oxygen versus nitrogen, nitrogen is a better nucleophile. Which is why you DMAP prefer to interact as compared to the alcohol. So now here alcohol will interact. Again you form this tetrahedral intermediate. And here again you see when the lone pair comes in you have a better leaving group here. So then you get your product after one more proton transfer.

So this is a mechanism of nucleophilic catalysis. Remember this is very different from pyridine acting as a base. So when pyridine acts as a base it will abstract a proton. Here it is acting as a nucleophile. So you see it actually attack the electrophilic centre. So remember there is a difference between an amine acting as a base and an amine acting as a nucleophile. So now I will introduce you to one another interesting concept. When you talk about nucleophilic catalysis you must have come across the tertiary amine example before but this is a fairly interesting concept.

So what you can do is you can use a Lewis base to increase the electrophilicity of a Lewis acid. So you must have studied several reactions where Lewis acids are used to improve the electrophilicity for example of a carbonyl. If you have the oxygen coordinate with the Lewis acid it improves the electrophilicity at the carbon centre.
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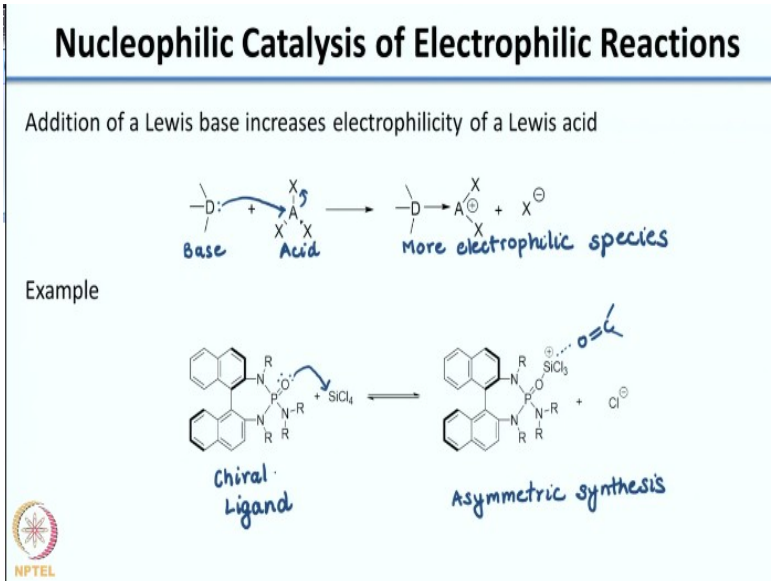


So here what you doing is your improving the electrophilicity of the Lewis acid further by adding a Lewis base. D here stands for donor. So this is your base. This is your acid. So this can add in here. So what you end up generating is; so this one kick out one X from the Lewis acid and what you generate is a more electrophilic species. Now how is this actually used? So shown is an example here where you have your Lewis acid. So you have your Lewis acid here and here what you see is you actually have a chiral ligand see you have a chiral ligand here.

So this is your donors here. So once it coordinates with the Lewis acid what you end up generating is a more electrophilic species. So this species can further coordinate to say carbonyl group to catalyze reactions and actually this catalyst has been used for an asymmetric synthesis because you are using this chiral ligand as your Lewis base. So this is a very interesting concept where you are actually increasing the electrophilicity of the Lewis acid by coordination of a Lewis base.

So now we will move on to the next type of catalysis which is covalent catalysis. Now in covalent catalysis the catalyst forms a covalent bond with the substrate. So in a way the examples that we have seen earlier using the pyridine and the nucleophilic catalysis examples there also what you see is, you can also called that is covalent catalysis because your catalyst forms a covalent bond with the reactant alright? So some of these different classifications that we

have seen of catalysis you can see that you can have one catalyst belonging to more than one of these classifications. Alright?

