Mechanisms in Organic Chemistry
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Lecture-33
Catalysis: Part B

Welcome back. In the last class we were looking at catalysis and we were first representing the whole process of catalysis using reaction coordinate diagrams. So shown on your screen is a representative reaction coordinate diagram in purple of a reaction which is being catalyzed.

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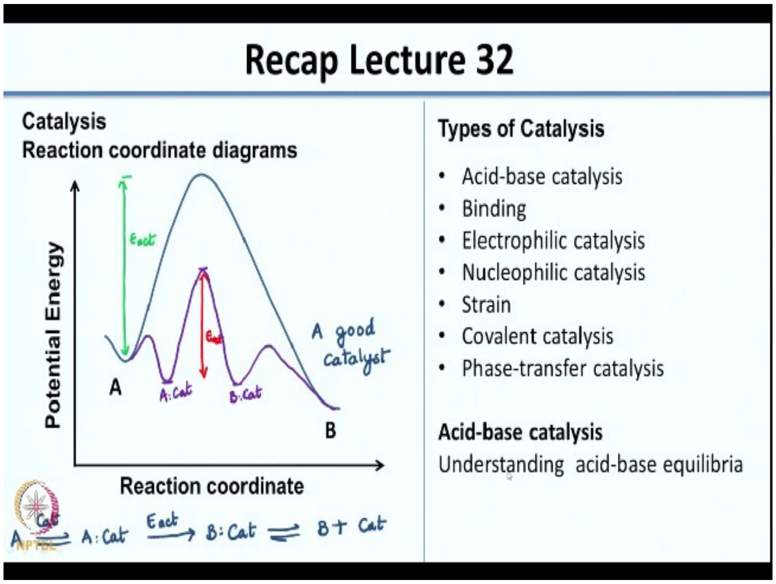

Recap Lecture 32

Catalysis
Reaction coordinate diagrams

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

Types of Catalysis

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

Acid-base catalysis
Understanding acid-base equilibria

And the transformation can be shown as below where you have A binding with the catalyst to give you A cat. This lowers the energy of activation to give you B cat and finally, you have B + catalyst. So, catalysis involves regeneration of the catalyst. The catalyst enhances the rate of the reaction by lowering of the activation energy. So, if you remember from the last class, the red line here is much smaller than the green line, which indicates that activation energy is lowered.

Then we looked at classification of catalysts. So, we looked at different types of catalysis and then we focused solely on acid base catalysis. So, this is what is found very often, which is why I will focus quite a bit on acid base catalysis. So acid base catalysis before we go on to catalysis we need to understand the acid base equilibria. So, we had looked at a simple transformation where you have acetone. So acetone in the presence of a base will give you an enolate.

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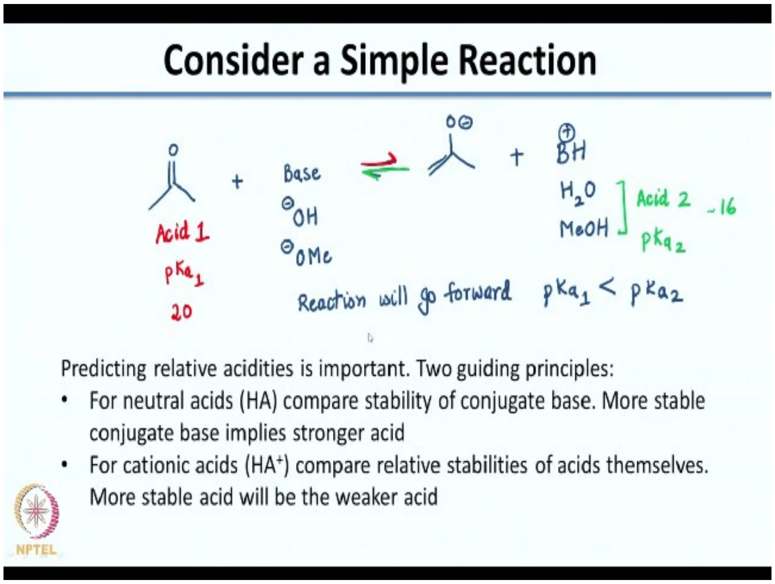

Consider a Simple Reaction

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

And then I had asked you to think about what would be a good base and relative acidities as I told you is important, because you have 2 acids here. One is the acid which is acetone, the other is the conjugate acid of the base, which is BH^+. So both have a tendency to give proton. So if acid 1 or acetone is a better acid, the reaction will go forward towards formation of enolate if the conjugate acid of the base.

