Indian Institute of Science Education and Research, Pune
National Programme on Technology on Technology Enhanced Learning
Medicinal Chemistry
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Tutorial – 01
Acidity, Basicity and Related concepts

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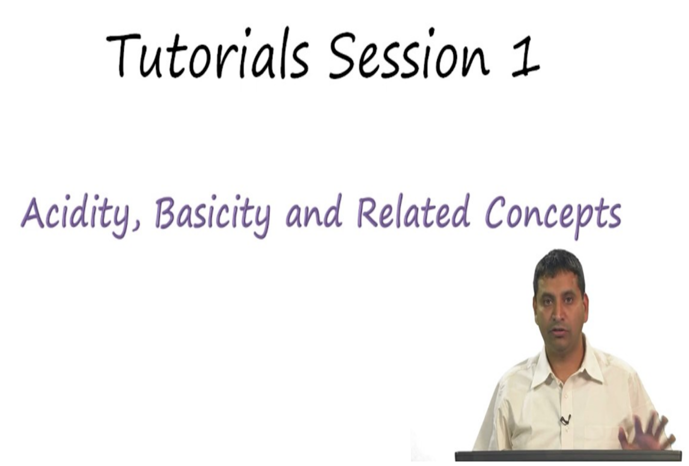

Tutorials Session 1

Acidity, Basicity and Related Concepts

Welcome to the tutorial session 1. So here we will look at the basics of acidity, basicity and related concepts so all though organic chemistry is a prerequisite for this course I thought it is a good idea for people to to go over some of the basic concepts so that we can all pretty much be on the same page when the advanced concepts are taught. So acidity and basicity these are very fundamental properties of a molecule.

And they help us understand number of aspects about the structure and it also gives us an idea about how changing the functional group on the molecule can have a major impact on a property so before we go into this concepts.

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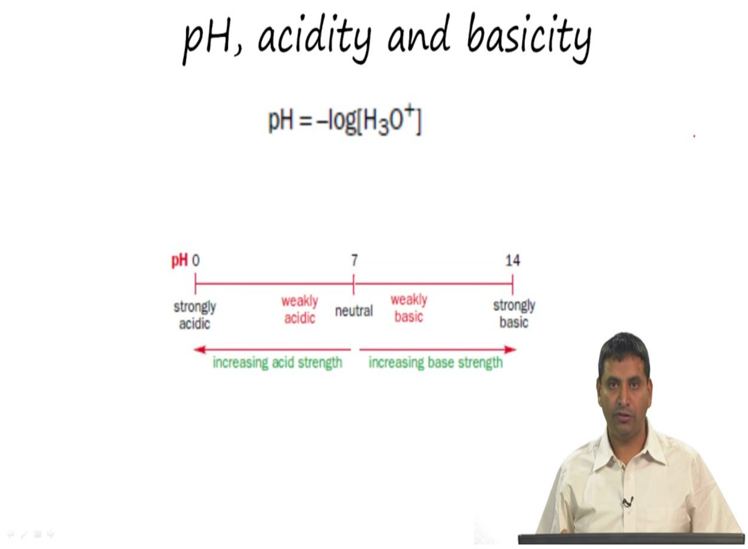

pH, acidity and basicity

$pH = -\log[H_3O^+]$

pH 0 — 7 — 14

strongly acidic | weakly acidic | neutral | weakly basic | strongly basic

← increasing acid strength | increasing base strength →

Let's first define pH so pH is define as negative log of concentration of H_3O Plus and this is definition that we have we have encountered in 8th or 9th standard perhaps and just to go this so ph 7 is considered neutral so you have its neither acidic nor basic and pH 14 is strongly basic while pH 0 is strongly acidic. Okay so as we proceed from 7.

And go towards left that is go to smaller values the pH of the solution becomes more and more acidic and similarly When we start from 7 and go up to 14 the solution becomes more and more basic so keep in mind that this is a scale so that to lower bound and upper bound of the scale is 0 and 40 so if you and this is a obviously operational in water because you're looking at hydronium ion right.

So therefore pH because since life as we know it exists in water so pH becomes an important parameter for us to understand what happens inside a cell so in certain compartments inside the cell the pH can vary it can become quite acidic and in certain compartments it can become a little bit basic so pH plays a very important role in many aspects of functioning of a cell so with that background.

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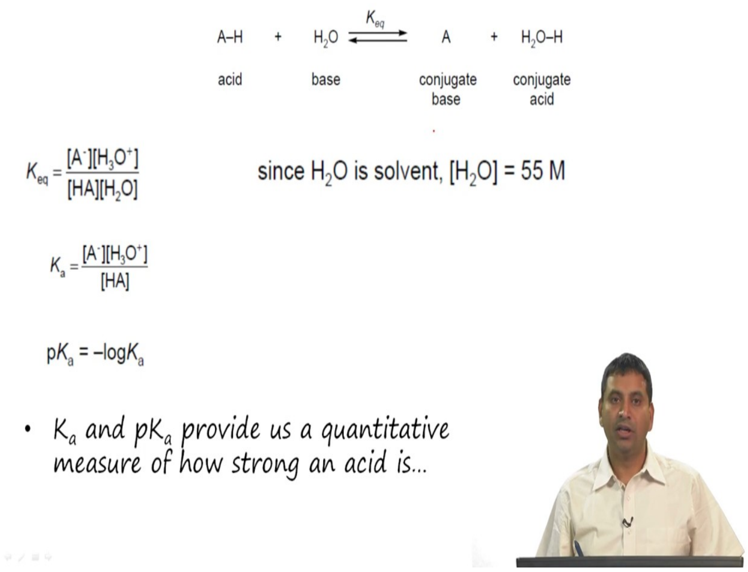

$$\begin{array}{ccccccc} \text{A–H} & + & H_2O & \underset{}{\overset{K_{eq}}{\rightleftharpoons}} & \text{A} & + & H_2O\text{–H} \\ \text{acid} & & \text{base} & & \text{conjugate base} & & \text{conjugate acid} \end{array}$$

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

since H_2O is solvent, $[H_2O] = 55$ M

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

$$pK_a = -\log K_a$$

- K_a and pK_a provide us a quantitative measure of how strong an acid is...

Now let's look at what pKa is. Okay so if I take an acid HA or AH and if I dissolved in water we can write an equilibrium constant such as this where conjugate base is A minus and the conjugate acid is H_3O plus and now if I have to write an equilibrium constant the equilibrium constant would be A minus multiplied by concentration of H_3O plus divided by concentration of HA times H_2O again this is pretty much stuff that we have learnt in a previously in high school.

So since the water as a solvent and the concentration of water in aqueous media is 55 molar and it is we can assume that it is a constant and so we can remove one of these terms which is this concentration of H_2O because whatever we do we multiply it by a very large number so we defined the storm called as KA which is nothing but the acidity equilibrium constant which is nothing.

But concentration of the A minus which is the concentration of the conjugate base multiplied by the concentration of the conjugate acid divided by the concentration of acid so what we deal with here is typically very dilute solutions of acid and what we determine here is if he take a very dilute solution of acid then one can measure what is known as the equilibrium constant and define it as Ka.

pka is defined as negative log of the equilibrium constant Ka so both these numbers Ka and pKa providers a quantitative measure of how strong and acid is.

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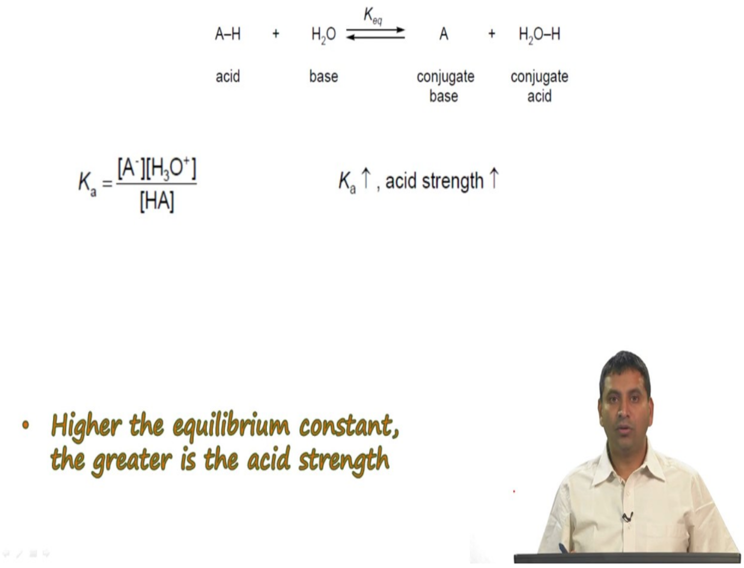
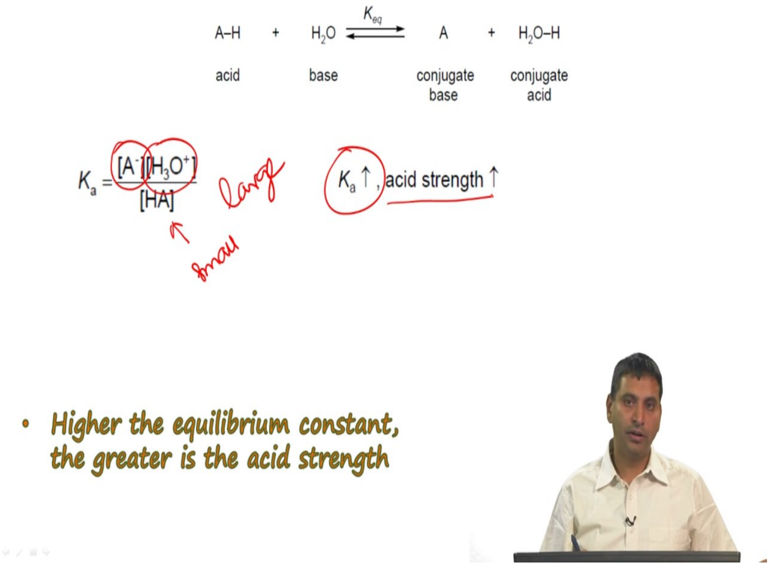


$$\underset{\text{acid}}{\text{A–H}} + \underset{\text{base}}{H_2O} \xrightleftharpoons{K_{eq}} \underset{\text{conjugate base}}{\text{A}} + \underset{\text{conjugate acid}}{H_2O\text{–H}}$$

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

$K_a \uparrow$, acid strength $\uparrow$

- Higher the equilibrium constant, the greater is the acid strength



$$\underset{\text{acid}}{\text{A–H}} + \underset{\text{base}}{H_2O} \xrightleftharpoons{K_{eq}} \underset{\text{conjugate base}}{\text{A}} + \underset{\text{conjugate acid}}{H_2O\text{–H}}$$

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

large

small

$K_a \uparrow$, acid strength $\uparrow$

- Higher the equilibrium constant, the greater is the acid strength

So if I have to look at how how an acid how strong and acid is then one would argue that if the concentration of a minus multiplied by concentration of H_3O Plus is a large number right. Which necessarily mean that concentration of HA is small then together the K value would go up okay. So therefore when the K value is pretty high the acid strength is quite high okay. So higher the equilibrium constant the greater the acid strength.