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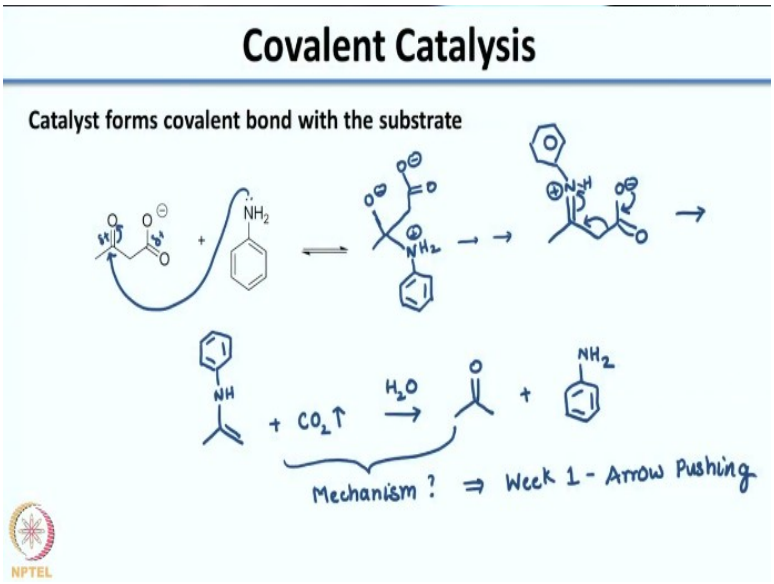


So here is a very interesting example. Now what is seen here is you must have studied this. If you have a species like this right and if you heat it in an acidic medium what happens? This is something you must have studied in your BSc. It can undergo decarboxylation alright? So typically what is seen is to undergo decarboxylation an acidic medium is required and you need to heat the reaction. But what is seen is if you add a small amount of aniline the reaction can go in several hours at room temperature alright? Or slight heating in some cases.

So now what I want you to do is, I want you to think of what is happening here. So what is the mechanism here to give you the decarboxylated product? So decarboxylated means you are generating the ketone from this substrate here alright? So you can press the pause button and work out the mechanism. So let us see if you got the answer correct. So now here your nucleophilic species is here. Right? You have to electrophilic centres here and here. So you have this 2 electrophilic centers. This is more electrophilic. So you will have the aniline add in here.

So what you would end of getting would be this tetrahedral intermediate. Now after you do this addition I am going to skip over multiple steps. I think you will be able to write the mechanism yourself because we had done a similar mechanism earlier for generation of the iminium ion. So

after this what you see is you will generate, you will generate this iminium ion alright? So these steps of the mechanism you should be able to write. Alright? So just to give you a hint, when we had looked at deviation from linear free energy relationships, we had done a similar kind of mechanism. So if you are not able to write it you can check back the lecture where we were looking at deviation from linear free energy relationships. So now that you have this here, this will come in here, these bonded electrons will come here and this will come here.

So what you would end of generating would be; so you will be generating this enamine. Alright? Now for conversion of the enamine to the ketone, if you remember our very first week we had looked at the mechanism for that so I will not write it again. So what you end up doing is you and up hydrolyzing this to give you the ketone + aniline. Okay? So you should be able to write this mechanism yourself.

So if you have any doubts you can look at week 1 where we had done a similar mechanism when we were doing arrow pushing. Alright? Hopefully by now you do not need to look back and you will be able to write the mechanism but if not do not worry you can go back and look at the mechanism and write this. Alright? So now what you see is formation of this iminium intermediate improves the reaction considerably. Alright? Because now you have a greater driving force for this elimination to take place.

So the formation of this iminium adduct has been used quite a bit even in asymmetric catalysis. So a very nice example of where covalent catalysis has been used is in peptide synthesis.

