Mechanisms in Organic Chemistry

Prof. Nandita Madhavan
Department of Chemistry
Indian Institute of Technology-Bombay

Lecture-16
Scales Used in Hammett Plots

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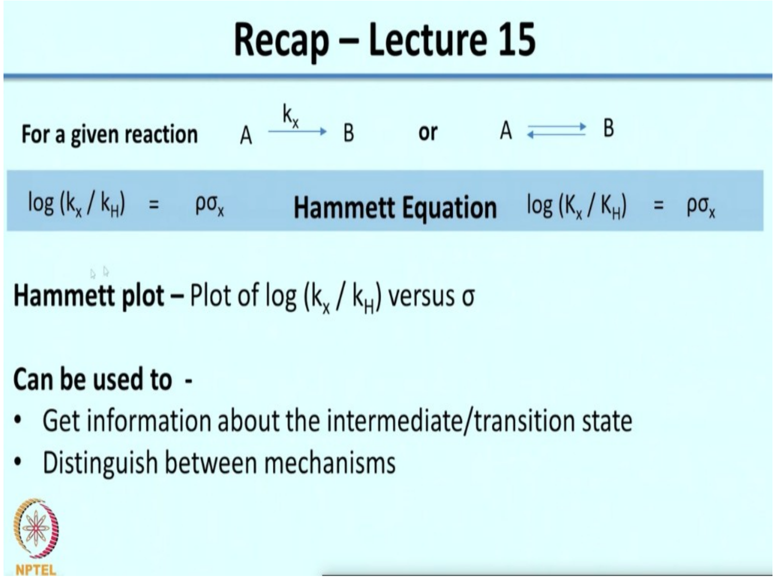
So, welcome back. In the last class, we had looked at the Hammett equation. So, essentially what the Hammett equation does is it correlates for any given reaction, log (K_X/K_H) where X is the substituent that is varied on the aromatic ring.



Recap – Lecture 15

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

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

Hammett plot – Plot of log (k_x / k_H) versus σ

Can be used to -
- Get information about the intermediate/transition state
- Distinguish between mechanisms

So, this correlation with σ which is the substituent constant and rho is called the reaction constant and it tells you how a particular reaction corresponds to the benzoic acid dissociation which is used for determination of the substituent constant.

So, we had looked at how this could be used to get what is called as a Hammett plot for a reaction. So, the Hammett plot is a plot of log (K_X/K_H) versus σ and the slope of the plot is your reaction constant which is rho and this info this could be used to get information about the intermediate or transition state of a particular reaction. We also saw how this could be used to distinguish between mechanisms.

We have viewed that we had used this to distinguish between S_N2 and S_N1 mechanisms. So, before leaving I had given you an example. So if you look at this reaction where you have deprotonation of an aromatic amine.

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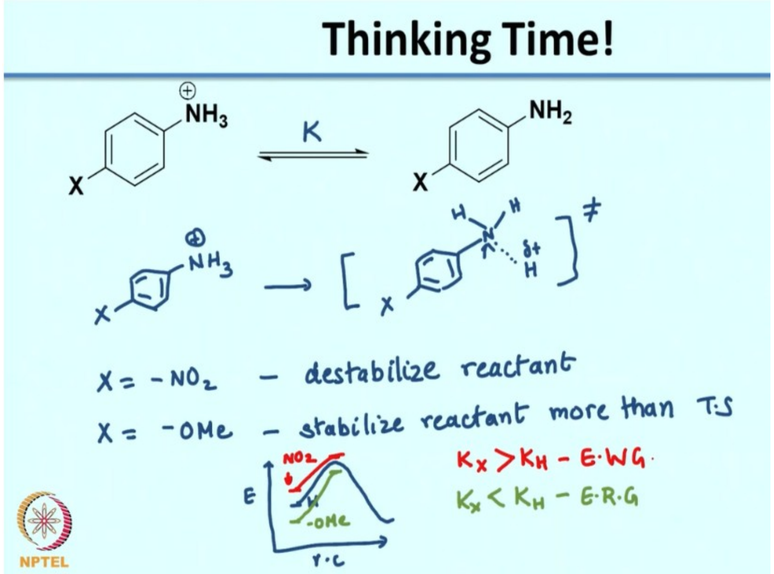

Thinking Time!

