Mechanisms in Organic Chemistry
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Lecture-36
General Catalysis: Part B

So welcome back in the last class we were looking at acid and base catalysis, so we had already classified acids as specific and general acid.

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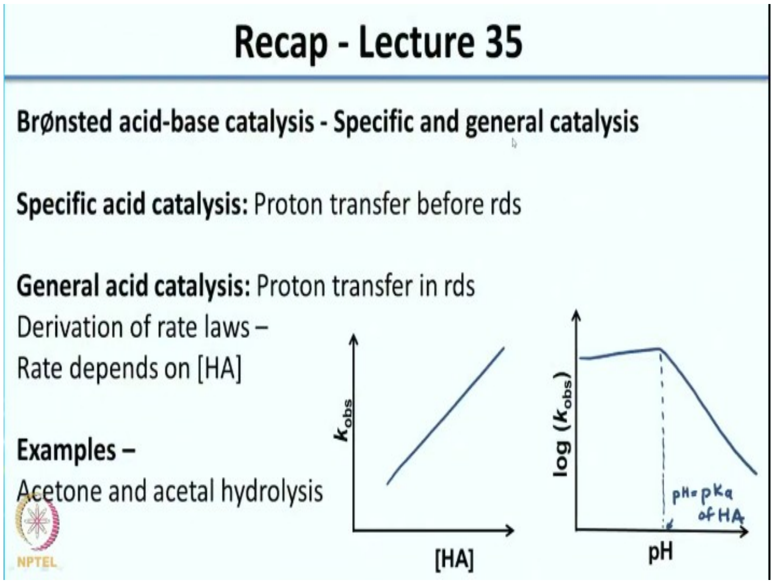

Recap - Lecture 35

Brønsted acid-base catalysis - Specific and general catalysis

Specific acid catalysis: Proton transfer before rds

General acid catalysis: Proton transfer in rds
Derivation of rate laws –
Rate depends on [HA]

Examples –
Acetone and acetal hydrolysis

And we had looked at specific acid catalysis in the earlier lecture where specific acid catalysis involves Proton transfer before the rate determining step in the last lecture we had focus mainly on general acid catalysis. So in general acid catalysis you have Proton transfer in the rate determining step. So as with this specific acid catalysis here also we had looked at the rate laws and here but we had seen is that the rate depends on concentration of HA.

So if you plot $k_{observed}$ versus concentration of HA you would see a steady increase. Similar trends are seen for general base catalysis as well, the other thing is if you look at dependence with pH what would you see is that it would remain constant for a while and then you would observe a dip in the log k value and that dip would be seen at the point corresponding to pKa of the acid which is HA.

Then what happens is when you cross the pKa of the acid you would have more dissociation of the acid and hence a smaller concentration of HA. So then we had also looked at examples of acetone and acetal hydrolysis acetone we had looked at both specific as well as general catalysis in acetal only looked at specific acid catalysis and I had asked you to work out the general acid catalysis, so let us see if you are able to work it out so hydrolysis of acetal to hemiacetal, how will you represent it when you are trying to represent it for general acid catalysis.

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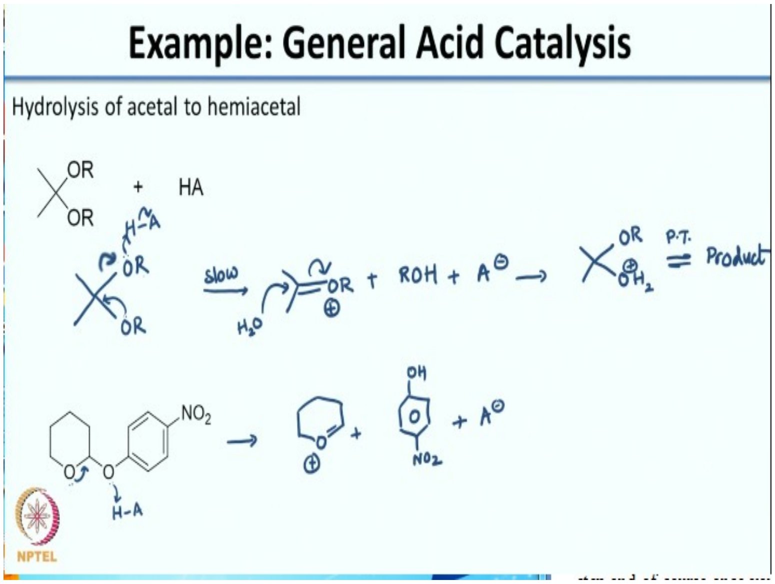