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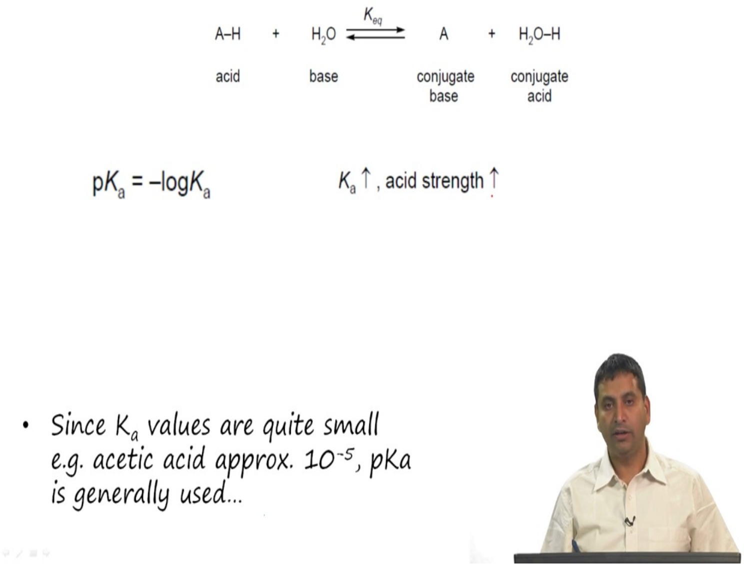

$$A{-}H + H_2O \underset{}{\xrightarrow{K_{eq}}} A + H_2O{-}H$$

acid, base, conjugate base, conjugate acid

$pK_a = -\log K_a$

K_a ↑, acid strength ↑

- Since K_a values are quite small e.g. acetic acid approx. 10^{-5}, pKa is generally used...

So similarly we look at pKa and because because Ka value is sometimes quiet small for example acetic acid value is around 10 power minus 5 and its difficult for us to think of differences between 10 power minus 5 and 10 power minus 4.8 and 10 power minus 4.7 and so on what we refer to is usually pKa. So pKa because it's a negative log value it makes makes it into a smaller number that we can easily understand.

So the pKa a scale so a unit difference in pKa means tenfold difference in the equilibrium constant.

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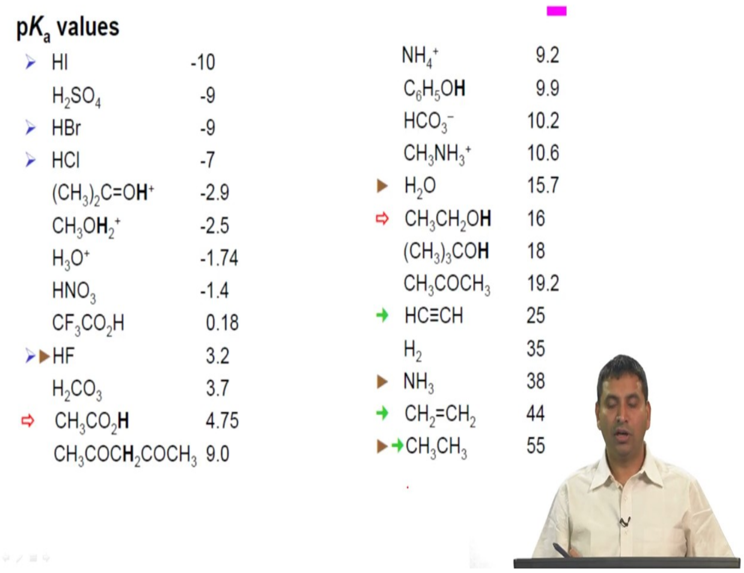

pK_a values

HI	-10	NH_4^+	9.2
H_2SO_4	-9	C_6H_5OH	9.9
HBr	-9	HCO_3^-	10.2
HCl	-7	$CH_3NH_3^+$	10.6
$(CH_3)_2C{=}OH^+$	-2.9	H_2O	15.7
$CH_3OH_2^+$	-2.5	CH_3CH_2OH	16
H_3O^+	-1.74	$(CH_3)_3COH$	18
HNO_3	-1.4	CH_3COCH_3	19.2
CF_3CO_2H	0.18	$HC{\equiv}CH$	25
HF	3.2	H_2	35
H_2CO_3	3.7	NH_3	38
CH_3CO_2H	4.75	$CH_2{=}CH_2$	44
$CH_3COCH_2COCH_3$	9.0	CH_3CH_3	55

So again we shall summarise some of the pKa values that we have encountered so let's start with something like HI which is a very strong acid the pKa value is minus 10 okay and let's go to a very weak acid such as ethane where the pKa values 55 okay. So this number is quite observed that is the concentration of CH_3 CH_3 minus in aqueous media is 10 power minus 55 which is essentially not measurable.

But it is an estimated pKa value so if you look at some other reasonable molecules such as Acetic Acid which we look that earlier the pKa values 4.75 so we shall come back to the pKa table once again later but this is a experimentally measurable quantity and therefore pKa value serve as a very important guide to understand the properties of a molecule.

And how it changing a particular functional group can have a profound impact on a property such as acidity or basicity or sometimes it may have no impact so both of these are important for us to understand because when we want to understand let's say how a drug functions or how a drug distribute itself one of the properties that becomes important is the level of ionisation which will depend on pKa okay.

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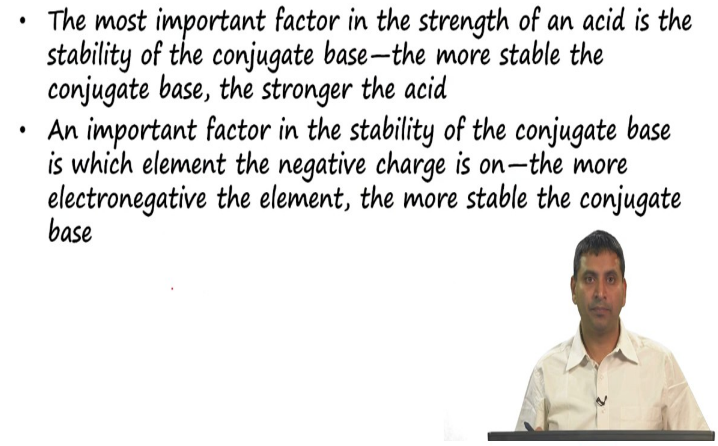
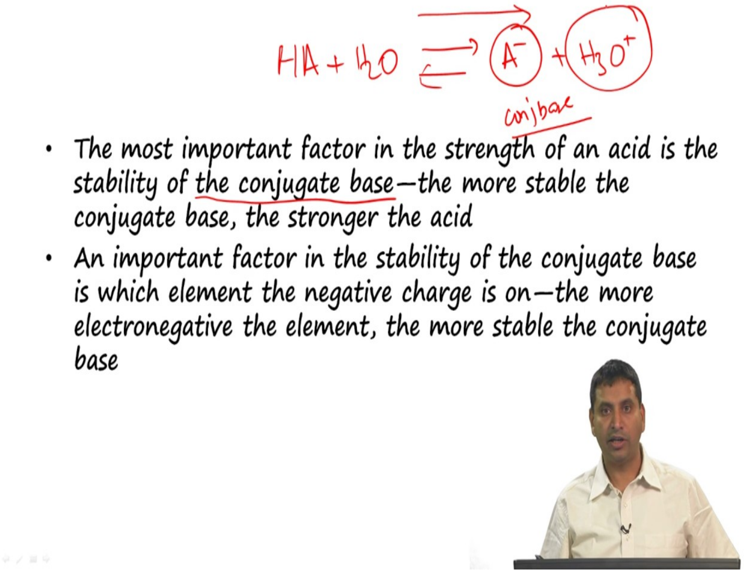


- The most important factor in the strength of an acid is the stability of the conjugate base—the more stable the conjugate base, the stronger the acid
- An important factor in the stability of the conjugate base is which element the negative charge is on—the more electronegative the element, the more stable the conjugate base



$HA + H_2O \rightleftharpoons A^- + H_3O^+$

conj base

- The most important factor in the strength of an acid is the stability of the conjugate base—the more stable the conjugate base, the stronger the acid
- An important factor in the stability of the conjugate base is which element the negative charge is on—the more electronegative the element, the more stable the conjugate base

So to understand how differences in acidity are going to manifest we would have to figure out what is important factor in determining the acidity strength so the most important factor in determining the strength of an acid is the stability of the conjugate base so that is basically HA + H_2O is in equilibrium with A minus plus H_3O plus.

So A minus here is the conjugate base and the stability of this conjugate base one of the most important factors in determining how strong the asset is so the more stable it is the more this equilibrium is pushed towards right and the stronger the acid another important factor to determine the stability of the conjugate base and an important factor in determining the stability of the conjugate base is the element on which the negative charges on okay.

So more electronegative the atom or element the more stable the conjugate base now we shall look at some examples and see how we can explain the trends in pKa.

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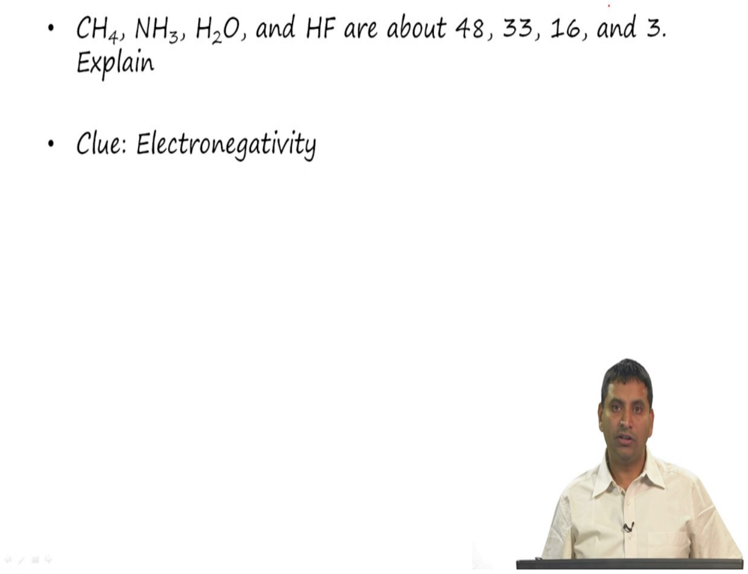
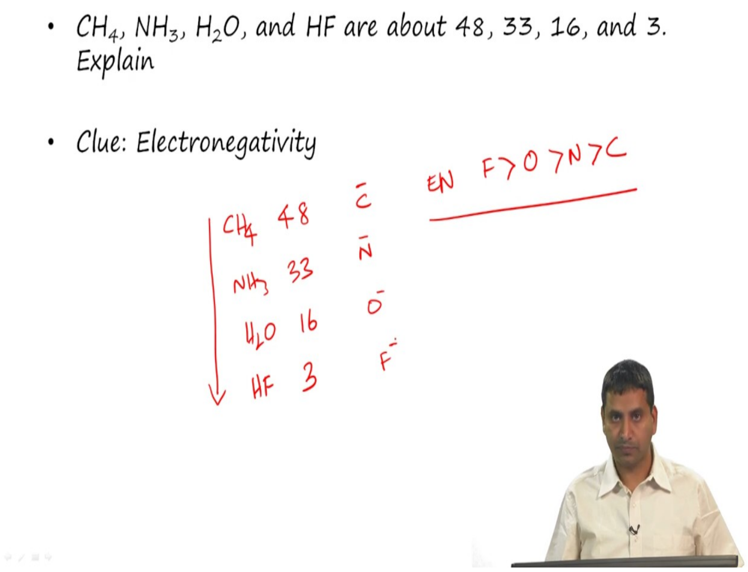


- CH_4, NH_3, H_2O, and HF are about 48, 33, 16, and 3. Explain
- Clue: Electronegativity



- CH_4, NH_3, H_2O, and HF are about 48, 33, 16, and 3. Explain
- Clue: Electronegativity

EN F > O > N > C

CH_4 48 $\bar{C}$
NH_3 33 $\bar{N}$
H_2O 16 O^-
HF 3 F^-

So let's look at these numbers CH_4, NH_3, H_2O and HF. CH_4 the pKa is 48, NH_3 pKa is 33, H_2O the pKa is 16 and HF the pKa is 3 So as we know from our fundamental concepts in general chemistry electro negativity of the molecule increases in the following order that is fluorine is greater than oxygen greater than nitrogen greater than carbon.

