Mechanisms of Organic Chemistry
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Lecture – 40
Course Summary

So welcome to the last lecture in this course and in today's lecture what will be doing is I would just be summarizing whatever you have studied from week one. So the overall picture that I had given you in the very first class is, when you think of reaction mechanisms, reaction mechanism tell you the pathway of a particular reaction and this is there in the introductory video as well. So what we have been doing over the past 8 weeks is, we have been looking at ways to propose a reasonable mechanism.

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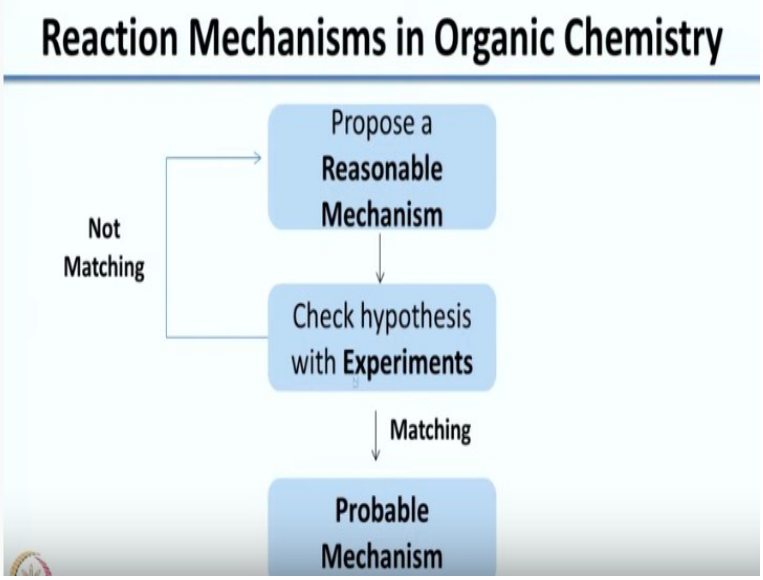

Once you propose the mechanism check the hypothesis using experiments. If the experiments are matching then you can say yes this is the correct mechanism. If not you need to go back rewrite your mechanism and again check it. So it is a cycle; a loop which will be useful in determining what is the probable mechanism. So I have show you examples from Chemistry and Biology where people have use these kind of experiments to confirm the most probable mechanism.

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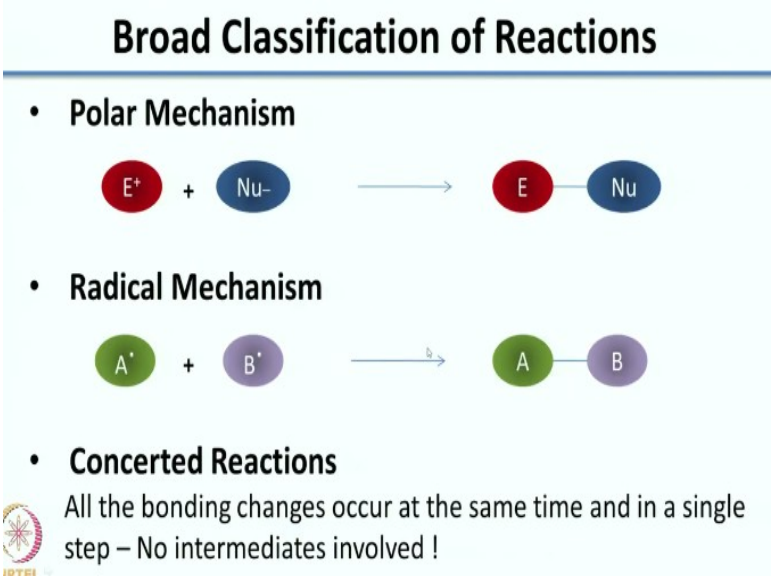

So initially in week 1 we have started with a broad classification of reactions so we had classify them as reactions that have a polar mechanism. So in polar mechanism you have charged intermediates or with intermediates with partial charge that is developed and you can think of electrophilic and nucleophilic species coming together to form this new bond. Then we had looked at radical mechanism

where you essentially do not have charge intermediate but you have intermediates containing single electrons called as radicals and how they come together to form products and the third classification was concerted reactions. So in these reactions all bonding changes occur at the same time and in a single step. So essentially you have no intermediates involved. So then what we had done is we had looked at how you actually right mechanism using arrow pushing or electron pushing.

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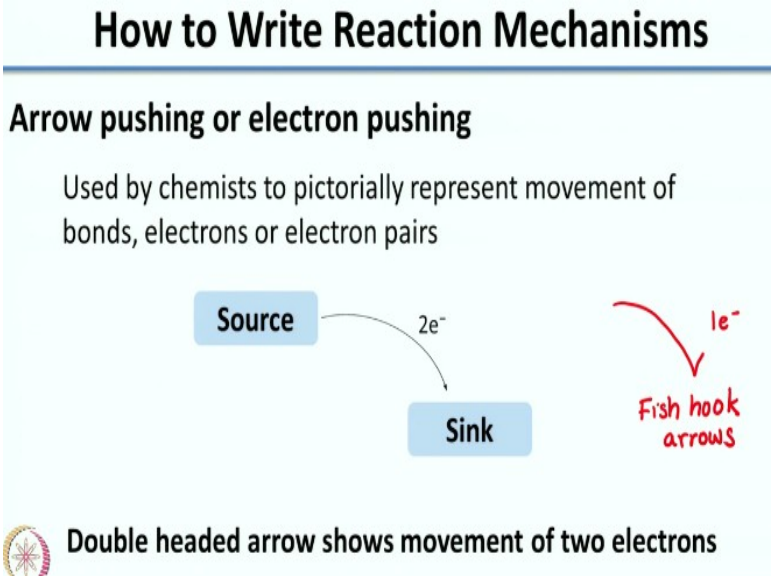

So arrow pushing is used by chemists to pictorially represent movement of electrons or electron pairs. So this is a convention and the convention is such that the arrow starts from what is called as a source. So source is your electron rich species and ends at what is called as a sink. So sink is your electron deficient species and you show 2 electrons moving by using double headed arrows.

