Mechanisms in Organic Chemistry
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Lecture-18
LFER for Sterics: The Taft Parameters

So welcome back to the lecture on reaction mechanisms. So, we were working with the Hammett equation and we had looked at several parameters for the substituents as well as reactions. So, the substitution constants we had looked at the values σ, σ^+ and σ^-.

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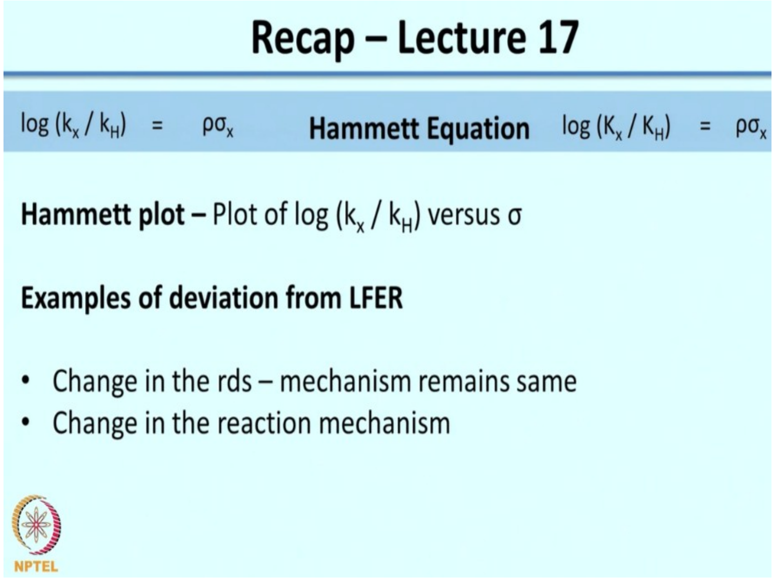

Recap – Lecture 17

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

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

Examples of deviation from LFER

- Change in the rds – mechanism remains same
- Change in the reaction mechanism

And in the last lecture specifically we had focused on examples of deviation from linear free energy relationships. So, typically you would expect that for a particular reaction you get a straight line plot but sometimes what happens is instead of straight line plot what you see is you would see a curved plot and that is because depending on the nature of the substituent the rho or reaction constant changes.

So, we had looked the two examples. One example where the change in the rate determining step leads to this deviation from linear free energy relationships. So, what happens is when you have an electron releasing substituent, one particular step becomes the rate determining step where as when you switch to electron withdrawing substituent, it is another step becomes slower. The other example which we seen is when the mechanism itself completely changes because of change in the reaction mechanism. So, these were the two things that we saw and now just to summarize whatever we have learnt so far,

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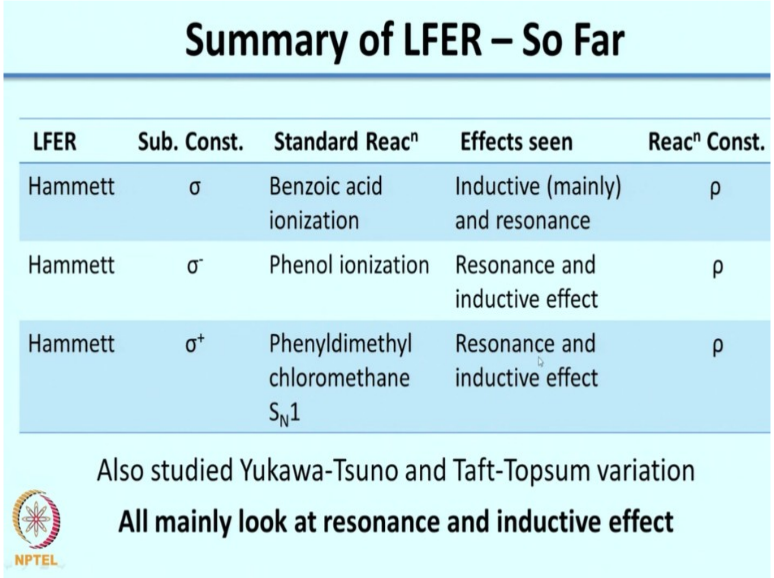

Summary of LFER – So Far

LFER	Sub. Const.	Standard Reac^n	Effects seen	Reac^n Const.
Hammett	σ	Benzoic acid ionization	Inductive (mainly) and resonance	ρ
Hammett	σ^-	Phenol ionization	Resonance and inductive effect	ρ
Hammett	σ^+	Phenyldimethyl chloromethane S_N1	Resonance and inductive effect	ρ

Also studied Yukawa-Tsuno and Taft-Topsum variation

All mainly look at resonance and inductive effect

What we have learnt so far is that the Hammett correlation which uses benzoic acid ionization as the standard reaction gives you the substitute constant σ and essentially the effects that it gives you is inductive mainly, and you also see some amount of resonance effect and the reaction constant for a new reaction is given by rho. And this works best for reactions that do not involve conjugation with the aromatic ring.