Electro negativity fluorine is greater than Oxygen greater than nitrogen greater than carbon so therefore you can understand that the negative charge that is formed on the element that is C -, N-, O - and F -, F - is stabilized far more compared to O minus which is an intern far far more stable than N minus and C - so therefore the this trend in pKa can be explained by invoking electro negativity.

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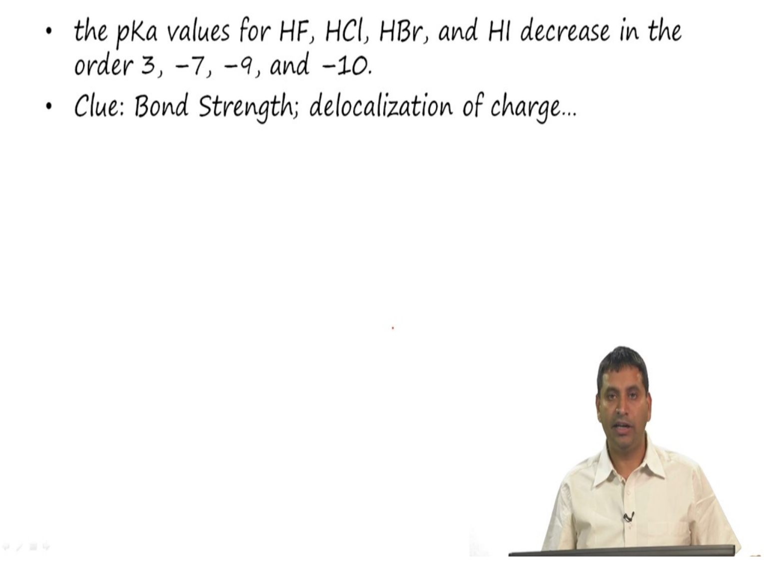
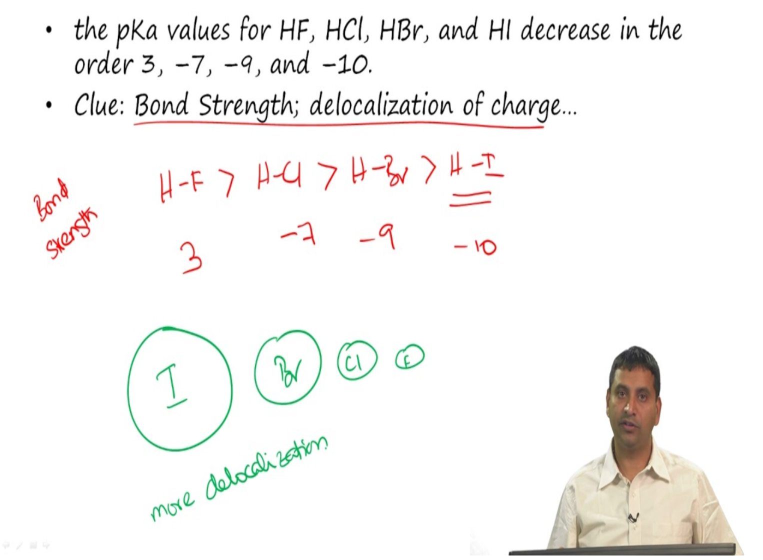


- the pKa values for HF, HCl, HBr, and HI decrease in the order 3, −7, −9, and −10.
- Clue: Bond Strength; delocalization of charge...



- the pKa values for HF, HCl, HBr, and HI decrease in the order 3, −7, −9, and −10.
- Clue: Bond Strength; delocalization of charge...

Bond strength

H-F > H-Cl > H-Br > H-I

3 -7 -9 -10

more delocalization

The pKA value of HF, HCl, HBr and HI decrease in the order 3, - 7, - 9 and minus 10 so here in order to explain this we would need to invoke bond strength and delocalisation of charge so the bond strength of HF is greater than bond strength of HCl which is greater than bond strength of HBr which is intern greater than the bond strength of HI.

Okay so therefore this bond is much easier to break when compared to HBr and so on. And so the pKa value is 3, -7, - 9 and minus 10 the second concept that we want to bring in here is the delocalisation of charge if you won't understand delocalisation of charge then let's look at iodine which is a much larger when compared to bromine which in turn is larger than chlorine which in turn is larger than fluorine.

So the negative charge is dispersed much larger in a much larger space and therefore there is more delocalization in iodine when compared to a iodide when compared to Bromide chloride or fluoride so this helps us understand the trends in the pKa values.

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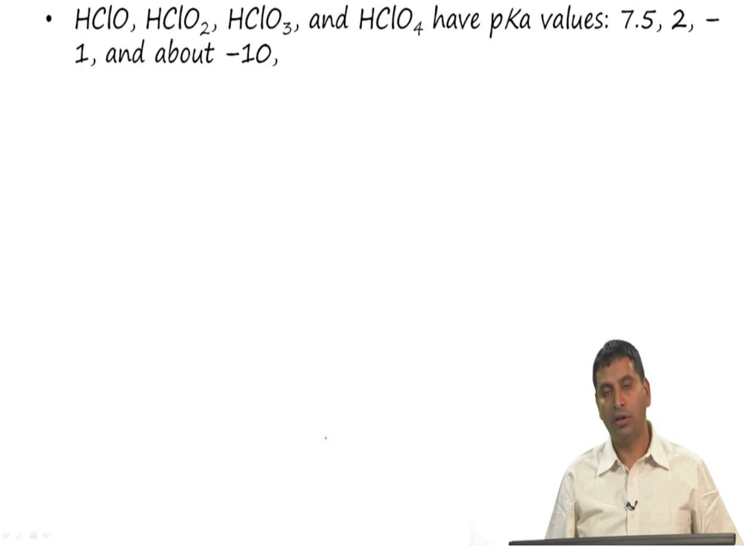
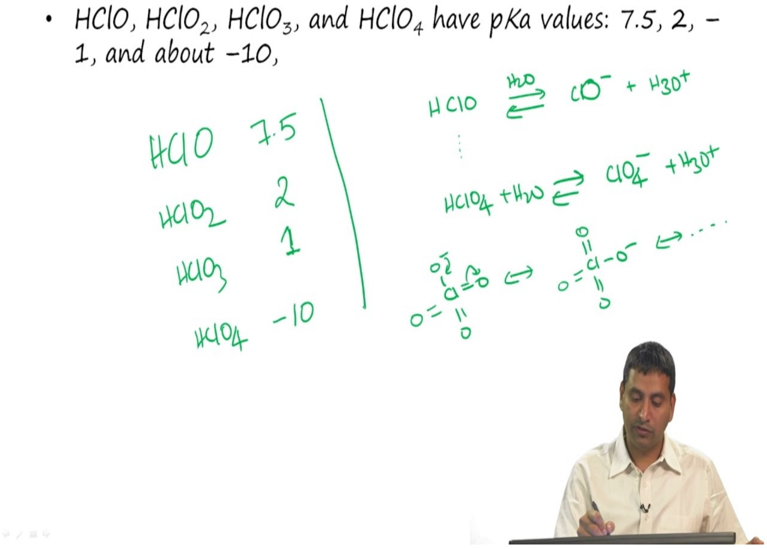


- HClO, $HClO_2$, $HClO_3$, and $HClO_4$ have pKa values: 7.5, 2, −1, and about −10,



- HClO, $HClO_2$, $HClO_3$, and $HClO_4$ have pKa values: 7.5, 2, −1, and about −10,

The next example is a series of perchlorate and related compounds so here again the pKa values are arranged in HClO is 7.5, $HClO_2$ is 2, $HClO_3$ is 1 and $HClO_4$ is a dramatic value of minus 10 right so it's a huge difference between $HClO_3$ and its $HClO_4$ so the way we would understand this is to draw the equilibrium HClO in equilibrium with ClO minus plus H_3O plus top of this is water.

Now if you do the same analogy analysis for $HClO_4 + H_2O$ going to $ClO_4^- + H_3O^+$ then you will understand the chlorate is actually the species like this and this can participate in resonance and you'll have ClO minus double bond O double bond O and so on and so forth therefore the negative charge on per chloride is far more stabilized when compared with HClO ClO_3 minus which in turn is more stable than ClO_2^- which turns more stable than ClO minus so this helps us explain this trend in pKa.

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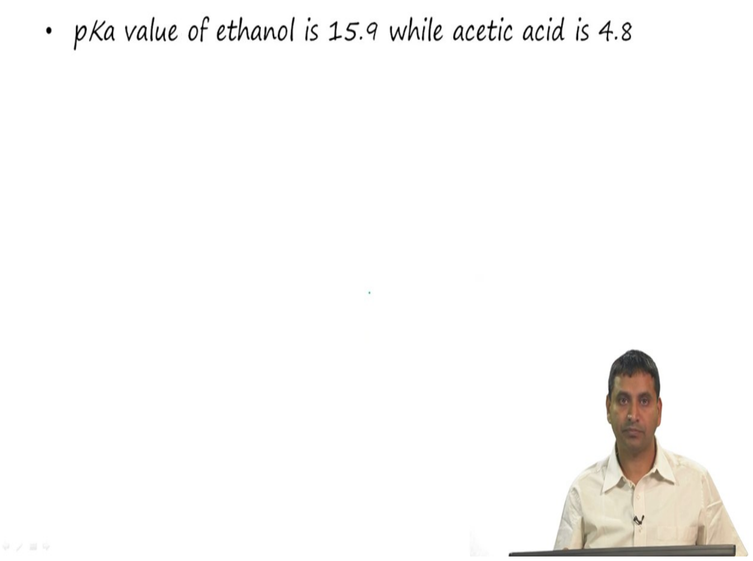
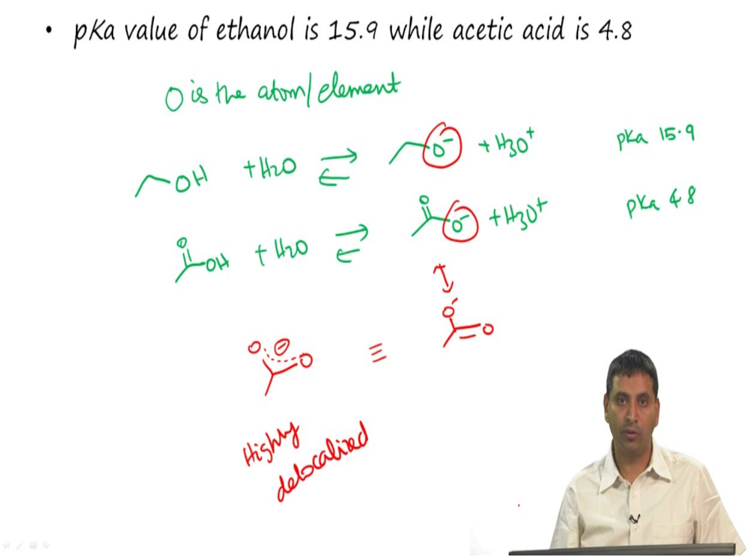


- pKa value of ethanol is 15.9 while acetic acid is 4.8



- pKa value of ethanol is 15.9 while acetic acid is 4.8

The next question is the pKa value of Ethanol is 15.9 while acetic acid is 4.8 how do we explain this. So here oxygen is the atom or element that we are considering so therefore there is no difference here pretty much so ethanol the structure is OH + H_2O which will give you ethoxide + H_3O^+ so here the pKa is 15.9 where as for Acetic Acid which is whose structure is this + H_2O in equilibrium with Acetate + H_3O^+. The pKa is 4.8

So one way we can explain this is that you can see that the element involved is oxygen in both cases right. But one important difference between Acetate and ethoxide is the fact that Acetate can actually involve itself in resonance as a resonance form you can draw this therefore this is nothing but the resonance hybrid O O minus so this negative charge is highly delocalised when compared with ethoxide.

