Mechanisms in Organic Chemistry

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Lecture-14
Linear Free Energy Relationships (LFER)

Welcome back. In the last class we were looking at experiments to determine the nature of the substituent and I had introduced you to the standard reaction used by Hammett to get what is called as the substituent parameter or the substituent constant.

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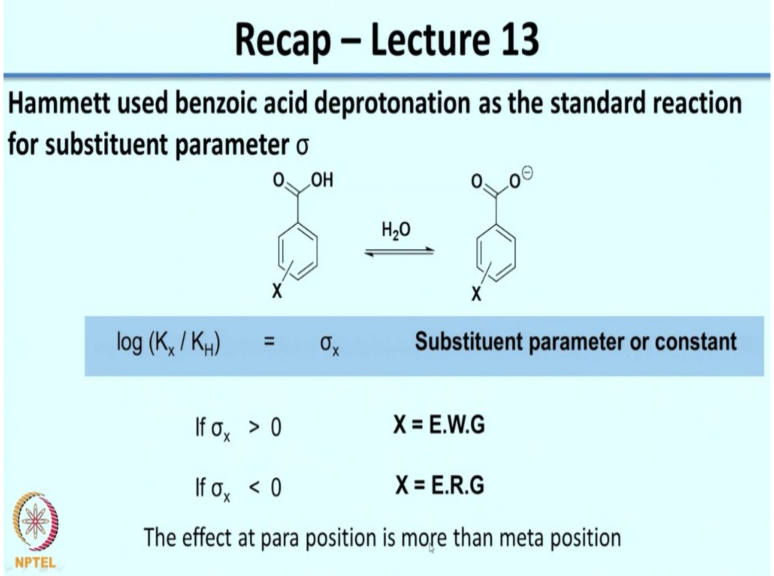

Recap – Lecture 13

Hammett used benzoic acid deprotonation as the standard reaction for substituent parameter σ

$\log (K_x / K_H) \;=\; \sigma_x$ **Substituent parameter or constant**

If $\sigma_x > 0$ **X = E.W.G**

If $\sigma_x < 0$ **X = E.R.G**

The effect at para position is more than meta position

So, the standard reaction is the benzoic acid dissociation to give the conjugate acid which is the benzoate iron and H_3O^+. Now for this reaction the effect of substituent was seen on the equilibrium constant K and the substituent parameter is given by log (K_X/K_H) where X is the substituent on the aromatic ring. So, for this reaction what was seen is this value of Sigma x is greater than 0 when you have an X which stabilizes the benzoate ion.

So, when you have X as an electron withdrawing groups such as nitro, cyano it stabilizes the benzoate ion and that is why you get σ_x greater than 0 if you have electron releasing groups such as OMe, Me it destabilizes this and that is why the value of K_X is less than K_H which means Sigma x is negative or less than 0 and what we had seen is the effect at para position is more than meta position in cases where you have more of a resonance effect whereas where you have an inductive effect you would see that the effect at meta position is higher. But in most cases we had seen that there was a combination of resonance and inductive effect.

So, now the question is we have this standard reaction which is benzoic acid dissociation or deprotonation. How do we use this to understand reaction mechanisms.