So if you use hydroxy, then the conjugate acid is water if you use methoxy the conjugate acid is methanol. So, this is a better acid, then what you would see is the reaction will go towards the left, so you will not get much of your enolate. So it is important to consider related acidities. So if pKa of 1 is lower than pKa of 2 the reaction will go forward and we had compared the pKa of acetone with methanol and water both are 16, acetone has a pKa of 20.

So we know that these are not great basis for you to deprotonate acetone. So there were 2 ground rules I had asked you to remember. So when you have neutral acids, if you are trying to compare their acidities, what you do is you compare the stability of the conjugate base. So in this case you are looking at enolate. The more stable conjugate base implies a stronger acid, if you are looking at cationic acids like HA^+.

In that case when you compare the relative stability of the acids themselves, what you would see is the more stable cation would be a weaker acid because obviously it would not want to give away its protons. So before leaving, I had asked you to look at this table and you already have the pKa values given of acetone, water and methanol.

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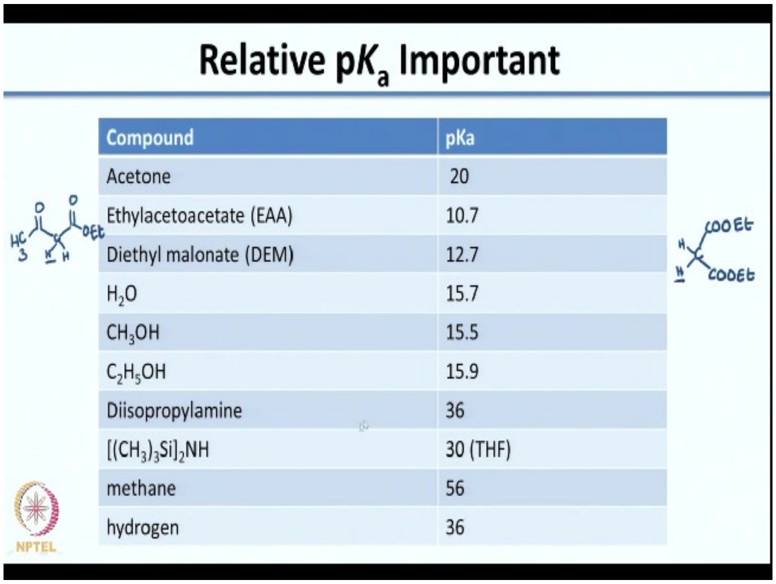

Relative pK_a Important

Compound	pKa
Acetone	20
Ethylacetoacetate (EAA)	10.7
Diethyl malonate (DEM)	12.7
H_2O	15.7
CH_3OH	15.5
C_2H_5OH	15.9
Diisopropylamine	36
$[(CH_3)_3Si]_2NH$	30 (THF)
methane	56
hydrogen	36

Now based on the pKa of acetone, if you write the structure of ethylacetoacetate and diethyl malonate, what do you expect the pKas is to be? Will they be lower than acetone or will they be higher? Also between these 2 which would be more acidic? So, I want you to write the structures of both of these and compare the pKas of the hydrogen which is α to the carbonyl group. So, if you do not remember the structure of ethylacetoacetate, ethylacetoacetate is you have CH_3C double bond OCH_2. So, this is the acidic proton that we are talking about.