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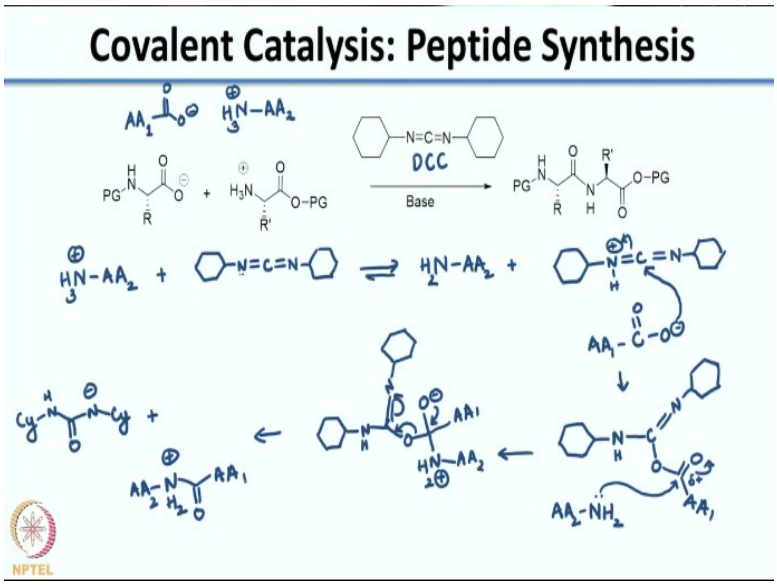


So peptide synthesis involves coupling of 2 amino acids to give you a peptide bond as shown on your screen. So you have amino acid 1 interacting with amino acid 2. So amino acids are interesting because they have an amine and a carboxylic acid. So what is done is this PG is a protecting group. It blocks an amine on one amino acid and a carboxylate on the other amino acid. So these two are the only ones that can interact to form an amide bond. So if you had not blocked it then all of these could interact with each other.

So imagine putting things together using lego or blocks. So what we are ensuring is that only these 2 blocks can fit together. Alright? The other sides of the block are capped. Alright? Or protected using a protecting group. So reagent which is used to catalyze this reaction, it is called as a coupling reagent or an acid activator, is the reagent shown here. You might have heard it as DCC. So it is dicyclohexyl carbodiimide and a base to give you that product.

So now what happens is this reagent helps in catalyzing the reaction. So what I want you to do is I want you to again press the pause button and try to write the mechanism yourself. To simplify it what you can do is you can call this as $AA_1$ so you need not write the whole structure $COO^-$. So again as I told you everything else is capped and then we can write this as $AA_2$. Alright? You need not write the whole structure. So go ahead and try to work out the mechanism for this synthesis.

So let us see if you got the answer correct. So what happens is in the reaction medium, so here again if you have your amine + DCC; now this can undergo proton transfer. So you can have the nitrogen here pick up a proton to give you to the free amine + the protonated DCC. Now this process is in equilibrium and actually you have a very small concentration of this in your reaction mixture but that is enough to catalyze the reaction.

So once you have this, you can have your $AA_1$ carboxylate; now what is your electrophilic centre here? What is this sink? It is here and you can push the arrows here. So then what you get is; so you get this intermediate. Alright? Now what you see in this intermediate is you have improved the reactivity of this carboxylate. Right? Initially you just had it as the $O^-$. So it was not as electrophilic for reaction of your amine. Also you did not have a very great leaving group.

So here what you have done is you have made this centre more activated. So this is how your covalent catalysis has worked. You have formed this covalent bond which makes your electrophilic centre more reactive. So now what will happen is when you have your amine; so the amine will come here. Again it will form the tetrahedral intermediate. So what you will get would be and then we will have this leave to generate.

I will just see write Cy because I am running out room here for cyclohyl + So you have formed your amide bond and now with a proton transfer you will get both these products. So one is urea by product and the other is your peptide. Alright? So this covalent catalysis concept is used a lot in peptide synthesis. I have just shown you one reagent here which is DCC but many other such reagents has been used to catalyze this coupling reaction. So now we will move on and we will look at strain catalysis. Now strain catalysis like the name suggests