So for polar reactions typically used the double headed arrows and the single headed arrows are used for movement of single electrons. So for single electrons you use single headed arrows. Alright? They are also called as fish hook arrows. So we had looked at multiple examples on how to push arrows and what we have done to summarize in week one is

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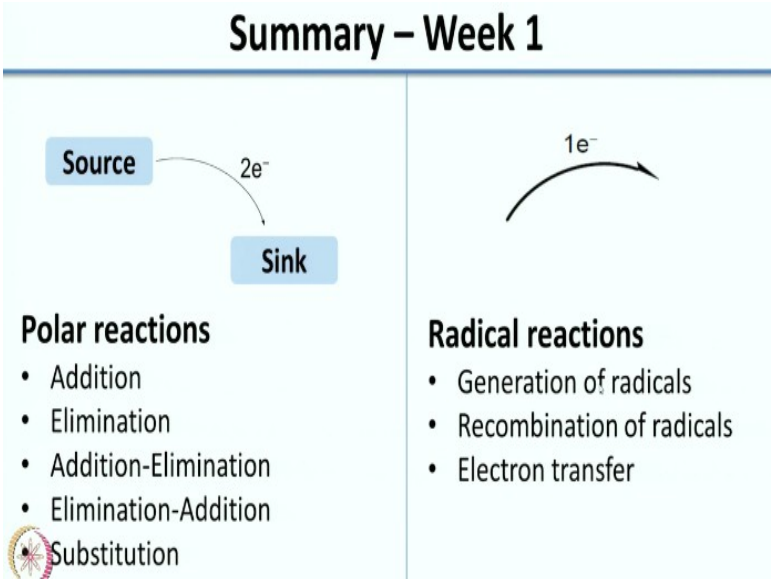

we had looked at polar reactions and we had looked at the basic mechanism type of addition, elimination, addition-elimination, elimination-addition and substitution. We had also classified various types of sources and sinks. This was just give you an idea of what are the different species that you would come across when you are writing a reaction that could be considered as sources and sinks and you must have seen all of this even tested in the assignments that you had taken.

Then we looked at radical reactions. So in radical reactions you have 1 electron transfer. As I said, so you show it using a single headed arrow or what is called as fish hook arrow. So in radical reactions we had looked at generic examples of how you push arrows for generation of radicals, for recombination of radicals and electron transfer. So we had also looked at specific examples where you could do the arrow pushing and rationalize what the product would be.

So the first week was essentially giving you a primer of reaction mechanisms, arrow pushing. We had also looked at how you can have an unequal distribution of electrons across 2 atoms. So we had looked at very basic concept such as inductive effect, resonance effect and hyper conjugation. Then we moved on in the second week look at how you can represent reactions in terms of energy and what is called as a reaction co-ordinate?

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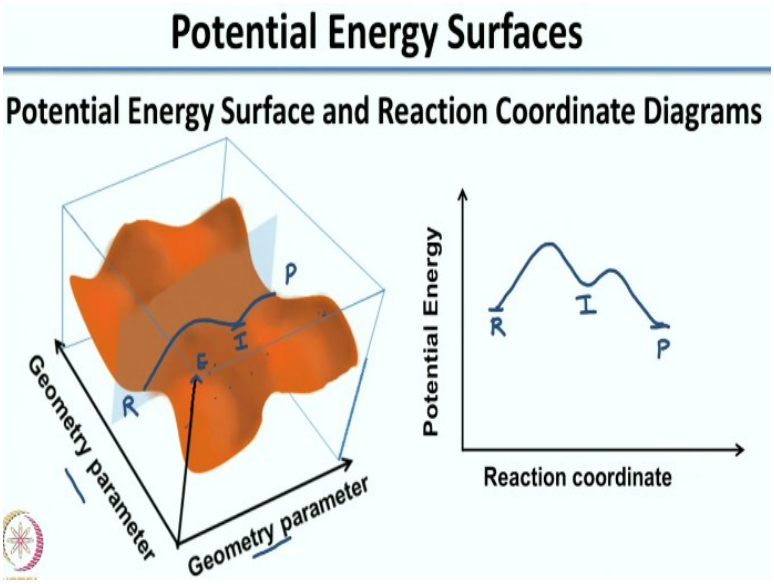

So I had introduced to this concept of potential energy surface. So, if you have a reaction taking place usually you can represent it in terms of a complex potential energy surface where on one access you have energy and on the other axis you have what is called as a geometry parameter and the geometry parameter essential tells you how the bonding changes are occurring in your reactants. Now the reaction coordinate diagram is actually a slice of this potential energy surface.

So shown here in blue, you can see a cross sections; so imagine your cutting the surface, slicing it like your essentially slicing a cake. So when you slice it what you see is your reaction for the diagram which is what is shown towards the right of your screen. So the reaction co-ordinate is actually the lowest energy path for your reactant to take. So I told you the example of say R is Mumbai and P is Pune and the potential energy surface is all the Ghats and the mountains that you have in the middle.

The reaction co-ordinate is the quickest path that you can take from Mumbai to Pune. Alright? and then when you slice it what you see is this 2-dimensional plot which is called as your reaction co-ordinate diagram. So what you would see is, since this is the lowest energy pathway whatever shows up as peaks on your reaction co-ordinate diagram would be valleys in your potential energy surface. Alright? And then we had looked at what all information you can get from this reaction co-ordinate diagram.

It is a very simple looking 2-dimensional plot but it is packed with a lot and lot of information and we had seen what all this information is. For example we had seen what information the Y-axis gives?

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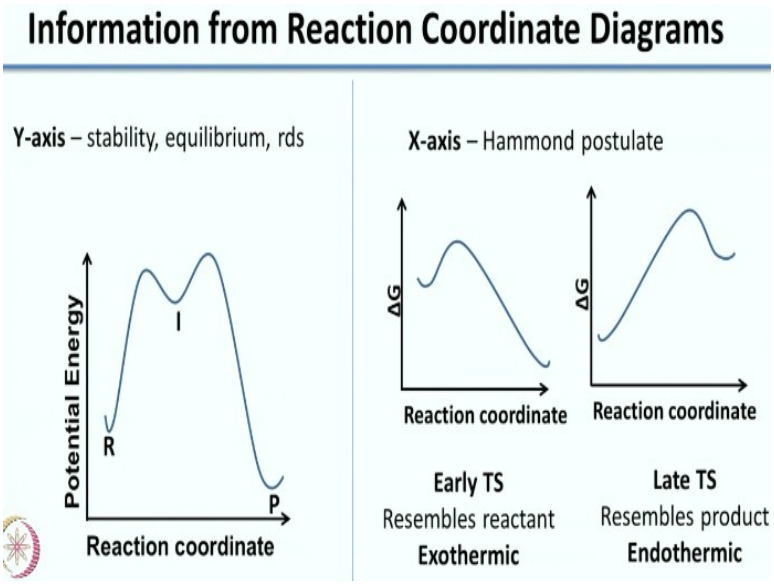

So the Y-axis as I told you deals with energy. So looking at the Y-axis you know the relative energy of the reactant, the intermediate and the product. Also looking at the reaction co-ordinate diagram you know that this reaction proceeds via 1 intermediate. So, so, rich in information and you also know that the intermediate is higher in energy than the reactant and product is lowest in energy. So it give you an idea of

Because you know the relative energy you know what is the rate determining step. Alright? and also you know whether a reaction is in equilibrium looking at the rate of the reverse reaction and the forward reaction. So lot of information packed in this simple diagram that we call a reaction co-ordinate diagram. Again in your assignment that you done, your assignment 2 in week 2 you looked at how you can I mean what all information you can get from reaction co-ordinate diagrams and we had looked at several examples as to how you can even predict

what the reaction co-ordinate diagram will look like if you are told the relative energy and what is the rate determining step. Then we had looked at the X-axis and specifically how the position of the transition state gives you a lot of information about the structure of the transition state. The Hammond postulate I had introduced you to and Hammond postulate says that if the transition state is close to reactant it will resemble the reactant and it is called as an early transition state.