So this is ethylacetoacetate and diethyl malonate the structure is here. Again, these are the protons we are looking at. So now if you compare the acidity of these 2 protons, in one case you have a proton next to alpha to two ester groups. In one case, it is alpha to an ester and alpha to a ketone. So this would be more acidic as compared to this and a if you see compared to acetone. Now in acetone, you have only one C = O next to the acidic hydrogen.

Whereas in this case you have two C = Os. So both these compounds would be more acidic than acetone, which means a lower pKa and among the 2 ethylacetoacetate would be a better acid. So it has a pKa of 10.7 as compared to diethyl malonate which has a pKa of 12.7. So these are commonly used compounds which have an acidic hydrogen, acidic alpha hydrogen, which is used in a lot of organic transformation.

So I would suggest you have some idea or maybe even memorize these pKas, because it would be very useful for you when you try to understand reactions involving these compounds. Now, let us look at the conjugate acids of the bases. So if you have ethoxide as the base, the conjugate acid would be ethanol. So now when you compare methanol with ethanol, methanol has a pKa of 15.5.

So what do you think would be the pKa of ethanol, will it be more than methanol, or less than methanol? So hopefully, I have gotten the answer correct. The pKa will be more because ethanol is less acidic than methanol. It has an extra releasing group, which is the CH_3CH_2OH as compared to CH_3. And the other thing is once you generate the ethoxide, the stabilization due to solvation is less as compared to the methoxide, which would be solvated more.

Ethoxide is solvated less because of the bulk. So if you had isopropoxide, that would have a further higher pKa, because solvation of the ion would be worse. Now, let us look at these two diisopropylamine and then you have another amine, but here you have two silyl groups next to the amine. So when you look at the pKas of these, these would be significantly higher than that of ethanol or methanol, right? Because you are generating the N^- ion here, and you have releasing groups on both sides.

So their pKas as you can see is 36 and 30. Then if you compare methane, so methane, what you would see is the conjugate base is CH_3^-. So this is not as stable as compared to methoxide. So what you see is, it has a very high pKa of 56. And hydrogen, if you compare with methane is slightly better, it has a lower pKa of 36. So it is good for you to have a feel of all this. So, based on this what do you know is any of these compounds would be very good bases to deprotonate.

So these are the conjugate acids, the BH^+ which we looked at the previous slide. So if you use a base such as LDA, we have seen that before, it is a very good base, because it is conjugate acid has a very high pKa. So the reaction will not go back towards acetone. So now are there some principles that you need to know in order to predict the relative acidities of 2 molecules? So there are several factors and usually what you see is a contribution of all of these.

It is not only one factor which predominates. So, let us look at what some of these factors are. So, this is the generic equation we had seen before. So you have an acid, a base, you generate the conjugate base of the acid and conjugate acid of the base. Now one thing which really has an effect on the pH or pKa is the reaction medium. So most organic reactions that you carry out you carry out in a solvent.

So the solvent we have seen earlier also plays a very very important role. But here, we are looking at specifically the role of the solvent on pKa. So if you compare a neutral acid, so when you compare the pKa of a neutral acid like acetic acid in different solvents, you would see that the pKa increases as you go from water to DMF.

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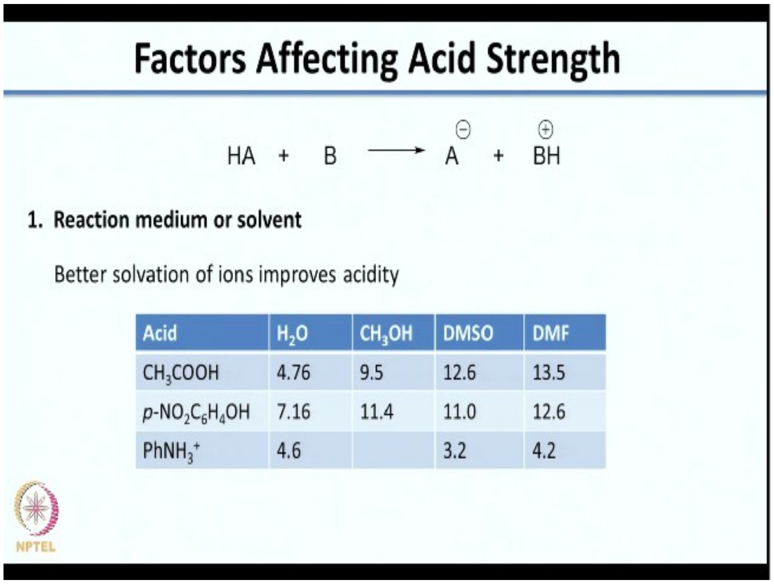