Example: General Acid Catalysis

Hydrolysis of acetal to hemiacetal

So let us see if you got this correctly, so when you think of general acid catalysis what you would have is? You would have so this is your acetal correct, so now you would have this coming in now as you know RO^- will not be as great leaving group, so what you would do is? You would have this being protonated at the same time. So what you would get would be and this would be the slowest step and of course once you have this intermediate you can then think of water adding in to give you to and of course further proton transfer will give you your product.

Now in which situation do you think you would observe general acid catalysis right, so if you want to think of a specific substrate, so earlier we had looked at the previous class substrate which underwent specific acid catalysis the hammet plot for that was also obtained which supported that, so now which kind of substrate do you think will prefer to undergo general acid catalysis. Logically it would be a substrate which would have a good OR leaving group and that is what is actually observed.

So this particular acetal here when you think of its hydrolysis, so if you have the p-nitro phenoxide as the leaving group, so it is assisted by this acid, so now what you will get would be this intermediate. So what is observed this for this particular acetal and it refers to undergo the hydrolysis by general acid catalysis mechanism, so what you see is looking at the substrate you can logically deduce whether it would undergo specific or general acid catalysis and of course experimentally it is easy to determine if you look at how the rate constants vary with pH.

Now there are several reactions where you actually have concerted or sequential general acid general base catalysis especially in biology see you have multiple species working together one is a general acid one is a general base and you have both of these actually working together to give you an intermediate which then gives you the product.

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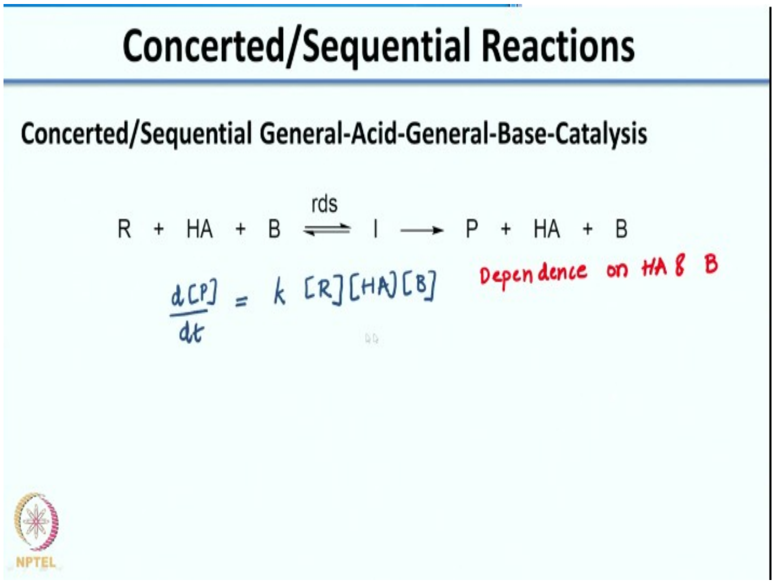

Concerted/Sequential Reactions

Concerted/Sequential General-Acid-General-Base-Catalysis

$$R + HA + B \underset{}{\overset{rds}{\rightleftharpoons}} I \longrightarrow P + HA + B$$

$$\frac{d[P]}{dt} = k\,[R][HA][B]$$

Dependence on HA & B

So if you were to write the rate law for this what would it be? The rate law would be, so this would be equal to concentration of R, concentration of HA and concentration of B. So here what would you see is you would actually see a dependence on both HA as well as HB sorry B. So you would see a dependence on both HA and B here, alright? So this is commonly seen in

Biology. So now if you have a situation like this I will go back for a second to the previous slide you have dependence on HA as well as B.

