Mechanisms in Organic Chemistry

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Lecture-32
Catalysis: Part A

So welcome back. In the last class we had looked at some other experiments to understand the reaction mechanism. So, one experiment is checking for a common intermediate and here what you do is you take 2 different reactants.

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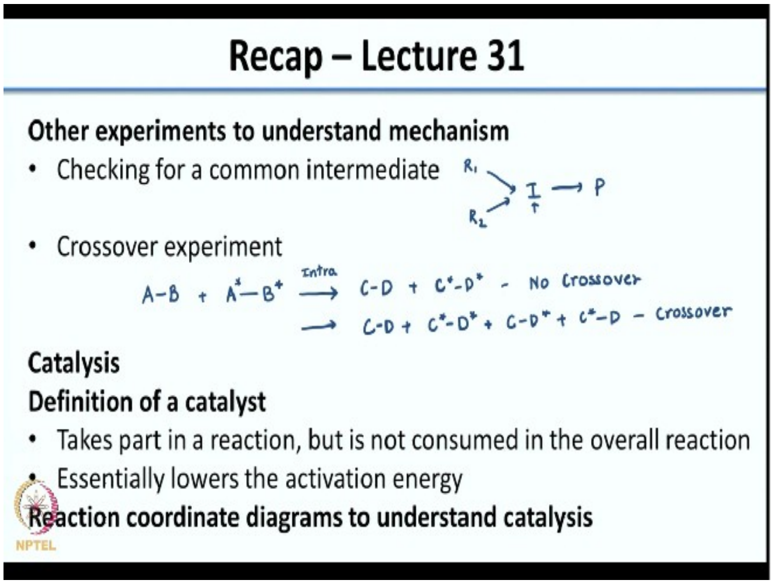

Recap – Lecture 31

Other experiments to understand mechanism

- Checking for a common intermediate

$$R_1 \rightarrow I \leftarrow R_2, \quad I \longrightarrow P$$

- Crossover experiment

$$A{-}B + A^*{-}B^* \xrightarrow{Intra} C{-}D + C^*{-}D^* \text{ - No Crossover}$$
$$\longrightarrow C{-}D + C^*{-}D^* + C{-}D^* + C^*{-}D \text{ – Crossover}$$

Catalysis

Definition of a catalyst

- Takes part in a reaction, but is not consumed in the overall reaction
- Essentially lowers the activation energy

Reaction coordinate diagrams to understand catalysis

And essentially, if both the reactants give the same intermediate I, which will essentially lead to the same product, you can say that I is the intermediate formed in that particular reaction. So, this is a nice trick that is used to determine the nature of the intermediate where you choose slightly different reactants by working out the mechanism. If you assume that both found the same intermediate, you can based on the product form you can say that this is the intermediate that is formed.

And we had looked at 2 examples as to how this method is used to determine the mechanism. The other experiment we had seen is a crossover experiment. This is usually used for rearrangement reactions. And in this what is taken is again you take 2 reactants, but these are taken together. So, in the earlier case, you are doing 2 parallel experiments. Here you are doing the same experiments where you are taking 2 reactants.

And this is used when you need to figure out if the reaction involves fragmentation or it goes via an intramolecular reaction. So, if the reaction is intramolecular, then the products you get would be CD and C* D*. So, there is no crossover. The other situation is where it involves ionization or fragmentation. In that case the products you get would be CD + C* D* as before, but you also see what is called as crossover.

So, you will see CD* and C* D. So, you see crossover. So, we also looked at examples as to how this can be used to determine whether the reaction is going by an intramolecular rearrangement or fragmentation. Then towards the end of the class we started the topic of catalysis. Now, we started with the definition of a catalyst. So, a catalyst is a molecule which takes part in the reaction but is not consumed in the overall reaction.

So, whatever the catalyst does during the reaction, by the end of the reaction you get back the catalyst and the main role of the catalyst is that it lowers the activation energy. So what that means is the reaction goes faster. So this is a term used in English also, when you think of something catalyzing a process, you talk about it making the process faster. So it is the same thing with reactions. A catalyst increases the rate and is regenerated at the end of the reaction.