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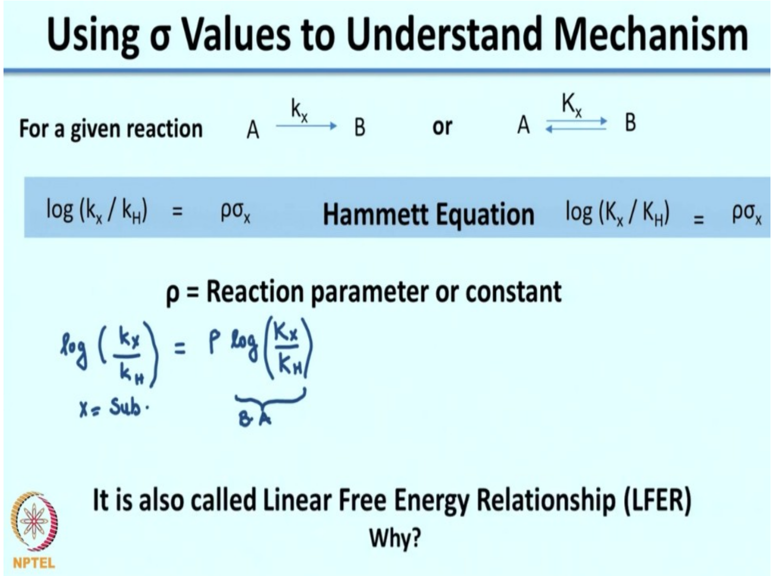

Using σ Values to Understand Mechanism

For a given reaction $A \xrightarrow{k_x} B$ or $A \xrightleftharpoons{K_x} B$

$\log(k_x / k_H) = \rho\sigma_x$ **Hammett Equation** $\log(K_x / K_H) = \rho\sigma_x$

ρ = Reaction parameter or constant

$$\log\left(\frac{k_x}{k_H}\right) = \rho \underbrace{\log\left(\frac{K_x}{K_H}\right)}_{B.A}$$

X = Sub.

It is also called Linear Free Energy Relationship (LFER)

Why?

So, for this, Hammett came up with what is called as the Hammett equation. So, in the Hammett equation for a given reaction, so now remember we are not talking about benzoic acid dissociation anymore. So, imagine any reaction you are taking you have A going to B and let us say it goes with a K observed of K_X. You can also have a process under equilibrium where you have A in equilibrium with B and the equilibrium constant given by K_X. Essentially what the Hammett equation says is that the log (K_X/K_H) for this equation, A going to B is $\rho\sigma_x$

So, we already saw in the last class what Sigma X is that is your substituent constant. Rho is now a new proportionality constant called as reaction parameter or reaction constant and that is specific to the reaction that you are studying that is A going to B. Similarly, for this reaction A and B in equilibrium, the log (K_X/K_H) is equal to $\rho\sigma_x$. So, here you are talking about the ratio of equilibrium constants.

So to give you a little bit more idea about this, so essentially what this means is if you have a reaction, so here again you would be varying the substituents at the aromatic ring of your react reaction. So, log of K of your substituent over hydrogen would be given by Rho times log of the equilibrium constant K_X/K_H, so log (K_X/K_H) and this is of benzoic acid, so this is the σ value or the standard value.

So, whenever you study a reaction you would need to determine the rate of the reaction by varying different substituents. So that is your numerator where X is equal to substituent just like that for Sigma. So, log (K_X/K_H) would be given would be directly proportional to σ. Now this is called a linear free energy relationship. So, can you say why this is called a linear free energy relationship? Linear you can understand we are talking about a direct proportionality but now what you need to think of is how do you equate the free energy with the rate constants or the equilibrium constants.

So, I will give you a minute to think about it if you want you can press the pause button on the video and think about it. So, why LFTR or linear free energy relationship?

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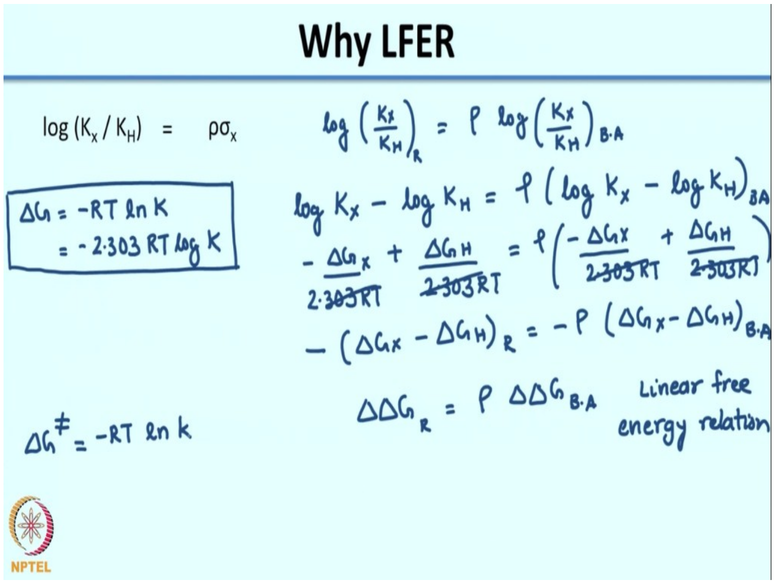

