Mechanisms in Organic Chemistry

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Lecture - 20
Solvent Effects: Part B

So welcome back. In the last class we had looked at the effect of solvents on reactions. So we had looked at first classifying solvents as aprotic and protic solvents and within aprotic solvents we had further classified them as polar and nonpolar and looked at examples under each of these classes. Then we had looked at how solvents affect reactions.

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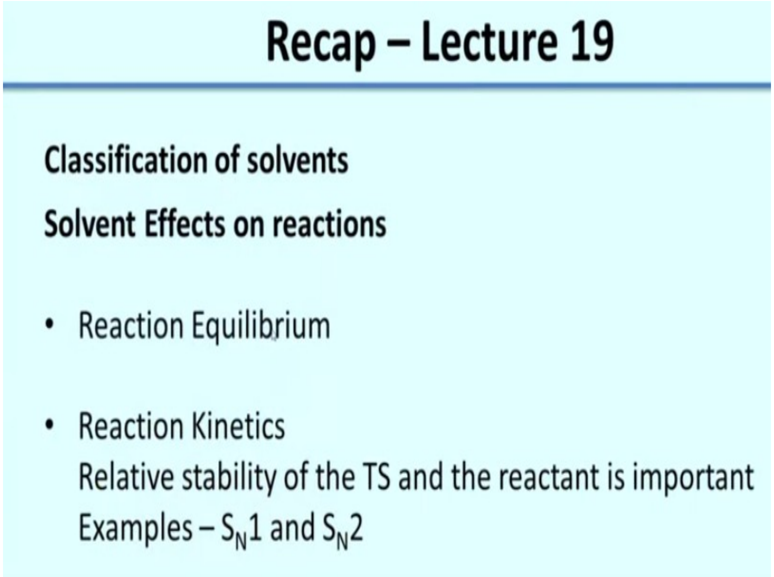

Recap – Lecture 19

Classification of solvents
Solvent Effects on reactions

- Reaction Equilibrium
- Reaction Kinetics
  Relative stability of the TS and the reactant is important
  Examples – S_N1 and S_N2

So first we had looked at the effect of solvent on a reaction equilibrium. So if you see that you have an equilibrium where you are going to a more polar compound, then a polar solvent favors that particular compound. We had also seen the effect of solvent on reaction kinetics and essentially what we had looked at is the relative stability of the transition state and the reactant.

And we had seen how it affects multiple reactions such as S_N1 and S_N2 and before leaving, I had asked you this question-

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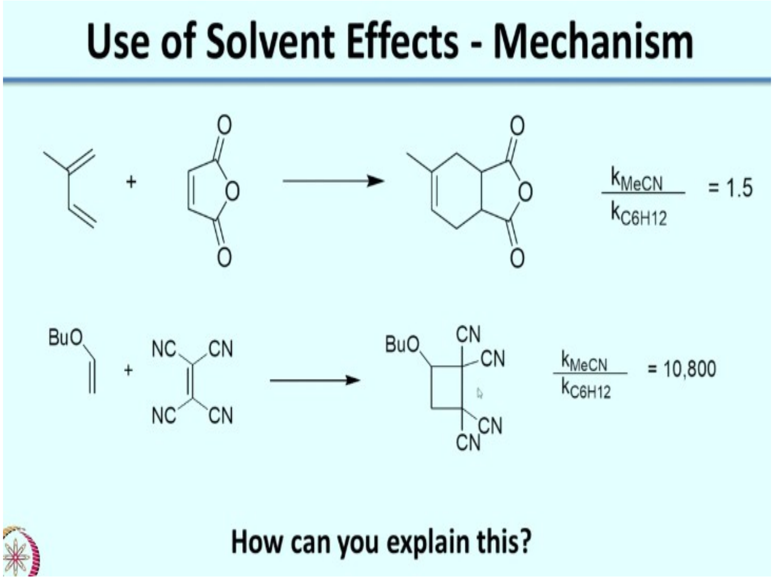

Use of Solvent Effects - Mechanism

$\frac{k_{MeCN}}{k_{C6H12}} = 1.5$

$\frac{k_{MeCN}}{k_{C6H12}} = 10,800$

How can you explain this?

So there were two reactions given to you. In the first case, you see that the solvent effect is not dramatic, whereas in the second case, you see a large effect on reaction rate, when you increase the solvent polarity from cyclohexane to acetonitrile. So how will you explain this? Hopefully, you had time to work out this problem. And let us look at the solution to this.