If the transition state is close to the product it will resemble the product and it is called a late transition state. So we had looked at this, which is called as the Hammond postulate and as an extension of that we had said is, if you have a highly exothermic reaction, so exothermic reaction is a reaction giving out heat, what you see is you would see an early transition state whereas if you have an endothermic reaction which is taking up heat,

what you see is a late transition state and of course we had looked at several examples on how you can use this Hammond postulate to explain selectivity. Then we had seen how we can use reaction co-ordinate diagrams to determine major products.

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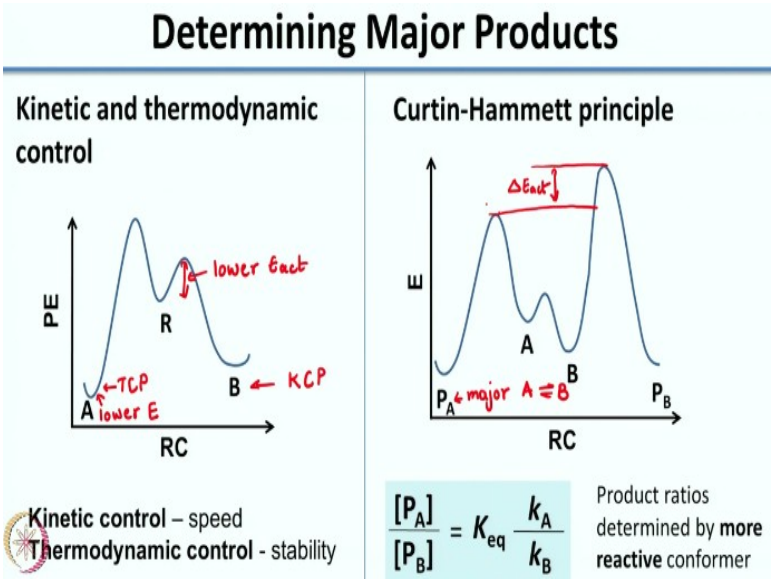

So we had looked at what is called as kinetic and thermodynamic control. So here you have a reactant are which can go to product A or product B. Now if the reaction is under kinetic control, kinetics- speed is more important, so speed is important it would prefer to form product B because it has a lower activation energy for product B but is stability is what is more important which is what you call thermodynamic control you would see product A being formed because product A is lower in energy. So this is lower in energy and this has a lower activation energy.

So this is the product that you would get if the reaction is kinetically controlled and this is the product that you would get if the reaction is thermodynamically controlled alright? Then we had looked at the scenario where if you have A and B. So A and B are actually conformers. So if you

have A and B which can interconvert and the energy of inter conversion is very small, so it can convert pretty quickly; the ratio of the product P_A verses P_B is given by the difference in activation energy for formation of these 2 products so in essence it is given by k_A over k_B.

So in this case based on the Curtin-Hammett principle although A is the higher energy conformer this would be the major product because the activation energy for this is lower and we had looked at multiple scenarios where depending on the relative energy of the conformers and their activation energy you can predict the product ratios. Alright?

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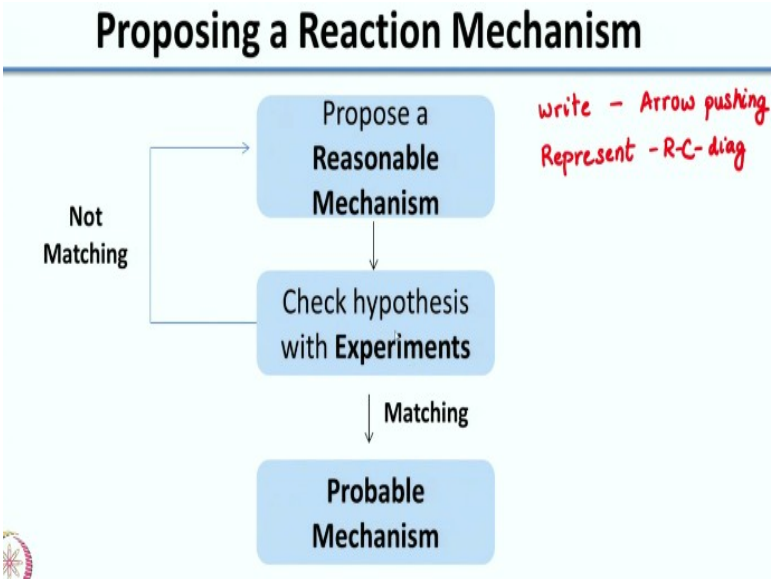

So then after week 2, we had looked at so now, we are looked at ways to propose which is write a reaction mechanism, so were able to write mechanism and we were also able to represent reactions using reaction co-ordinate diagrams. So I will just call them a R-C diagrams and writing was using arrow pushing. So then we move down to what are the experiments that people usually use. So we moved on to what are the experiments people use to check reaction mechanisms.

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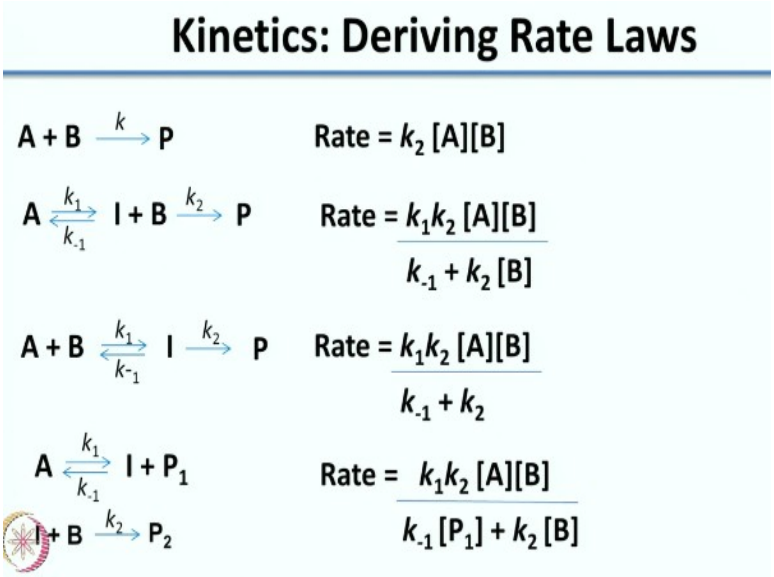

So we started with kinetics. So we looked at simple reactions, elementary reactions, much more complex reactions and we, we were able to systematically derived rate laws for all these reactions. So if you look at all of these together you might feel that it is overwhelming but go back to that week and it was quite easy for you to systematically derive the rate law for each of these complex reactions and again this was tested in your assignment.