Why LFER

$\log(K_x/K_H) = \rho\sigma_x$

$$\boxed{\begin{aligned}\Delta G &= -RT \ln K \\ &= -2.303\,RT \log K\end{aligned}}$$

$$\Delta G^{\neq} = -RT \ln k$$

$$\log\left(\frac{K_x}{K_H}\right)_R = \rho \log\left(\frac{K_x}{K_H}\right)_{B\cdot A}$$

$$\log K_x - \log K_H = \rho\left(\log K_x - \log K_H\right)_{BA}$$

$$-\frac{\Delta G_x}{2.\cancel{303RT}} + \frac{\Delta G_H}{\cancel{2.303RT}} = \rho\left(-\frac{\Delta G_x}{\cancel{2.303RT}} + \frac{\Delta G_H}{\cancel{2.303RT}}\right)$$

$$-\left(\Delta G_x - \Delta G_H\right)_R = -\rho\left(\Delta G_x - \Delta G_H\right)_{B\cdot A}$$

$$\Delta\Delta G_R = \rho\,\Delta\Delta G_{B\cdot A}$$

Linear free energy relation

So, let us look at the case where you have log $(K_X/K_H) = \rho\sigma_x$ which is your Hammett equation so what that means is as I said earlier log (K_X/K_H) for the reaction is equal to Rho log of K_X/K_H benzoic acid. Correct? So, now you know ΔG is equal to that is, so log K would be - ΔG/2.303 RT. So, with this in mind we can substitute here. So essentially what this makes this equation becomes this log of K_X for your reaction - log of K_H for your reaction is equal to Rho of again log of K_X for benzoic acid - log of K_H for benzoic acid. And this is for the reaction.

So, now we can go ahead and write this in terms of ΔG. So this would be $-\Delta G_X + \Delta G_H / 2.303$ RT this would be equal to Rho of again minus so this will go, so essentially what you would get is, so this is for your reaction would be equal to -Rho for benzoic acid. So, essentially what that means is the ΔΔG for a particular substituent for your reaction would be equal to Rho of; so essentially the free energy of your reaction is directly proportional to benzoic acid, which is why it is called a linear free energy relationship.

Now if you were to think of it in terms of rate constant, you can also think of the rate constant where instead of ΔG you will essentially have ΔG of your transition state so $\Delta G^{\neq}$ would be given by -RTlnk. So, even when you are looking at rate constants you can still get this linear free energy relationship. So, now mathematically we have written what this means but what this tells you is that whatever reaction you take you are talking about a linear correlation with benzoic acid when you vary the substituent.