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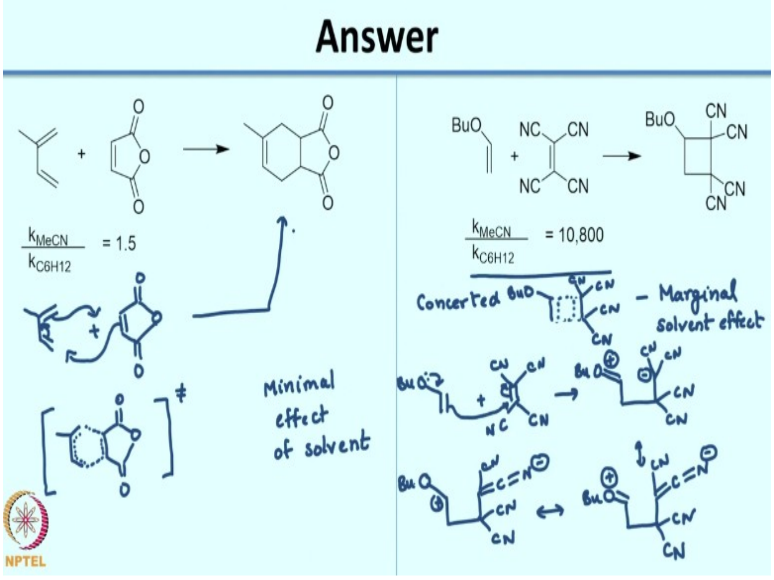

Answer

$\frac{k_{MeCN}}{k_{C6H12}} = 1.5$

Minimal effect of solvent

$\frac{k_{MeCN}}{k_{C6H12}} = 10,800$

Concerted – Marginal solvent effect

So the first reaction as I told you is an example of a four pi plus two pi cycloaddition reaction also called as the Diels-Alder reaction. Now the Diels-Alder reaction is a concerted reaction. What that means is you do not have an intermediate, what you essentially have is a cyclic transition state. It comes under a class of reactions called as pericyclic reactions. And if I were to draw the mechanism for this, so the mechanism would look like this.

It is a one step reaction. And I can push arrows in either direction. So essentially I am forming a new bond to give you the product. So in the transition state, what I have is, I have partial bond formation. The rest of the molecule remains unchanged. And then I have shifting of the pi bonds. So this is what the transition state will look like. Now as you can see there is no development of charge in the transition state and there is not any charge in the reactant either.

Therefore, you see a minimal effect of solvent. Now if I were to draw a similar mechanism for the reaction shown on the right it would not show the solvent effect seen here, right? If I were to draw a concerted process I would have a transition state which would look like the earlier case, right? Marginal solvent effect. But is that what is seen? No, correct? So what you see is a large solvent effect.

So how do you explain this large solvent effect? Obviously, there has to be some charged intermediate being formed. So if you think of a stepwise mechanism for this reaction, you can draw, redrawing the reactants. You have the lone pair here, you can either use it to push the electrons. So what you would get would be an intermediate which is charged.

Now this charged intermediate would be definitely stabilized by an increase in solvent polarity. So does this mechanism match with what is experimentally observed? Yes. And further if you were to rationalize this, you can understand it by the fact that you have an intermediate which is stabilized by resonance, right? So you can have also a resonance structure. You can also have a resonance structure.

So the very fact that you can write multiple resonance structures tells you that this intermediate is highly stabilized due to resonance. So that is why this reaction prefers to go via a stepwise process and not a concerted process. So if I were to argue I have the proof right here, where with a concerted process I would have observed a marginal solvent effect. But what is observed is a huge solvent effect.

So what that tells you is that the reaction goes by a polar intermediate. So such a simple experiment can help you distinguish between two mechanisms and shown here is a very good example, where you can just use solvent effects to determine the reaction mechanism. So now, we were looking at linear free energy relationships. So connecting with that there are also free energy relationships for looking at solvent effects.

And we have so far looked at Hammett plots, we have also looked at the Taft equation for looking at sterics. So now we are looking at a third aspect of reaction mechanisms, which is the solvent.