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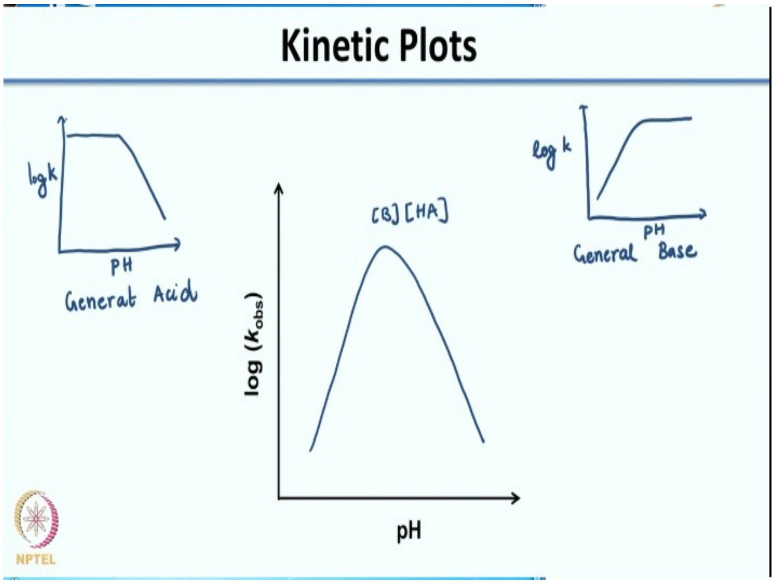

Kinetic Plots

So here if you were to plot log of k observed versus pH what do you think the plot will look like? Alright? So we have already seen in the previous 2 classes what the plot will look like in the case of a general acid and a general base right? In the previous class actually we looked at what the plot will look like for a general acid and a general base. So now what you need to do is you need to figure out when you have both of these together what will the kinetic plot look like. Obviously look like a mix of the 2. So I want you to press the pause button and try to work out what this plot will look like.

So let us see if you have this correctly. So what you would see is it would be a bell shaped plot. Right? So what you get actually is a hybrid of both the plots. So for a general acid what did the plot look like when you are plotting it? And you can remember what it looked like for a general base as well. So in the general acid what you had is the plot looked like this. And in general base you had the plot look like this. So here what you see is at low pH what would happen is because you have a lower concentration of B, right so as you increase the pH you have more of BH^+,

so as you increase the pH you will increase the concentration of B till you reach the state where you have maximum amount of rate, so you will have maximum rate when you have both good concentration of B as well as HA. Now what will happen as you again go on increasing the pH HA will now disassociate to H^+ and A^-. So now what you would see is again you would have the rate drop off. So you have a high concentration of B but the concentration of HA will decrease. So this is what the kinetic plot will look like.

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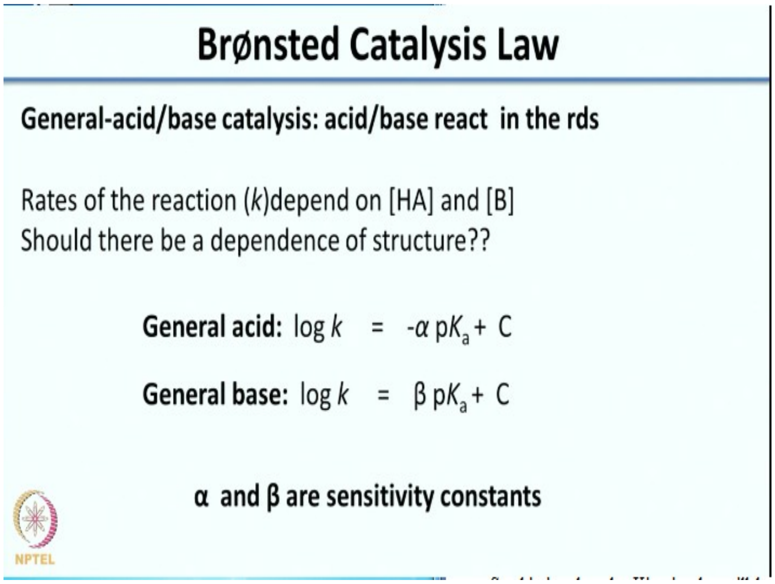