And we had started looking at reaction coordinate diagrams to understand catalysis. So typically, when you think of catalysis, you think of the catalyst lowering the activation energy.

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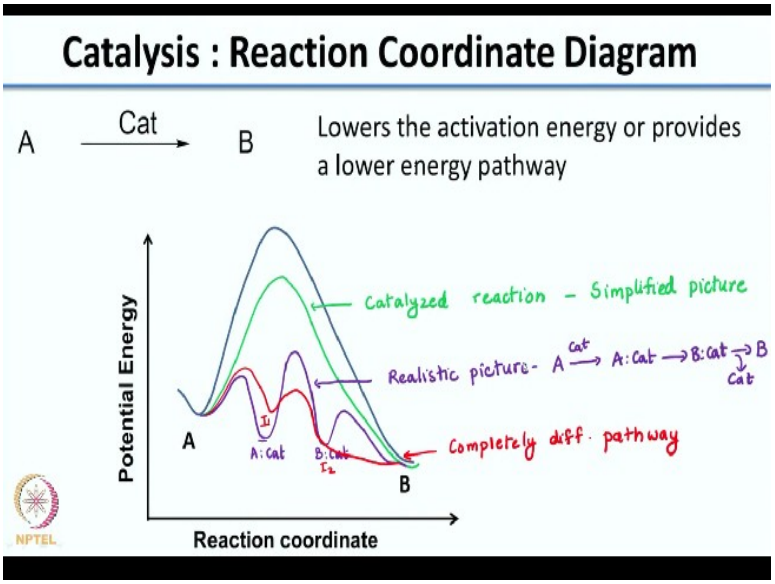

Catalysis : Reaction Coordinate Diagram

$A \xrightarrow{Cat} B$

Lowers the activation energy or provides a lower energy pathway

And we had done this towards the end of the last class and this is the highly simplistic reaction coordinate diagram, that a lot of books will show or you will be tempted to write. But in reality, what is observed is, the catalyst forms are complex with the reactant A to give you a lower energy complex with a lower activation energy. This then reacts to form the product which is again complexed with the catalyst and finally you form the product.

So, this whole pathway is lower in energy compared to the activation energy for uncatalyzed reaction. Another way by which catalysts work is, sometimes a completely different reaction coordinate is followed. So, the pathway is completely different. So, we will look at what is most commonly observed and try to understand this process a little bit more. So, let us see the scenario shown in purple, which I call the realistic picture here.

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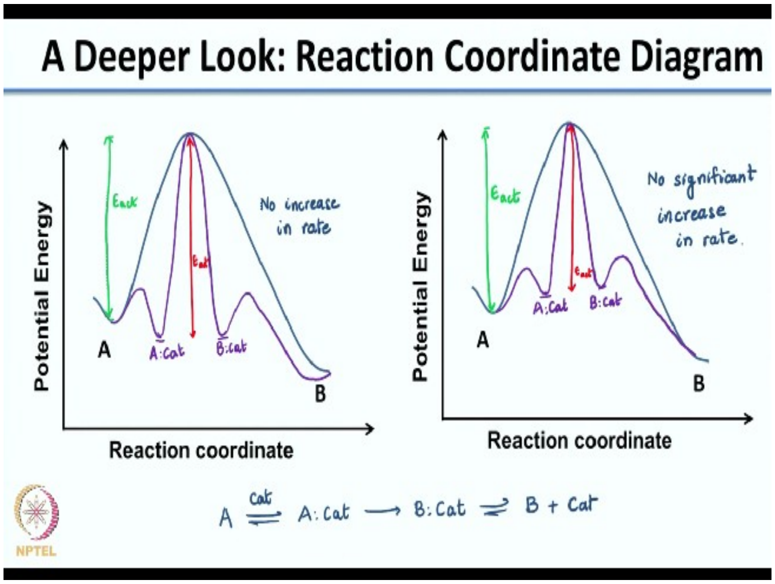