$X = -NO_2$ – destabilize reactant

$X = -OMe$ – stabilize reactant more than T.S

$K_X > K_H$ – E.W.G.

$K_X < K_H$ – E.R.G

So, let us look at the K value for this reaction. So, now I had asked you to do firstly write the mechanism for this reaction. So the mechanism for this is straightforward, it is just a deprotonation as is shown here. But now what you need to think of is when you look at the reactant, which is protonated, when you go from reactant to your transition state, so this is the transition state, so in the transition state the NH bond is partially broken.

So, what that does is, that would reduce the charge on, so that would reduce the charge on the nitrogen here. So, now what you need to think of is, as you vary the substituent on the aromatic ring what effect it would have on the reaction. As I told you the easiest thing to do is look at two extreme situations where you have X as NO_2 and X as say OMe or OH. You can use either of these cases. Now in this case, when you have X as OMe what it does is, this would stabilize the reactant and this would stabilize reactant more than the transition state whereas X as NO_2 would destabilize your reactant.

So, as I told you last time, if you now think of the reaction coordinate diagram, where you look at E versus reaction coordinate, in the case of an electron releasing group what would happen is if this is H and this is your reaction profile diagram, in the case of an electron releasing group, let us say X is OMe, it would stabilize your reactant. But it would not stabilize the transition state to the same level. So what you would have is, you would end up having a greater activation energy barrier.

So, what you would have is for an electron releasing group, you will have K_X less than K_H for an electron releasing group. Whereas for an electron withdrawing group what will happen is, since the reactant is destabilized, so let us look at this case where this is NO_2, now because the reactant is destabilized its energy has increased, so, now what will happen is and the corresponding increase in transition state energy is not as much.

So, now what you have is you have a decrease in activation energy. So what you would have is you will have K_X actually greater than K_H when you have an electron withdrawing group. So, now this is a case very similar to the benzoic acid case. So, again remember the weighing scale that we were talking about. You have hydrogen in the middle, electron withdrawing groups to the right, electron releasing groups to the left.

So electron withdrawing groups are increasing the rate of the reaction. So now what you have is a positive slope. So, in this case the rho value is actually positive and if you see the value is quite high in magnitude it is 3.19 and that is because the positive charge in your reactant is in conjugation with the aromatic ring. So, whenever you are you are analyzing any particular reaction to determine the rho value it is very important that you understand how the reaction works.

You cannot directly jump and say that you see a negative charge, the rho will be positive or you see a positive charge the rho will be negative. So, we have done two examples now where this is not the case but then what you would see in both of these examples is that, in this case for example what you see is that the positive charge is reducing from the reactant to the transition state. Now let us look at an interesting application of the Hammett plot. This is again to determine the mechanism of a particular reaction.

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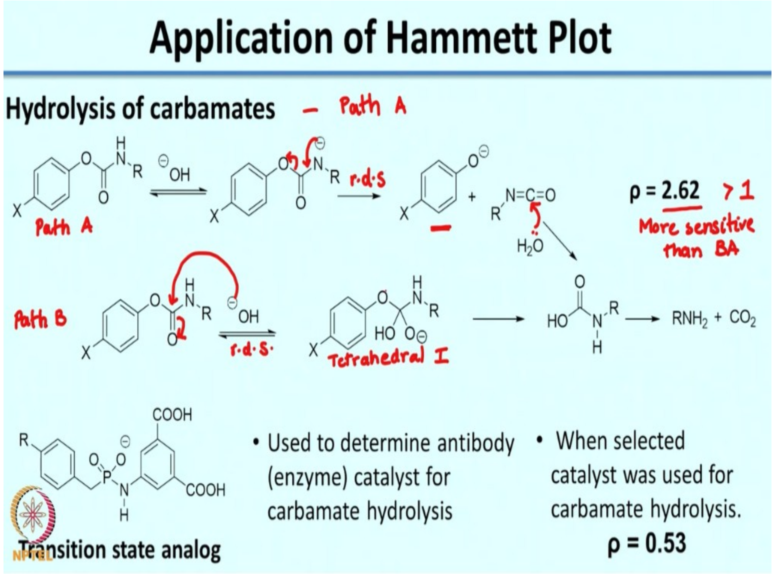

Application of Hammett Plot

Hydrolysis of carbamates – Path A

ρ = 2.62 >1

More sensitive than BA

Transition state analog

- Used to determine antibody (enzyme) catalyst for carbamate hydrolysis
- When selected catalyst was used for carbamate hydrolysis. ρ = 0.53

The reaction that we are looking at is hydrolysis of carbamates. So this functional group here is called a carbamate. So you must be aware of Co NH which is an amide, just the NH which is an amine, OCO NH, this functional group is called a carbonate. So, while considering the base assisted hydrolysis of carbonate, one can imagine a mechanism where OH^- first deprotonates this NH to generate the anion.