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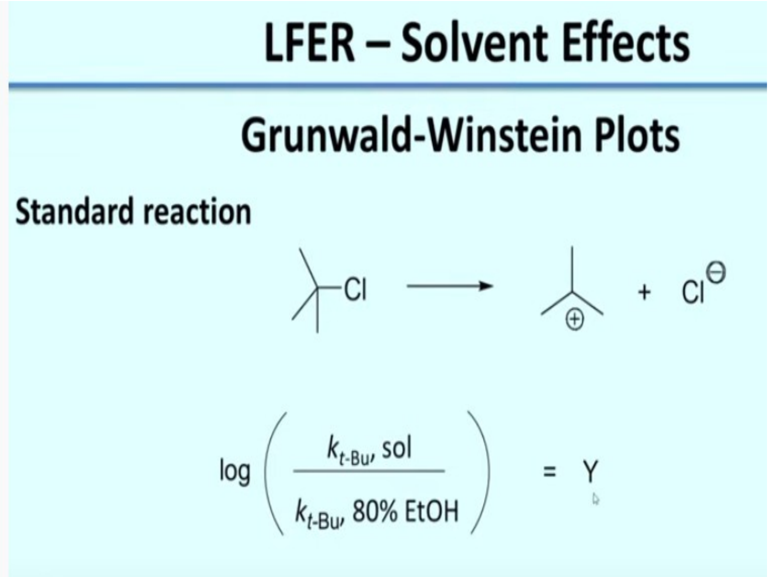

LFER – Solvent Effects

Grunwald-Winstein Plots

Standard reaction

$$\log\left(\frac{k_{t\text{-Bu}},\ \text{sol}}{k_{t\text{-Bu}},\ 80\%\ \text{EtOH}}\right) = Y$$

And the plots are given by what are the Grunwald-Winstein plots. Now the standard reaction for this is the dissociation of t-butyl chloride. So t- butyl chloride when it dissociates gives you this highly stabilized carbocation and chloride and this is the rate determining step of an S_N1 one like reaction.

Now when you have such a polar intermediate based on whatever we have seen in the last lecture and the previous example, what it tells you is that the solvent will have a major role in improving the reaction kinetics. So based on whatever we have studied, what you get a feel of by now is that if I increase the solvent polarity, the rate of the reaction will I am leaving a pause here for you to answer.

But the rate of the reaction will increase when I increase the solvent polarity. So now, the scale that was developed is $\log(k_{\text{t-butyl,sol}} / k_{\text{t-butyl,80\% EtOH}})$. So unlike the previous cases where we were changing the substituent, here what you are doing is you are keeping the reactant same, but you are changing the solvent, okay?

So you understand this? What we are doing here is again maintaining the reactant, but changing the solvent because you want to see how the solvent affects the reaction, alright? So for that you have to vary the solvent. For the standard reaction, the solvent chosen is 80% ethanol. So if you look at the standard reaction in the denominator, what is chosen is 80% ethanol.

So whatever solvent you have in the numerator, you will be comparing with 80% ethanol. So this is similar to the cases where we had looked at no substituent in the denominator and some substituent in the numerator. So whenever you think of enhancement of rate remember you are thinking with respect to 80% ethanol and the value that you get, which tells you how the solvent affects the reaction is given by this Y. So Greek alphabet Y is epsilon.

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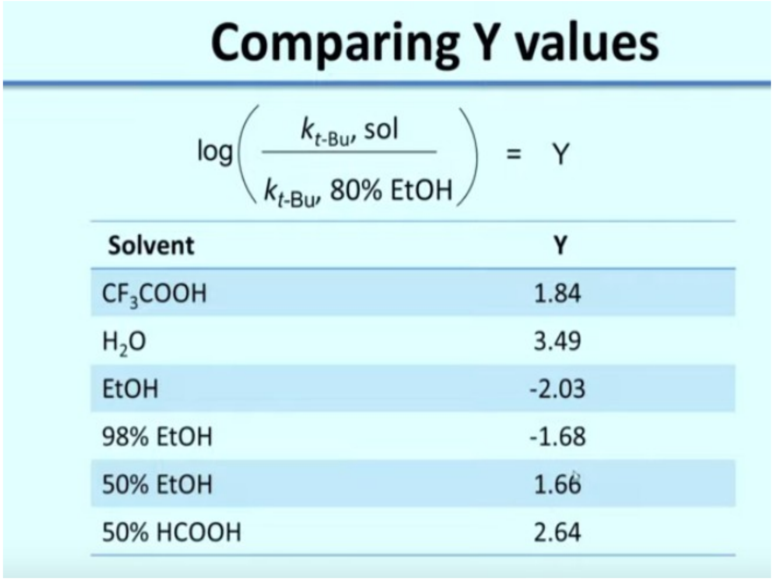

