Medicinal Chemistry
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Quantitative Structure-Activity Relationship (QSAR) Part-2

So far we have looked at what is the effect of hydrophobicity on activity. So when we have a series of compounds where we systematically vary the hydrophobicity by measuring what is known as log P, we can study the effect of activity on log P ok. So we looked at the possibilities of even varying a substituent on a benzene ring or an aliphatic ring and what the effect of a single substituent is on the hydrophobicity of the molecule, so we looked at P, we looked at Pi ok. Now hydrophobicity is one of the important characteristics of a molecule, so today or now we will look at what are the other effects that can come into play.

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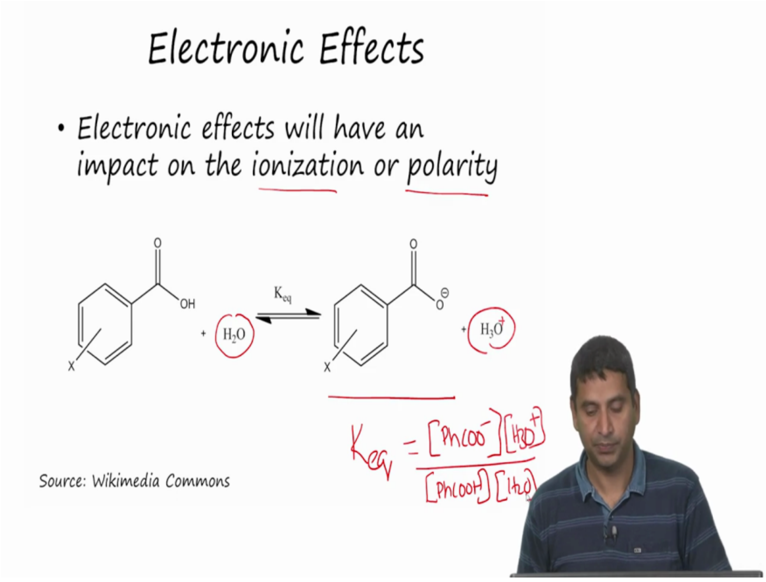

Electronic Effects

- Electronic effects will have an impact on the ionization or polarity

$K_{eq} = \frac{[PhCOO^-][H_3O^+]}{[PhCOOH][H_2O]}$

Source: Wikimedia Commons

So the 1st effect is an electronic effect okay, so as you know that molecules have an electron cloud around it and this electronic effect can play a major role in binding specially in non-covalent interactions. Now one of the important electronic effects is on ionisation or polarity okay, so one of the standard ways of looking at ionisation is to look at acid-based equilibrium ok. So if I take benzoic acid and dissolves in water I can determine, what is the ratio of benzoate to benzoic acid so benzoic acid equilibrates in water to produce benzoate and H3O+ ok. Now we can take benzoic acid and put it in water and measure the amount of benzoate that is produced and from that we can determine the equilibrium constant.

K eq is nothing but the concentration of benzoate COO – times H3O + divided by concentration of benzoic acid times water ok, this equilibrium constant will help us understand how the benzoate acid partitions into the corresponding conjugate base ok.

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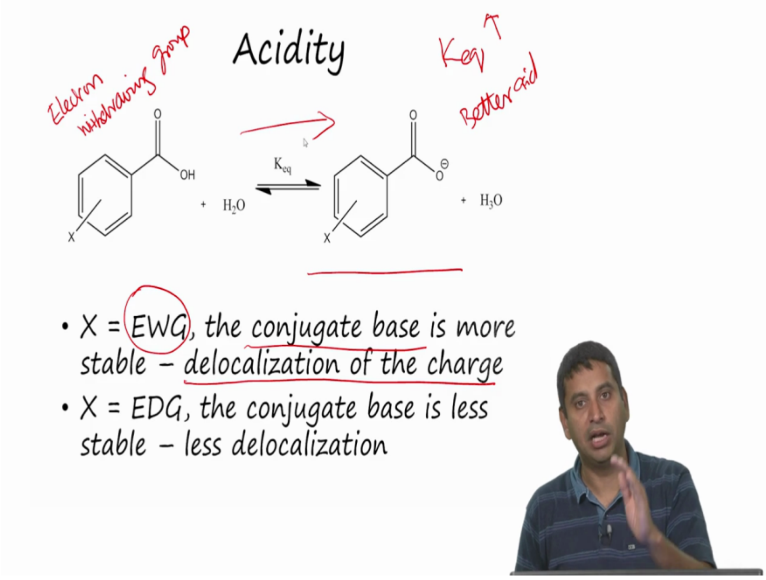