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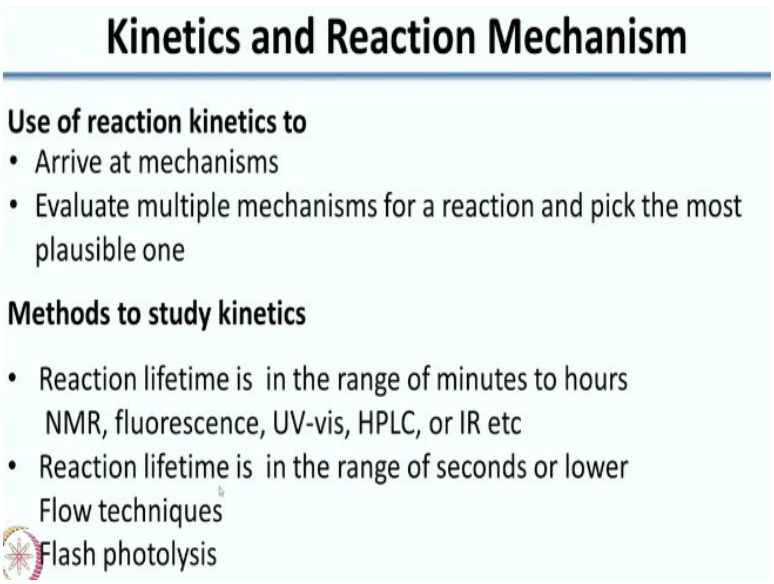

Then we had seen how you could use reaction kinetics to arrive at mechanisms and we had also seen how you can evaluate multiple mechanisms for a reaction and pick the most plausible one using reaction kinetics. We had also looked at methods to actually measure the concentration because you would need that data write when you are doing the experiment? So we looked at

methods for reactions with lifetimes of minutes to hours and we had also looked at methods for reaction which have a lifetime of few seconds or lower.

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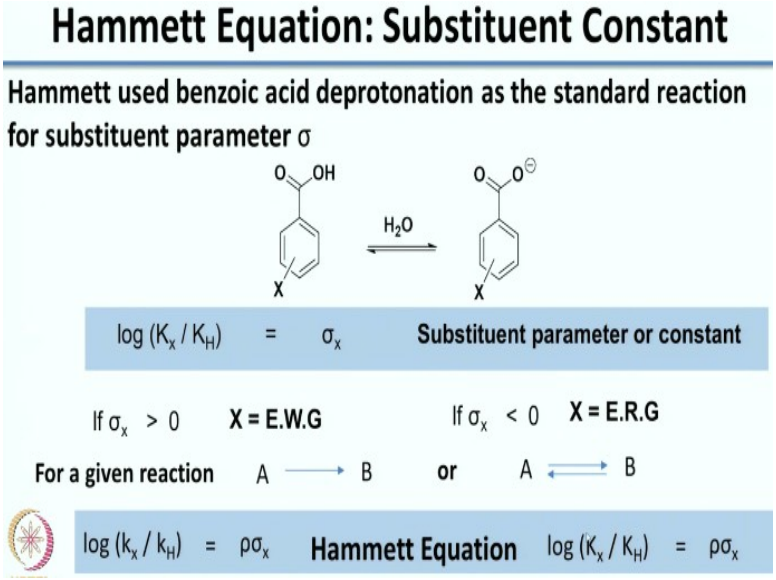

Then we moved on to another very interesting experiment. This is called as a linear free energy relationship and the plot that you get is called the Hammett plot and it tells you how or what is the nature of the intermediate in a particular reaction. So what Hammett did is used the benzoic acid deprotonation to derive or get what is called as the substituent parameter. So what the substitution parameter tells you is, how changing the substituent, changes the rate of benzoic acid deprotonation so, this is the equation that is given.

Where you have log (Kx/K_H) where Kx is equilibrium constant for the substitute X and H when you have no substituent. So that gives you σ_x which is your substituent parameter or your substituent constants and what we are seen is if σ_x is greater than 0 then X is an electron withdrawing group, because as you know electron withdrawing groups health in stabilizing the conjugate base here and now is σ_x is less than 0 then you know that X is an electron releasing group because it destabilizes it.

And then we had seen how the substituent constant can be used or extended to give you the nature of the intermediate for any reaction. So you have what is called as the Hammett equation where you have log (Kx/K_H) for any reaction which where you have A converting to B given by

$\rho\sigma_x$ where σ_x is your substituent constant that you get from benzoic acid and ρ is what is called as the reaction constant. Alright? This could also be used for equilibria and ratio of equilibrium constant.

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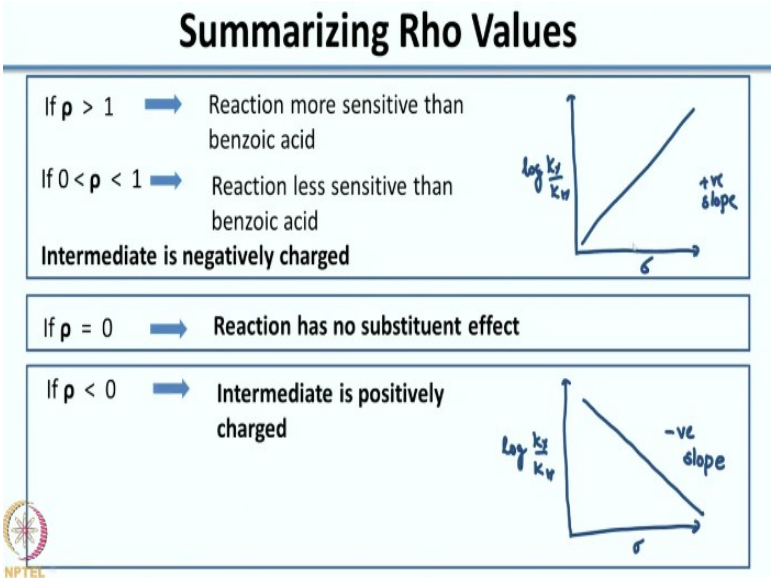

And from the value of ρ you get lot of information about the reaction this is a plot of log (K_x / K_H) over σ if ρ is positive you know that the reaction is similar to benzoic acid. That is you have a negatively charged intermediate. If ρ is between 0 and 1 you have that you know that the reaction is less sensitive than benzoic acid but intermediate would be negatively charged. If you have ρ as 0 you know that the reaction has no substitute effect and if you have ρ less than 0 you know that the reaction is positively charged because it has a negative slope.