And therefore one can understand why this Acetate is so stable and the acid is such a good acid so this is actually quite similar to the example of perchlorate that we looked at in the previous case.

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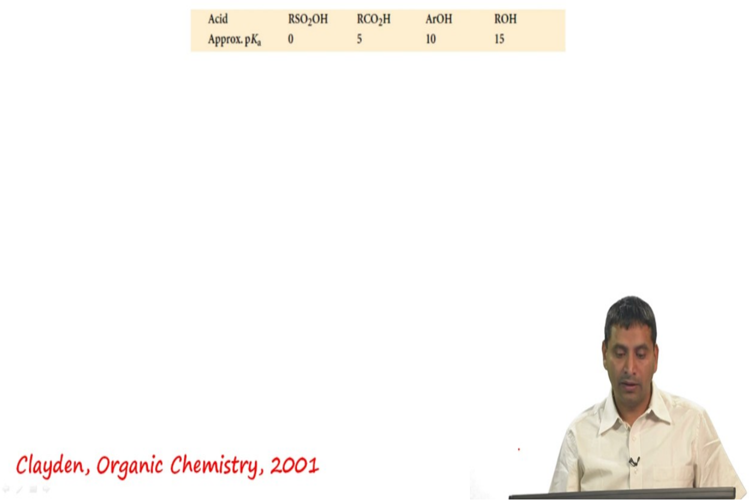
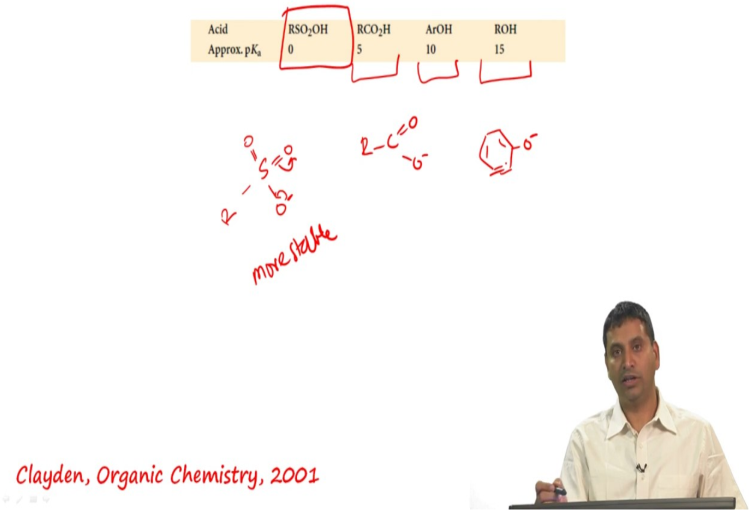


Acid	RSO_2OH	RCO_2H	ArOH	ROH
Approx. pK_a	0	5	10	15

Clayden, Organic Chemistry, 2001



Acid	RSO_2OH	RCO_2H	ArOH	ROH
Approx. pK_a	0	5	10	15

Clayden, Organic Chemistry, 2001

The next case is RSO_2OH has pKa of 0, RCO_2H is a pKa of 5, aryl alcohol such as phenols have pKa of 10 and regular alcohols have pKa of 15 so again this will have to do with the stability of the conjugate base RC double bond O O minus this we already looked at exists as resonance hybrid S double bond O double O O minus is the structure of sulphite and again this can involve itself in various resonance forms and therefore you can understand that this is more stable compared with the alcohol.

And between phenol and alcohol since there is a scope of delocalization within the aromatic ring the aryl alcohols I mean the phenols are typically more acidic compared to aliphatic alcohols.

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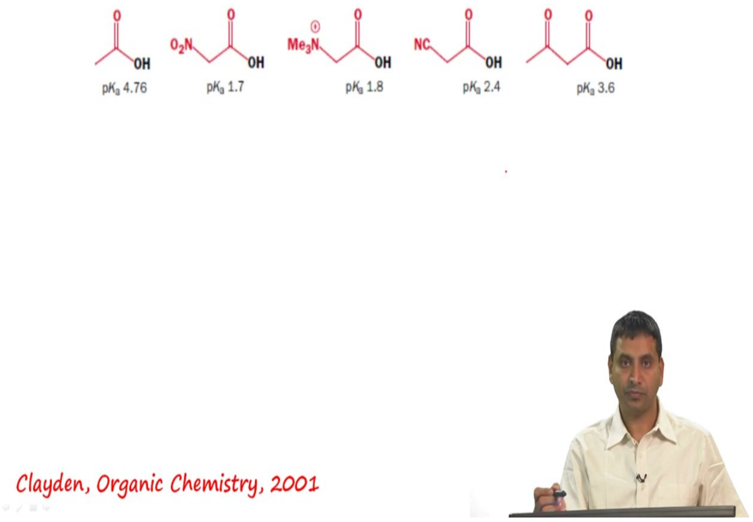

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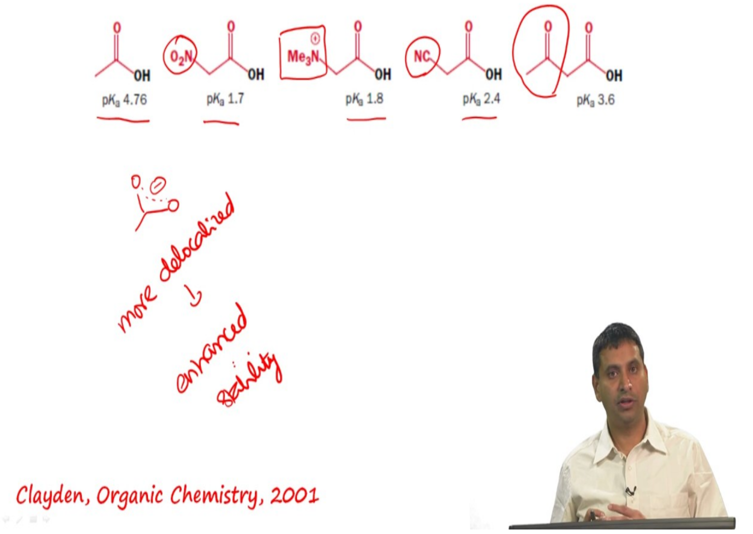

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Next example we look at pKa amongst various Carboxylic acids so here you see acetic acid is a starting point the pKa is 4.76. Once I introduce a nitro group here the pKa drops 1.7 and also when I have NMe_3^+ which is a positively charged amine then the pKa is comparable in 1.8 I have an electron withdrawing group in cyano the pka is 2.4

And here is the electron withdrawing group of a carbonyl with pKa is 3.6 so in order to understand this again we need to look at resonance forms here you have O it is an negative charge that is formed and the more stable this negative charges that is the more delocalised then the more stable this species is right.

So therefore if you see how nitro group is going to pull electrons it is going to pull pull the electrons from the carboxylate and it going to make the negative charged more delocalised similarly a fully charged ammonium species is good again result in significant amount of delocalisation.

Where as neutral electron withdrawing groups such a cyano and carbonyl are pretty good but they are not as effective as nitro group or a positively charged ammonium salt so this helps us understand the trend in pKa values.

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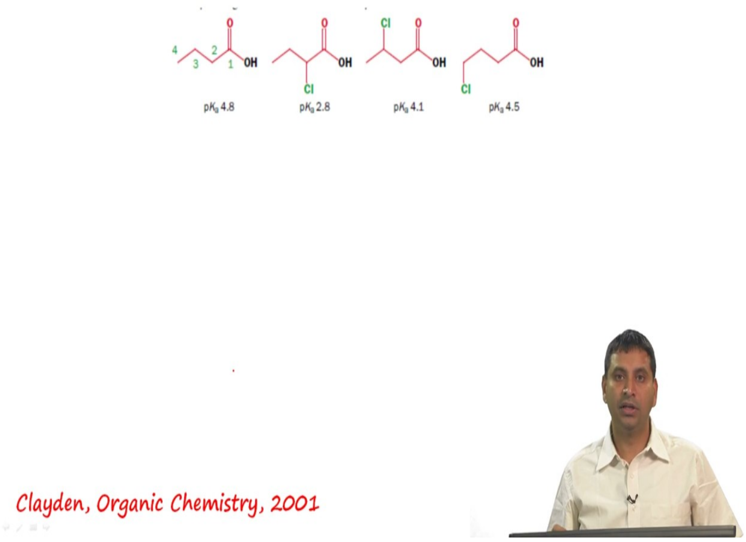

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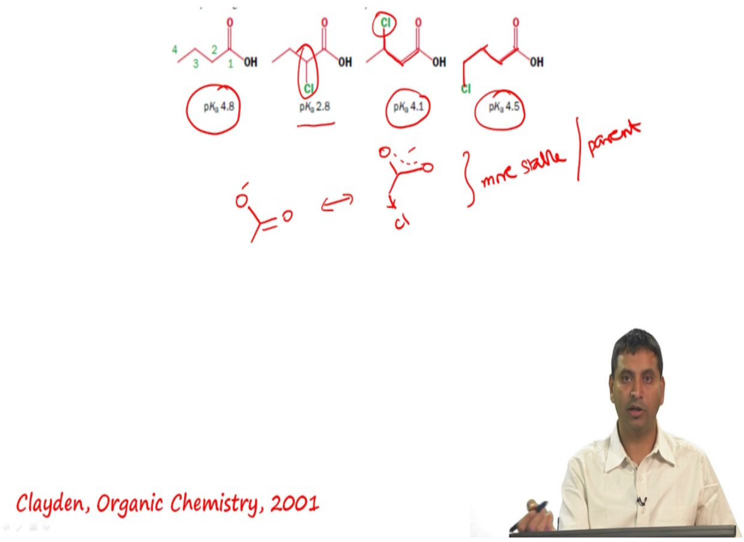

Clayden, Organic Chemistry, 2001

Now let's look at another example of structural effects on acidity in Carboxylic acids so here we have given four acids so the pKa of a starting molecule is 4.8 its very similar to acetic acid. Now when I introduce a chloro group at this position then the pKa drops by couple of units ok so 2 units of pKa means hundred folds difference in the Ka and pKa here is comparable to as there is a drop in the next case.

But it is comparable to the acetic Acid or the carboxylic acid while last example the pKa is 4.5 which again similar to what we would see with the parent molecule so the major difference in the pKa comes in the case of the second example where there is a two chloro functional group.

So the way we understand this again is to look at how delocalisation occurs so as we discussed earlier this can be a resonance hybrid in the form of a molecule here this resonance hybrid once you have an electron withdrawing chloro it's going to pull electrons towards itself being an electronegative atom and therefore this will be more stable when compared with the parent okay.

So that helps us understand why this molecule has a significantly lower pKa or it significantly more acidic than the parent molecule whereas as you go as the chloro moves further away from the carboxylic acid the inductive effect goes down in as the number of bonds increase and so it helps us explain why there is a not not a huge difference in the pKa values because here you will have 123 bonds and here you are 1234 right so as you go as the number of bonds increase the inductive effect becomes weaker.