A Deeper Look: Reaction Coordinate Diagram

$A \overset{Cat}{\rightleftharpoons} A{:}Cat \longrightarrow B{:}Cat \rightleftharpoons B + Cat$

So, here essentially what we had shown was that you have A going to A catalyst complex, this will go to B, which will still be attached to the catalyst and finally you have B + catalyst. So, as you can see the catalyst is regenerated in this entire pathway and then the cycle can repeat again. Now, there are certain parameters that you have to think of when you think of this representation of catalysis in terms of energetics.

So, as we said the overall goal that or the overall role played by the catalyst is to lower the activation energy. So, let us look at different scenarios. So, let us say that you have a situation where the catalyst binds quite tightly to the reactant. So when it binds tightly to the reactant what you have is you have a lowering in energy. So, this would be A catalyst complex. Now say it does not have a great affinity to the transition state. It just stabilizes the reactant. Now, what happens?

The activation energy for formation of B will still be very high. Let us call this B and then you have since B is bound, you have the product that is formed. So, this is one scenario. Another scenario is say the catalyst binds very weakly to the reactant. So, again you get the A catalyst complex, then again it does not bind to the transition state. So, let us call this B catalyst and then finally you get your product.

So this is the second scenario. Now what I want you to think about is look at both of these scenarios shown in purple. And tell me will that be a case of catalysis where the activation energy is lowered? So I repeat again, I want you to look at both these diagrams in front of your screen and what I want you to do is tell me whether the activation energy is actually lowered in any of these cases.

So, again you have to look at activation energy for formation of B from A. So you can press the pause button on your screen and try to work this out in your notebook and when you come back, we will see if you are able to understand this. So, let us see if you were able to understand this reaction coordinate diagram. So, now what is happening is, you have the activation energy for the process given by E_{act}.

So, this is the activation energy in the presence of catalyst. I will show it in both the cases. Now, your original activation energy I will show it in a different color. Let us choose green here. So, your original activation energy is given by this energy difference. So, this is your original activation energy. Similarly, in this case this is your. So, if you compare now the green line with the red line, if the red line is smaller than the green line that means it has a lower activation energy.

If the red line is almost same as the green line that means there is no improvement in the reaction rate. So what do you see in the first case? You see that the red line is actually slightly larger than the green line. So what that indicates is that you have no increase in the reaction rate. You would also see a slight decrease because you see that the red line is slightly more than the green line. Here again, when you compare in the second case, the red line and the green line, what you see is the red line is slightly lower than the green line.

But you see no major difference. So you would see no significant increase. So, will these two be good catalysts for a reaction? The answer is no. If the rate is not being increased, then these are not very good catalysts. Now, let us look at 2 different scenarios.

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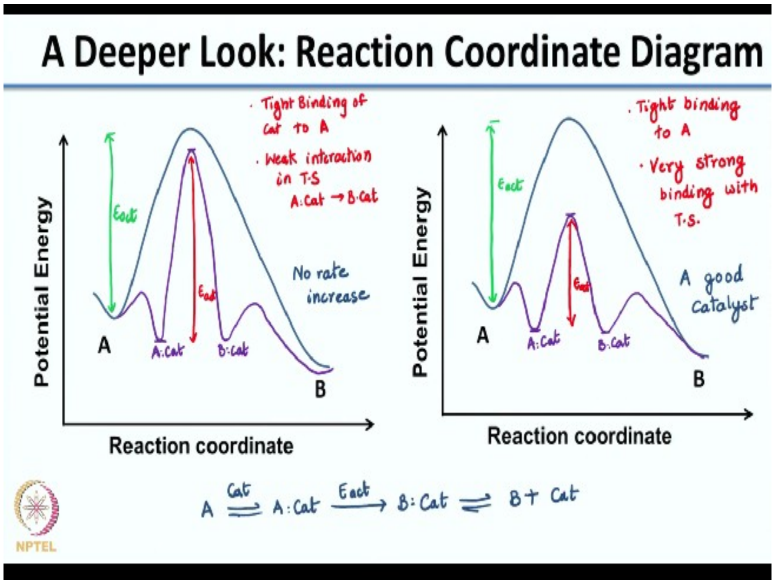