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LFER - Summary

LFER	Sub. Const.	Standard Reac^n	Effects seen	Reac^n Const.
Hammett	σ	BA ionization	Inductive (mainly)	ρ
Hammett	σ^+	Phenol ionization	R and I effect	ρ
Hammett	σ^-	Phenyldimethyl chloromethane S_N1	R and I effect	ρ
Taft	E_s	Hydrolysis of methyl acetate	Steric (and electronic)	δ
Grunwald-Weinstein	*Y*	Dissociation of *t*-BuCl	Solvent effect	*m*

Also looked at Schleyer adaptation

So then we did multiple free energy relationship and shown here the table of all the free energy relationship we did so we looked at the σ scale, σ^+, σ^-, E_s where we use the linear free energy relationship to understand steric and how steric effect reaction and we also looked that effect of solvent using free energy relationship so this was why? So we had instead of σ all these new substituent constants and all these new reaction constants.

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Kinetic Isotope Effect

A method that gives insights into the rds.

The Experiment:

- Substitute a particular position of reactant with an isotope
  Typically H with D
- Determine *k* values of reactant and labelled reactant
- Compare k_H versus k_D

The Principle for Primary KIE – The C-H bond that is substituted breaks in the rds

- Effect seen due to the symmetric vibrational stretch
- Effect is maximum for the symmetric transition state
- Theoretical maximum value of effect is 7
- If $k_H / k_D > 2$, **Primary KIE**
- Linear TS show a greater PKIE than non-linear TS

Then we moved on to another interesting experiment which is the kinetic isotope effect. So this is a method that gives insights into the rate determining step. So in this experiment a particular position of a reactant is substituted with an isotope. So typically hydrogen with deuterium is what we study. So the *k* values of the reactant and the label reactant is determined and you

compare the ratio. So, what is seen is a primary kinetic effect is one where the bond breaks in the rate determining step.

So what you see is the effect is due to a symmetric vibrational stretch and the effect is maximum when you have a symmetric transition state. So the theoretical maximum value of this effect was seen as 7 and if k_H over k_D is greater than 2, you have a primary kinetic isotope effect; that means that your C-H bond is breaking in the rate determining step and we also so that a linear transition state shows a greater primary kinetic isotope effect than a nonlinear transition state.

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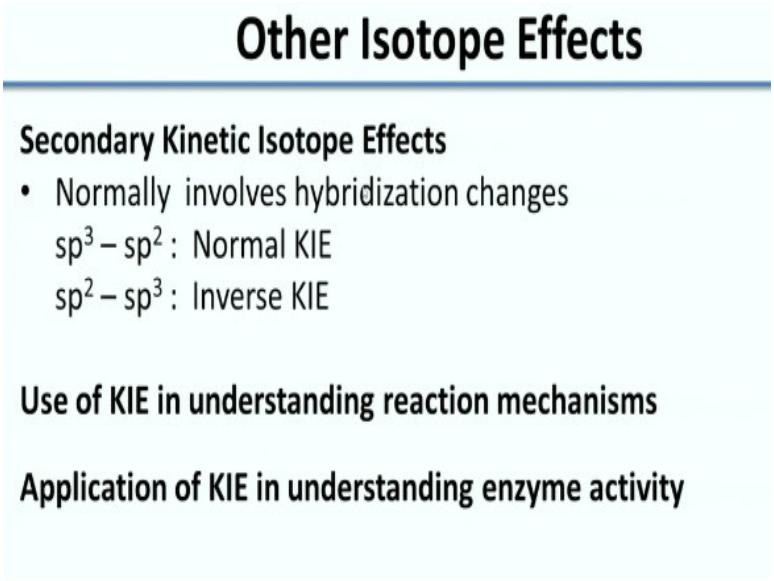

We also looked at other isotope effects. So we looked at secondary kinetic isotope effects. So these are usually seen when you have hybridization changes and here I told you that it is mainly because the C-H bond length is greater than the CD bond length which is shorter and here you see the changes mainly due to the bending vibrations and not the stretching vibrations like the primary kinetic isotope effect. So when you have a reaction where you have sp^3 converting to sp^2

hybridization in going from the reactant to the product or the intermediate you see a normal kinetic isotope effect but if you have sp^2 going to sp^3 you see a reverse which is an inverse kinetic isotope effect and again we saw this in understanding mechanisms and application in understanding biology.

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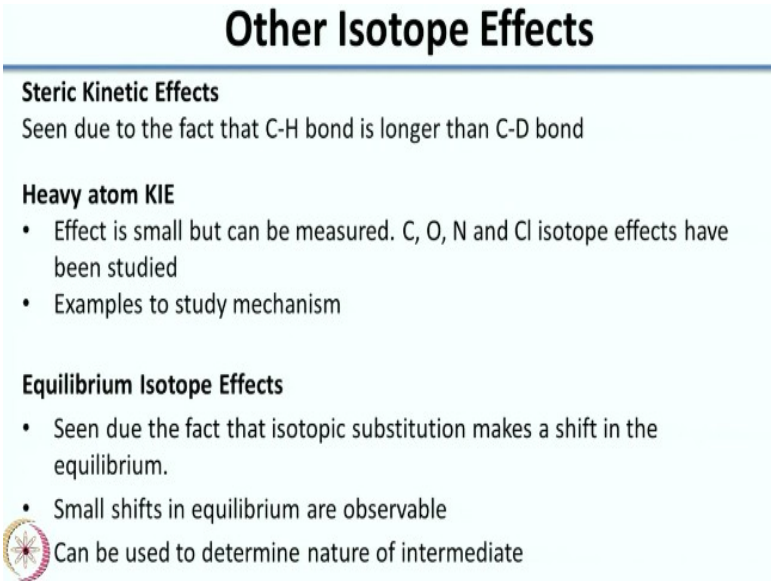

We also looked at steric kinetic effect. Here again the effect is due to the fact it is C-H bond longer than C-D bond. We looked that heavy atom kinetic isotope effect, so as I told you when you replace hydrogen with deuterium you see the maximum effect because the difference in mass is higher or reduced mass is higher for these 2 CH verses CD bond but when you have heavy are isotopes of carbon, oxygen, nitrogen, Cl you do not have much difference in the reduced mass.

So you are talking about very small difference in the kinetics but we also showed you how this could be studied and finally we looked at equilibrium isotope effects where we saw that small isotopic substitution makes a shift in the equilibrium and we saw that this could actually be used to determine the nature of the intermediate.