Factors Affecting Acid Strength

$$HA + B \longrightarrow \overset{\ominus}{A} + \overset{\oplus}{BH}$$

1. **Reaction medium or solvent**

   Better solvation of ions improves acidity

Acid	H_2O	CH_3OH	DMSO	DMF
CH_3COOH	4.76	9.5	12.6	13.5
p-$NO_2C_6H_4OH$	7.16	11.4	11.0	12.6
$PhNH_3^+$	4.6		3.2	4.2

So what is happening here? Remember the 2 guiding principles I told do. So for a neutral acid when you compare the acid strength, it is important to look at stability of the conjugate base. Now what happens is if you have a solvent like water, which is very good in solvating your conjugate base, which is an anion, you would see that the acidity is improved. So what you see is in water acetic acid has a pKa of 4.76

because the conjugate base is solvated very well. But as you go to methanol, the pKa increases, because now salvation is less. And then as you go to DMSO and DMF, you see that there is a increase in pKa. Similarly, with para nitrophenol, you would see that to start with you have a pKa in water at around 7.16. But then as you vary the solvent from water to methanol, DMSO and DMF, the pKa increases.

Now we look at the second example here. Here what you see is you have a protonated acid. So when I told you the guiding principle, this comes in the second category where you have a cationic acid. So here what you see is in water the pKa is 4.6. But when you go to DMSO and DMF, the pKa decreases. So why is this the case? Now I want you to think before I tell you the answer. What happens when you change the solvent from water to DMSO or DMF?

So hopefully, you have understood and gotten the answer correct. What happens is in water now your acid which is charged is more solvated or more stabilized. So what happens is, when you go from water to DMSO, DMSO does not solvate the acid as well. So it is easier for the acid to give away the proton. So here what you see is you see a reverse trend, because the solvent stabilizes the acid more than the conjugate base. So hopefully you have understood how the reaction medium or solvent has an effect on pKa.

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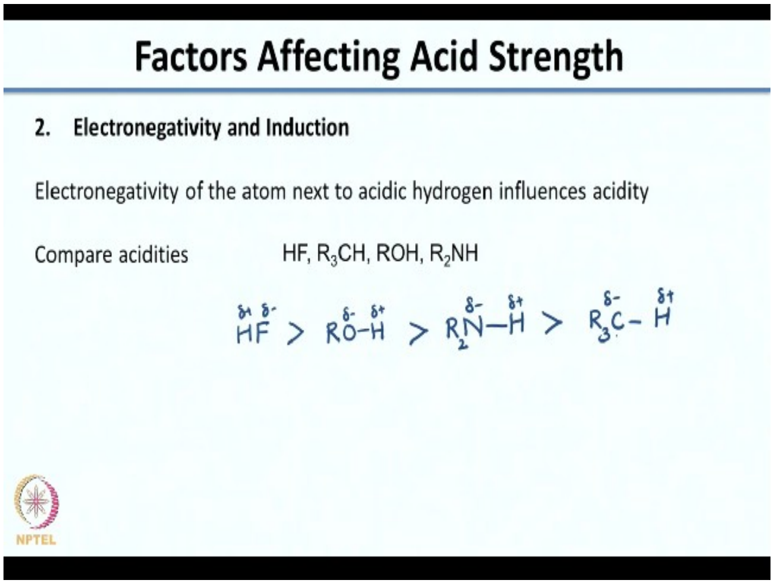

Factors Affecting Acid Strength

2. Electronegativity and Induction

Electronegativity of the atom next to acidic hydrogen influences acidity

Compare acidities HF, R_3CH, ROH, R_2NH

$\overset{\delta+}{H}\overset{\delta-}{F} > R\overset{\delta-}{O}-\overset{\delta+}{H} > R_2\overset{\delta-}{N}-\overset{\delta+}{H} > R_3\overset{\delta-}{C}-\overset{\delta+}{H}$

The other factor is the electronegativity and what is called as the inductive effect. So if you remember the very first class with that we had for this course, we had looked at inductive effect.