A Deeper Look: Reaction Coordinate Diagram

$$A \overset{Cat}{\rightleftharpoons} A{:}Cat \xrightarrow{E_{act}} B{:}Cat \rightleftharpoons B + Cat$$

So, in this case, again I will write the generic equation below to help you. So, the generic equation is A getting complex with the catalyst. So, you are adding the catalyst and then you have A going to B. Again, B is bound to the catalyst. And then you have dissociation of B and the catalyst. So, this is the process what we are interested in. A catalyst going to B catalyst. Now, I will tell you what the scenario is and I want you to try to draw the reaction coordinate diagram.

So in the previous slide I had drawn it for you. In this slide now you try to draw it yourself. So, here the scenario is that you have, let us say case A. In this case, I will write the conditions here. You have tight binding of catalyst to A. Second condition-weak interaction in transition state going from A cat to B cat. So, again I repeat. Scenario one is you have a tight binding of catalyst to A, but then a weak interaction in the transition state.

So, tight binding means high stabilization, weak interaction means less stabilization. So what I want you to do is I want you to go ahead and draw the reaction coordinate diagram for this scenario. You can press the pause button on your screens and try to draw the reaction coordinate diagram. So, let us see if you have the reaction coordinate diagram. So in this case, a tight binding means a lower energy for the A cat complex.

So it will be weak interaction in the transition state means a slight lowering in energy of the transition state. Not as high as the reactant but you have just a slight lowering of the energy of the transition state. So this is what it will look like and then again you have your B catalyst and then you have your product. So now tell me in this case will the catalyst enhance the rate? So, this is one scenario where we have shown that you have a weak interaction at the transition state and a strong interaction with the reactant.

If you remember all the experiments we had studied so far the kinetic isotope effect, the linear free energy relationships. In all these cases, what was important was the relative stabilization. Even solvent effects. So, now what do you see again, you can go ahead and try drawing the green line and the red line and see what is happening. So, let us go ahead and do that. So, the red line is the catalised activation energy.

So, this is E_{act} and the green line is for the un-catalysed. So now what do you observe when you compare the green line and the red line? Do you see an increase in rate? No, because what is happening is the catalyst is actually stabilizing the reactant a lot more than the transition state. Again, the same thing we had spoken about earlier. Think of a mountain, if you are at 2 positions, if you are at a much lower position, there is a greater height you need to climb.

So it is the same case here, you do not see rate enhancement. So this is again, not a great catalyst. So you see no rate increase. So now I want you to draw the reaction coordinate diagram for this scenario where you have a tight binding. You can even choose the scenario where you have a moderate binding to A and a very strong interaction with the transition state. So now go ahead and draw the reaction coordinate diagram for this.

And you can again press the pause button and also do one more thing. Try to figure out if this will be a good catalyst with the green line, red line that we were doing so far. Alright. So, let us see. So in this case you have a tight binding. So, you have this as the A catalyst complex and you have a very strong binding with the transition state. So, it indicates a large stabilization of the transition state.

So, now when I draw this process, it will look something like this. I have B cat and this finally goes to the product P. So now if you draw the red line and the green line, what do you see? If you draw the red line, this is the energy of activation and if you draw the green line this is for the un-catalysed reaction. So now you see the red line is much, much smaller than the green line. It is very visible. So that means this is a great catalyst.

So this is a very very good catalyst because what it does is, it lowers the activation energy. Or in other words, increases the rate of the reaction. So, the lesson that you learn looking at all of this is that a good catalyst should be designed such that it has a greater affinity for the transition state as compared to the reactant. Alright? So lot of times when people also try to inhibit enzymes. So in our body a lot of problems or diseases that we get, is due to some enzyme catalyzed reaction.