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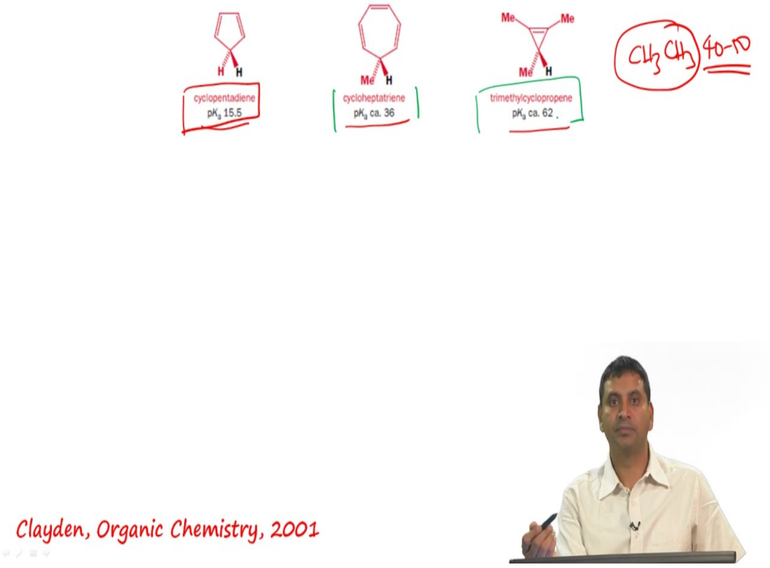
Clayden, Organic Chemistry, 2001



Clayden, Organic Chemistry, 2001

Lets look at one more example here this is an example of a carbon acid so if you take cyclo pentadiene the pKa is 15.5 where as in the case of this cyclo heptatriene the value is 36 and tri methyl cyclopropene is 62 so to put these numbers and perspective CH_3 CH_3 the value is around somewhere between 40 to 50 okay so compared to a regular alkane like methane for example there is a huge difference in the pKa when it comes to cyclopentadiene.

So cyclopentadiene is significantly stronger acid when compared to a regular alkane where as in the case of cycloheptatriene there is there is a drop in there is a shift of about 3 to 4 units perhaps but in that case of trimethyl cyclopropane there is an increase in pKa value that means it becomes of poorer acid when compared to aliphatic or alkanes.

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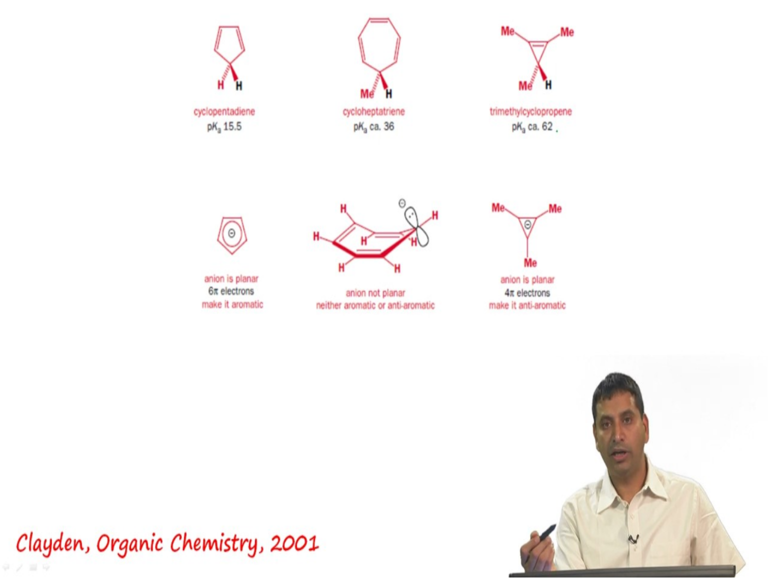

Clayden, Organic Chemistry, 2001

So this can be explained by invoking the concept of aromaticity again because the anion that is formed is 6 pie electrons in this as we know aromatic and aromatic compounds are generally more stable than the corresponding unconjugated or molecules therefore the possibility of aromaticity enhances the stability of the conjugate base.

Here the compound is neither aromatic nor antiaromatic and the negative charge is not really planar because you are you it is a assuming a puckered structure and so there is no stabilization or destabilization and so the value difference in pka is not very large in the last case if you generate an anion you generate a 4 Pie electron system which is antiaromatic in nature.

And therefore it becomes very difficult to make this molecule and the pKa values substantially higher than the parent one.

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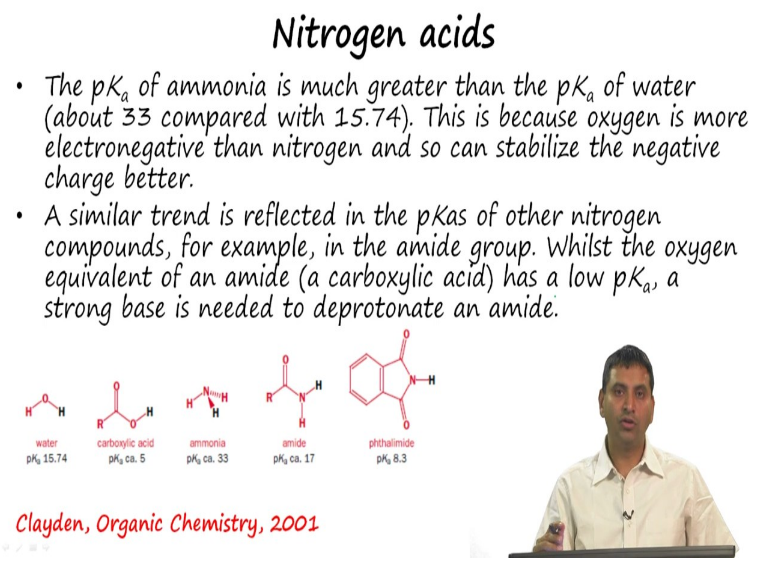

Nitrogen acids

- The pK_a of ammonia is much greater than the pK_a of water (about 33 compared with 15.74). This is because oxygen is more electronegative than nitrogen and so can stabilize the negative charge better.
- A similar trend is reflected in the pKas of other nitrogen compounds, for example, in the amide group. Whilst the oxygen equivalent of an amide (a carboxylic acid) has a low pK_a, a strong base is needed to deprotonate an amide.

Clayden, Organic Chemistry, 2001

So very similar to carbon or oxygen or sulphur based acids we also have nitrogen acids so nitrogen acids for example Ammonia the pKa value is being around 33 now when you move to an amide pKa value is 17 and phthalimide which who structure is shown here the pKa value is 8.3 okay so the trend in the acidity of Nitrogen acids is quite similar to the trend in oxygen acids.

So the difference or the concept that we need to look at again is the stability of the conjugate base.

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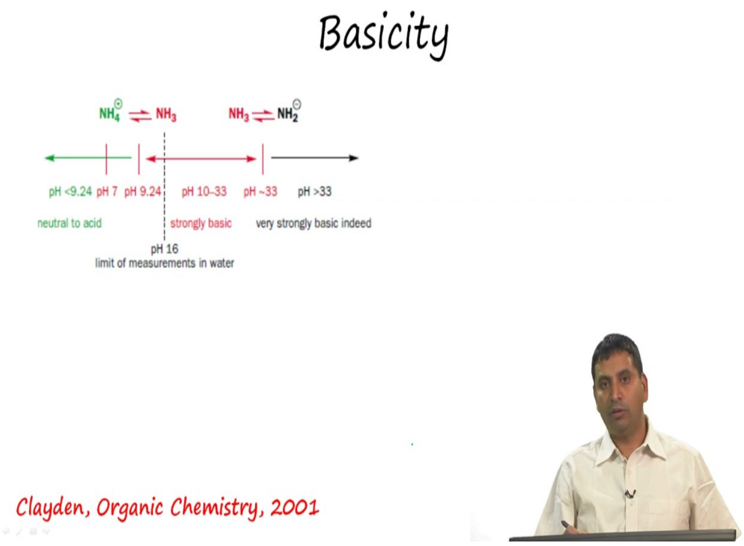

Basicity

Clayden, Organic Chemistry, 2001

So with that in mind we let’s look at basicity so nitrogen containing molecules such is amines are very unique so we just showed you that Amin Ammonia can act as an acid ok so this actually acts as an acid and produces NH_2^{-}, NH_2^- the pKa is going to be as we just looked that is around 33.

And so for this to occurred you need a very strong base for the deprotonation of ammonia to produce amide however what is more common is that you have Ammonia getting protonated to form NH_4^{+} so here in low pH that is below 7 for example Ammonia can be protonated to form NH_4 plus in mildly basic pH it forms Ammonia again the pKa value of ammonia ammonium is around 9.2 and therefore at Higher pH it's going to be Neutral.

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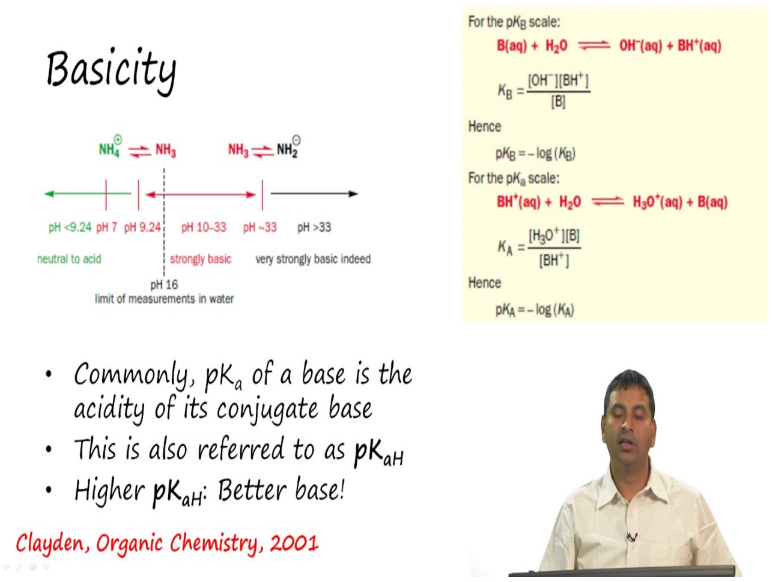

Basicity

For the pK_B scale:

$$B(aq) + H_2O \rightleftharpoons OH^-(aq) + BH^+(aq)$$

$$K_B = \frac{[OH^-][BH^+]}{[B]}$$

Hence

$$pK_B = -\log(K_B)$$

For the pK_a scale:

$$BH^+(aq) + H_2O \rightleftharpoons H_3O^+(aq) + B(aq)$$

$$K_A = \frac{[H_3O^+][B]}{[BH^+]}$$

Hence

$$pK_A = -\log(K_A)$$

- Commonly, pK_a of a base is the acidity of its conjugate base
- This is also referred to as pK_{aH}
- Higher pK_{aH}: Better base!

Clayden, Organic Chemistry, 2001

So with this in minds lets define another equilibrium constant known as Kb much like Ka is for acidity, Kb is for basicity. So Kb is nothing but you take B + H_2O going to give you hydroxide and BH^+ so here is the conjugate acid and here is OH minus is the conjugate base and the scale can be defined as pKb is nothing.

But - log of Kb because pKa is also commonly used if we want to understand the symptoms of pka since its in equilibrium its just have to swap the numbers so you can imagine this as BH^+ + H_2O going to H_3O^+ +B so here the acidity is defined in the following manner which is H_3O plus times B divided by BH^+. So, here pKa is nothing but negative of log of K. So commonly pKa of a base is the acidity of its conjugate base.

So therefore it is also referred to as pKaH its not a very commonly used term but pKaH is nothing but the way how good are acidity of the conjugate base so higher the pKaH the better the base so what we need to understand in determining basicity is what happens in the to the electron density on the nitrogen when it is acting as a base so the lone pair of on the nitrogen.

If it is less available for protonation then the molecule would be less basic right so the nitrogen atom is attached to an electron withdrawing group so in such a situation lone pair on the nitrogen becomes less available because you have an electron withdrawing group available attached to it and therefore it makes it less basic if the Lone pair is on sp or sp^2 hybridised orbital as opposed to an sp3 hybridised orbital then it becomes less basic if the lone pair is conjugated with an electron withdrawing group not just attached and but it can also be conjugated to an electron withdrawing group then again the basicity it goes down. If the lone pair is involved in maintaining aromaticity of the molecule that absolutely you will find that the molecule is going to be very resistant to giving away this lone pair.