So now we are essentially looking at the same concept towards the end of the course. But in a very different context. We are looking at inductive effect in the context of acidity. So if you have HA, where A is more electronegative,

that is a has a greater tendency to pull electrons towards itself, then it would be easier for it to dissociate because the conjugate base that you get A^- would be stronger, right? So the more electronegative atom attached to the hydrogen would be very good to improve its acidity. So that is one of the factors as I told you. So now I have shown you on your screen 4 different acids. So based on this concept, what I would like you to do is I would like you to compare their acidities.

So which would be most acidic and which would be least acidic? So if you were to compare the acidities you will see HF would be most acidic greater than that would be ROH, greater than that would be R_2NH and greater than that would be R_3CH and you can easily explain this in terms of the electronegativity. So as the electronegativity increases you see in this case across a group, the acidity increases. So this is quite straightforward and something I am sure you must have studied earlier as well.

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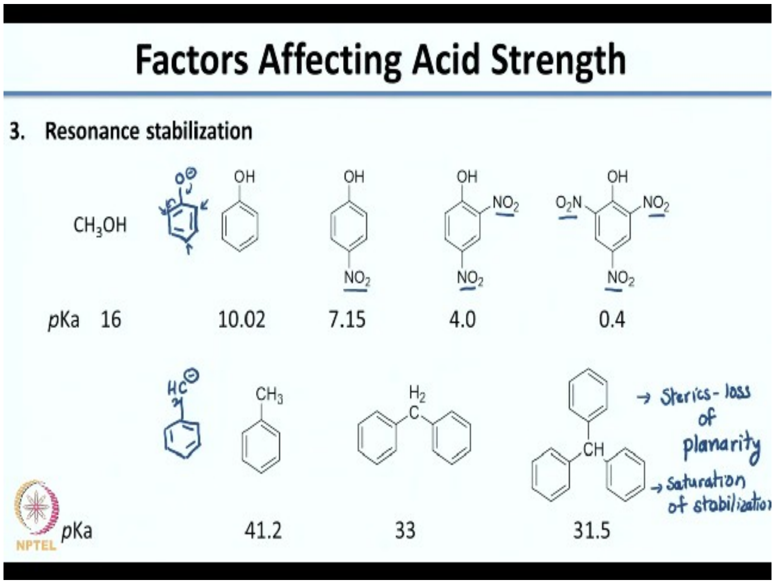

Factors Affecting Acid Strength

3. Resonance stabilization

CH_3OH

pKa 16 10.02 7.15 4.0 0.4

pKa 41.2 33 31.5

→ Sterics - loss of planarity

→ Saturation of stabilizatio

The other thing is resonance stabilization. So if I compare methanol with phenol, now we have seen this when we were looking at linear free energy relationships. The phenoxide ion is stabilized by resonance. So you can write resonance structures of this. You can write multiple resonance structures where the negative charge would be either at the oxygen or it would be at the 2 position, or the 4 position or the 6 position. Ok?

So you can have the negative charge delocalized, which is why it is stable. Now what happens is, as we are looking at stability of the conjugate base, if I put electron withdrawing groups at these 3 position, so in this case, I have one electron withdrawing group at the 4 position. In this case I have two electron withdrawing groups. And in this case, I have 3 electron withdrawing groups. So what do you think will happen to the pKa, as I go from methanol to picric acid?