Once you have generated the anion you can imagine the anion pushing in the electrons here and this bond cleaving. So what you end up generating is a phenoxide and then what you can imagine is you can imagine water attacking the carbon here to give you the hydrolyzed carbamate, which would further decompose to give you the amine and carbon dioxide. Now another mechanism for this would be where you have the OH^- acting as a nucleophile instead of the base. So the OH^- now is a nucleophile, it will attack here and what you end up getting is a tetrahedral intermediate.

Now, when the Hammett analysis was done for this reaction what was found was that the rho value is 2.62. So, now which of these pathways is the reaction going through? So you can carefully look at both mechanisms. Let us say call this path A and we can call this path B. So, now what I want you to think about is, based on the rho value, which is a positive slope, positive slope indicating electron withdrawing groups increase the rate electron releasing groups decrease the rate.

So, now if you have a positive slope which of these pathways is operative? Pathway A or pathway B? I will give you some time to think about it. You can press the pause button on your video. So, if you are confused, I can give you one more hint. What is known is that whenever you have an acid base kind of equal equilibrium, that would happen pretty quickly as compared to the dissociation we are talking about. So, for path A the rate determining step is the second step whereas for path B the rate determining step is the first step.

Now with this information, are you able to say which is the pathway for hydrolysis of carbamate? Now the magnitude of this is greater than 1. So what that indicates is that it is more sensitive than benzoic acid, correct? We had seen that in the previous two lectures. So, now that you know this is more sensitive than benzoic acid, what you can say is that the negative charge that is formed in the intermediate, would be highly influenced by the substituent. Which could be seen in this case because you have the negative charge in conjugation with the aromatic ring.

So, by this we can say that hydrolysis of carbamates is going through path A. Now is there a way in which we can force the hydrolysis to go through path B? Now this might seem very confusing at first when I tell you that can we actually design a catalyst such that the catalyst will allow the reaction to go only by path B or in other words it would stabilize the transition state for path B more than path A? Is this possible?

So, to do that, an approach that was followed in a research lab was that this particular molecule was taken as what is called as a transition state analogue. So, it was taken as the analogue of the transition state going from the starting material to this tetrahedral intermediate in path B. The only difference being that instead of oxygen you have a carbon here and you have a phosphorus here instead of carbon.

Now this was used to determine the antibody catalyst, or you can think of it as a particular kind of enzyme for carbamate hydrolysis. So, multiple enzymes were taken and their interaction with this transition state analogue was determined. As you know, for a reaction to be catalyzed by an enzyme it is very important that your state fits in very nicely into the enzymes catalytic or active site catalytic pocket or active site.

So, in this case the transition state analogue was taken and multiple enzymes were screened to see which enzymes fit very well with this transition state analogue. So it is like a selection. You have this molecule and you are interacting it with bunch of different enzymes to see which enzyme is stuck to this molecule the best. Now that enzyme was chosen to be the catalyst for the reaction above, which is hydrolysis of carbamate.

The logic being that, because this is so similar to the transition state shown here, what would happen is the energy for this transition state would be significantly lowered as compared to the transition states in pathway A. So, with this idea what was done was, the enzyme that was screened, that is the enzyme which stuck best with the transition state analogue was taken and the selected catalyst was used for carbamate hydrolysis.

And what was observed was that the rho value now decreased dramatically from 2.66 to 0.53

which indicated that the pathway actually switched from A to B. and why is the value low? Can you again look at the structure of tetrahedral intermediate I and try to reason why this is the case? You can pause your video and think about it. So, now in the case of the tetrahedral intermediate the negative charge is quite far away from the aromatic ring.