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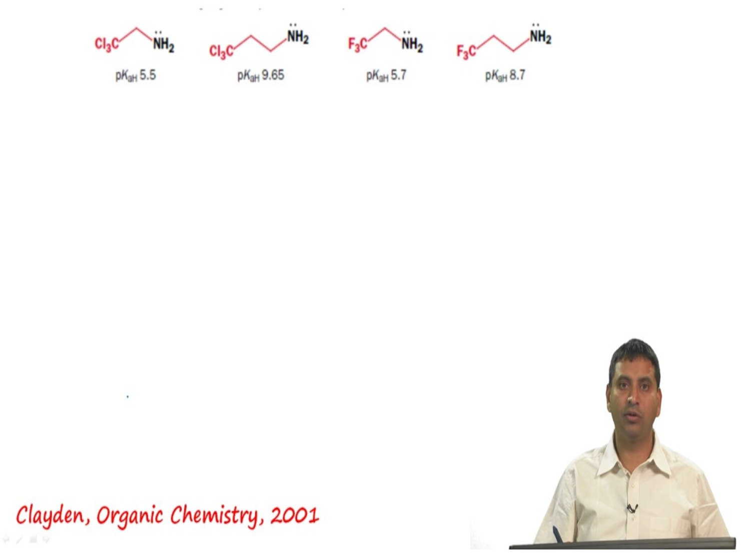

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So with this in mind let's look at some examples of pKaH values so if you take this molecule here which is trifluoro analogue of Ethylamine you have $CH_3CH_2NH_2$ the pKaH of this molecule is 5.7 where as of the CF_3 is moved by one carbon to the left then the value goes up to 8.7

So here you can understand this because the Lone pair on nitrogen is being pulled by induction by the flourine groups and since the number of bonds intervening here are increasing inductive effect becomes weaker and so the pKaH increases and this becomes a better base. very similarly you have the example of the chloro where you are 5.5 and 9.65 ok so this helps us understand how changing the group on the neighbouring carbons of the nitrogen can have an important effect on the basicity of the amine.

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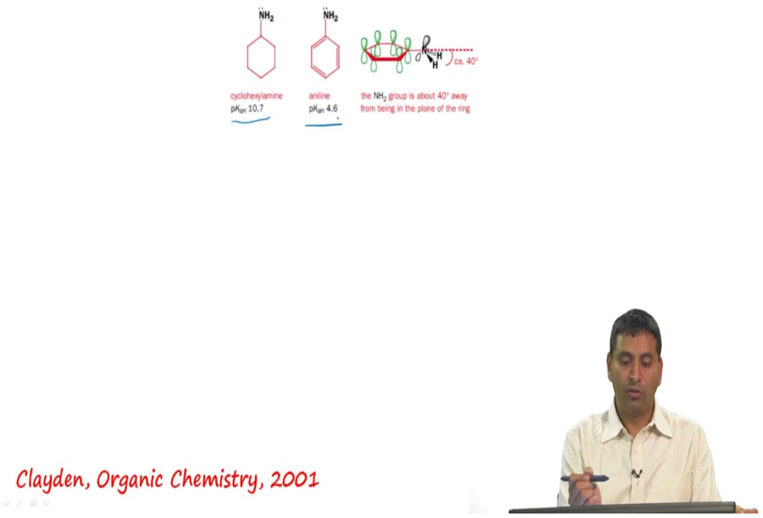

the NH_2 group is about 40° away from being in the plane of the ring

Clayden, Organic Chemistry, 2001

Now let's look at the example of cyclohexylamine and aniline so cyclohexylamine has pKaH of 10.7 where is aniline has pKaH of 4.6 so what happens here is that NH_2 here is quite available for donations so in the case of aniline since it is about 40 Degrees away from being in the plane it is not participating in resonance as much but it is it does have the opportunity to have some delocalisation therefore the pKaH of aniline is lower than pKaH of cyclohexylamine.

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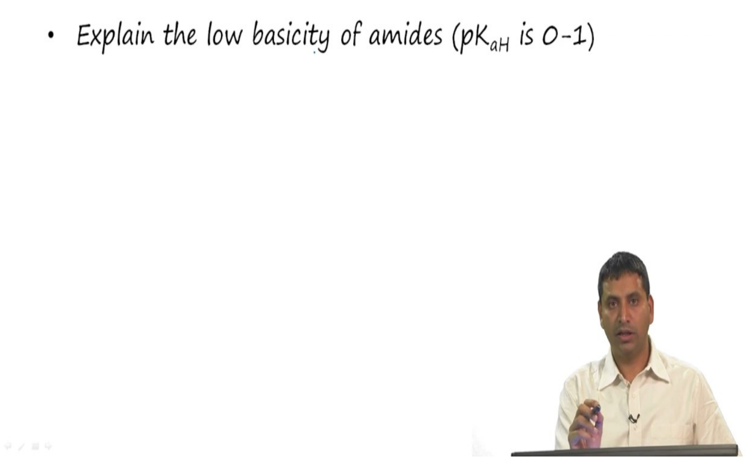

- Explain the low basicity of amides (pK_{aH} is 0-1)

The next question is explain the low basicity of amides the pKaH of amides is somewhere in the range 0 to 1.

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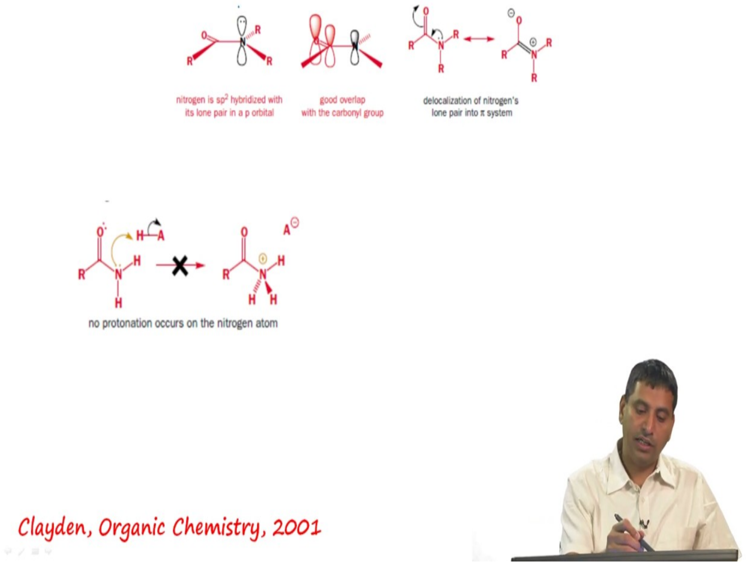

nitrogen is sp² hybridized with its lone pair in a p orbital

good overlap with the carbonyl group

delocalization of nitrogen's lone pair into π system

no protonation occurs on the nitrogen atom

Clayden, Organic Chemistry, 2001

So amides have the nitrogen is sp^2 hybridised and it occupies a p orbital but we also know that this amide can involve in self-resonance and it can form a structure such as this is. So therefore the lone pair is not really available for the amine for the nitrogen on the nitrogen to donate.

And so indeed if the lone pair does is there is donation that occurs you will form a positively charged nitrogen molecules such as this which is going to be situated right next to an electron withdrawing carbonyl group so this is highly unstable and is quite unlikely that this will be it will occur and before the pKaH of this molecule is substantially lower is between somewhere between 0 and 1.

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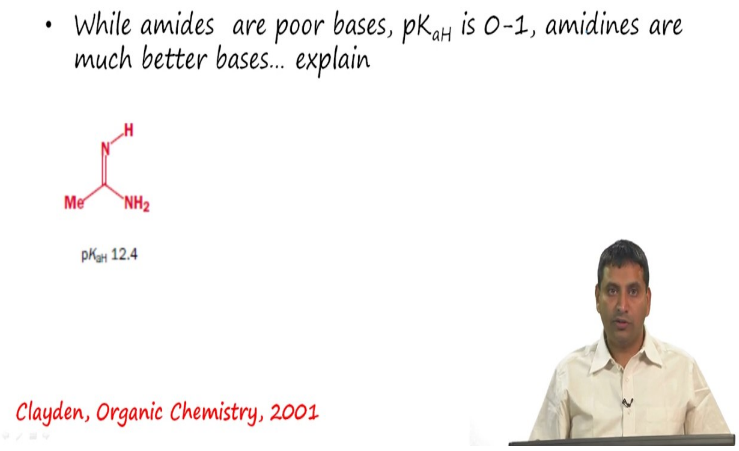

- While amides are poor bases, pK_{aH} is 0-1, amidines are much better bases… explain

Clayden, Organic Chemistry, 2001

Okay for the next question while amides are poor basses but pKaH 0 to 1 amidines the structure is shown here are much better bases so we need to explain this so amidine whose structure is shown here is basically there nitrogen analogue of an amide in order to understand this huge difference of a about 12 units in pKaH it let's look at the structure of amidines.

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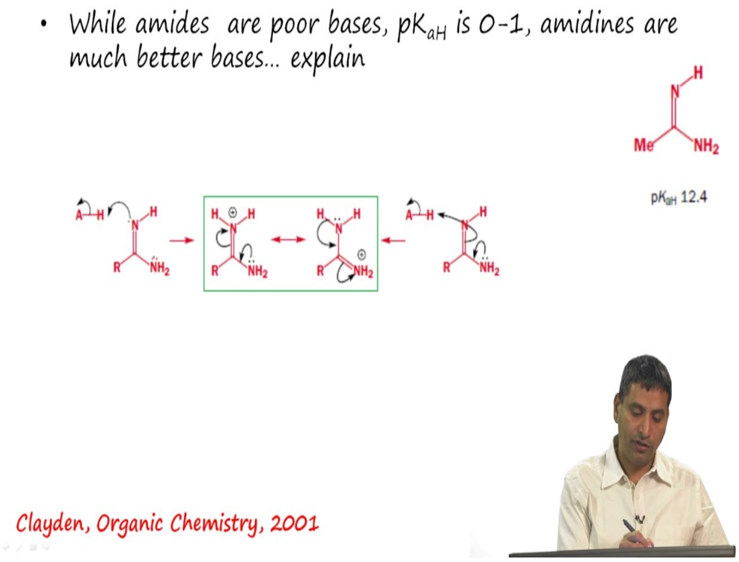

- While amides are poor bases, pK_{aH} is 0-1, amidines are much better bases… explain

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So amidines have nitrogen lone pair and they have a C double bond N now this lone pair on this nitrogen can be donated to an acid to produce a positively charged nitrogen species are shown here which can then subsequently delocalised by arrow pushing as shown here forms another resonance form which is shown here. So together you can propose that this nitrogen lone pair can move into and form a double bond with this carbon which in turn can pick up a proton from AH.

So this helps us understand why this molecule is substantially more acidic than the corresponding oxygen analogue which is an amide okay.