This is called picric acid, which is the 2,4,6-trinitrophenol. So what do you think will happen to the pKa? Think about it, I will wait for a minute or you can press the pause button. So now what you would see is as you increase the number of electron withdrawing groups, there is a major effect on the pKa. So we start with a pKa of 16 for methanol. And already when you put an aromatic ring instead of methyl, you see a drop in pKa to 10.

Then when you start putting electron withdrawing groups, you have a further drop. So you go to 7.15, then 4, and when you have 3 nitro groups, it goes as low as 0.4. So what you see here is a great decrease in pKa because you are adding electron withdrawing groups. So this is due to the resonance stabilization. Now we will take another case here. So here you have toluene. So imagine you are thinking of the deprotonation of toluene, the CH bond, as you increase the aromatic rings here.

So here the conjugate base that you are generating will be. So this again is stabilized by resonance. Now, what you see is, you would assume that as you increase the number of aromatic units, you would see a decrease in pKa. What you see is, you do see a decrease in pKa, so for toluene, it is 41.2. But when you put 1 aromatic ring, it drops down to 33, which would make sense because now you have 2 aromatic groups, which can be involved in stabilization due to resonance.

But you put the third aromatic unit, you see that the decrease is not much. Now again, I will ask you a question. Why do you think this decrease is not much? So think about it, there are 2 reasons you can think about it, press the pause button. So one, one reason is sterics. So what happens here is due to sterics there is a loss of planarity. So what happens is, when you have 3 aromatic rings, there is it is almost like a fan that you have here you have a slight loss of planarity.

And because of this resonance essentially involves conjugation or delocalization. And in order for delocalization to happen you need to have a planar structure. So, if planarity is lost delocalization is reduced, which is why you do not see as much as an effect that you saw in the earlier case of picric acid. Now the second reason is, there is what is called as a saturation of stabilization due to delocalization.

Now, in the case of picric acid there were 3 positions where you had negative charge which could be stabilized by electron withdrawing groups. But in this case the additional stabilization that you get by adding aromatic units is not significant. Which is why adding 3 aromatic groups is not as useful as just having 2 in terms of improving acidity. So, this is again, this shows you that there are multiple factors that you need to consider when you think of pKa.

So in this case one is the sterics and the second is what is called as saturation of stabilization. So, so far we have looked at solvent effects, we have looked at inductive effects and we have looked at stabilization due to resonance. Now, let us look at some more effects. One is the bond strength. So, so as I told you earlier within a row as the electronegativity increases the acid strength increases.

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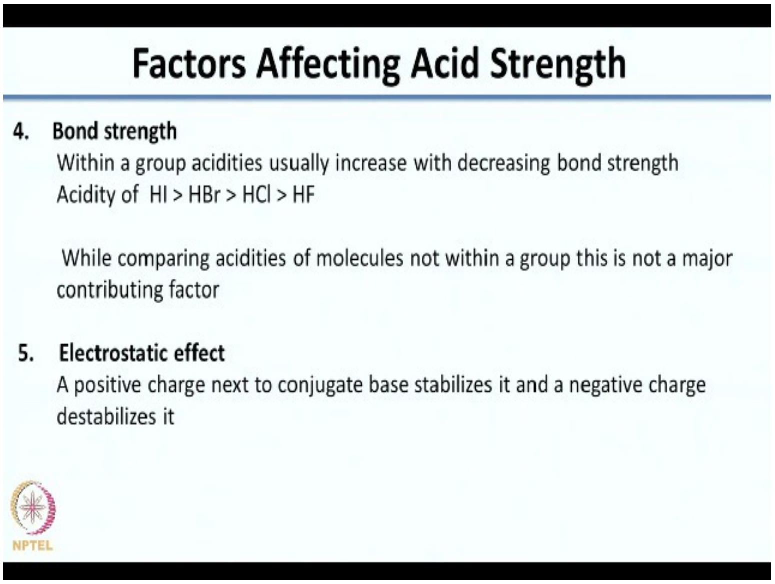

Factors Affecting Acid Strength

4. **Bond strength**
   Within a group acidities usually increase with decreasing bond strength
   Acidity of HI > HBr > HCl > HF

   While comparing acidities of molecules not within a group this is not a major contributing factor

5. **Electrostatic effect**
   A positive charge next to conjugate base stabilizes it and a negative charge destabilizes it

But what happens within a group? So let us say we compare the acidity of HI, HBr, HCl and HF. Now, fluorine is the most electronegative, but what you see is that the most acidic is HI and that is because the bond strength is lower for HI as compared to HF. So it is very easy to break the HI bond as compared to the HF bond. So within a group, you can use the bond strength as a criteria.