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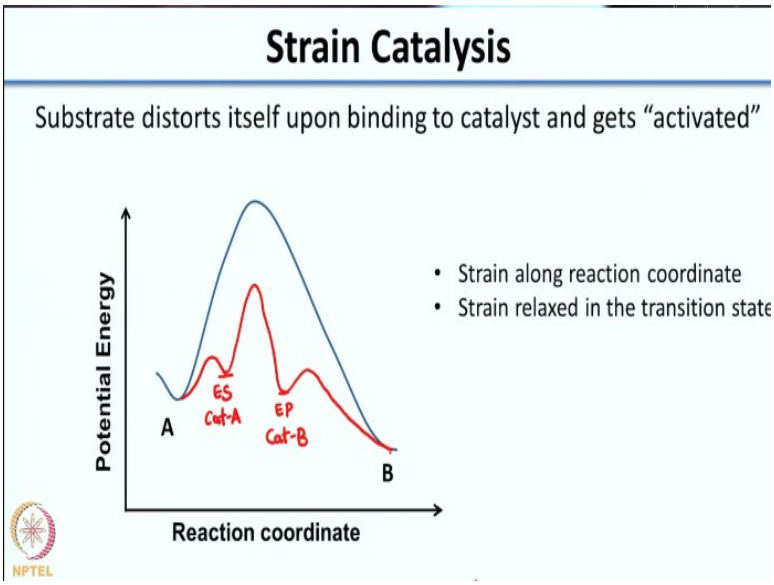


what happens is the substrate distorts itself upon binding to a catalyst and get activated. Alright? So distorts means there is some change in the structure of your reactant and this helps it get activated. So in terms of the reaction coordinate diagram one way for you to think about it is, so imagine that you have your reactant which is A. As it goes to your catalyst it forms a more strained complex. So what you are doing is your getting a higher energy as compared to your reactant.

So it will look something like this. Alright? Now what happens is after this you have the usual thing - the formation of the product. Now here what happens is as it goes to the transition state probably there is a release of strain. Alright? So what happens is the transition state is stabilized but your reactant is more strained. So this kind of catalysis works when the strain is along the reaction coordinate and leads to this increase in energy of the enzyme substrate; I have written enzyme-substrate but you can also call a catalyst.

So since we are looking at A this would be a catalyst A-complex and this would be catalyst-P. ES, EP correspond to enzyme substrate. Because this is seen very often in enzymes I by mistake wrote ES and EP but you can equate to cat-A and cat-P or cat-B actually since B is the product here. So what you see here is, you have the enzyme substrate or the catalyst reactant being more strain at a higher energy but you have the transition state at a lower energy.

So you have a net stabilization. So that is what I have written here saying that the substrate distorts itself upon binding to catalyst and gets activated. So again, back to our old analogy. We think about climbing a mountain. Here the substrate is going closer to the mountain by binding to this catalyst and the transition state is lowered in energy because this strain is released in the transition state. Alright? So let us now look at an example of this.

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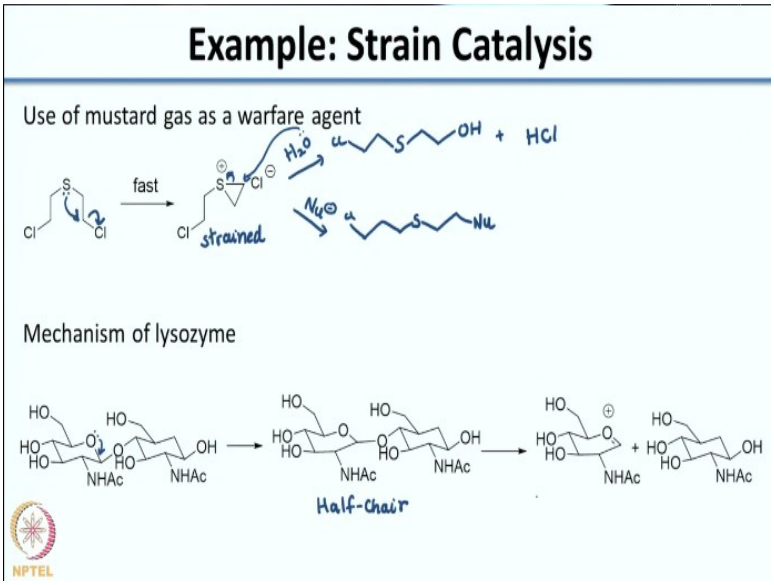


So this is a classic example of mustard gas which was used as a warfare agents in world war and what you see is with mustard gas, so it is known to interact with DNA, proteins and how it works is you have this compound here and you have an intra-molecules reaction so you have the lone pair on the salphur which can come in and kick out the chloride. So what you generate is this strained species. Now this is far more reactive than a direct substitution here because now the strain takes up or increases the energy of the reactant. So remember the reaction coordinate we had seen earlier.