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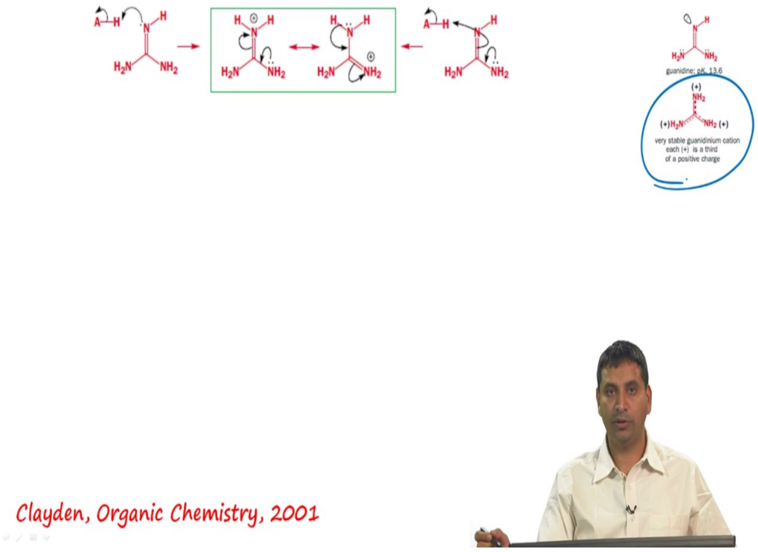

guanidine: pK_a 13.6

very stable guanidinium cation each (+) is a third of a positive charge

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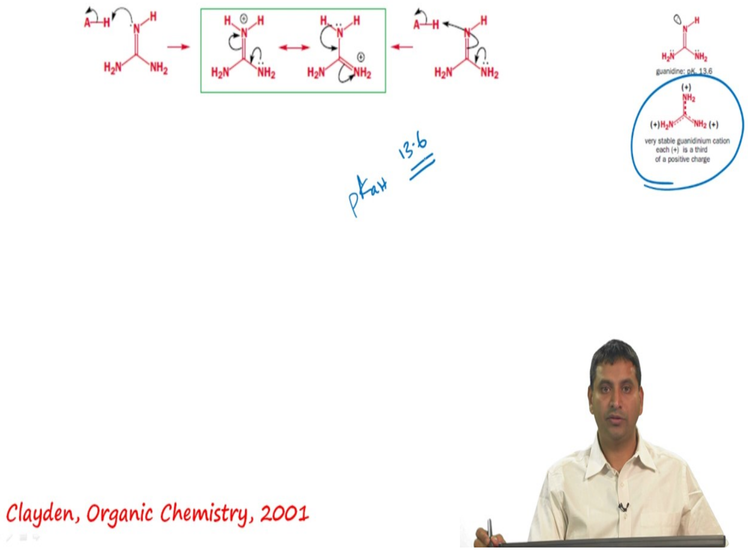

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So similarly if you push a one more nitrogen into this C double bond N into this picture. You form guanidines. Guanidines have three nitrogens on them and again why just showing a similar structure you can find out you can infer that these are going to be substantially more stable. pKaH of guanidines is in the range 13.6 which is again quite high compared to amidines.

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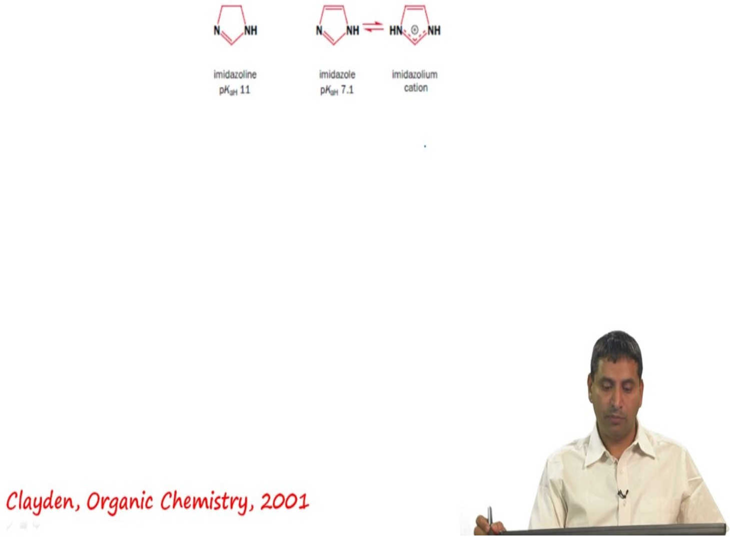

Clayden, Organic Chemistry, 2001

The next example we look at imidazole imidazoline whose pKaH is 11 imidazole whose is pKaH 7.1 and how we want to understand this difference so in the case of imidazoline.

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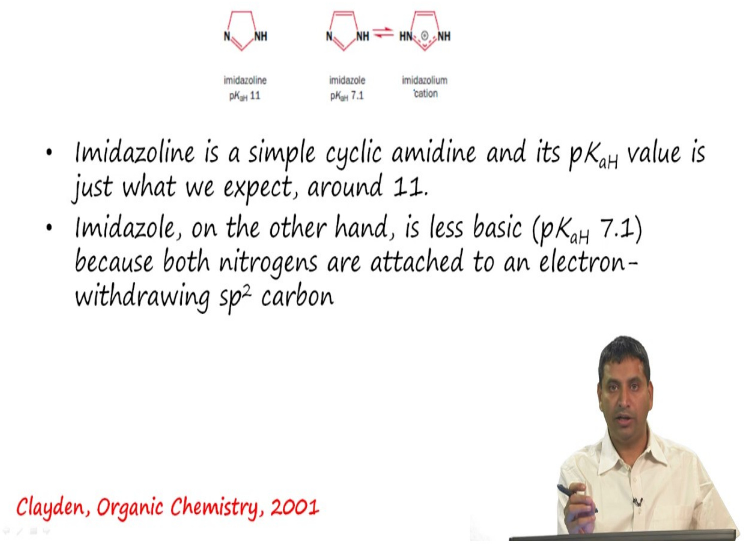

- Imidazoline is a simple cyclic amidine and its pK_{aH} value is just what we expect, around 11.
- Imidazole, on the other hand, is less basic (pK_{aH} 7.1) because both nitrogens are attached to an electron-withdrawing sp² carbon

Clayden, Organic Chemistry, 2001

It is a simple cyclic amidine and its pKaH value is just what you would expect is around 11 right but in the case of imidazole on the other hand, it is less basic that is it is more resistant to giving awaits lone pair because both the nitrogen that are attached to an electron withdrawing sp^2 carbon so here you see this sp^2 carbon in this another sp^2 carbon so since sp^2 carbon are going to be electronegative and they pull electrons towards themselves the lone pair on the nitrogen is less available for donation.

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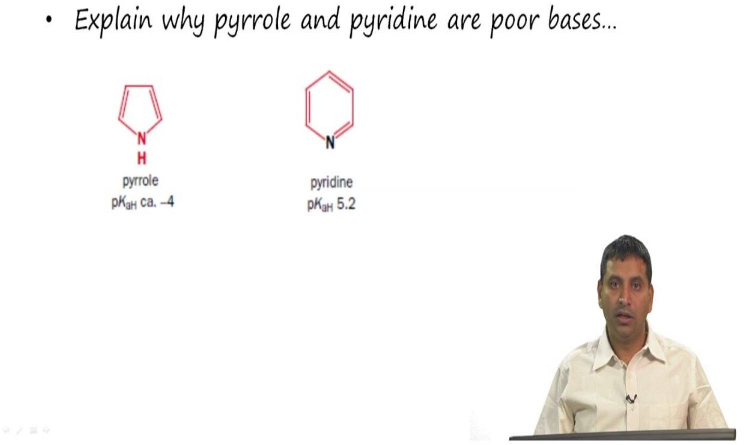

- Explain why pyrrole and pyridine are poor bases…

Now let's look at the next example of a cyclic nitrogen base base so pyrrole its an extremely weak base and the value is -4 where as pyridine the pKaH is 5.2 but both of these are actually poor bases when compared to a regular amine whose pKaH is substantially higher.

so the way we understand this is basically pyrrole has its lone pair involved in resonance and it can form a 6 pie aromatic system if I include the lone pair.

And so therefore this lone pair is not really something that is easy for donation. Pyridine, on the other hand, the lone pair is not involved in resonance but since it is to as a electronegative sp^2 system it’s again less available for donation.

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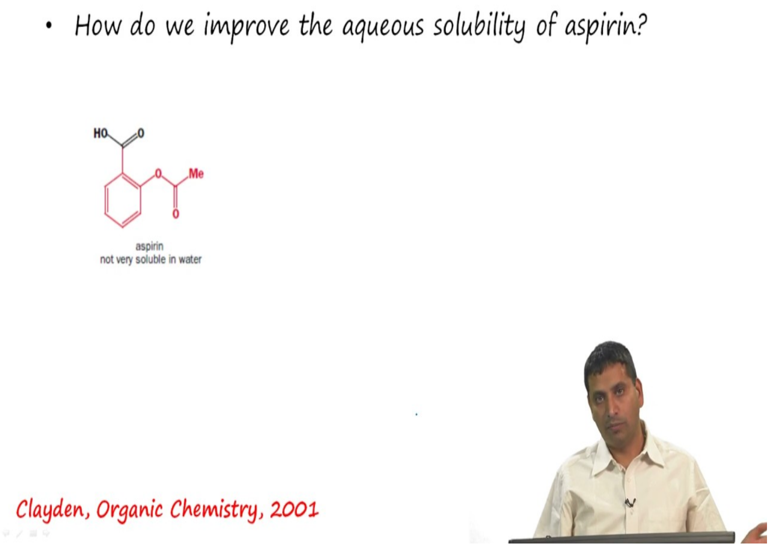
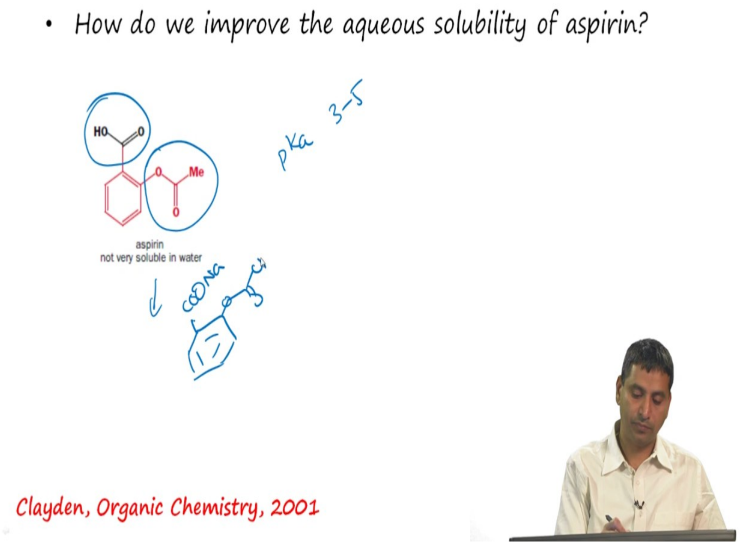


- How do we improve the aqueous solubility of aspirin?

aspirin
not very soluble in water

Clayden, Organic Chemistry, 2001



- How do we improve the aqueous solubility of aspirin?

aspirin
not very soluble in water

Clayden, Organic Chemistry, 2001

Lets look at with this concepts in mind let's look at another question how do we improve the aqueous solubility of Aspirin. Aspirin is very poorly soluble in water so if you have to address this problem let's look at the various functional groups that are available here aspirin has carboxylic acid it has an ester and we already know that carboxylic acids have pKa values somewhere between 3 to 5.

So if we were to make the medium slightly basic or if the pKa if the pH of the medium is little bit higher than the pKa value then it is quite possible or quite likely that the carboxylic acid will be deprotonated. So what we need to do is to be able to increase the pH that is make it into a slightly basic pH and then you can make it as a sodium salt of aspirin which will be freely soluble in water.