But when you compare acidities of molecules across different groups, it is not very useful to use this criteria because a lot of other factors will play a more dominant role. The other thing is, when you think of bond strength you are typically thinking of a homolytic bond cleavage, whereas in this case what you have is a heterolytic bond cleavage. So, it does give you some idea about predicting acidities within a group.

But as I said, you cannot compare it across different acids which are atoms across different groups. The other is what is called as an electrostatic effect. Electrostatic as the name suggests we are talking about charges. So you can have the case where you have a positive charge next to the conjugate base. So a conjugate base is negatively charged. Now if you have a positively charged species next to your conjugate base obviously it will stabilize your conjugate base due to electrostatic interactions.

And if you have a negative charge, it will destabilize it due to repulsion. So let us see a classic example for that, I will come back to acetic acid.

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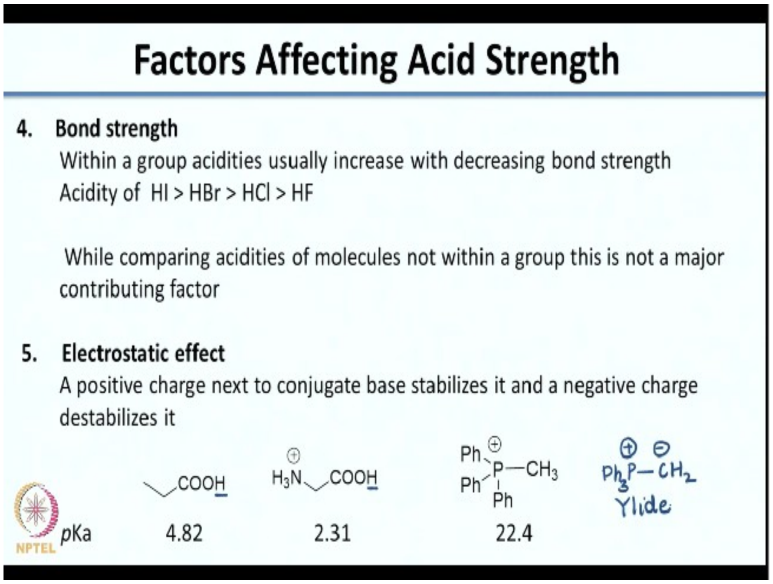

Factors Affecting Acid Strength

4. **Bond strength**
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5. **Electrostatic effect**
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pKa 4.82 2.31 22.4

Now instead of acetic acid we have propanoic acid here. So the pKa would be quite close to acetic acid slightly higher. Now shown here is glycine, glycine is an amino acid. So if I asked you to compare the pKa of these 2 hydrogens, so we are comparing the pKa of carboxylic acid from propanoic acid and the carboxylic acid from glycine, which do you think would be more acidic? So let us see if you have the answer correct.

Between these 2, glycine would be more acidic, because it has a positively charged NH_3^+ right next to it. So if you compare the pKas of these two propanoic acid has a pKa of 4.82. Whereas glycine has a lower pKa of 2.31 and you see this a lot in biology, all the amino acids have a structure like this. And their pKas are in the range of between 2 to 2.5. And what you see is in our body at neutral pH, what you would see is these would have a zwitterionic form. Another example I have here is where you have positively charged phosphorous right next to the methyl group.

And where have you seen this? You have probably seen this when you have studied Wittig reaction. Having this positive charge next to methyl reduces the pKa of that methyl and it is easy to generate this species which you know as you are ylide which is used in Wittig reactions. So shown here is another example where the electrostatic effect is used a lot organic synthesis to stabilize this particular ylide structure.