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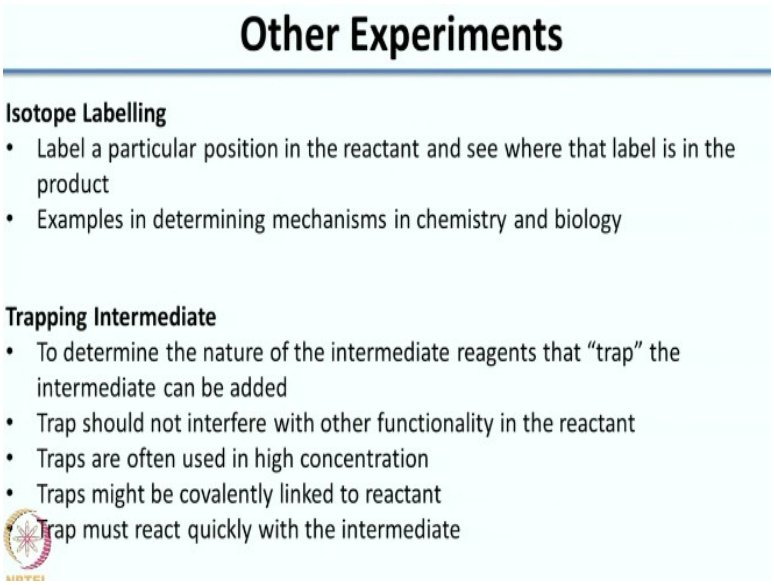

We also looked at other experiments such as isotope labelling. Like I said you label your book you label an atom of reactant and then follow how that label moves in your product and that would give you lot of valuable information especially when you are looking at reactions where you are trying to figure out the difference between 2 mechanisms. We also saw the application in biology. Then we looked at other methods such trapping intermediate. So traps are reagents that are used to sort of freeze the intermediate or trap it.

This reagent can be used depending on the nature of the intermediate you vary the nature of the trap. You have to remember that the trap should not interfere with the rest of the reaction. Traps are often used in very high concentration because you want to increase the probability of collision of the trap with the intermediate instead of the intermediate reacting with other like your solvent or something to give you the product.

We also saw that traps could be covalently linked to improve the again probability of collision and we saw that traps must react quickly with the intermediate. So we saw multiple traps for anions, cations and radicals. Then we looked at competition experiments.

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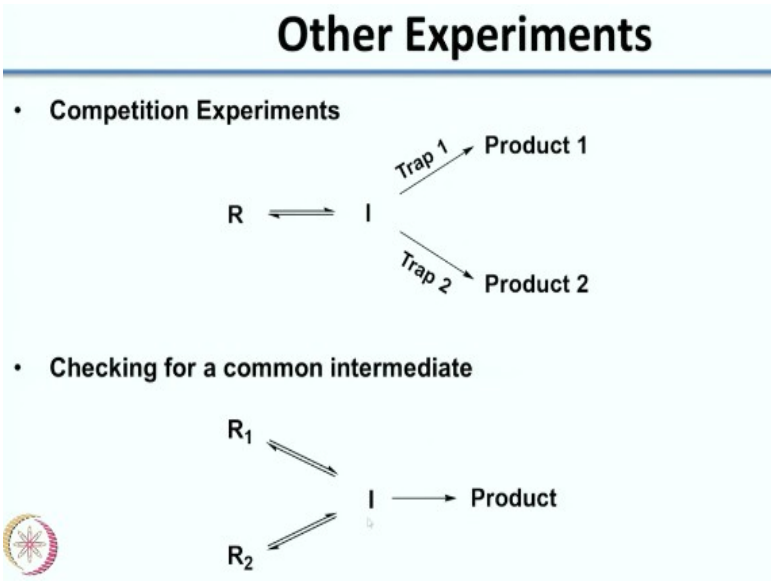

So competition experiments is where? So where the reactant forms an intermediate I and you use 2 different traps to get two products and the product ratio could be used for you to understand what is the nature of the intermediate and the reverse of that is checking for a common intermediate where you start with 2 different reactants, if you get the same intermediate which will give you the same product, you know that that is the intermediate form for that particular reaction.

Then we looked at crossover an experiments. So this is very useful for rearrangement reactions. So what is seen as you are 2 sets of reactions.

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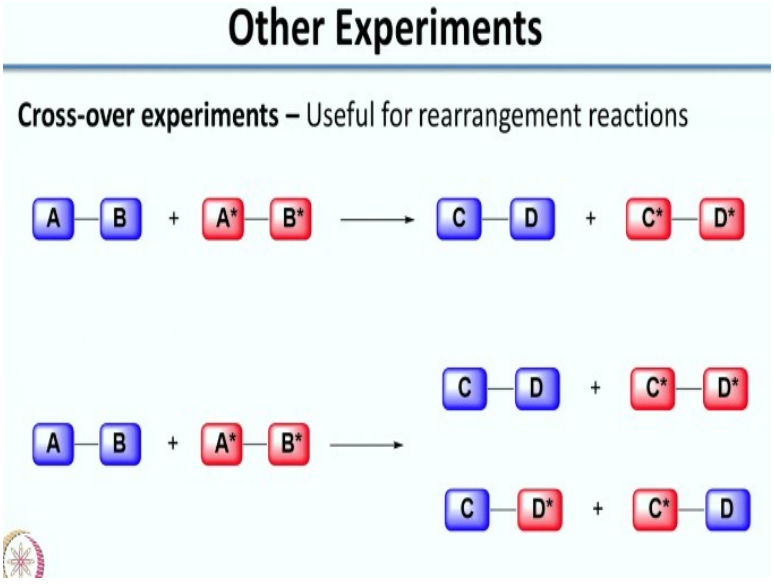

If the reaction is intra-molecular then you will have products corresponding to the blue reagent or the blue reactant and the red reactant. You will not have blue and red mixing with each other. Whereas if you have 2 of these reagents, so you have the blue reagent and the red reagent and you have what is called as a crossover, so distinct intermediates and not an intra-molecular reaction, you will have only blue, only red and a mix of red and blue. So it is called as the crossover takes place and you know that the reaction goes over via this formation of an intermediate.