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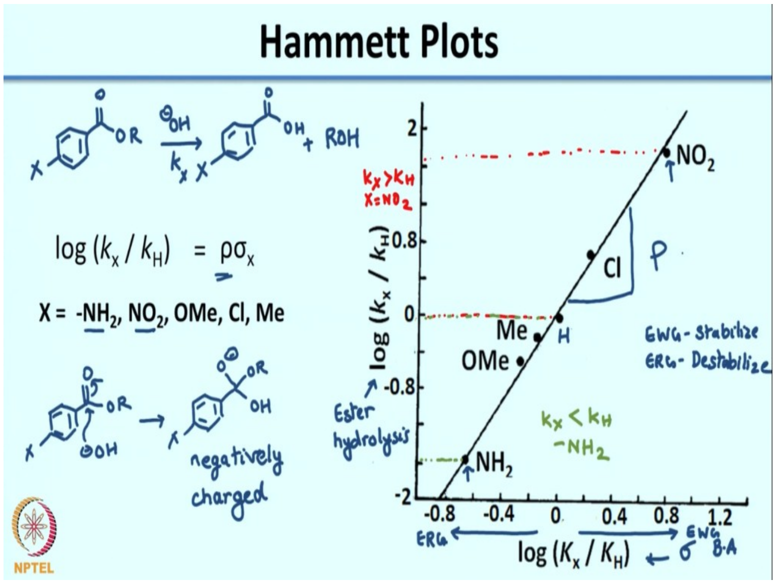

Hammett Plots

$$\log(k_X / k_H) = \rho\sigma_X$$

X = -NH₂, NO₂, OMe, Cl, Me

So what does this mean? let us try to understand a little more, Shown here is one of the earlier examples shown by Hammett. So, this is for the reaction of ester hydrolysis in the presence of base, so this is the reaction for ester hydrolysis in the presence of base. So, on your Y-axis you are looking at log (K_X/K_H) for ester hydrolysis and again what was done was you put substituents here and you vary it from electron releasing electron withdrawing to see how it has an effect on this rate constant which is small k.

So, for every substituent you will have a rate K_X, So on your Y-axis you have the log (K_X/K_H) for the different substituents and the substituents studied where NH_2, NO_2, OMe, Cl and Me as shown on your screen. Now on the X-axis what you have is Sigma so that means the substituent constant which you get from benzoic acid. As I told you this value you need not experimentally determine because it is already been done and you have these values that can be picked out from any textbook which has the table on your substituent constants all the Sigma value.

So, now if you were to think, I am not showing you which of these corresponds to which substituent because I would like you to think about it. Match the substituent is given here with the 5 points that is shown on the screen a one clue I can give you is the X axis corresponds to the substituent constant. So, now you have a value of 00 corresponds to hydrogen. So, you can take some time to solve this, pause the video and match these substituents with the points on the graph.

So now if you look at the substituents based on the X axis the most electron withdrawing substituent would stabilize the benzoic ion would, more so most electron-withdrawing here is your NO_2 group and most electron releasing substituent which is your amine will actually destabilized your benzoate ion so that would be the most negative. So, this would correspond to the most electron releasing and this would correspond to the most electron withdrawing substituent.

So, now that you have this hint can you now try to fill out the values for the electron releasing and electron withdrawing substituents? So, what you would see is you have NO_2 which is most electron withdrawing then you have Cl followed by Me, OMe and then NH_2. So, you can understand this looking at the X-axis which is your substituent constant. Now what this tells you is that let us now focus on the Y-axis, even for this particular reaction which is the ester hydrolysis,

What you see is when you have electron withdrawing substituents the K value your Y-axis is higher than what you have for hydrogen. So, what you will see is if you compare it with hydrogen and your NO_2 group the value for nitro is greater than K_H. So, essentially even in your Y-axis you have K_X greater than K_H where X is equal to NO_2 .So what do you see in the case of amine? In the case of amine what you see is that now, again this will be the same.

Your K_X is actually less than K_H for NH_2. So what this tells you is that electron withdrawing groups stabilize stabilize this reaction and electron releasing groups destabilize this reaction. So, now let us try to look at the mechanism for this reaction. So, if you think of the mechanism a plausible mechanism could be; now if you generate an intermediate like this which is negatively charged. So, this is similar to the case of your benzoic acid dissociation.

So, which is why the effect that you see is also similar where you have electron withdrawing groups actually stabilizing this and electron releasing groups destabilizing this. So in this case what you see is you see Rho which is the slope of this is positive. Right? So, Rho is positive because just imagine as I said these two points you can imagine the amine and the Nitro what happens is if you think of this as a weighing scale 00 is where you have hydrogen.