Acidity

- X = EWG, the conjugate base is more stable – delocalization of the charge
- X = EDG, the conjugate base is less stable – less delocalization

We already know that this is a measure of acidity, the higher the equilibrium constant that is greater the K eq, the better the acid okay so we already know this right. And the acidity of a molecule is determined by the stability of the conjugate base, so the stability of this conjugate base here going to determine the position of the equilibrium. Now the stability of the conjugate base is determined by how delocalise the charges, the more delocalised the charge the more stable the molecule is. So by putting an electron withdrawing group EWG, EWG is Electron Withdrawing Group ok, what happens is that we pull the electrons from the carboxylate and help it delocalise and the more delocalised it is, the more stable it is right.

So by putting an electron withdrawing group I am going to push this equilibrium towards the right and therefore the acidity improves right. Conversely if I have an electron donating group that increases the localisation of the charge on the carboxylate and therefore the K equilibrium is going to go down. So therefore in order to study the effects of electron withdrawing or an electron donating group, I can use benzoic acid, benzoate equilibrium as a model system.

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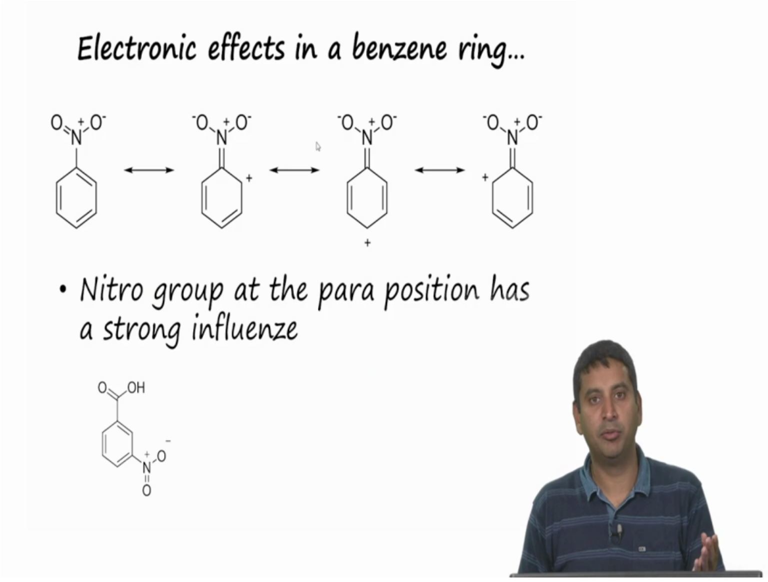

Electronic effects in a benzene ring...

- Nitro group at the para position has a strong influenze

Now we already are familiar with how a particular substituent can have an influence whether it is on the para-position on the meta position. So here is an example of a nitro group on a benzene ring, so if I draw the resonance form, I see that there is a charge being localised in the ortho position and the para-position and whereas the meta position the charge localisation is not very good right. So therefore there is a differential in the way in which the electron cloud is going to distribute itself in this particular case. Now similarly when I have a substituent nitro group in the meta position, the influence on the carboxylic acid is far lesser then when we have it in the para-position, so these are concepts that we have studied previously in our organic chemistry courses, I am not going to repeat these things at this point right.

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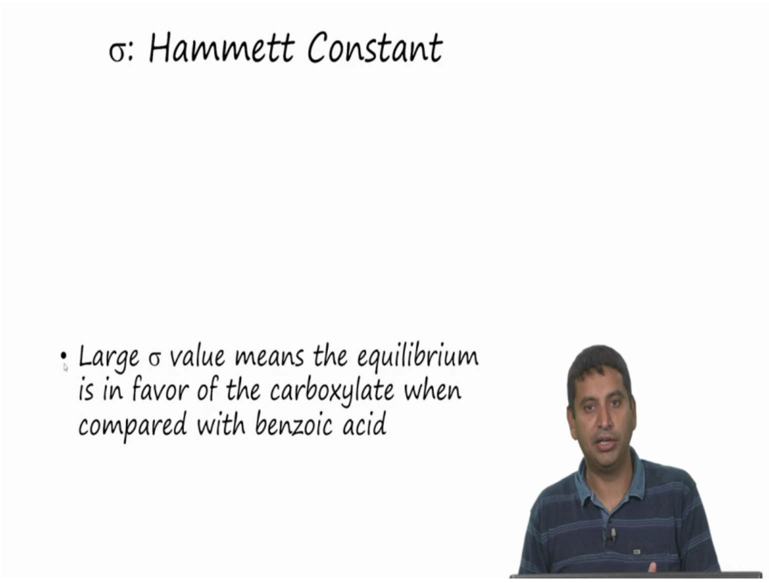