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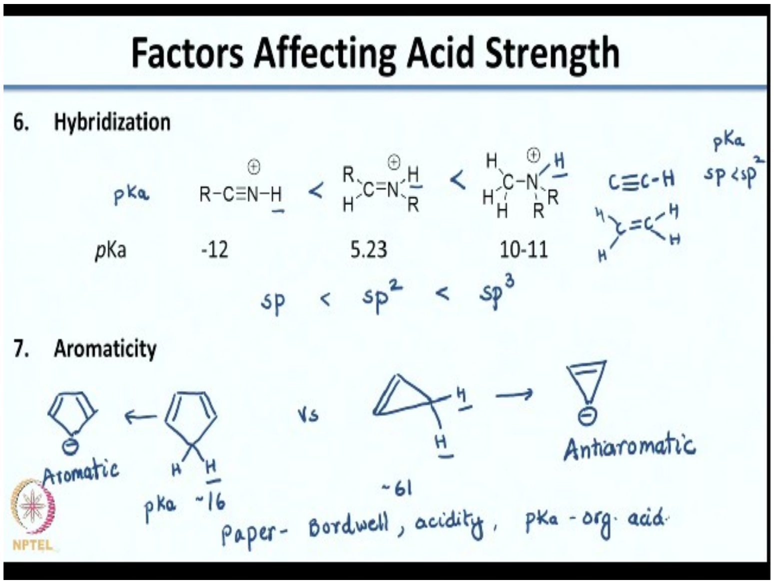

Factors Affecting Acid Strength

6. Hybridization

pKa	-12	5.23	10-11

sp < sp² < sp³

7. Aromaticity

So now we will go ahead and look at two other factors. One is hybridization. So Shown here are 3 species. And what I want you to do is I want you to compare the pKas of these hydrogens, hydrogen missing here. So I want you to compare the pKas of these three hydrogens. You can press the pause button. Alright. So let us see if you have gotten this correct. Out of these the most acidic is this species.

So if I were to compare the pKa, the pKa of this is lower than and these are the values. It is as low as -12. So, you have the pKa here as –12 compared to 5.23 to 10 to 11 and what is the major difference between these 3 species? It is the hybridization because if you see the electronegativity of the atoms is very similar here. What you see is you have an sp hybrid hybridization here as compared to an sp^2 here as compared to an sp^3.

So as the percentage s character increases, the acidity of the species increases. So what you see is, if you this will also work if you were to compare alkyne versus alkene versus alkane. So you will see the same trend where the pKa of sp would be less than a sp^2 alright? We are talking about pKas . So, sp hybridization leads to greater acidity. And the last factor that we are going to look at is aromaticity and this is something which you would have probably studied in 12th standard. So, if you were to compare these 2 species, so we are looking at acidity of this hydrogen versus acidity of this hydrogen. So, what you see is the pKa of this molecule cyclopentadiene is 16 whereas, the pKa of this is around 61. So, you see a major difference in pKa. This is quite acidic as compared to the cyclopropene and the reason being that, in this case the conjugate base that you generate is aromatic.

So you have added stabilization due to aromaticity, whereas, in this case, the conjugate base that you generate is antiaromatic. So, which makes it highly unstable. So, these are some of the factors that affect acid strength. So, if you go back and look at the table that I showed you earlier, you can try to figure out each of these factors playing a role in the pKa that is shown here. There are also several papers where people look at relative a pKas of organic acids.

And this is very very useful when you are trying to do organic reactions. You can specifically look up this paper. So, you can look up this paper by Bordwell, which compares the pKas of organic acids. This gives you an extensive list of pKas of several organic acids in water and DMSO. Mainly you would see that the pKas are measured in the DMSO. So with this we will end today's lecture.

In the next lecture, we will look at acid base catalysis and now that we have a general idea of how the acid base equilibria works, I think it will be easier for us to figure out how acids or bases catalyze reactions. Thank you and see you in the next lecture.