So, in the case of benzoic acid you had carbon and then O^- in this case you have an oxygen you have another carbon and then you have O^-. So, it is pretty far away from the aromatic ring which is why the effect is lesser than benzoic acid. So, it is less than 1 because the negative charge is farther away from the aromatic ring. So, this is a very beautiful illustration of how a catalyst was actually designed such that the pathway switches from the uncatalysed reaction.

So, in this case uncatalyzed reaction went by pathway A whereas the catalyzed reaction went by pathway B. Now what was observed when these correlations were being made was that if you compare a reaction,

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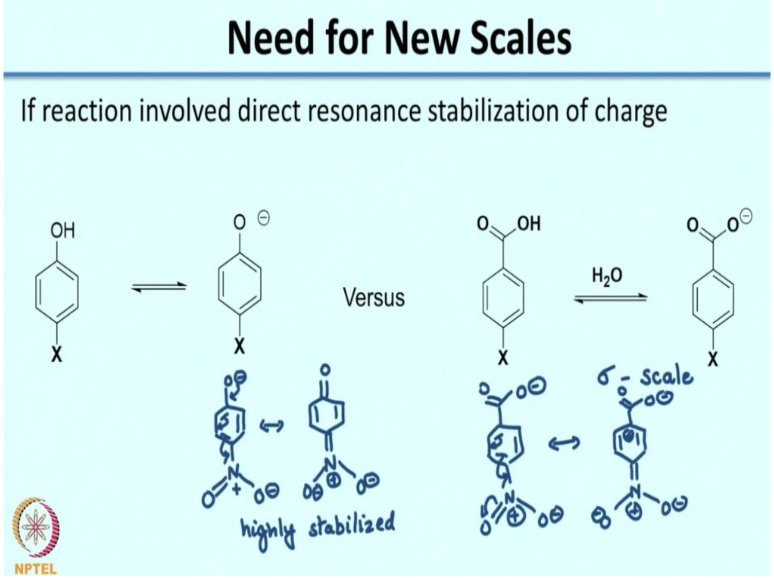

Need for New Scales

If reaction involved direct resonance stabilization of charge

For example, this is your standard reaction for getting the σ scale. Now suppose I am comparing a reaction, this is also a deprotonation reaction in this case we are looking at deprotonation of a phenol to phenoxide. Now in this case what is happening? If I have a substituent, say I have O^- , now in this case the negative charge is directly in resonance with the ring. So, there is a high degree of stabilization. So, this is highly stabilized right? Similarly, if I have an electron releasing group, it will make it highly destabilized. So, now if I compare it with the case of benzoic acid, if I have a nitro group here, if you remember when we had written the resonance structures earlier.

So, when you have a nitro group, you just end up generating a positive charge, O^-, so this is not as stabilizing as the case of the phenoxide. So, what was seen was that in cases where the reaction involves a direct interaction between the substituent via the aromatic ring, the correlation was not as great with benzoic acid. So, you will not find all the dots corresponding to substituents lying on a straight line.

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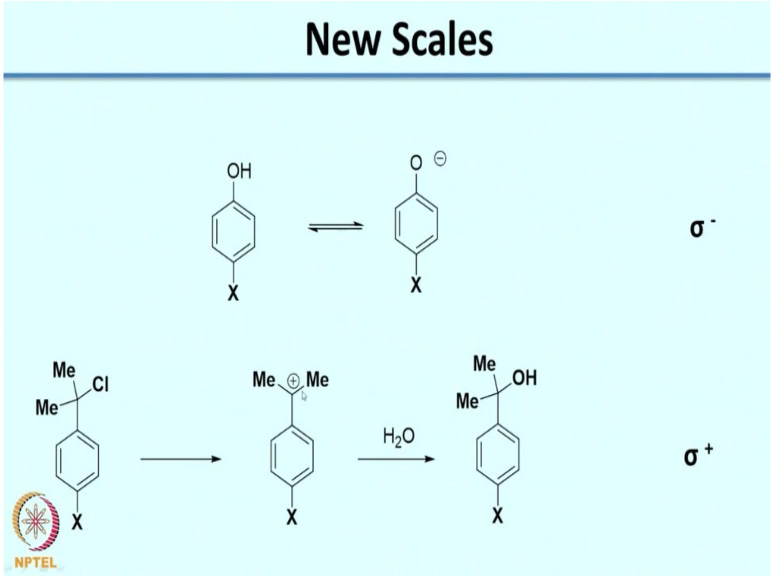

New Scales

σ^-

σ^+

So, then what was said is that for these reactions to new scales would be introduced. So, for a negatively charged intermediate, a new scale which is the σ^- scale was introduced. So, in this case as you can see the negative charge is in conjugation with the aromatic ring and for a positively charged intermediate a new σ^+ scale was introduced because here this is an S_N1

reaction so the carbo cation that is generated is in conjugation with the aromatic ring.