σ: Hammett Constant

- Large σ value means the equilibrium is in favor of the carboxylate when compared with benzoic acid

So what Hammett did many years back was to introduce a term called as Sigma which is nothing but the Hammett constant ok. So what Hammett did was he took this equilibrium of benzoic acid which I am drawing over here C double bond OH + H2O giving you an equilibrium with, so he took this equilibrium, what we write in this is actually K ok, and this by putting a substituent X on this he defined a parameter known as log of K X by K H, this he called as Sigma okay.

So if I have a substituent X that increases the equilibrium constant which means that it becomes a better acid which means that the conjugate base is more stable than I would have a higher Sigma value ok. Conversely, if we have a substituent which decreases the stability of the conjugate base and as a consequence the log K X by K H would be lower okay, in this case it can be negative right. So therefore Sigma is the measure of how well the substituent influences the position of the equilibrium of benzoic acid and benzoate ok assuming that benzoic acid is the benchmark.

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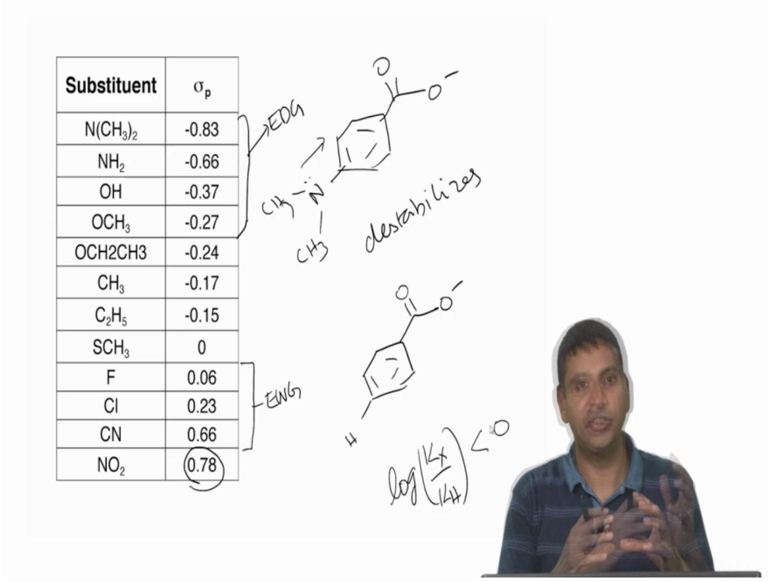

Substituent	σ_p
$N(CH_3)_2$	-0.83
NH_2	-0.66
OH	-0.37
OCH_3	-0.27
OCH2CH3	-0.24
CH_3	-0.17
C_2H_5	-0.15
SCH_3	0
F	0.06
Cl	0.23
CN	0.66
NO_2	0.78

Now based on this we can derive Sigma values for various substituent are so let us go through a few of them now for us to have a better understanding. So keep in mind what we looked at was nitro group, so nitro group basically can help stabilise the negative charge on benzoate much better and therefore the position of the equilibrium is going to favour the benzoate when compared with the corresponding benzoic acid okay, I will repeat this. So when we compare the stability of the conjugate base with Para Nitro benzoic acid which is Para Nitro benzoate, it is significantly more stable than benzoate therefore, the position of the equilibrium in the case of Para Nitro benzoate as it will be far more in favour of the conjugate base and therefore log of K X by K H is greater than 0 right.

So the value for nitro is 0.78, and as you can see here there are bunch of electron withdrawing groups, and all these values are somewhere in the positive region. So SINO is a very good electoral withdrawing group, chlorofluoro are by electronegativity they are quite good at pulling electrons towards themselves. Now let us look at the case of an electron donating group, so if we have benzoate as I have drawn below, and look at the conjugate base. The example we take is N and CH3, CH3, this has a lone pair of electrons which can be pushed into the benzene ring and it can destabilises the conjugate base.