So for reactions involving conjugation with the aromatic ring, a good standard reaction if you have negatively recharge intermediate would be σ^-. Where the standard reaction is phenol ionization and here what you see is both resonance as well as inductive effect play an important role. And here the reaction constant is rho. And if you have a positively charged intermediate the reaction is, standard reaction is phenyl dimethyl chloromethane dissociation. So, like and S_N1 reaction and substituent constant is σ^+.

And here again you see an effect which is contributed both due to resonance as well as an inductive effect and here again the reaction constant is rho. We also studied some other variations. But what you see is in all these cases, we were mainly looking at electronic effects of the substituent. So, essentially either inductive or resonance but mainly electronic effects. So, can you have a scale which will actually tell you how the sterics of a substituent actually affects the reaction?

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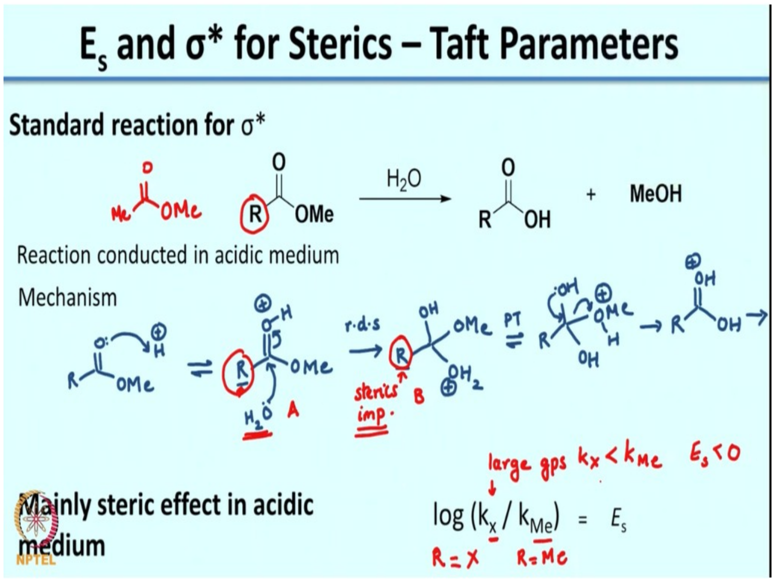

E_s and σ* for Sterics – Taft Parameters

Standard reaction for σ*

Reaction conducted in acidic medium

Mechanism

Mainly steric effect in acidic medium

$$\log (k_X / k_{Me}) = E_s$$

So, this is what we will look at in today's class. So, now just as we had a standard reaction before like the benzoic acid dissociation whenever you want to develop a relationship like this, you need to first find an appropriate standard reaction. In this case, the standard reaction is given below which is the ester hydrolysis. When you think of ester hydrolysis, the reaction can be conducted in an acidic medium or a basic medium.

So, the first thing I want you to do is, since we have also practiced writing reaction mechanism, write the reaction mechanism for ester hydrolysis in acidic medium. So here remember the medium is acidic so you will have protons in the reaction medium. So, with this information I want you to press the power button on your video and draw the reaction mechanism for this ester hydrolysis. So we draw the mechanism together, in case you had trouble writing the mechanism.

So now the reaction medium is acidic. So I will start with first my ester. So in an acidic medium, the first step would be protonation of the C=O. So, what this protonation does is, it increases the electrophilicity at the carbon. Now the next step is addition of your nucleophile. Remember the reaction is under acidic medium. So, you will not have OH^- in the medium. So, what you will get is; and subsequent steps, all those will not be of much consequence because this is your rate determining step.

So, then what you would have is, you would have a proton transfer. Now you are converting this into good leaving group. Once this proton transfer is done, we will have coming in to give you, the protonated product which would then deprotonate to give you the desired product. So, this would be the mechanism for the ester hydrolysis under acidic medium or under acidic conditions. So, now let us look at the rate determining step.