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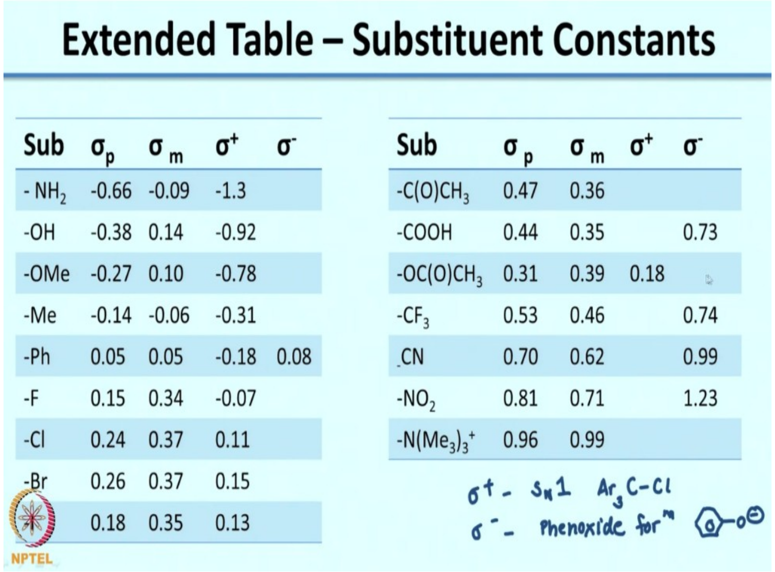

Extended Table – Substituent Constants

Sub	σ_p	σ_m	σ^+	σ^-
$-NH_2$	-0.66	-0.09	-1.3	
-OH	-0.38	0.14	-0.92	
-OMe	-0.27	0.10	-0.78	
-Me	-0.14	-0.06	-0.31	
-Ph	0.05	0.05	-0.18	0.08
-F	0.15	0.34	-0.07	
-Cl	0.24	0.37	0.11	
-Br	0.26	0.37	0.15	
	0.18	0.35	0.13	

Sub	σ_p	σ_m	σ^+	σ^-
$-C(O)CH_3$	0.47	0.36		
-COOH	0.44	0.35		0.73
$-OC(O)CH_3$	0.31	0.39	0.18	
$-CF_3$	0.53	0.46		0.74
-CN	0.70	0.62		0.99
$-NO_2$	0.81	0.71		1.23
$-N(Me_3)_3^+$	0.96	0.99		

σ^+ - S_N1 Ar_3C-Cl

σ^- - Phenoxide for^n

So with these two new scales we can again look at the extended table for substituent constants. So, we had already looked at σ_p and σ_m what you would see is now in the case for example NH_2 what you see is that σ^+, so, what was the reaction for σ^+? For σ^+ it was the S_N1 reaction. So, at S_N1 reaction where you had the Ar 3 C Cl and σ^- it was deprotonation of the phenol.

Now if you think of an electron releasing substituent let us look at a highly electron releasing substituent which is NH_2. When you have NH_2 it will highly, highly stabilize the reaction which is your S_N1 reaction. So, what you would see here is when you have NH_2, the magnitude is much higher. So, σ_p for benzoic acid was .66 whereas for the new scale which is the σ^+ scale the value goes up to 1.3.

Now one might wonder why is the value negative? Because as what we have studied when you have an electron releasing substituent and a positively charged intermediate, the electron releasing substituent should actually stabilize it. So, the K_X should actually be greater than K_H. But in order to keep the scales consistent were always negative σ values correspond to electron releasing groups,

In this case it is switched such that the negative value is maintained. So, the negative value is just put in order to maintain consistency. It is the magnitude which is important. What you see here is now a large increase in the value of σ^+. Similarly, when you have OH again there is a large increase, because now you are taking into account resonance. So, the same effect can be seen for OMe and Me and very interestingly when you look at Ph, it has now gone from a withdrawing group or one with marginal effect to a releasing group in the σ^+ scale.