Therefore the position of the equilibrium in the case of N dythmethal amino benzoic acid is going to be far more and favourable benzoic acid when compared with the parent benzoic acid. Therefore, electron donating groups such as here are going to have a negative sigma value, is what we looked at earlier is log of K X by K H is going to be less than 0. And therefore this gives us an estimate of how a particular substituent in this case in the para-position influences the electronics of the benzoate of the carboxylate and it helps us understand what is the influence on the level of ionisation and also on the level of polarisation right so this parameter is very useful to study electronics.

Now this also works for a substituent in the meta position, but once they start putting substituent in the ortho position, statics will come into play and therefore we do not consider ortho substituted benzoic acids in this analysis. We will look at in detail the effects of Sterics in the later part of this course right, so the effect of electronics can be studied using this Hammett scale.

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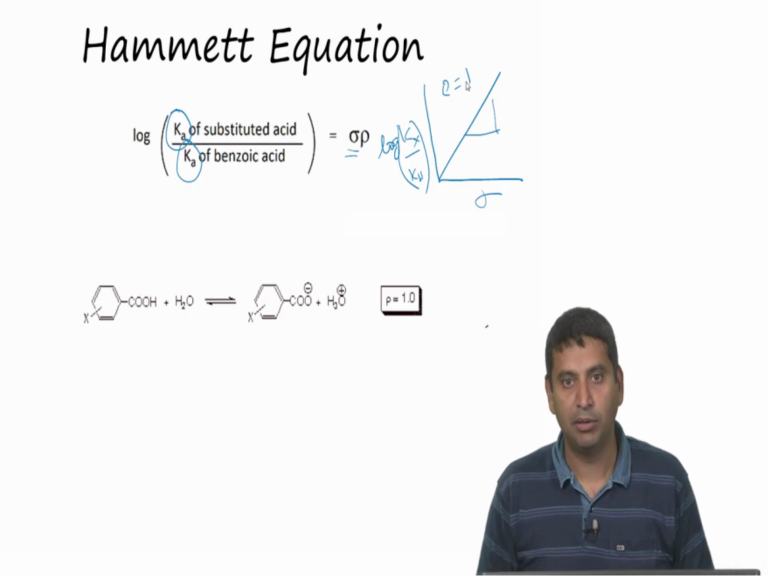

Hammett Equation

$$\log\left(\frac{K_a \text{ of substituted acid}}{K_a \text{ of benzoic acid}}\right) = \sigma\rho$$

$\rho = 1.0$

So here is the equation that Hammett defined, so if I take the K of substituted acid, so K equilibrium can be converted to K A by factoring in water, so if I consider the K A of a substituted acid and compare it with the K A of benzoic acid, so if I take a log of this then we have already defined Sigma as being the ratio of these 2 parameters, and now the slope in this case would be 1. So if I take log of K X by K H for the case of benzoic acid and plot it versus Sigma then I would get a straight line on the slope of 1 and interceptive 0. Now this is because we are comparing the values of benzoic acid with benzoic acid.

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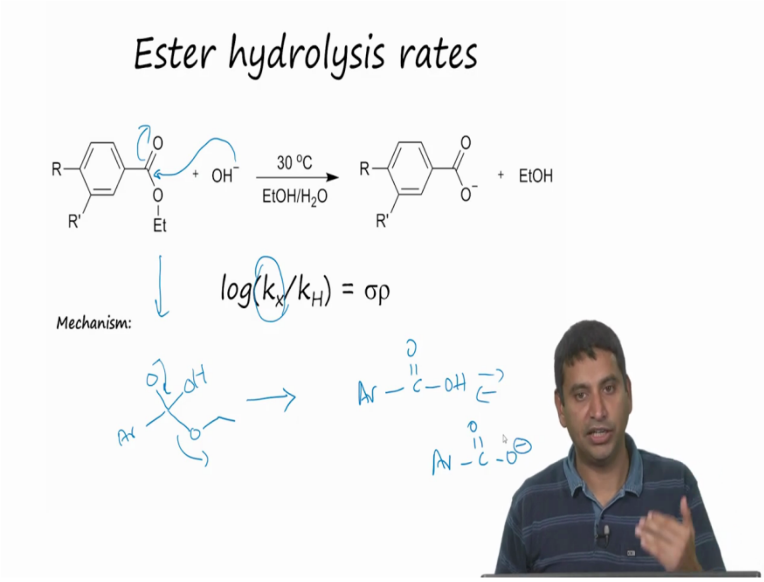