Because we are trying to determine the role of the substituent and let us assume, now we are looking at the substituent at this position R. So in the rate determining step I have A going to B. Now what is happening here is both A as well as B is protonated. So, if I have an electronic effect on A, say electron releasing or electron withdrawing R group, a similar effect will also be felt on B. So if the energy of my reactant as well as my transition state is increased or decreased it will not have much of an effect on the reaction kinetics.

So, this is a very nice example where the electronics actually does not play much of a role at all in dictating the energy of activation or kinetics of the reaction. So, then what will play an important role? Sterics. So, this is very nice example, where, if I consider the R group, sterics is actually very important, electronics is not. So, this equation or this reaction can be used for you to determine the effect of sterics. So that is essentially what was done.

So, if you do this reaction and here the standard reaction is the one where you have R is equal to Me. So, in the benzoic acid case we were looking at an aromatic substitution, remember here we are not talking about substitution on an aromatic ring. What we are saying is that the whole R group, essentially is Me. So, in the standard reaction, we are looking at; Alright? So we are essentially looking at methyl acetate here.

So here, this is your denominator and your numerator has K_X where X is essentially different R groups. So, X is where you have different R groups. So, I; specifying this again because I do not want you to confuse this with the earlier examples we had done where we were only looking at substituents on the aromatic rings. Here we are talking about changing the whole R group. So, for your basic reaction or your standard reaction, you have R as methyl and then to look at the effect of sterics,

what you do is you vary R. So instead of methyl, you can have ethyl and you can have hydrogen, you can have phenyl. So that how you very X. Now log(K_X /K_{Me}) gives you Es. Based on what you have studied earlier with σ, so if you have a group which is bulkier than Me what would that do to your numerator here? So K_X, if you have a bulky group will that be greater than or lower than K_{Me}? I want you to think about this.

So, again let us look at the reaction. You have A going to B and sterics is important that we have already seen. Now if sterics is important, if you have large groups there they will actually make it more difficult for your nucleophile to approach. So, large groups will actually lower the rate. So, just like when you have a traffic jam, if you have large substituents it will be very difficult for your nucleophile to come in.

So, what that would do is that would decrease the numerator here. Alright? So, if you have large groups, K_X would be less than K_{Me} and if K_X is less than K_{Me} what would that do? You would have Es, which is negative. Whereas, if you have small groups, where small group as in you are comparing it with respect to Me, So if you have group smaller than Me then K_X will be greater than K_{Me} and then you will have a positive values. So you will have Es greater than 0.

So, now that we have understood this reaction under acidic medium, can you also use this reaction to get the effect of electronics on a particular reaction such as this? So to study the effect of electronics or to decouple the sterics with electronics a very clever experiment was done. So, here what is done is, you consider the same reaction, now under basic medium. So, now what I like you do is, I would like you to write the mechanism for this reaction under basic medium.

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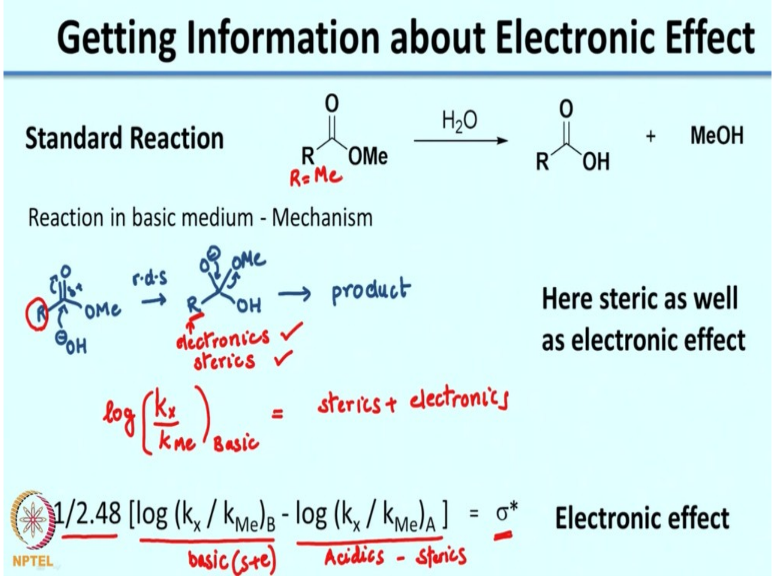