Comparing Y values

$$\log\left(\frac{k_{t\text{-Bu}},\ \text{sol}}{k_{t\text{-Bu}},\ 80\%\ \text{EtOH}}\right) = \text{Y}$$

Solvent	Y
CF_3COOH	1.84
H_2O	3.49
EtOH	-2.03
98% EtOH	-1.68
50% EtOH	1.66
50% HCOOH	2.64

So now let us try to do the same exercise as we had done in the earlier cases. Remember, we are looking at ionization of t-butyl chloride. On the denominator 80% ethanol. And based on this, can you comment on the relative trends for the values of Y? So you can try to fill out these values of Y in your notebook. It need not be exact, but what I would like you to get is the relative trends, as in, in which case would Y be greater than 1.84.

In which cases will Y be a positive value and in which cases Y will be a negative value. So I will give you some time to work this out. You can press the pause button and try to work out the Y values for all these solvents. All right, so let us look at the first case which is water. So if I compare water with 80% ethanol, now 80% ethanol means you have 80 of ethanol and 20 of water.

So when you think of water, you are looking at 100% of water. Whereas in this case, you have 20% of water. So between water and ethanol, which is more polar? Water is more polar. So now what have you done? In your numerator, you have a more polar solvent. So when you have a more polar solvent, the Y value will be positive. Now let us compare this with trifluoroacetic acid.

So if I were to compare trifluoroacetic acid with 80% ethanol what you see is you have a more polar environment. So you get a Y value of 1.84. Now with water, the value is much higher because you are talking about a much much polar solvent. What will the value be in ethanol? Now you are looking at 100% ethanol divided by 80% ethanol.

So the value will be negative, because now your numerator rate is actually lower than your denominator rate. Now what about 98% ethanol? That would be also negative, but the value is less negative than 100% ethanol. 50% ethanol will be now positive, because it has greater amount of water as compared to 80% ethanol. And if you compare this with 50% formic acid since formic acid is more polar than ethanol, you would see a value which is greater than 50% ethanol.

So having a feel for polarity of the solvent and the reaction you are looking at, you can get a good idea of what the trends will be for Y values. So similar to the other constants we had looked at earlier, which is sigma you also have tables which you can find in textbooks of physical organic chemistry, which will give you this Y scale to give you an idea about solvent polarity and how much a solvent will stabilize a particular reaction.

Now this case that we had seen is for t-butyl chloride. So similar to your Hammett equation, you now want to determine how sensitive a reaction is to solvent polarity.

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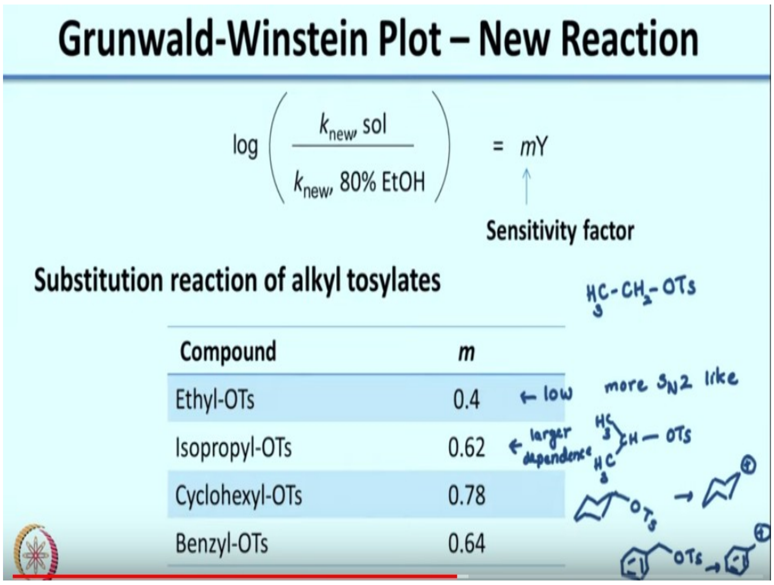