Because now the resonance contribution is much more important than the inductive contribution. Similarly fluoride has also gone slightly towards the electron releasing side in the case of the σ^+ scale. With the other halides what you see is that the magnitude slightly decreases because now the effect of resonance is slightly more than the inductive effect. In the case of σ^-, what is seen is that, when you have Ph so σ^- is the phenoxide, there is not it much difference between the σ_p and the σ^- scale.

But if you look at the other withdrawing substituents such as carboxylic acid, what you see is the magnitude has gone up. So, now you have .73 as compared to 0.44 for carboxylic acid. Similarly, if you see CF_3 you see a great increase in magnitude or CN for that matter where you have the largest increase in magnitude where it goes to 0.99. Similarly for NO_2 it goes to 1.23. So, what you see is the σ^- scale is very, very useful for electron withdrawing substituent's which will stabilize the phenoxide via conjugation.

Similarly the σ^+ scale is very important for electron releasing groups which will stabilize the carbocation which is in conjugation with the aromatic ring. So, now that we know multiple scales so we have now looked at σ scale, which corresponds to benzoic acid dissociation σ^+ scale which corresponds to the S_N1 reaction, and σ^- scale which corresponds to the phenoxide ion formation. So, there are equations that people have used instead of the Hammett equation to see if the inductive and resonance effects can be decoupled.

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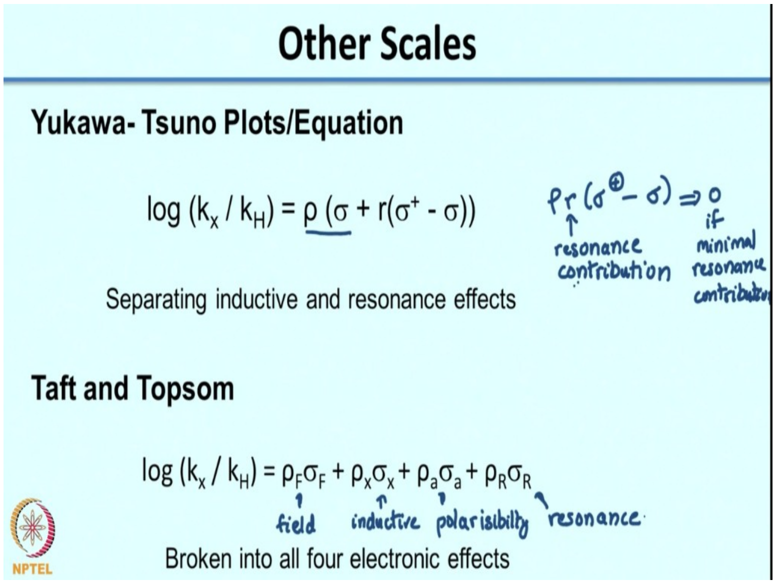

Other Scales

Yukawa- Tsuno Plots/Equation

$$\log(k_x / k_H) = \underline{\rho\ (\sigma} + r(\sigma^+ - \sigma))$$

$$\underset{\substack{\uparrow \\ \text{resonance} \\ \text{contribution}}}{\rho r}(\sigma^{\oplus} - \sigma) \Rightarrow \underset{\substack{\text{if} \\ \text{minimal} \\ \text{resonance} \\ \text{contributi}}}{0}$$

Separating inductive and resonance effects

Taft and Topsom

$$\log(k_x / k_H) = \underset{\substack{\uparrow \\ \text{field}}}{\rho_F\sigma_F} + \underset{\substack{\uparrow \\ \text{inductive}}}{\rho_x\sigma_x} + \underset{\substack{\uparrow \\ \text{polarisibility}}}{\rho_a\sigma_a} + \underset{\substack{\nwarrow \\ \text{resonance}}}{\rho_R\sigma_R}$$

Broken into all four electronic effects

So, one example is the Yukawa-Tsuno plot or equation. In this case, what you see is on the right instead of just the simple ρσ, you have an additional term which is ρ_r (σ^+- σ). The r stands for the resonance contribution. The logic being that σ^+ is a combination of the resonance as well as inductive effect whereas the σ scale, because you do not have direct conjugation with the benzoate ion, is mainly the inductive effect.