So if you want to make a drug that blocks the activity of the enzyme, it is better to design a drug, which is similar to the transition state of the molecule that is actually interacting with the enzyme. Because if you have the drug, which resembles the transition state more than the reactant, that means the enzyme will bind stronger to it. And it would help in blocking the enzyme because nature is so good that a lot of these reactions catalyzed by nature naturally does what we are talking about in a good catalyst.

The transition state is bound very tightly to the enzyme. So when you have a drug, which competes for the transition state of the regular substrate of the enzyme, that would be an excellent drug. So this gives you an idea of what are the characteristics you need for a catalyst. And doing the systematic process of drawing it actually made you see it visibly that the case where you had the smallest red line was the case where you had the greatest stabilization for the transition state.

So now we will move on and we will look at the different types of catalysts. So, there are several types of catalysis. Some of these could be put within one category or the other. I start with acid base catalysis. Now acid base catalysis is what is most common.

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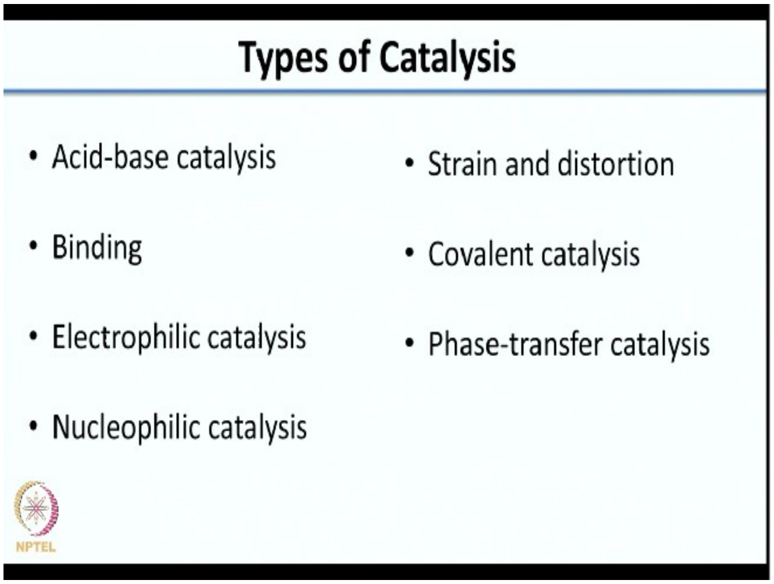

Types of Catalysis

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

You have some acid or base catalyzing reaction. Even so far we looked at several examples of writing reaction mechanism. And we came across acids catalyzing the reaction or bases catalyzing the reaction. The other important form is binding which we saw earlier where you have the catalyst binding with the reactant and this leading to lowering of the activation energy. This is seen a lot in biology and enzyme catalysis.

Then you have electrophilic catalysis where do you have an electrophilic species catalyzing the reaction. You have nucleophilic catalysis. Then you have strain catalyzing reaction sometimes strain is a great catalyst because when the molecule has strained it wants to release that strain and that is a driving force for the reaction. Then you have covalent catalysis and phase transfer catalysis. So, we will start with acid base catalysis

because that is seen very very often, but before we even go to acid base catalysis, I had told you earlier that we will look at understanding pH, pKa and that is what we will be doing first. So, first we need to have a good understanding of what exactly is this acid base equilibrium.