Grunwald-Winstein Plot – New Reaction

$$\log\left(\frac{k_{new},\ sol}{k_{new},\ 80\%\ EtOH}\right) = mY$$

Sensitivity factor

Substitution reaction of alkyl tosylates

Compound	*m*
Ethyl-OTs	0.4
Isopropyl-OTs	0.62
Cyclohexyl-OTs	0.78
Benzyl-OTs	0.64

So to do that you use the Grunwald-Winstein plot. And here what you have is you have log of k new which is your new reaction, not your t-butyl chloride in your unknown solvent divided by k new in 80% ethanol and you compare that with Y which you get from the t-butyl chloride reaction. So this is exactly like what we had seen in the Hammett case.

What you have is on the left you have your new reaction or unknown reaction. On the right you have your standard reaction, which in this case is ionization of t-butyl chloride. And this proportionality factor, which is *m* gives you the sensitivity of a particular reaction for solvent polarity. So if you look at the earlier two examples that we had done the Diels-Alder reaction and the two plus two stepwise process in one case, you saw that the reaction did not depend much on the solvent.

So one can say if you do this analysis, the m value is probably very low for that reaction. Whereas, in the other case where you had a polar intermediate, you see a huge difference with the change in solvent polarity. So what that tells you is that m value for that reaction will be very high. This is exactly like the rho value, except that you are now looking at solvent effects.

So now to give you an example of how this works, let us consider the reaction of alkyl tosylates. Now you have studied earlier that when you have S_N2 it would go via a concerted process. When you do the reaction or when the reaction goes by an S_N1

process you expect a stepwise dissociation. First dissociation followed by attack of nucleophile.

So now, if you were to look at these different reactions, so here what you have is you have in the first case ethyl tosylate. Now ethyl tosylate because you have here CH_2 OTS if it were to dissociate it would generate a primary carbocation which is not very stable as compared to a secondary or tertiary. It would prefer to go via an S_N2 reaction and not by an S_N1 reaction.

So what you see is in this case the value is quite low, right? So more S_N2 like. Now if I look at isopropyl tosylate, so isopropyl tosylate is, now here we are looking at somewhere between S_N1 and S_N2. It is not sure which mechanism would be favorable. So here what you see is you have a larger dependence, not a very large value, but a larger dependence.

So what it means is that when you increase solvent polarity, the reaction will have a tendency to go from S_N2 to S_N1 because the polar solvent will provide extra stabilization to the carbocation that is formed. The other example is of cyclohexyl tosylate. In this case also, you see that the dependence is actually larger than that of isopropyl tosylate because in general this molecule has a greater propensity to form the carbocation as compared to the isopropyl.

And what you would see is the effect is also much larger in this case. The last example is benzyl tosylate. Here you see that the effect is almost similar to the isopropyl tosylate. It is slightly higher. Here you also have the additional stabilization due to resonance which is why solvent per se does not affect it as much as one would think. But if you see the effect is larger than ethyl tosylate, Okay?

So in this case, what you see is that based on the solvent, the reaction has a propensity to go towards S_N2 or S_N1 like mechanism especially for cases like this, where it is somewhere between S_N2 and S_N1. Now one thing that was thought of by scientists is that solvents need not only stabilize the cation based on its polarity, it can also provide nucleophilic assistance.

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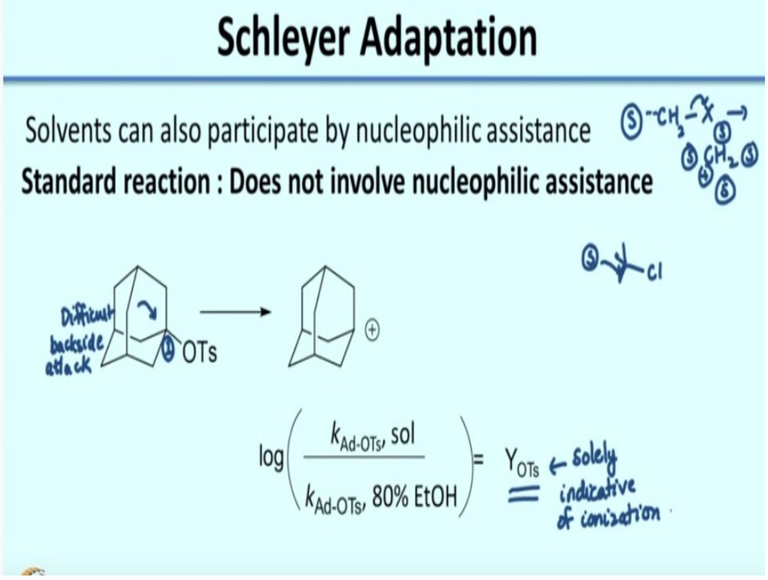