Brønsted Catalysis Law

General-acid/base catalysis: acid/base react in the rds

Rates of the reaction (*k*)depend on [HA] and [B]
Should there be a dependence of structure??

General acid: $\log k = -\alpha \, pK_a + C$

General base: $\log k = \beta \, pK_a + C$

α and β are sensitivity constants

So now we will go to what is called as the bronsted catalysis law. So now I will go to what is called as the bronsted catalysis law alright? So when you have the general acid base catalysis you have the acid or base react in the rate determining step correct we have done that since the last class there is no doubt there. So the rate of the reaction *k* depends on concentration of HA and B depending on which reaction you looking and general acid or general base.

Now should there be a dependence on the structure. Alright? so do you think there would be a dependence of the K value on the structure, so say if you have a stronger acid or a stronger base do you think that would have an impact on the K value? So remember when you talk about acid base and acid strength it is a thermodynamic property right you are talking about the pKa but when you look at the reaction kinetics you are talking about the kinetics are the rate at which you are protonating or adding OH^-.

So that is the difference between these 2. So the question to use do you think that the kinetics of the reaction will depend on strength of the acid or base and the answer is yes it will. and this dependence is given by what is called as the bronsted catalysis law so in the bronsted catalysis law log of k is given by is equal to - α pKa + C. C is just a constant to show you the intercept of the graph that you get if you plot log k versus pKa. α is a sensitivity factor.

So just like the name suggests, α will tell you how sensitive your reaction is to the acid strength or in other words pKa. Similarly for a general base log of K is given by β pKa + C and both α and β are called as sensitivity constants. So I want you to closely look at these equations. Now if you notice there is a negative sign in the case of general acid catalysis whereas there is no negative sign for general base catalysis.

So why is that do you think? Again look closely at the expression you can press the pause button and look closely at the equation to figure out why there is a negative sign that is put? So if you were not able to figure out I will give you hint as the pKa of the acid increases again, as the pKa of the acid increases would you expect the rate to increase or decrease? So pKa increases means less acidity, so with the less acidity will the K value increase or decrease?

It will obviously decrease right? You looking at acid catalysis if the acid strength is decreasing how will catalysis increase? So essentially because of this inverse relationship a negative sign is put when you look at α but that is not the case for β because here you are looking at pKa of the conjugate acid alright? So you need an put this negative sign here. So now let us try to understand this more closely. So does this remind you of any equation that you had seen earlier where you are correlating the rate to some sort of a dissociation constant? Think little more it is similar to the Hammett equation correct?

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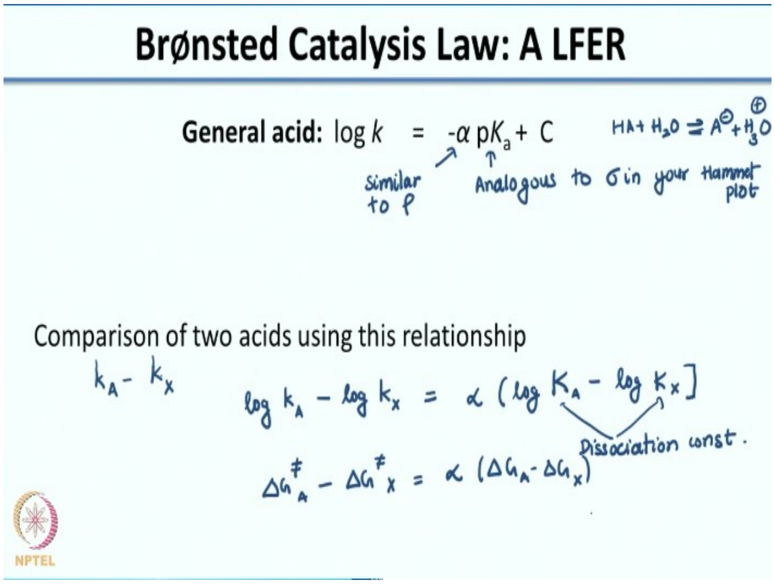