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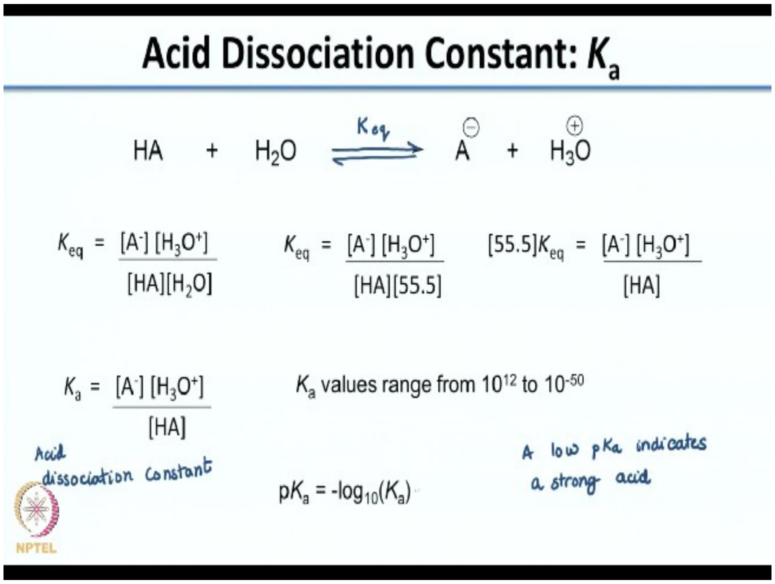

Acid Dissociation Constant: K_a

$$HA + H_2O \overset{K_{eq}}{\rightleftharpoons} \overset{\ominus}{A} + \overset{\oplus}{H_3O}$$

$$K_{eq} = \frac{[A^-][H_3O^+]}{[HA][H_2O]} \qquad K_{eq} = \frac{[A^-][H_3O^+]}{[HA][55.5]} \qquad [55.5]K_{eq} = \frac{[A^-][H_3O^+]}{[HA]}$$

$$K_a = \frac{[A^-][H_3O^+]}{[HA]}$$

Acid dissociation constant

K_a values range from 10^{12} to 10^{-50}

$pK_a = -\log_{10}(K_a)$

A low pKa indicates a strong acid

So, shown here is a generic equation. So when you have HA + B giving A^- + BH^+ a better arrow for this would be the equilibrium arrow. So when you have an equilibria like this, so this is your acid, this is your base, this is your conjugate base. And this is your conjugate acid. So you get the conjugate base by the dissociation of the acid. Now, if you look at the right you have now another acid and another base.

If the conjugate acid gives its proton, you get the base. If the conjugate base grabs a proton, you get the acid. So now you have to understand that this process is in equilibrium. Now a lot of times we consider reactions in water. So, here what is happening is your water acts as a base. So, the water acts as the base and the conjugate acid that you have is H_3O^+. Again better way to represent this would be by the equilibrium sign.

Similarly, water in the presence of a base, in this case, water now acts as an acid and then you have your conjugate base of water which is OH^-. alright? So, this is your acid, in this case, this is your base and this is your conjugate base and this is your conjugate acid. And as I told you earlier this process is also in equilibria. So, this is a better arrow to represent this. Now, whenever you have multiple acids or bases in a media, the relative acidity or basicity is very important.

Because as you see, if you look at this equation on the left side you have an acid, on the right side you have an acid. So, then which acid will give a proton will depend on which is the stronger acid. So, you need to have an understanding of acid strength. So, let us look at the case where we are looking at the dissociation in water. Again, the arrow that you have to use is the equilibrium arrow and the equilibrium constant for this is given by K_{eq}.

So, now K_{eq} would be given by $[A^-]$ $[H_3O^+]$ which is your product divided by [HA] times concentration of water. Now, water is the solvent. So typically water is in large excess, so water is in large excess here. So, a lot of times people do not consider it or in other words, if you consider a very dilute solution of the acid, you can consider the concentration of water to be 55.5 molar. So then this equation reduces to the one shown on your screen.

And further if you take the water concentration to the left, this is what the equation becomes. So it is $[A^-]$ $[H_3O^+]$ / [HA]. And this is called K_a where K_a is called your acid dissociation constant. So K_a is called the acid dissociation constant. So you have varied acids of different strengths. Can you even guess how different these strengths are? So just to give you a feel, the K_a values can range anywhere from 10 to the power 12 to 10 to the power -50.