Getting Information about Electronic Effect

Standard Reaction

Reaction in basic medium - Mechanism

electronics ✓

sterics ✓

Here steric as well as electronic effect

$$\log\left(\frac{k_x}{k_{Me}}\right)_{Basic} = \text{sterics} + \text{electronics}$$

$$\underline{1/2.48}\ [\underbrace{\log (k_x / k_{Me})_B}_{\text{basic (s+e)}} - \underbrace{\log (k_x / k_{Me})_A}_{\text{Acidics - sterics}}] = \underline{\sigma^*}$$

Electronic effect

So, you can go ahead, press pause button on your video and write the reaction mechanism under basic medium. So, let us see if you have the mechanism correct. So, I will start with R and then I have; So which is the most electrophilic centre here? It is the carbon here, you have your δ+ so then you add OH^-. Remember now your reaction medium is basic, so you will not have protons but you will have OH^-. So what you will get would be; you will form this tetrahedral negatively charged intermediate.

And then once you from this intermediate you will get your product. So, here your first step, which is the attack of the hydroxide is your rate determining step. So, now let us look at this carefully. Now in this case, if you compare R in the reactant with R in the intermediate what you would see is the reactant is neutral whereas your intermediate has a negative charge. So, this is similar to the benzoic acid case.

So, when you have electron withdrawing R groups, they will actually stabilize the intermediate more than the reactant. So, will electronics make a difference in this particular reaction? Yes. So, electronics important. Now what about sterics? So, even here, since you have the R group close to the carbonyl group here, so, if you have the nucleophile coming in, again the same traffic jam concept.

If you have a large R group it will be more difficult for the nucleophile to come in. So does sterics play a important role? Absolutely. So you will have both electronics as well as sterics play a very important role in this reaction. So, now if you were to vary the substituents just like you did in the previous case. I do not want you to get very stressed looking at this large equation. I will help you understand it, so that it does not look as scary. So, what we will do is, if you have

So, let us look at each term. For now I want you to neglect the first term which is 1 divided by 2.48. This term here corresponds to log($K_X/K_{Me)}$ in a basic medium. So for the reaction above in basic medium, if I do log of; So this will give me sterics plus electronics. So this is in basic medium. So, the first term you get from the reaction which is shown on the screen in front of you, where you talk about the reaction happening in basic medium.

The second term here, after minus is for the reaction under acidic conditions. So, this deals with only sterics and this deals with sterics + electronics. So if I subtract these two terms what is the effect that you get? It is the electronic effect. So again, I will repeat in basic medium you have sterics + electronics. So I will call it s+e. In acidic medium you have only s which is sterics. So, when you subtract basic and acidic what you get is only the electronic effect.

And that is what is given by sigma star. So, σ* gives you only the electronic effect which has been gotten by subtracting the K_X/K_{Me} in the acidic medium from the basic medium. Now let us come to the factor of 1 divided by 2.48. Why this has been added is, when you compare all the values, so we have the scale right for the substituents, the σ scale. So, we want this electronic effect σ* to be comparable in magnitude to that obtained from the Hammett equation.

So, Hammett gives your value σ for certain substituents. Now in the case of Hammett, you have the substituent attached to the aromatic rings; so it is farther away from the negative charge whereas in this case you have the substituent right there close to where the charge has been generated. So, that both these sigma values are comparable a normalisation factor of 2.48 is added. So, which is why the value is divided by 2.48 to give you σ* so that you can put all these values in a single table: the σ, σ^+, σ^- and now the σ*. Alright?

So again, I will give you a summary before we move on to see how we can use this for any reaction. Remember we are still at the standard reaction which is similar to benzoic acid dissociation. So, here the standard reaction is hydrolysis of an ester. In the basis reaction you choose R is equal to Me. So you have R is equal to Me, which is in your denominator and this reaction can be done in an acidic medium and a basic medium.

So, to get the constant which responds to sterics, you look at $\log(K_X/K_{Me})$ in acidic medium and if you want to get both sterics + electronics you look at the reaction in basic medium and just to extract the electronic effect for the substituent you subtract acidic from basic. So, now we have looked at the standard reaction for getting an idea about sterics.