Brønsted Catalysis Law: A LFER

General acid: $\log k = -\alpha \, pK_a + C$ $\quad HA + H_2O \rightleftharpoons A^{\ominus} + H_3O^{\oplus}$

similar to ρ

Analogous to σ in your Hammett plot

Comparison of two acids using this relationship

$k_A - k_X$

$$\log k_A - \log k_X = \alpha\,(\underbrace{\log K_A - \log K_X}_{\text{Dissociation const.}}]$$

$$\Delta G^{\neq}_A - \Delta G^{\neq}_X = \alpha\,(\Delta G_A - \Delta G_X)$$

So in the Hammett equation what you had is you were looking at a reaction and correlating that with the dissociation of benzoic acid. So this here was your substituent constant for Hammett equation. But here what you have is the pKa instead and what is pKa how do you define the pKa? The pKa tells you what is the tendency of the acid to give proton to water correct? So when you think of acid dissociation constants you are thinking of HA^+ water giving $A^- + H_3O^+$.

So when you talk about pKa you are talking about the ability of the acid to give proton to water right, so this is similar to sigma in your Hammett plot and α is similar to rho. So what it tells you is that for any particular acid you are looking at a particular reaction now, for that particular reaction what is the tendency of the acid to protonate that substrate? So you are comparing that tendency to protonate with its tendency to protonate water. Alright? So this is analogous to a hammet plot.

So you have log k = - α pKa where this α which is the sensitivity coefficient tells you how sensitive the reaction is to this protonation. Alright? So now you can even compare 2 acids using this relationship. As you know you can correlate the K value with the Δ G right? So you can so this is similar to a linear free energy relationship. So I am going to write it directly in the form of the K value but to compare 2 acids, say your comparing an acid k_A with any other acid k_X. alright?

It is you are trying to compare how good these 2 acids would be for a given reaction. So you can give that by log of k_A - log of k_X = αlog of K_A – log of K_X. Alright? Where both of these are the dissociation constants. You can also look at it in terms of ratio if you so wish. Alright? And again if you were to write it in terms of free energy it would be when you talk of k if you are talking about the Δ G for the transition state based on the Eyring equations.

So you have, again this would correspond to the acid dissociation, free energy for the dissociation of the acid in water. So now we have found out another free energy relationship which compares the acidity of two general acids alright and this coefficient that you have α tells you how sensitive a particular reaction is to protonation or deprotonation. Alright? maybe if you look at some more examples this will make a little more sense to you.

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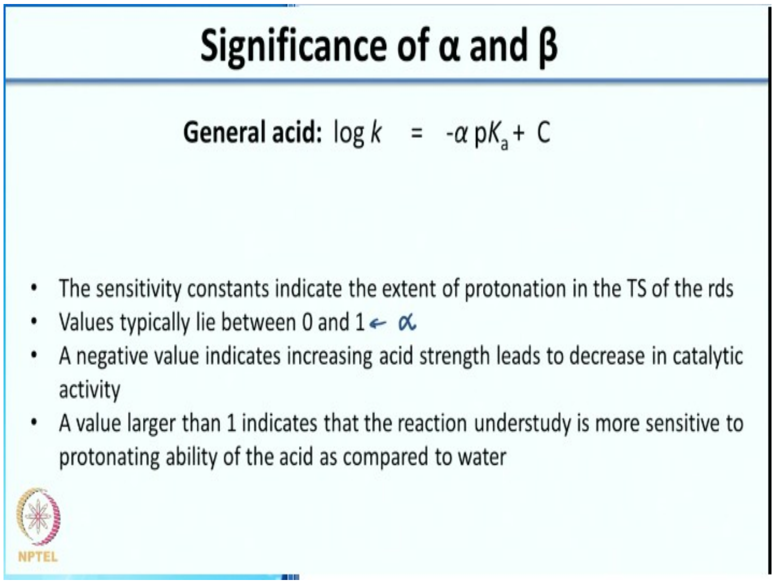