So, that is a big range. So, when you're trying to compare acidities, it becomes very difficult when you are looking at such large differences. So to make it easier for you to compare another scale is used very often, which is the pKa. So, when you compare pKa of 2 acids, it gives you an indication of the acid strength. So pKa is defined as $–\log_{10}K_a$. So now, pKa is defined as $–\log_{10}K_a$.

So what does that tell you if you were to compare 2 acids, and one is much stronger than the other. what that indicates is that the pK_a of that acid is much lower. So what you need to remember is a low pK_a indicates a strong acid. So especially when you are trying to compare 2 acids you can compare their p K_a s and the one with the lower p K_a would be the stronger acid. And that makes sense because pK_a is nothing but $–\log_{10}K_a$.

So that is quite straightforward and easy to understand. Now let us see what that actually means in terms of an organic reaction.

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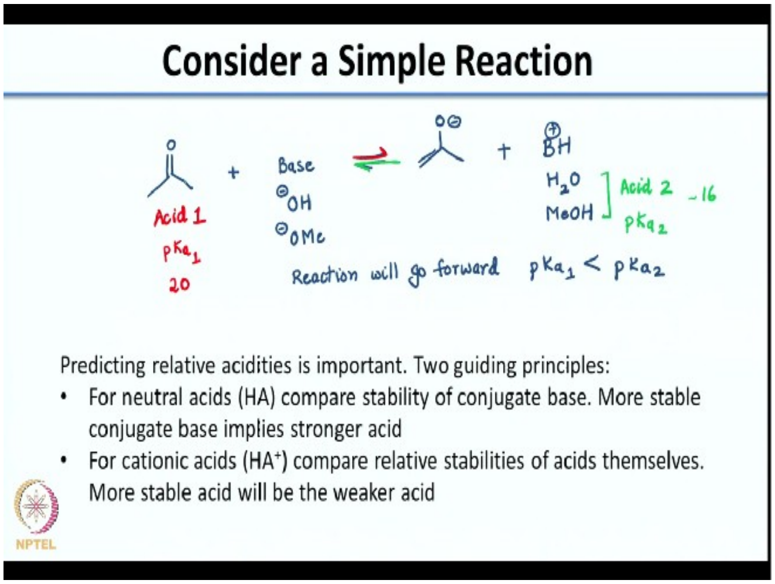

Consider a Simple Reaction

Reaction will go forward $pK_{a_1} < pK_{a_2}$

Predicting relative acidities is important. Two guiding principles:

- For neutral acids (HA) compare stability of conjugate base. More stable conjugate base implies stronger acid
- For cationic acids (HA^+) compare relative stabilities of acids themselves. More stable acid will be the weaker acid

So, let us consider the simple reaction. If I have acetone and I am treating that with a base. So let us say I will first put it as base. So then what do you generate? You generate the enolate + BH^+. Now let us consider a specific example. So let us consider the base as OH^- and then so if the base is OH^- what would be the conjugate acid? It will be water. Let us say another example, the base as OMe^-. methoxide, what will be the conjugate acid?

Now, how do you decide whether this is actually a good base for this reaction? So, I want you to carefully look at this reaction. And if I were to ask you which of these would be a good base, or any of these a good base to ensure deprotonation, how will you go about thinking about it? You can spend some time press the pause button and think carefully. Alright. So, what would be important is, as I said, you have now, 2 acids here, right?

Acetone, I will call it as acid 1 and what is your second acid? These are acid 2. Now, if acid 1 is a strong acid that means there is a greater tendency for it to give away the proton. So, what will that indicate? That will indicate that the reaction will go forward in this direction. Right? Because it likes to give proton. Now let us imagine that acid 2 is the stronger acid. If acid 2 is the stronger acid, then there is a greater chance for it to give a proton.

So that means the reaction will go in the opposite direction. So, if you were to compare both of these, what do you need to compare? You need to compare the pK_a of acid 1. So let us call it pK_a 1, you need to compare that with pK_{a2}. So the action will go forward in which scenario? When pK_{a1} is less than pK_{a2}, remember lower pK_a means stronger acid. So if pK_a of 1 is less than pK_a of 2 you will have the reaction go in the red direction.