So let us imagine 00 is where you have hydrogen, so I will try to show this from your perspective so if this is the graph this is hydrogen on the right you have electron withdrawing groups on the left you have electron releasing groups So, what happens is in the case of electron withdrawing groups, if the rate is increased you have a slope which goes up like this so what will happen is the slope would be positive similar to that for because the effect is similar to what is seen for benzoic acid.

So, now it is very useful for us because the slope of the plot which is Rho gives you lot of information about the nature of the intermediate.

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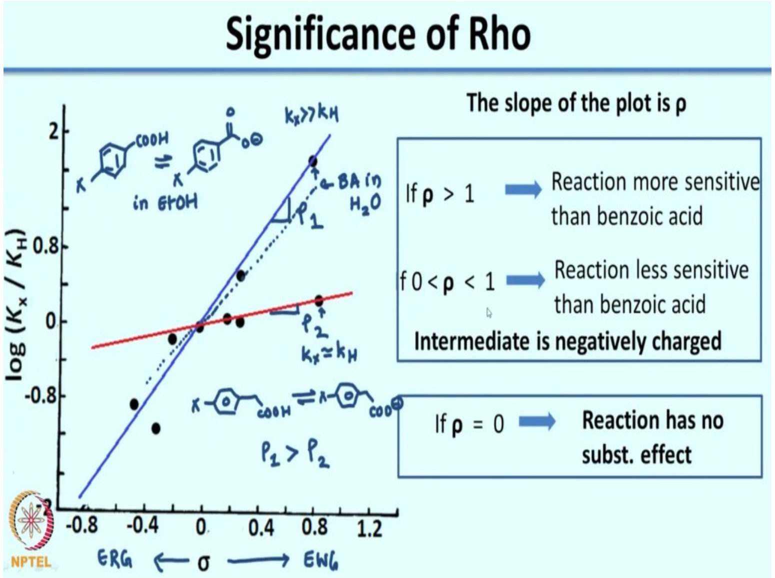

Significance of Rho

The slope of the plot is ρ

If ρ > 1 ➡ Reaction more sensitive than benzoic acid

f 0 < ρ < 1 ➡ Reaction less sensitive than benzoic acid

Intermediate is negatively charged

If ρ = 0 ➡ Reaction has no subst. effect

So, now let us see what information we can get from these slopes. So, here you are seeing two different slopes one is larger and one is smaller so this corresponds to Rho 1 and this corresponds to Rho 2 and what we see here is that Rho 1 is greater than Rho 2. So, what that means is on your x axis as I told you anything greater than 0 corresponds to electron withdrawing groups and less than 0 corresponds to electron releasing groups.

So, what this means is that when you have an electron withdrawing group let us say this these 2 points the effect that you see in the case of reaction 1 where you have Rho 1 as the slope is much higher than Rho 2. So, in this case you can say K_X is much more than K_H whereas in this case what you see is K_X is almost equal to are just slightly greater than K_H. Now if you look at these two reactions it would make sense to you as to why this is the case.

So, the reaction below is so it is again the dissociation of a carboxylic acid but what you see here is the carboxylic acid is farther away from the aromatic ring as compared to benzoic acid so what you see is that the effect is not as pronounced. The other reaction is actually dissociation of benzoic acid in ethanol. So, now if I were to compare it with benzoic acid dissociation for benzoic acid dissociation so since the equation your Hammett equation is log (K_X/K_H) is equal to

$\rho\sigma$.

Since on the left also you have σ you are talking about a slope which is 1. So, what that means is that it would be slightly lower than this at an angle of 45 degrees. So, it will be slightly lower than this, this is for benzoic acid in water. Now the interesting question is why is the dissociation of benzoic acid in ethanol affected more by substituents as compared to benzoic acid in water? I would like you to think about this it is a slightly challenging question so do not feel bad if you are not able to get the answer immediately.