Ester hydrolysis rates

$\log(k_x/k_H) = \sigma\rho$

Mechanism:

But now if I take a hypothetical reaction which let us say is Ester hydrolysis and if I measure the rate constant of hydrolysis then I can determine K X which is basically the rate of the reaction with a substituted benzoyl ester with an un-substituted benzoyl ester. So here is the example that we are taking, so we take this ethel benzoates and react them with hydroxide ions at 30 degrees in ethanol and water, so what we would expect would happen is OH minus attacks here and then this goes back out and it generates tetrahedral intermediate which then can subsequently collapse and kick out ether oxide which will give you A r C double bond OH which is going to rapidly equilibrate with A r C double bond O O minus.

This is an example of a reaction that we want to study and how the reaction is affected by changing electronics, so what I need to do is to determine the rate constant of the reaction and then study what happened when I change the substituent.

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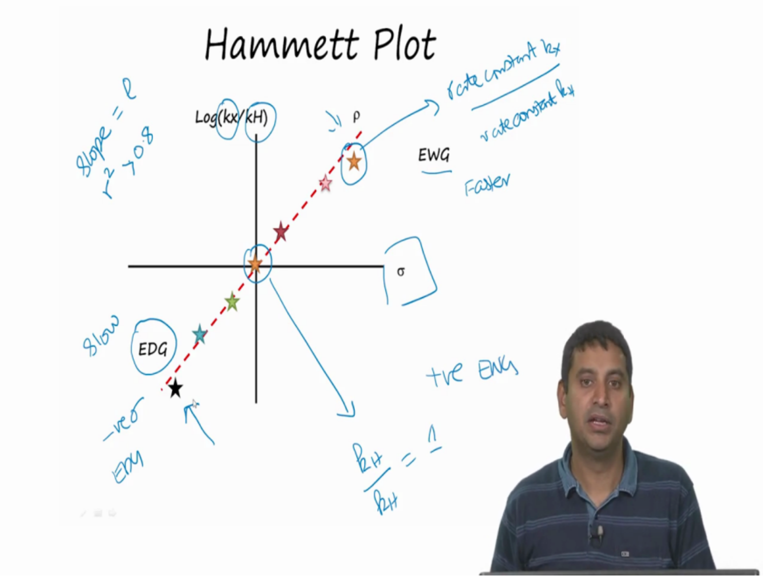

Now what we do is we take the log of K X by K H and then plot it versus Sigma, so this is how a typical Hammett plot would look like ok. So keep in mind a positive Sigma value means that it is in the electron withdrawing group, and negative stigma value means that it is in electron donating group. So when I plot this ester hydrolysis versus Sigma, I get points such as this, so each of these is the individual rate constant K X divided by rate constant for H ok. So if I take this point here, this is nothing but K H divided by K H that is equal to 1, the log of that value ends up being 0.

Now if you look at this plot you can see that electron donating group has a slower reaction compared to hydrogen whereas in electron withdrawing group has a faster reaction ok that is the 1st observation we make. Second observation is you can actually fit it to a line, what we learned earlier which is linear regression analysis and then you can determine the slope which is nothing but Rho ok. And you can also determine the linear regression coefficient which is R square which we have said that if it is greater than 0.8 then it is a good fit to a line, so this study allows us to predictably study what happens when I change a subsequent on the rate of a reaction, in this particular case we have taken the rate of ester hydrolysis right.

Once I fit this into a line, let us say I want to accelerate the rate of reaction, I know that I have to look at higher Sigma values, and if I want to slow down the reaction of ester hydrolysis then I need to go to lower Sigma values okay. And therefore it is a predictable mechanism that one can use to design the next set of compounds if needed.