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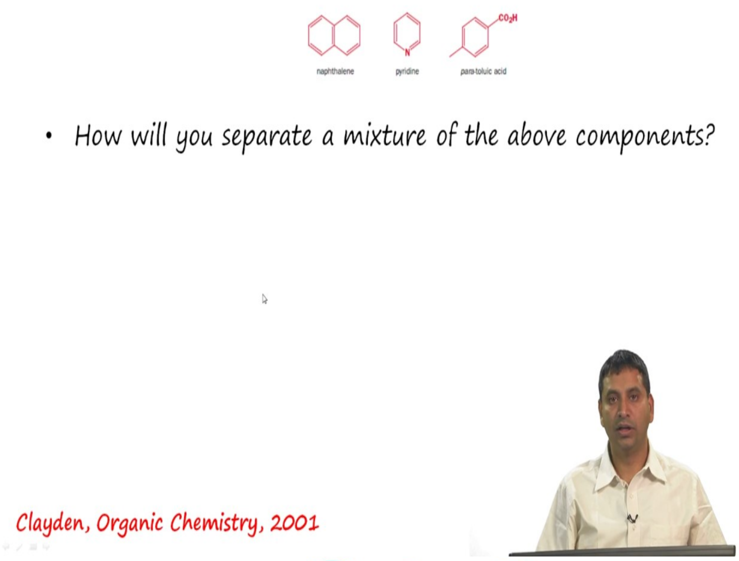
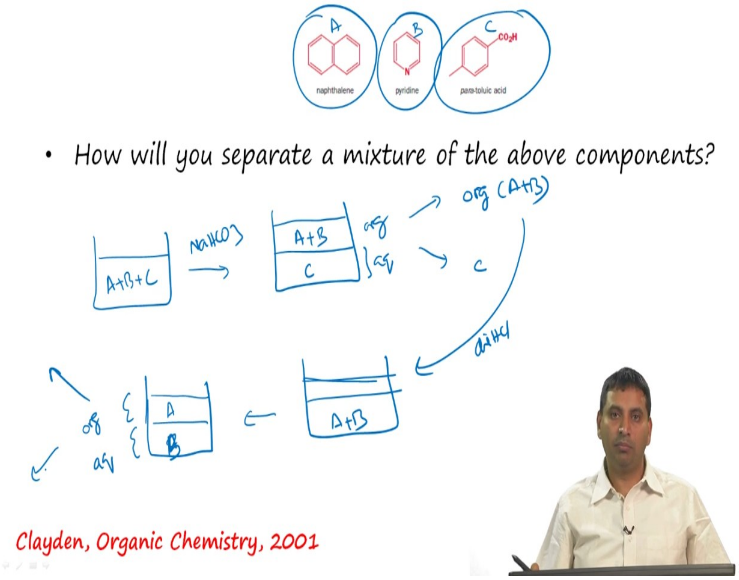


- How will you separate a mixture of the above components?

Clayden, Organic Chemistry, 2001



- How will you separate a mixture of the above components?

Clayden, Organic Chemistry, 2001

Next question is how will you separate a mixture of the above components that is naphthalene pyridine and *para*-toluic acid so if you want to do this lets again look at the functional group here this is an acid this has a base always not a very strong base and it has a neutral molecule so if you have a mixture of these three components the best way to do this would be the first dissolve this in an organic medium so in this organic medium you will have all three components A + B + C let's call this is as A let’s call this as B, let's call this as C.

Now if you let’s say to begin with wash it with sodium bicarbonate then you have the organic layer or the aqueous layer below the organic layer above now the organic layer will take an A and since bicarbonate is a base it's going to convert the carboxylic acid to carboxylate. The carboxylate will remain here in the aqueous medium and A + B are is going to remain in the organic medium.

Now what you do as you separate the organic layer which will contain A plus B and you get your C. To this organic layer which contains A + B, you treat it with a weak acid such as so now if you dissolve it in dilute HCl then the aqueous layer which is here will contain B where as the organic layer will contain A so now you can separate these two by this process. So by using simple acid base chemistry we can separate complicated mixtures even if you are able to understand how the acid base properties are manifesting themselves.

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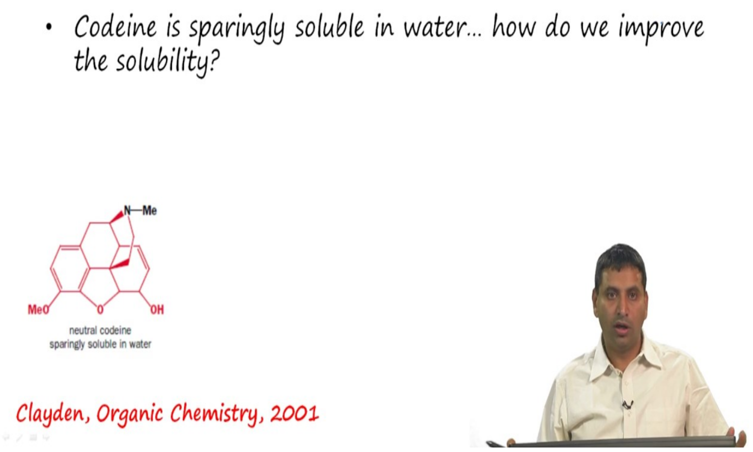

- Codeine is sparingly soluble in water… how do we improve the solubility?

Clayden, Organic Chemistry, 2001

So the next question is Codeine is sparingly soluble in water how can we improve the solubility so codeine is this molecule that shown here it looks very complicated but an important functional group here is the amine the other one is a phenol the others that not really going to contribute to acid base.

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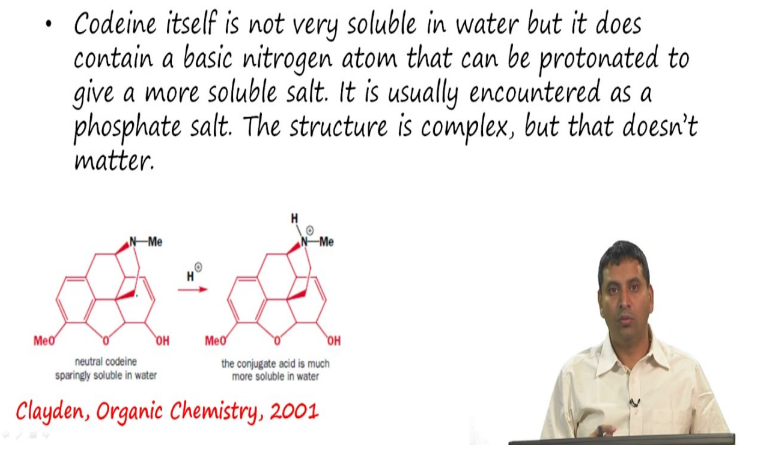

- Codeine itself is not very soluble in water but it does contain a basic nitrogen atom that can be protonated to give a more soluble salt. It is usually encountered as a phosphate salt. The structure is complex, but that doesn't matter.

neutral codeine sparingly soluble in water

the conjugate acid is much more soluble in water

Clayden, Organic Chemistry, 2001

And so as we have looked at earlier what we can do is to treat it with a mild acid and so this nitrogen is going to get protonated and it'll form NMeH plus which is going to improve the solubility. So despite the structure of being Complex you can make a very simple modification of adding an acid to make the molecule more soluble in aqueous media.

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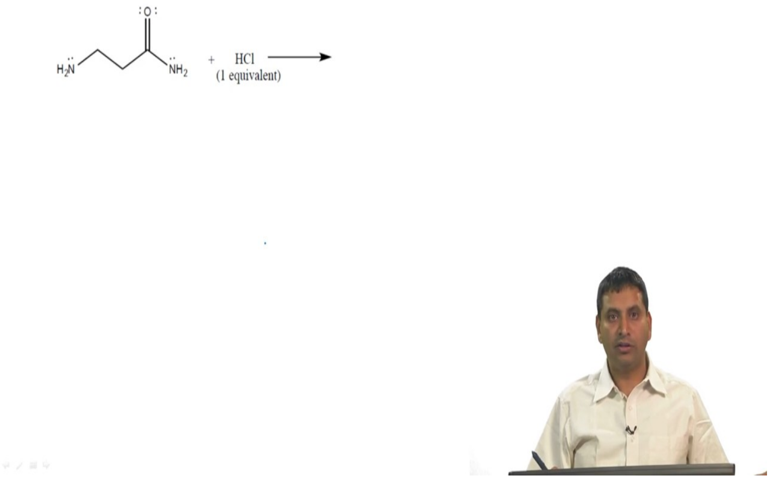

So now with this let's move on to the next question which is if I take this molecule shown here and add 1 equivalent of HCl which of the three lone pairs are going to get protonated so if you look at carbonyl. Carbonyl is a base but it's extremely weak base we already look at amide whose pKaH is somewhere between 0 and 1.

So its also going to be a weak base now the last option is an amine whose pKaH is estimated to be around 8 to 10 or something like that so if I add exactly one equivalent of HCl the first nitrogen that will get protonated would be the NH_2 as shown here.

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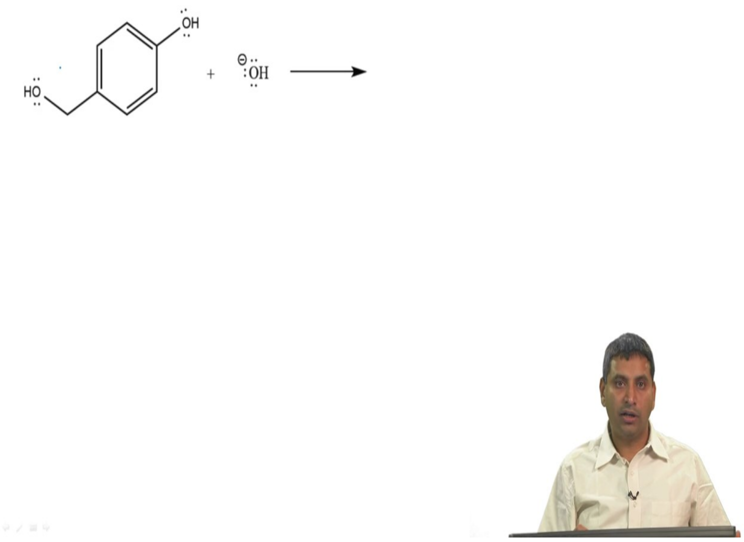

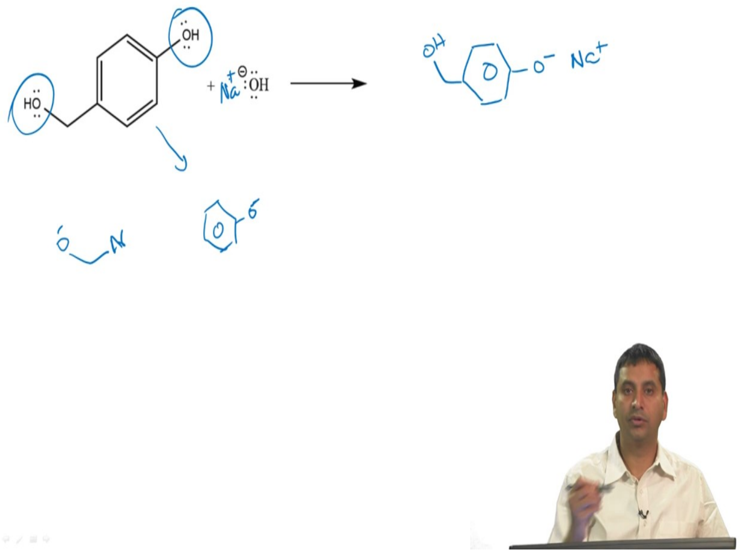

The next example will look at two different alcohols so you have a phenol and you have an aliphatic alcohol so if I had one equivalent of Hydroxide Ion if we want to look at what would happen first then if you generate a phenolate which is as shown here and and O minus with an aromatic alcohol over here we already know that a phenolate is actually more stable when compared with an aliphatic alkoxide.

And so I would expect that phenolate would be the only product that would be formed that is you will get O^- CH_2OH assuming that NaOH is the base used here.

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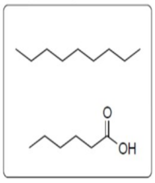
- Separate a mixture containing nonane and hexanoic acid:



So next question is separate a mixture containing nonane and hexanoic acid. So we already looked at the example of the ternary mixture so this is much simpler compared to that so here this is an organic soluble molecule this is also soluble in organic solvent but then we were treated with a mild base can generate RCOO minus which was then be moved to the aqueous layer in the organic layer will retain nonane.