So when you subtract both of these, what you get would correspond to the major contribution from resonance. So, this if you notice for a reaction where you do not have much contribution of resonance, similar to the benzoic acid case, this term would reduce to 0 if minimal resonance contribution. So, then essentially the Yukawa-Tsuno equation will boil down to the Hammett equation. So, this again is completely logical where you say that if the resonance contribution is minimal, essentially Yukawa-Tsuno equation is your Hammett equation.

But if there is a significant resonance contribution, the resonance R value would be high and then the second term would have a considerable value. People have also used equations, so this is the

Taft and Topsom equation where it has broken down the Hammett equation to all four effects, where you have the field effect, so this is for the field effect, this is for the inductive effect, this is for polarizing, so this for polarisibility

So, this is for and this is for resonance. So, when you do the experiment, essentially to get one of these plots, what you determine on the Y-axis which is log (K_X/K_H), let us say we are taking a new reaction, whatever you plot on the Y-axis is experimentally determined. So, you would do the reaction for a substrate with substituent X and then you will do another reaction where you do not have such a substituent and you would take the log (K_X/K_H).

So, this is experimentally determined for all these other values, you can get this from a book or from the literature So once you get the Y-axis what you can do is you can fit the line that you get versus σ into various equations shown here and figure out which gives the best fit.

And based on that you can tell, say if it fits better to a σ^+ scale you can say that the reaction involves direct resonance interaction with the aromatic ring. But in principle, although there are many of these other complicated equations, for all practical purposes what is used most is the σ, σ^+ and σ^- scales. So, you need not worry about all these other scales.

Now something very interesting is observed. What is observed is that in some reactions, you do not have a linear relationship throughout the reaction. As in you do not have a linear relationship across all substituents.

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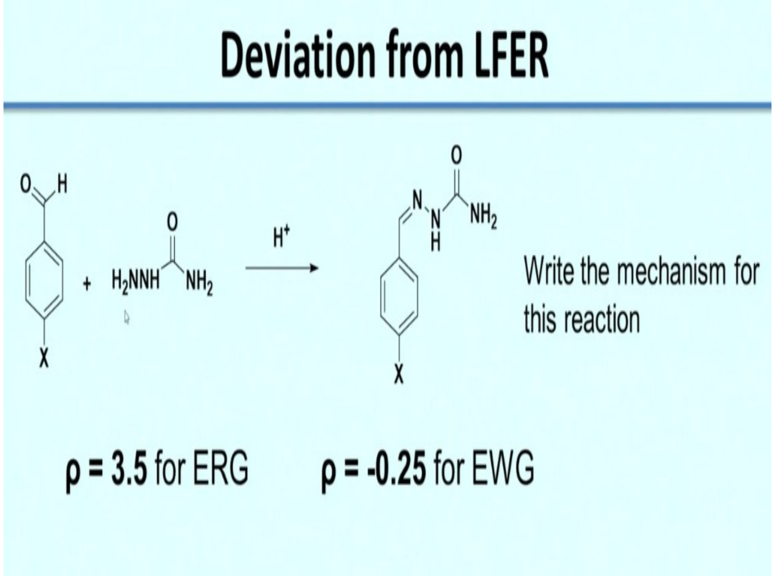

Deviation from LFER

Write the mechanism for this reaction

$\rho = 3.5$ for ERG $\rho = -0.25$ for EWG

So, one example this particular reaction, you might find it familiar. So you have formation of semi-carbazone. So you are interacting the aldehyde with the NH_2, here to form the product, what is seen is depending on the nature of X, so if you have electron releasing groups the rho value is found to be 3.5, whereas if you have electron withdrawing groups the rho value is found to be -0.25. So, why is this? This is actually very interesting.

So, to understand this, the first thing that you would need to do is, you would need to write the mechanism for this reaction. So, we will take this as homework for you, where you first drive the mechanism for this reaction and try to rationalize as to why is it that you have different rho values for electron releasing groups and electron withdrawing groups. So, we will meet in the next class where we will discuss this reaction and also other examples where you see a deviation from linear free energy relationships. Thank you.