Significance of α and β

General acid: $\log k = -\alpha \, pK_a + C$

- The sensitivity constants indicate the extent of protonation in the TS of the rds
- Values typically lie between 0 and 1 ← α
- A negative value indicates increasing acid strength leads to decrease in catalytic activity
- A value larger than 1 indicates that the reaction understudy is more sensitive to protonating ability of the acid as compared to water

So what is the significance of α and β? I am just focusing on α hear the same you can think of when you think of β. So shown is on your screen the equation for general acid catalysis. Now sensitivity constant as I told you indicate the extent of protonation in the transition state of the rate determining step. So I had not explicitly told this to you earlier but if you have extensive protonation in the transition state that would indicate that the acid strength actually has an effect on the reaction rate.

So more protonation in transition state implies the acid has a greater effect. Typically, values lie of α between 0 and 1. So we are talking about values of α. Now why is that? What would the value of 1 indicate? A value of 1 in this equation indicates that you have a linear correlation between the rate constant and the pKa of the acid. So what does that tell you? The kinetics depends directly on the acid dissociation strength. So which indicates that you essentially have complete protonation in the transition state.

So this is the best possible scenario for you to see an effect right on the reaction rate to have a correlation with pKa. So that effect would be most when you have complete protonation in the transition states. So if that is the case that means you have a direct correlation of k and K. So that is why the maximum possible value would be 1. What will the value of 0 indicate? 0 indicates that the acid strength has absolutely no effect on the k observed or the k value. So essentially what that tells you that is the transition state is probably not yet protonated.

So it is probably a very early transition state and you probably do not see much of an effect on the acid. Sometimes a negative value is seen. So what a negative value indicates is that increasing the acid strength leads to decrease in catalytic activity. This is usually not very common but we will look at an example so that it makes sense because usually if the acid strength increases the understanding is that its ability to protonate any other substrate will also increase proportionally. but a negative value indicates that that is not the case and we will look at an example

so that it makes more sense to you. A value larger than 1 would indicate what? The value greater than 1 would indicate that the reaction that you are studying is actually more sensitive to protonating ability of the acid as compared to water. And why do you say as compared to water? Because when you talk about pKa you are looking at the ability of the acid to protonate water. The value greater than 1 indicates that whatever reactant you choose that has that is more sensitive to protonation that even water.

So this is again not very common. So let us look at again with respect to numbers what these values of α and β mean. So we will come back to hydrolysis of acetone. So if you have acetone alright,

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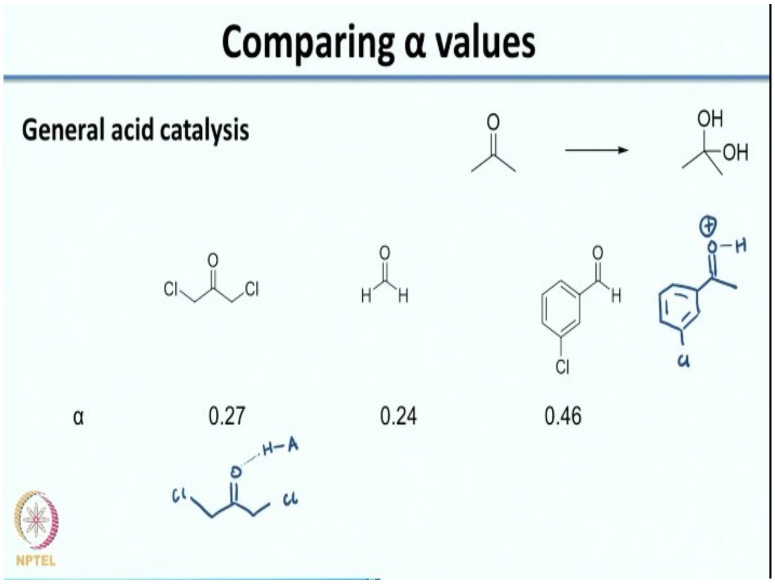