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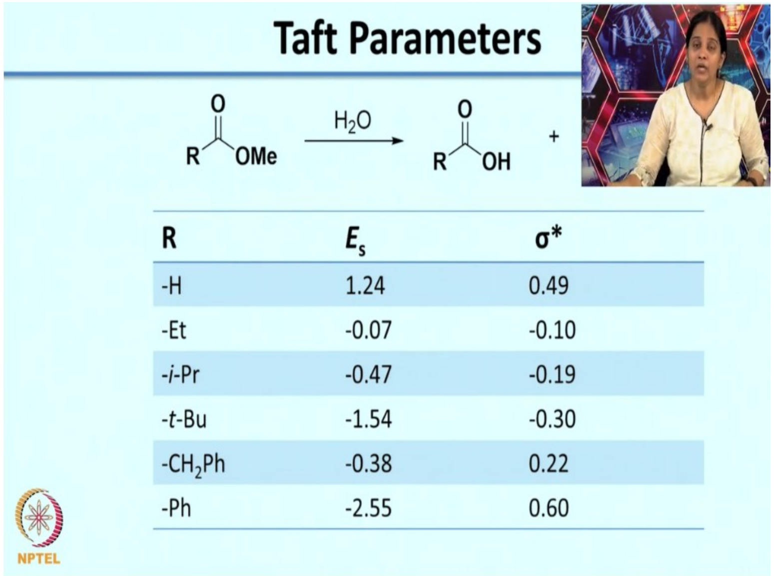

Taft Parameters

R	E_s	σ*
-H	1.24	0.49
-Et	-0.07	-0.10
-*i*-Pr	-0.47	-0.19
-*t*-Bu	-1.54	-0.30
$-CH_2Ph$	-0.38	0.22
-Ph	-2.55	0.60

So, now that you understand the steric factor Es and σ* which is electronic factor, let us see if you can predict some of these values. As I told you before, you need not know the exact value but you should have an idea about the trend. So, as I told you, the basic reaction of the standard reaction you looking at is where R is methyl. So, let us look at the first case where you have R is equal to hydrogen.

So, in terms of sterics, you have to think of whether hydrogen is smaller and or larger than methyl. The same thing you do for each of the other substituents show here. As a hint, I have shown you the value for ethyl so that based on that you can predict the values for the other substituents. So go ahead and try to do this exercise. You can press the pause button on the video and work on it. So alright let us start with hydrogen.

What will the value for hydrogen be Es? Will it be positive or negative? Now I am sure most of you have gotten this correctly. Hydrogen is smaller than methyl. Now since hydrogen is smaller than methyl, the reaction will be faster when you have hydrogen. So, K_X/K_{Me} would a value which is greater than 1. Which is why you will get positive value. Now what about Isoprophyl? Isoprophyl is bulkier than methyl so K_X/K_{Me} would be a fraction value.

So, if you take log of that you would get a negative value and it would be more negative than .07 which is given for ethyl here. t-butyl now? As you know t-butyl is known to be super bulky so you would see a much larger value. It is -1.540. So, it shows you how bulky t-butyl is and how small hydrogen is. Now what about the benzyl group? Benzyl group comes out to be somewhere between isopropyl and ethyl.

Remember in benzyl you have a CH_2 whereas in isopropyl you have CH Me Me. Now phenyl, this is very surprising. For this particular reaction, what is seen is that phenyl is found to be even more bulky than t-butyl. So, this is not always the case. But in this particular reaction what is seen as that phenyl group appears to be more bulky than the t-butyl group. Now the electronic parameter, so this would be similar to the Hammett trend when you have hydrogen; so if you have hydrogen here instead of methyl what you would have is methyl is more releasing,

So what you would have is you would have hydrogen being better because it increases the electrophilicity of your starting material. Now after hydrogen, if you have isopropyl, in the case of isopropyl compared to ethyl what would it do? Or compared to methyl?, it would be slightly more releasing which is why you have a negative value. t-butyl again slightly more releasing so you have a more negative value and then benzyl and phenyl would work better than methyl which is why they have positive values. Alright?

So, this is a very good example of how one can use the simple ester hydrolysis reaction to get both electronic as well as steric factor. So, the Taft equation is the only one where we look at the effect of sterics on the reaction.