But the question is when you think of dissociation of benzoic acid in ethanol why is that more affected by substituents as compared to the dissociation in water? One possible answer is that when you have water, solvation plays an important role in stabilizing your benzoate ion. In the case of ethanol, the extent of solvation is not much.The effect by substituent is a lot more.
So that is why you see that the slope and the magnitude of the slope can give you lot of information about the nature of the intermediate. So, to summarize if you have a Rho value which is greater than 1 which indicates the reaction is more sensitive than benzoic acid. As I told you for benzoic acid since you would have a slope of 1 because your Y-axis and X-axis are both benzoic acid you will get a slope of 1 it is a direct correlation.

If you have a magnitude greater than 1, so here I have shown you an example where it is just slightly greater than 1 so slightly greater than benzoic acid. So, if you have a slope which is slightly greater than 1 or much greater than 1 it will tell you the reaction is more sensitive than benzoic acid and depending on how large the magnitude is you can say how much more sensitive it is as compared to benzoic acid.

The other thing is if you have a slope between 0 and 1 you can say the reaction is less sensitive than benzoic acid but the fact that you have a positive slope, again remember the balance thing that I told you about you have a positive slope implies that electron withdrawing groups stabilize it more than electron releasing groups. So, what that indicates is that the reaction probably goes through an intermediate where you have negative charge, because negative charge will be more stabilised by your electron withdrawing group.

Do not use this as a blanket thing to memorize but any reaction you get you try to see how electron withdrawing and electron releasing groups will affect the intermediate. So, these are the two scenarios where I showed you can look at the value and the magnitude of Rho to understand what could be the nature of the intermediate. Now if the value of Rho is 0 that means whatever substituent you put it has no effect on the reaction, so it essentially tells that the reaction is not affected by any substituent.

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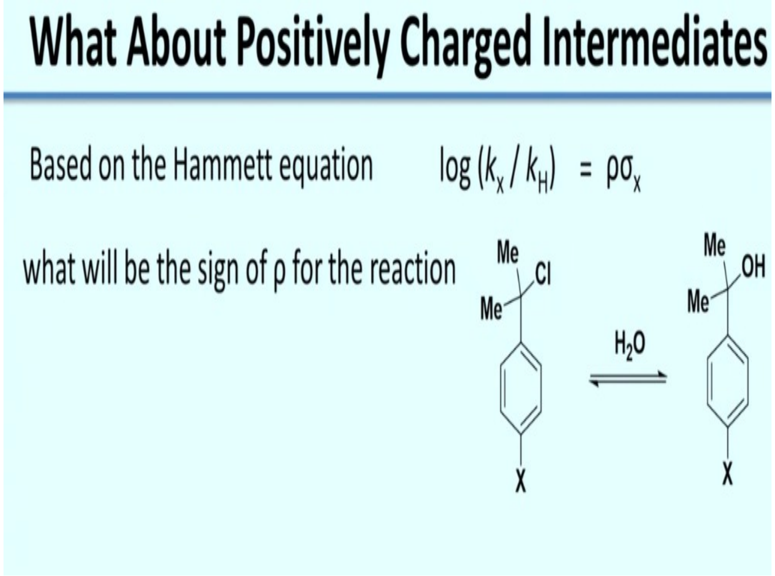

What About Positively Charged Intermediates

Based on the Hammett equation $\log(k_X / k_H) = \rho\sigma_X$

what will be the sign of ρ for the reaction

So now what about positively charged intermediates? Based on the Hammett equation you have log (K_X/K_H) given by ρσ. So, what I would like you to do is I would like you to think about this where if you have a reaction like this. so you have a displacement here, Cl is being displaced by OH so what I want you to think about is what would be the sign of Rho for this reaction. What will this reaction look like? So, you can think about it and we will come back to this in the neck in the next lecture. Thank you.