Schleyer Adaptation

Solvents can also participate by nucleophilic assistance

Standard reaction : Does not involve nucleophilic assistance

$$\log\left(\frac{k_{\text{Ad-OTs}}, \text{sol}}{k_{\text{Ad-OTs}}, 80\%\ \text{EtOH}}\right) = Y_{\text{OTs}} \leftarrow \text{solely indicative of ionization}$$

So what is meant by nucleophilic assistance is if you have and this is the solvent, the solvent might participate in some sort of a backside attack, which would help in the process of ionization. So what you end up getting would be, which is further stabilized by solvation. So now one would not expect much of nucleophilic assistance for the t-butyl chloride dissociation.

So when you think of t-butyl chloride, so such kind of backside assistance might not be as much but what was observed is that it is still present. So in order to ensure that there is no backside attack or nucleophilic assistance by solvent, there was an adaptation made by Schleyer and what Schleyer did was he used this standard reaction, where you look at dissociation of adamantyl tosylate.

So in one of the cases he looked at the tosylate at one position of adamantane. The logic being that because you have so much steric bulk at the backside of tosylate this backside attack would be very difficult. So if the backside attack is difficult, essentially what that means is the reaction, the solvent will not participate in nucleophilic assistance.

So this scale was developed where you have log of adamantyl tosylate in a solvent divided by adamantyl tosylate in 80% ethanol gives you Y tosylate and this is solely indicative of ionization and how the solvent actually stabilizes the ionized intermediate. So now, another adaptation was where instead of the one tosylate the two tosylate was used. This was just because of the ease of synthesizing this.

It is easier to synthesize the two substituted tosylate as compared to the one substituted tosylate. So this was also used to develop a solvent scale similar to the one we had seen earlier. But here we are only focusing on how the solvent stabilizes the ionized intermediate. So now here is a comparison of both these scales.

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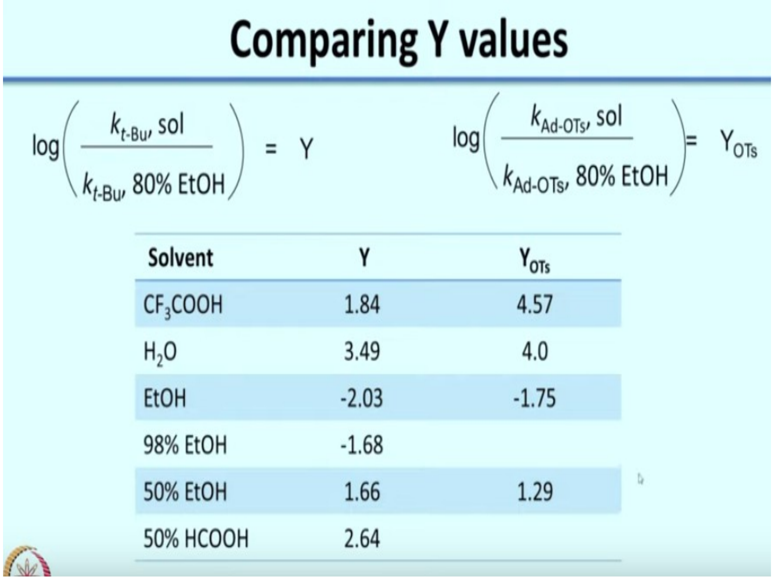

Comparing Y values

$$\log\left(\frac{k_{t\text{-Bu}},\ \text{sol}}{k_{t\text{-Bu}},\ 80\%\ \text{EtOH}}\right) = Y \qquad \log\left(\frac{k_{\text{Ad-OTs}},\ \text{sol}}{k_{\text{Ad-OTs}},\ 80\%\ \text{EtOH}}\right) = Y_{\text{OTs}}$$

Solvent	Y	Y_{OTs}
CF_3COOH	1.84	4.57
H_2O	3.49	4.0
EtOH	-2.03	-1.75
98% EtOH	-1.68	
50% EtOH	1.66	1.29
50% HCOOH	2.64	

So Y is the earlier scale, which is the Grunwald-Winstein scale, which looks at both nucleophilic assistance as well as ability of the solvent to stabilize the ionized intermediate. The other scale is the Y-OT s which looks at only ability of the solvent to stabilize the ionized intermediate. So if you compare the values here in the case of TFA for Y the value is 1.84 whereas in the case of the Schleyer adaptation, the value is 4.57.