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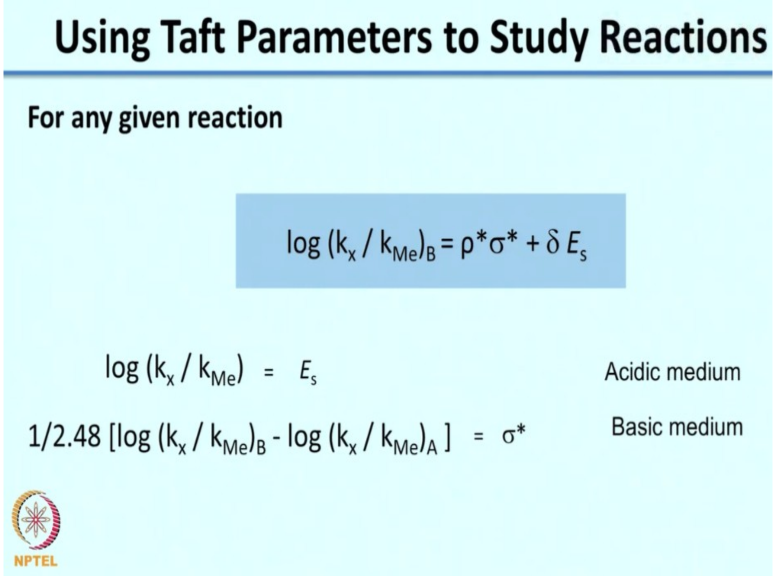

Using Taft Parameters to Study Reactions

For any given reaction

$$\log (k_x / k_{Me})_B = \rho^*\sigma^* + \delta E_s$$

$\log (k_x / k_{Me}) = E_s$ Acidic medium

$1/2.48 [\log (k_x / k_{Me})_B - \log (k_x / k_{Me})_A] = \sigma^*$ Basic medium

Now, if you have a new reaction, so your basic reaction is the one where you had the ester hydrolysis of methyl acetate. So, now for any given reaction if you want to see how the reaction behaves in terms of the steric parameters and the electronic parameters, you have a reaction an equation your Taft equation which says log (K_X/K_{Me}) is given by rho * σ* + Delta Es. So, essentially for any reaction you compare it with R as Me and you see how it correlates with sigma star for the electronic parameters and how it correlates with Es to give you how the sterics has an effect on a particular reaction.

So, now again just to revise, log (K_X/K_{Me}), the steric factor Es is given by the reaction under acidic medium, the ester hydrolysis reaction whereas your sigma star is obtained from this equation that we had seen earlier from ester hydrolysis under basic medium. So, what can be done is for any new system or a new reaction you see how it correlates with σ* and Es. If there is a correlation the sigma star you know that electronic effects are important for the reaction. If it correlates with Es you know that sterics are important for that particular reaction.

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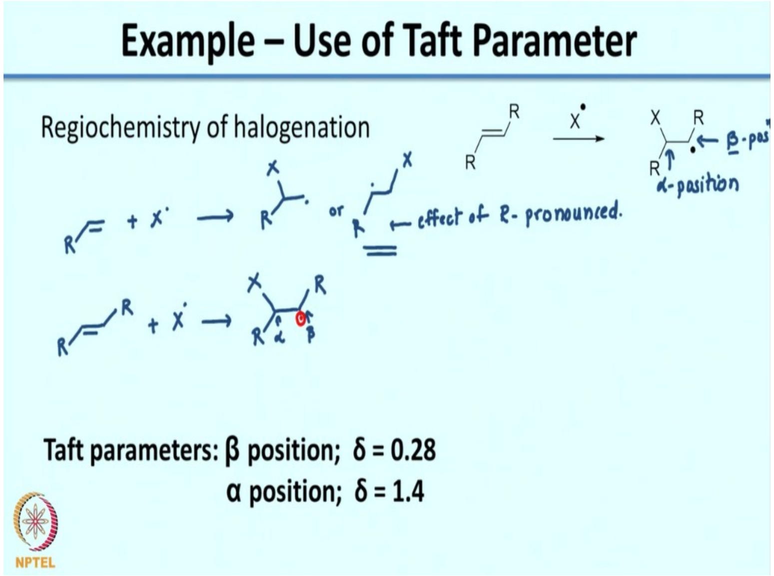

Example – Use of Taft Parameter

Regiochemistry of halogenation

Taft parameters: β position; δ = 0.28

α position; δ = 1.4

So, just to give you an example so that this makes more sense to you, let us look at the free radical reaction. So, here you are taking an alkene or an olefin and a free radical so we can think of halogenation, $X^{\cdot}$ reacting with the olefin to generate a new radical. The position where the X has come in, so we will call this as the alpha position and then the position right next to it we will call you as the beta position.