Because now red is the stronger acid, but if pK_{a2} is lower than pK_{a1}, then it will go in the green direction because green is the stronger acid. So now understanding relative acidities is very very important for you to understand a reaction. And there are 2 guiding principles that you can use to predict relative acidities. For neutral acids such as this case where you are looking at acetone, we called it HA in the previous slide, you usually compare the stability of the conjugate base.

So you can compare the stability of the enolate versus the OH^- or OMe^- and the second case is, for catatonic acids like HA^+, you compare the relative stability of the acids themselves. So what you would compare is that the more stable acid, so the one HA^+ which is more stable. Obviously if it is stable, it will not like to lose its proton, right? Because it is highly stable. As I said, molecules are just like us. If they are very comfortable, they would not like to react.

So if it is a very stable molecule, it will not want to react. So if HA^+ is more stable, it will be the weaker acid. So now that you have understood this, what I want you to do is, here now I am comparing the pK_as of acetone, water and methanol.

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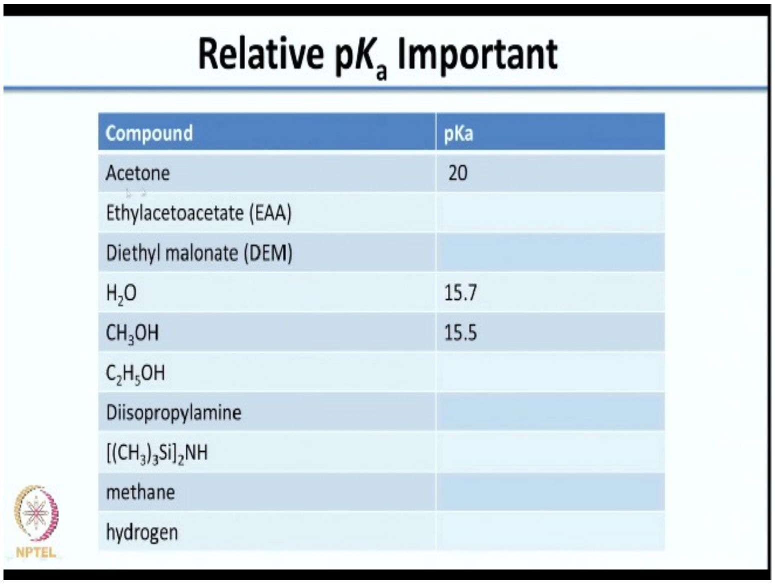

Relative pK_a Important

Compound	pKa
Acetone	20
Ethylacetoacetate (EAA)	
Diethyl malonate (DEM)	
H_2O	15.7
CH_3OH	15.5
C_2H_5OH	
Diisopropylamine	
$[(CH_3)_3Si]_2NH$	
methane	
hydrogen	

So what you see is acetone has a pK_a of 20, whereas water and methanol both have lower pK_as of 15.7 and 15.5. So now if you look at the previous slide that we were looking at, you have the pK_a of acetone, now we have values for this. So, I will put it pK_a of acetone is 20 and this is around would say around 16. So, now when I compare this what it tells you is that, it will have a greater tendency to go in the reverse direction.

So, water and methanol are stronger acids than acetone because the methoxide and the OH^- that you generate is highly solvated. So, you have a highly polarized OH bond here as well, as compared to the OC bond although this is resonance stabilized, but what you have here is this is highly solvated, so you have water to be a better acid as compared to acetone. So then these 2 will not be great bases for you to deprotonate.

So, what would be great bases? In order to understand you would have to get an idea about the pK_a of all these conjugate acids shown. So, these are some compounds shown here on the top which has acidic hydrogen similar to acetone, and here these are some compounds, which are conjugate acids of bases. So what I want you to do before the next class is, I want you to look at this table and try to predict what would be the relative acidity for each of these.

So, I leave you with this problem and we come back in the next lecture, we will look at all of these and also look at factors that affect acidity. So, thank you and see you in the next class.