So what has happened is it is increase the reactant, so here this is essentially a neighboring group participation. You have not added an external catalyst but it just explains the concept of strain catalyzing a reaction which is why I have shown it here. So you have the strained molecule and what is seen here is, if you add water to it, so you will have it add in here and this bond will

cleave, so what you end up generating would be OH + HCl and this HCl is known to cause the damage to human beings. The other thing is it is also known to interact with other nucleophiles.

And you can also think of it because of its charge interacting with the negatively charged DNA backbone. Alright? So shown here is now an example of a of how strain can help increase the reaction rate. Alright? So here you have not added an external catalyst. It is a neighboring group participation. This as I told you in the previous slide is seen a lot with enzymes and one such enzyme is lysozyme. So when you have dirt coming in or something in your eye you have these tears that are formed. You see this in the tears and this helps in killing the bacteria.

And how it kills bacteria is it destroys its cell wall and its cell wall has this linkage shown here. So these 2 sugars connected by this which is called as a glycosidic linkage. So the lysozyme chops this glycosidic linkage and destroys the bacteria. So how this works is, for this linkage is to be destroyed in the mechanism, what you need is you need these lone pairs to come in and kick out your other sugar alright? But what is seen as when it fits into the enzyme it takes up a half chair conformation.

Now if you remember studying the conformations of cyclohexane half chair is a very high energy conformation compared to the chair. So now what you are forming is a more strained conformation inside the enzyme and because of this strain you are essentially decreasing the activation energy for this transformation and the strain the conformation not only helps in increasing the activation energy but what happens is once it is in the half chair conformation the orientation of the lone pair with respect to the leaving group is also more favourable for the elimination.

So what you get is end up generating this oxocarbenium ion and the sugar which leaves out but the transition state actually alleviates this energy due to strain. So that is how you have the catalysis where your reactant has this strain but the transition state does not see this strain. So a lot of other enzymes also use this concept for catalyzing their reactions. The last example we are going to see is phase transfer catalysis

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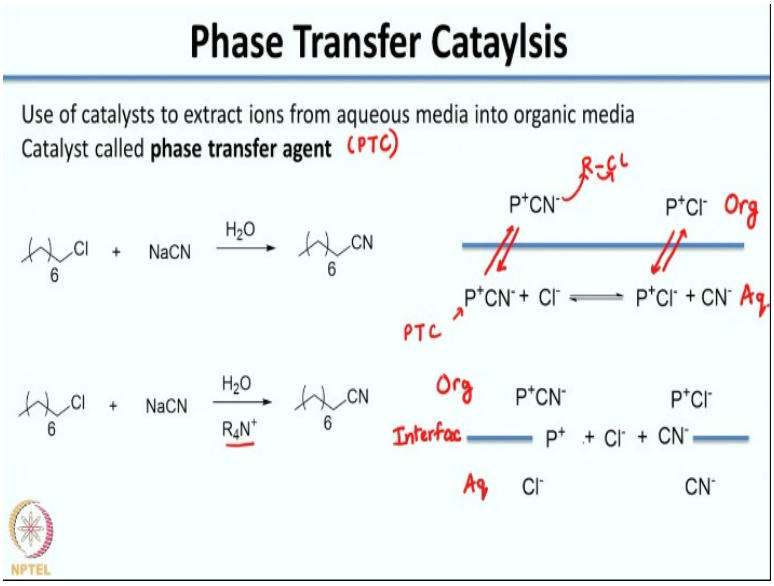


Now this it is used to extract ions from aqueous media into organic media. So if you remember when we studied solvent effects, if you have charged species in a reaction medium, organic solvents are not that great in solvating them. So if you want to get it to react with an organic compound which is highly in soluble in aqueous solution you would need some sort of catalyst to take this reaction forward. So show here is a classic example you have a alkyl chloride getting converted to a nitrile using sodium cyanide in water.