Comparing α values

General acid catalysis

α	0.27	0.24	0.46

and you are converting it to this diol. So when you convert it to the diol; let us look at 3 different reactions. So these 3 different reactions is so I have shown you 3 different substrates on your screen. So what these, in each of these case you are talking about hydrolysis of this instead of acetone alright? So you are measuring k for this particular reaction in the presence of different acids. So just so that you are not confused

I will repeat again. The reaction we are looking at is hydrolysis of a ketone to the diol. So for each of these ketones or aldehydes; you have 2 aldehydes and ketones here what is done is say for this aldehyde the first one here the reaction is carried out with different acids. Alright? To give you a correlation like we saw in the earlier slide and what you would get out of that would be the α value. Alright? Similarly it can be done for formaldehyde and this benzaldehyde derivative.

So the α values were determined for each of these and remember to determine α value on the left side you have the rate constant on the right side you have the acid dissociation constant. So what you see is that the α values follow this trend of 0.27, 0.24 and 0.46. So what is it tells you is that the extent of protonation is probably not as much in the transition state. It is probably partially protonated. Just like how you would think of; so you are looking at a situation where you have, so where you do not have complete protonation in the transition state.

And if you see the value is lower for formaldehyde and the dichloroacetone derivative as compared to the benzaldehyde derivative. In the benzaldehyde derivative you have a value closer to 0.5 which indicates that you have greater protonation in the transition state, which might also be explained by the fact that if you have a greater protonation here, this is again in conjugation to the aromatic ring, so maybe in this case you see a greater extent of protonation as compared to the other 2 cases.

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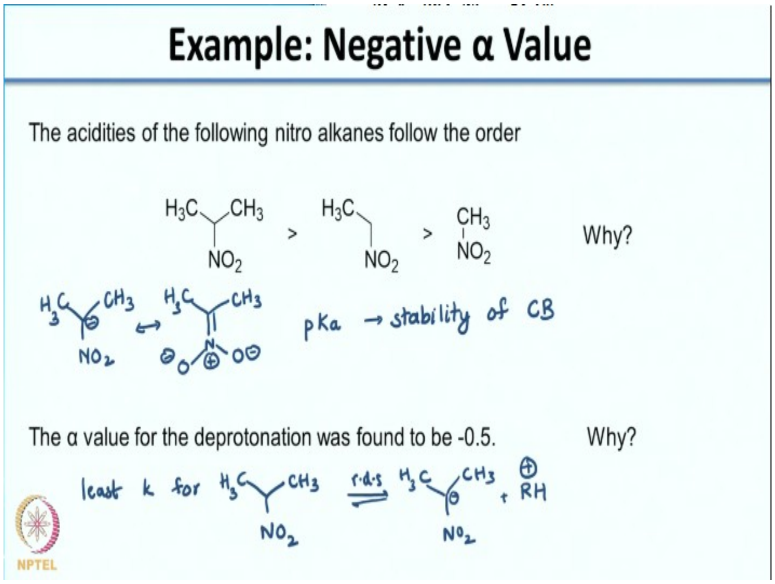

Example: Negative α Value

The acidities of the following nitro alkanes follow the order

Why?

pKa → stability of CB

The α value for the deprotonation was found to be -0.5.