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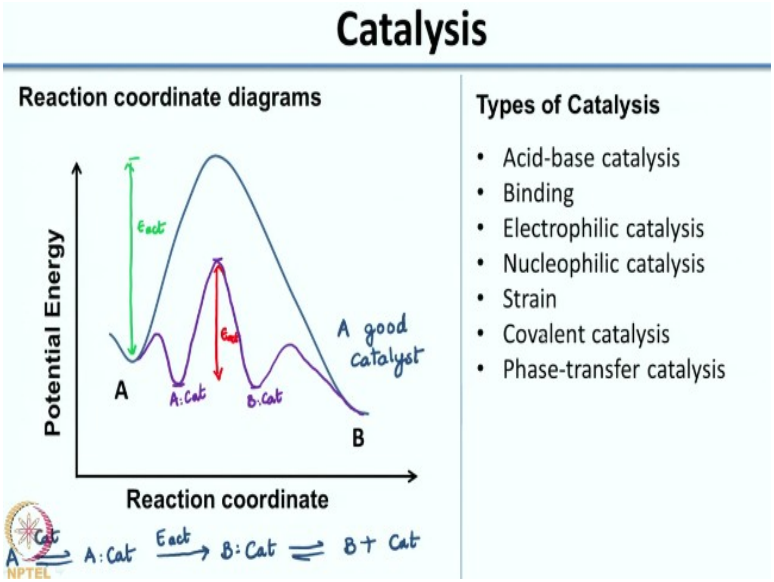

Then in the last 2 weeks we looked at catalysis and we saw how you can represent catalyst using reaction co-ordinate diagrams. So catalyst is essentially something which lowers the activation energy barrier for a reaction to take place. So this could either be by formation of a complex of the reactant with the catalyst or it could be by a totally different pathway and looked at different types of catalysis. So we looked at acid base catalysis, binding, electrophilic catalysis, nucleophilic catalysis, strain, covalent catalysis and phase transfer catalysis.

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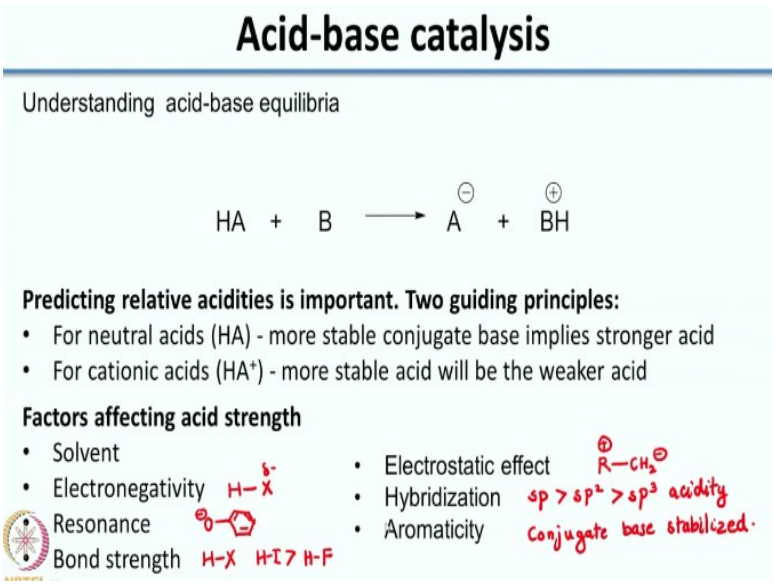

So in acid base catalysis we saw how first you get an understanding of acid base equilibria and the we saw how you can predict acidities by 2 guiding principles. So for neutral acids I told you the more conjugate base implies a stronger acid. For cationic acids we saw that the more stable acid will be the weaker acid. Then we also look that multiple factors favoring the acids strength such a solvent, electronegativity, resonance, bond strength, electrostatic effect, hybridization and aromaticity.

So I am not going to discuss all of this in detail because we had done that in week 7. You can go back and look at week 7 notes to understand each of these effects. Then we had looked at specific acid catalysis and general acid catalysis.

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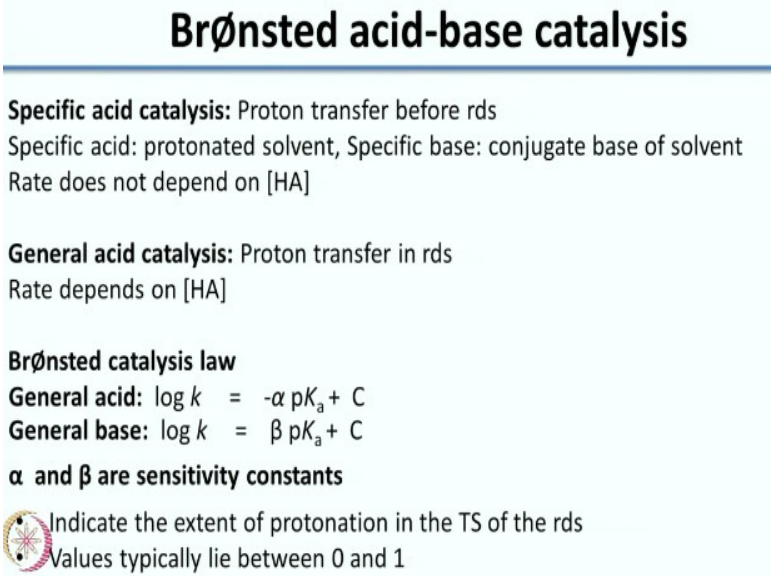

Specific acid catalysis is where proton transfer takes place before the rate determining step and it is only the protonated solvent concentration or the conjugate base of solvent that is important. The rate does not depend on HA. We had also looked at general acid catalysis where proton transfer occur in the rate determining step and the rate depends on the concentration of HA. Then we had derived another free energy relationship which is the Bronsted catalysis law where α and β give you what are called as sensitivity constants.

So it indicates the extent of protonation in the transition state of the rate determining step and of course it is values somewhere between 0 and 1 alright? So we had seen how you can use the α and β to tell you how sensitive the reaction is towards protonation or the extent of protonation.

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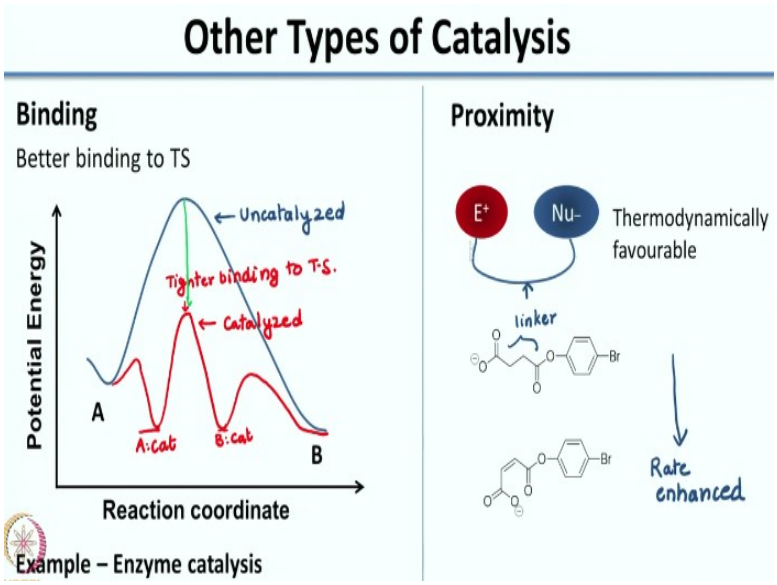

And in the last week we had looked at other forms of catalysis such as binding and here we actually focus a lot on enzyme catalysis. So again what binding does is you form a substrate catalyst complex which is lower energy and the substrate actually binds tighter to the transition state because you have then a lower dip in energy as compared to that for your reactant and then this leads to a lower energy pathway or catalysis of the reaction.