Now you can see this reaction for 2 days 3 days, does not matter the reaction does not take place because your alkyl chloride is not very soluble in water and it does not react with your $CN^-$ which is completely solublized in water. So what is seen is if you add this reagent which is a tetraalkyl ammonium salt, this acts as a phase transfer agent and helps in doing this reaction in like 2 to 3 hours. So now you can see the extent of catalysis using this reagent and what is the mechanism? So if you consider this as water so this is the aqueous part and this is the organic part.

So in the aqueous part you have, P is your tetra butyl ammonium; so this is your phase transfer catalyst we will call it. So this is your phase transfer catalyst. So what it does is, because you are using a cation here you have a counter ions $CN^-$ and this can exchange with $Cl^-$ also to give you P + $Cl^-$. Now in your reaction you have your alkyl chloride in your organic layer. So that is your RCl and what happens is

because this phase transfer catalyst has it typically has alkyl chains which are little long like tetra butyl attached to it so it has some solubility in the organic medium as well. So what it does is it takes this to the organic medium. That is why phase transfer. It can transfer the ion from aqueous to organic. So it takes it to the organic layer. The reaction takes place and once the reaction is done, so you have the $CN^-$ attack and once the reaction is done you have this salt here.

So where you have your phase transfer catalyst coordinated to $Cl^-$ and that is brought back again to the aqueous layer and again this is in equilibrium so you can have this process go on. So this is one explanation for the mechanism. So another explanation is where in the aqueous layer you just have the ions. At the interface is where you have the phase transfer catalyst sitting along with the $Cl^-$ and $CN^-$ and what it does is it takes this in the organic layer and now it does the catalysis.

So this is an alternate mechanism but experimentally what you observe is, the phase transfer catalyst is able to take these ions from the aqueous layer to the organic layer. So to summarize what we have done over the last 2 weeks when we studied catalysis is,

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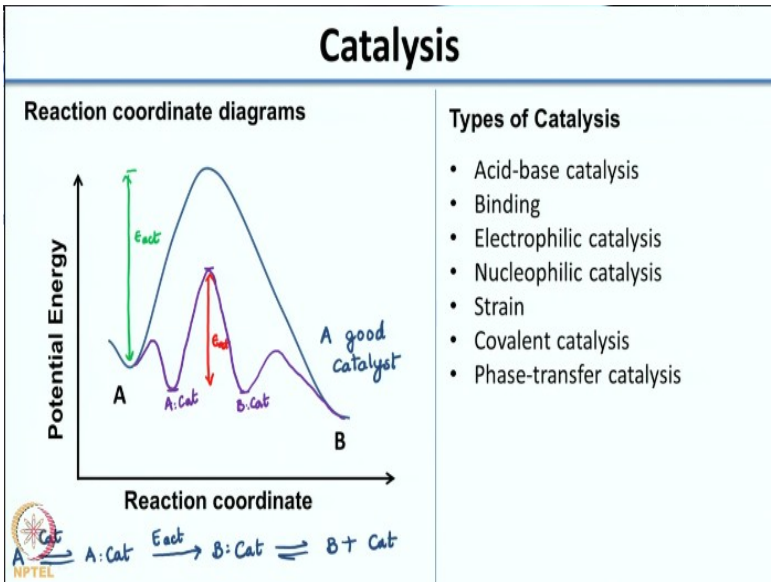


we looked at reaction co-ordinate diagrams where we saw how adding a catalyst helps in lowering the activation energy of a reaction. We also looked at several types of catalyst. So we

looked at acid catalysis, binding, electrophilic and in this class we looked at nucleophilic, strain, covalent catalysis and phase transfer catalysis. So over this entire 8 weeks, you have gotten a glimpse of how you can write mechanisms and how you can devise experiments to understand or to confirm whether the mechanisms your proposed is correct.

So in the very last lecture of this course what we will be doing is we will be summarizing whatever we have learnt from week 1 to week 8 and hopefully that will be useful for you in your final exam. So thank you and see you in the last lecture.