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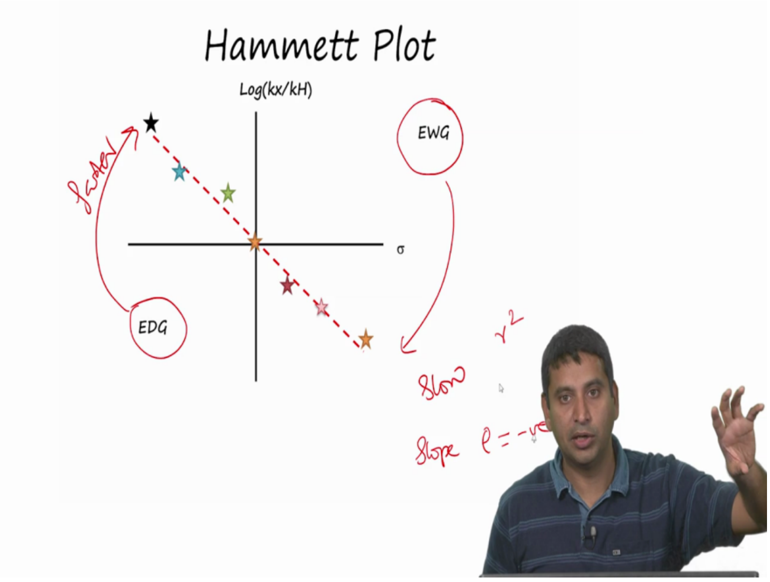

Now let us look at another example that we have a similar Hammett plot for another reaction where the trend is exactly the opposite. And electron withdrawing group which has high sigma value seems to slow down the reaction, while electron donating group which has a negative sigma value makes the reaction go faster ok. So now if I fit this to a straight line I can get a linear regression coefficient R square, I can determine the slope which is basically Rho, here in this case Rho would be negative ok. What this tells me is that in a particular series of reactions the mechanism of the reaction involves a transition state that is sensitive to electronic effects, so therefore you can have a situation where the electron donating group can accelerate the reaction whereas the electron withdrawing group can slow it down.

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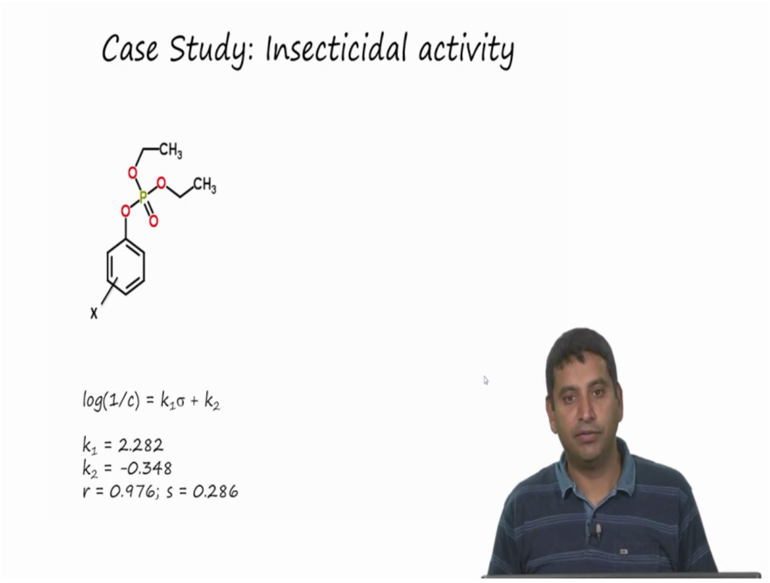

Case Study: Insecticidal activity

$\log(1/c) = k_1\sigma + k_2$

$k_1 = 2.282$
$k_2 = -0.348$
$r = 0.976;\ s = 0.286$

We would not go into too much details about the Hammett plot, now let us look at a case study where we have looked at the insecticidal activity of this organophosphate ok. So here what we have done is we have taken this prospect and there is a we have systematically changed the group on the benzene ring And when I studied the insecticidal activity, I get a QSAR equation of this sort and it showed that the electronic defect had a tremendous influence on the inhibitory activity by this set of molecules ok. So these molecules we find that electron withdrawing group on the aryl ring enhances the activity. So electron withdrawing group on differing increases the activity whereas in electron donating group slows it down that is indicated by the slope K 1 ok.

And K 1 being a positive value means that electron withdrawing group would increase the activity. These molecules were later found to be targets for acetylcholinesterases which are expressed outside the membrane and therefore it is understandable that the organophosphate will get hydrolysed better when you have an electron withdrawing group because the Phenylhyde becomes a living group in this case. So the QSAR on hydrophobicity shows no dependents right, so these 2 data are actually consistent in what we would expect that A insecticidal activity depends on electronics because better the conjugate base better the living group, number 2 the enzymes that are expressed are expressed outside the cell membrane so therefore there is no need for it to get across the cell and get into the cell to exert its activity ok.