So here further we looked at proximity, we looked at proximity catalysis as I told you when you have 2 reactants floating around in solution, you have to wait for them to meet each other but what you are doing is linking these 2 reactants would help in increasing the probability of their collision and it also makes the process thermodynamically favored and we have seen several linkers that could be used to actually improve the catalysis of intra-molecular reactions.

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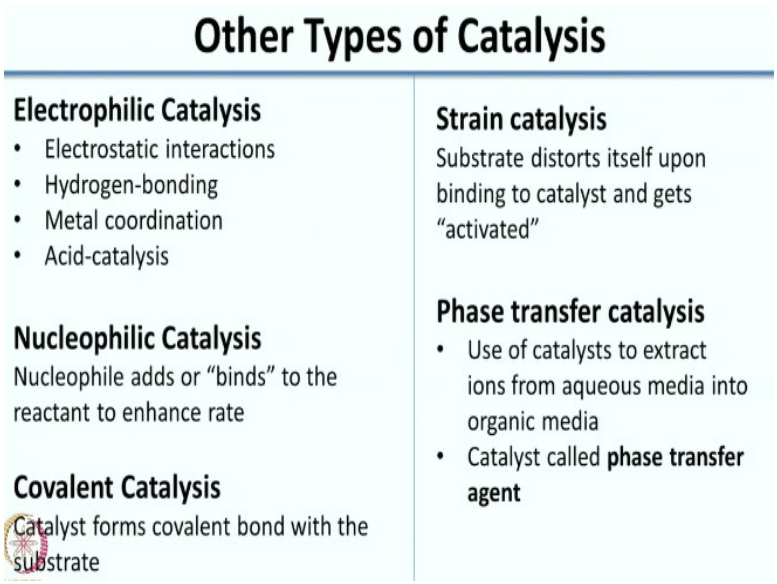

Then in the last few lectures we looked at electrophilic catalysis where we were looking at electrostatic interactions, hydrogen bonding, metal coordination and acid catalysis. We also looked at nucleophilic catalysis where a nucleophile binds to the reactant to enhance rate. Then we looked at covalent catalysis where the catalyst forms a covalent bond with the substrate to improve the rate. Then we looked at strain catalysis where the substrates distort itself upon binding to a catalyst and gets activated and then we did phase transfer catalysis in the end

where we use catalyst to extract ions from the aqueous media into organic media. So that was really quick overview of what we did over the last 40 lectures. So hopefully when you see this closer to your exam and you are thorough row with all the other concepts it would be easier for you to understand. Which is why I just breezed through it very very quickly just to give you a snapshot. Just reading the slides itself would be useful for you for this last lecture because essentially I was just trying to highlight all the information that was given on the slides.

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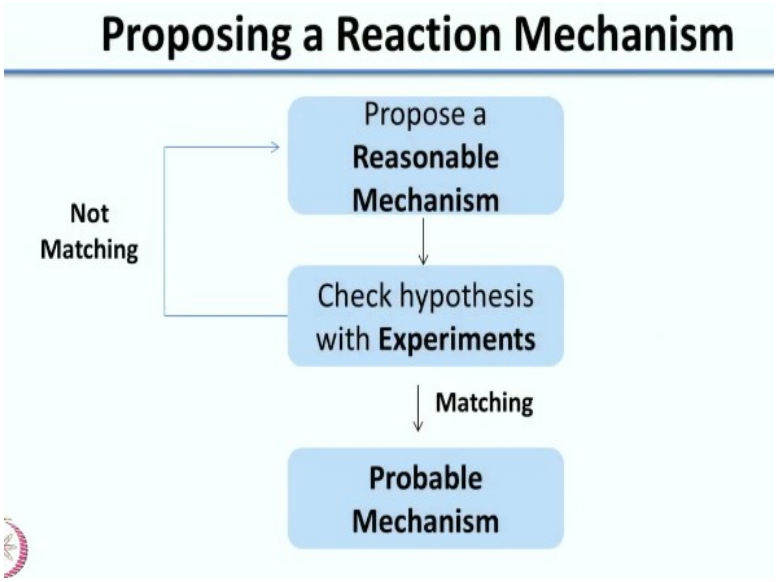

So now to just summarize the class overall. So we started with methods to propose a reaction mechanism. Then I taught you experiment that you could choose to check whether the hypothesis is correct and then we saw examples where you had multiple mechanisms and depending on the experiment the scientists were able to say which was the mechanistic pathway which was correct and we saw this in chemistry as well as in biology.

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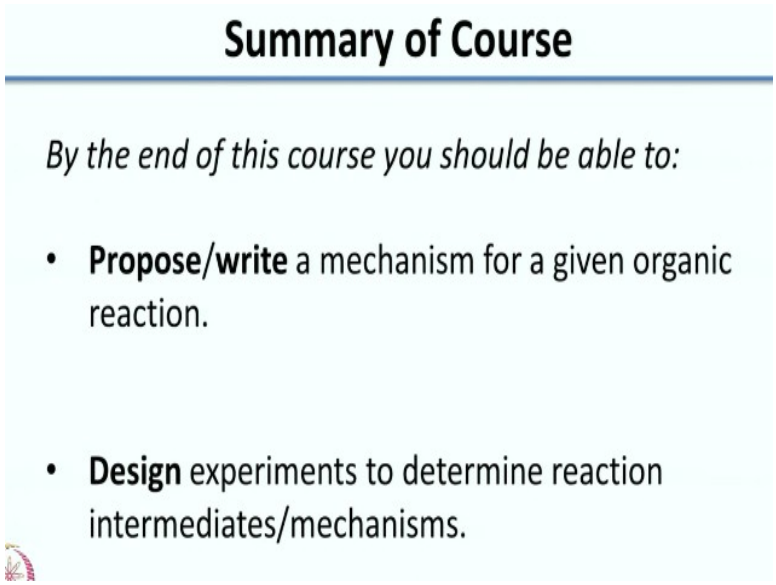

So the learning outcomes that I told you in the introductory lecture is, by the end of this course you should be able to propose or write a mechanism for a given organic reaction. So I hope these lectures have given you enough tools to be able to do that and I also told you that you would be

able to design an experiments to determine reaction intermediates. So depending on the nature of the mechanism I have given you several tools.

We saw them all in the lecture and you should be able to now pick which tool will actually be useful for you to be able to check your reaction mechanism. So it was a pleasure teaching this course and I hope you have benefited from it and I wish you all the very best for the exam. I hope you do well and I hope to interact with you in the future. So thank you and all the best.