So, now if you have a terminal alkene and you are doing this reaction, so what you will get is, you can have two possibilities or, we have done similar examples earlier. So, you are looking at generating a primary versus a secondary radical. So this is more stable, further what is seen here is that, so effect of R is pretty pronounced. So, the R groups can actually stabilize the radical. So if were to look at this R group would have a very important effect here. Ok? and effect would be mainly electronic.

Now let us look at the situation I had shown you earlier. Now suppose you have; where you have substituents on both sides. So, here again I had already defined your α and β positions. Highlighting the radical here. So this is your radical. So, what we need to figure out is, does sterics play an important role in this case? As you see in this case, you have 2 R groups, so the effect of electronics is similar at α and β position. Correct? because you have 2 R group at both sides.

So, electronics will not play a major role in deciding regiochemistry for this particular reaction because you have electron releasing groups or electron withdrawing groups on both positions. So, when you have the situation like this, sterics can actually play a very important role in deciding what is the regiochemistry of the product. Now if you think carefully, if I compare α position versus β position where do you think steric will play a very important role? Will it be alpha or β position?

Steric actually plays a very important role at α position. So, here for this particular reaction the value of delta was determined. So, if you look at the previous slide, Delta gives you correlation with Es. Alright? So, here you are looking at how it correlates with Es. So what you see is at β positions the correlation is very small in magnitude it is 0.28 but at the alpha position you have a very large correlation of 1.4.

So, what that tells you is that at alpha position, sterics plays a much, much more important role than the beta position. So, here you can use the Taft equation to actually correlate at the two positions to determine what would be the regiochemistry for the product and this can be done both looking at strecis and electronics in this particular example, sterics is what place very important role. So, this is an illustration of how you can use that Taft parameter.

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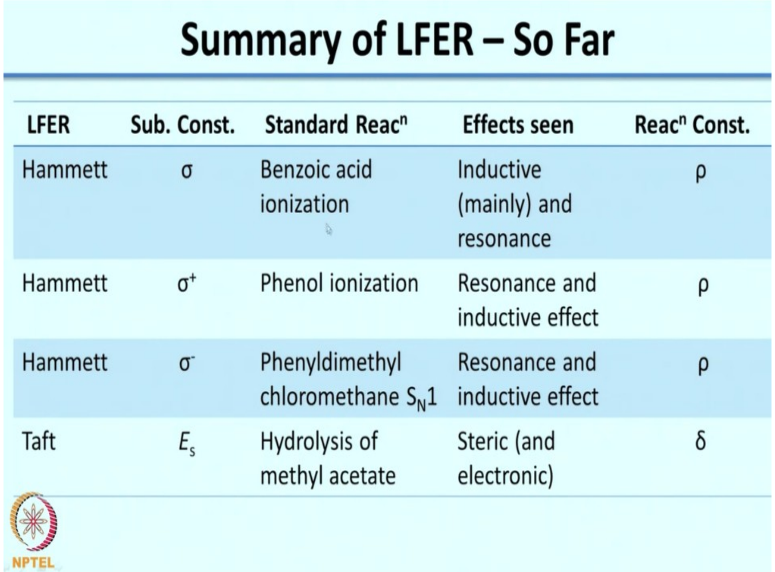

Summary of LFER – So Far

LFER	Sub. Const.	Standard Reac^n	Effects seen	Reac^n Const.
Hammett	σ	Benzoic acid ionization	Inductive (mainly) and resonance	ρ
Hammett	σ^+	Phenol ionization	Resonance and inductive effect	ρ
Hammett	σ^-	Phenyldimethyl chloromethane S_N1	Resonance and inductive effect	ρ
Taft	E_s	Hydrolysis of methyl acetate	Steric (and electronic)	δ

So, what we have studied so for under linear free energy relationship is we have looked at the Hammett equation, σ, σ^+ in σ^- and these are again the standard reactions for each of these and all of these tell you important information regarding how electronic effects are seen due to change in substituents. So only electronic effects are mainly seen for these equations. Today I have introduce you to the Taft equation, where you get a substituent constant Es which solely tells you the effect of sterics.

And the reaction constant here for sterics is given by Delta and here you have steric effect so this shows you how you can use linear free energy relationship very nicely to give you an idea about how a particular reaction behaves by changing its substituent which in turn tell you a lot of information regarding the nature of the reaction intermediate or the reaction transition state.