Why?

least k for $\xrightarrow{r.d.s}$ + RH

I had told you will look at an example of a negative α value. So shown on your screen are 3 different acids so these are nitroalkanes. So what you see on your screen is that the 2 nitropropane is more acidic than nitroethane, which is more acidic than nitromethane. So what I want you to think about is why this order of acidities? So you can press the pause button and think about it. So here this is your acid right? So the conjugate base that it generates is, so you can write a resonance structure for this which will look like this.

So now what you see is when you think of the pKa, you are looking at stability of the conjugate base. Right? We had looked at this earlier. I will put that as CB. So what you see is in the case of propane when you have this double bond structure, resonance structure which has a significant contribution, what you see is that due to hyper conjugation interaction the propane derivative is more stable than the ethane which is more stable than the methyl.

So which is why if you compare the acidities 2 nitropropane is more acidic than nitroethane which is more acidic than nitro Methane. Now what is seen as that the α value for the deprotonation was found to be -0.5. So what is that mean? It means that the kinetic for the deprotonation follows the reverse order of the acidity. So in other words what it means is that it is least for the most acidic nitroalkane and why is that? Because in this case what you see is you do not have complete deprotonation.

So when you look at your rate determining step, so this will be protonating some reactants, so let us call it RH^+. So what happens is probably in the transition state you do not have complete deprotonation. So it does not have any substantial amount of double bond character like you saw for the conjugate base. So in this case what you see is it is the inductive effect or the electronic properties that play a larger role. So what you see is, propane which has the 2 methyl groups is more releasing and it destabilizes the transition state as compared to methyl which has only one releasing group.

So which is why the kinetics of protonation is much faster for nitromethane as compared to 2-nitropropane whereas if you compare the acidity it is just the reverse. So shown here is an example where you can get a negative value of α. But typically, as I told you the value is between 0 to 1. So again, coming back towards the end of this class, so so far we have looked at acid base catalysis.

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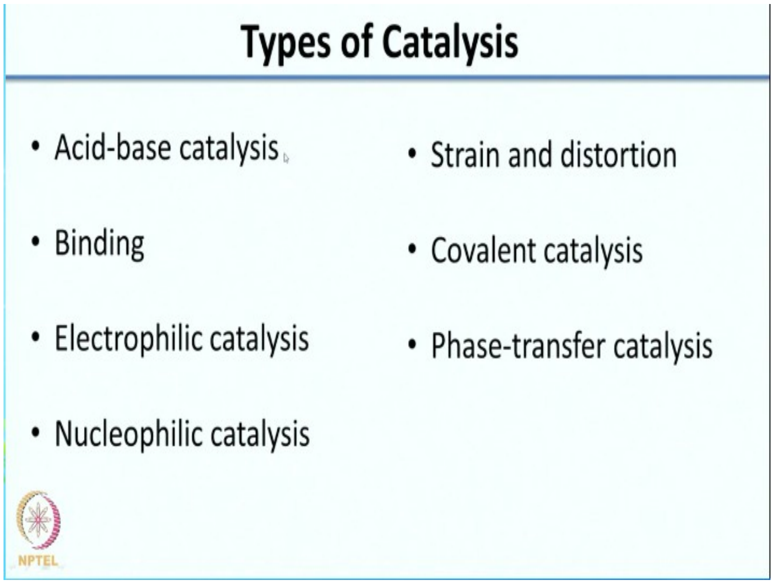

Types of Catalysis

- Acid-base catalysis
- Binding
- Electrophilic catalysis
- Nucleophilic catalysis
- Strain and distortion
- Covalent catalysis
- Phase-transfer catalysis

I spent a lot of time on this because that is what you see most often when you think of catalysis and reaction mechanisms. So over the next 2, 3 classes remaining, what we will do is we will quickly look at the other types of catalysis and towards the end of this week we will wrap up with a summary of whatever we have done so far. So thank you and see you in the next class.