So just to illustrate how LFER can actually be used to even understand biology or can be used for important applications is shown here.

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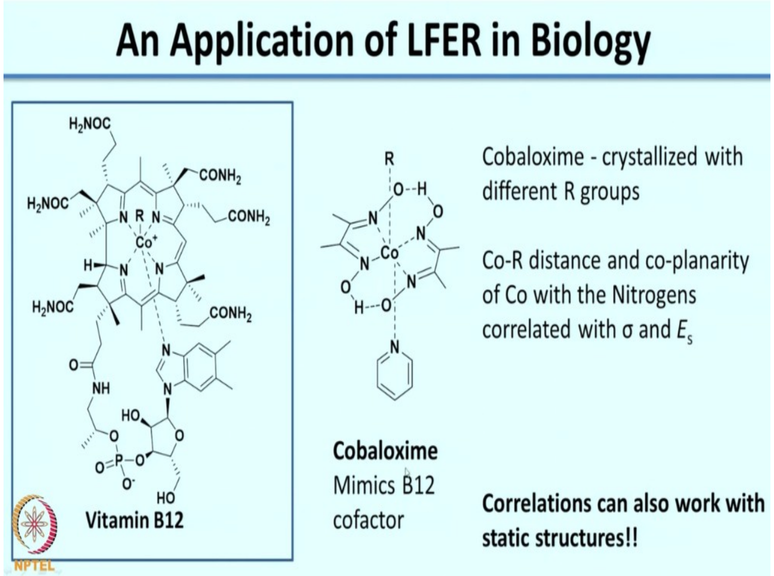

An Application of LFER in Biology

Cobaloxime - crystallized with different R groups

Co-R distance and co-planarity of Co with the Nitrogens correlated with σ and E_s

Correlations can also work with static structures!!

Shown here you have the structure of vitamin B12. As you can see, it is a very large molecule and looks quite complicated right? It is really big. So, now what scientist have tried to do is they have tried to use the small molecule, it is called cobaloxime to imitate or mimic this cofactor of vitamin B12. This part of the vitamin B12 is its cofactor which has the metal. So, this molecule has been used to imitate the cofactor.

Now if you look at the structure very carefully, this is actually not a cyclic molecule. It is an acyclic molecule which is coordinated with this cobalt and due to hydrogen bonding interaction it gives you a feel of the cyclic molecule seen here in vitamin B12. So is it not quite clever where scientists have used a small acyclic molecule which can essentially hold hands with each other to give you a cyclic structure which looks like this large molecule here.

Now what scientists wanted to see is, they wanted to see which would be a great mimic for vitamin B12. So, what they wanted to do is, they wanted to see how the R group has an effect on the properties of cobaloxime and this in turn would give them some idea about the effect of R group on vitamin B12. So, what they did is, they crystallized different molecules where the R group was varied. So, you must have studied what crystallization is right?

If you take salt and convert it to a crystalline form that process is called as crystallization. In biomolecules and organic molecules what is done is, if you are able to get an organic or biomolecules to form a crystal, you can actually get a almost photograph of molecule to show you how the molecule looks in the crystal or in the solid form. So, what was done is different crystals were made of molecules where the R groups were different.

And once you have a picture of the molecule, you can measure the distance between this R group and the cobalt centre. So what was done was, the COR distance was measured and also what was seen was, because of this R group how much the CO group goes out of the plane of this linear molecule. Remember we are trying to make a cyclic molecule. So they wanted to see by changing the R group how much the C was pushed out of the play.

So, what they did is for each of these crystal structures they correlated the COR distance with Sigma as well as Es using the Taft equation. So, what they found was that the COR distance correlated with σ, so that mainly indicates that the COR distance is affected mainly by electronic parameters. So what was seen is that how much CO is pushed out of the plane correlated better with Es indicating that it was more of a steric effect.

So, what was seen is that one can use the Taft equation to figure out a very important property of these cobaloximes and what is even more interesting is, so far even we are talking about rate constant right, we were seeing how are you vary K_X/K_{Me} but in this particular example a correlation was seen using static images or photographs of these molecules. So, using static images also, you can draw linear free energy relationships.

So, this is an example of its utility in biology and we will stop here today and in the next class, we will move on to see how solvents can have an important role in understanding or understanding the reaction mechanism and also improving the efficiency of a reaction Thank you.