Especially interesting is when you compare water and TFA. In the case of the Schleyer adaptation, what you see is these values are very similar. So what one can say is in terms of stabilization of the polar intermediate, presumably both of these solvents play a very similar role. But what you see is in the t-butyl chloride reaction, you have a greater effect of water.

So what that means is that the nucleophilic assistance by water is probably greater than that of TFA. Similarly, what you see is that when you compare ethanol versus Y-OTS in this case, you see that you have a lower reduction in the case of the Schleyer adaptation. Because in this case, when you have a lesser proportion of water, remember 100% ethanol versus 80% ethanol.

So when you have a lower proportion of water, the effect is a lot more pronounced in the case of the Grunwald-Winstein scale. So this just shows you different ways of comparing solvent effects and these can be used to determine the nature of the intermediate. So similar to whatever we had done earlier for the different correlations this is another scale which tells you the effect of solvents.

Some other solvent effects is solvents are shown to improve reactivity by improving solvation of salts.

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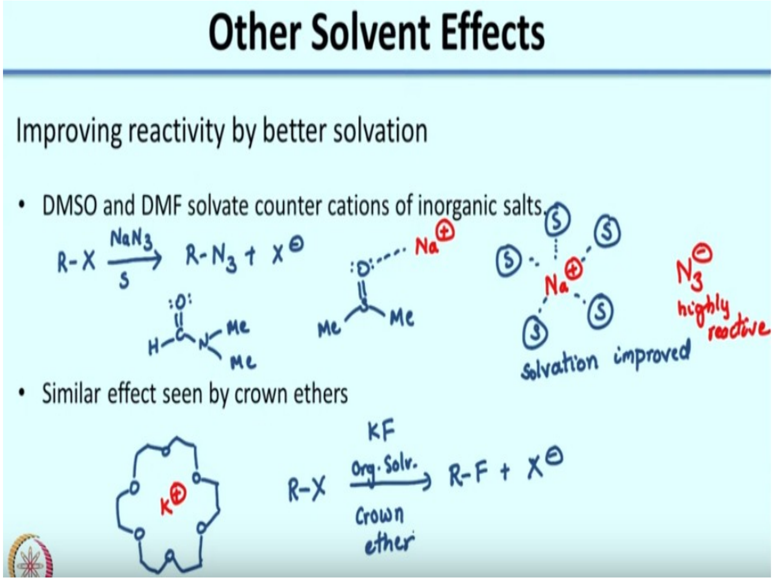

Other Solvent Effects

Improving reactivity by better solvation

- DMSO and DMF solvate counter cations of inorganic salts
- Similar effect seen by crown ethers

So what is seen is solvents such as DMSO and DMF solvate counter cations in inorganic salts. So to give you an example, if I take the reaction of R where X is a leaving group with sodium azide let us say I will put this as S as solvent. So what is seen is if you take DMF or DMSO because you have these lone pairs on the oxygen, this can coordinate to only the counter cations. So this can coordinate to Na^+.

So what will happen is if you have Na^+ and I will call both of these as solvent as S. So you will have coordination of the solvent. So you will have coordination of the solvent, so this improves solvation. So now that this solvent is coordinating to the counter cation what it does is you have the azide which is free and so the azide is highly reactive.

Otherwise, when you have salts like this and you choose an organic solvent, one of the major challenges is ensuring the salt is dissociated and then it can attack your electrophilic center. But choosing a solvent such as DMF or DMSO what you are doing is you are selectively solvating the cation and also making the nucleophile or the anion more available to nucleophilic attack.

So one of the major challenges in using salts like this in organic solvents is that it is very difficult to solvate them. But using a solvent such as DMF or DMSO ensures that these salts are solvated because they coordinate with the counter cation ensuring that the azide or the anion is highly available for nucleophilic attack. So solvation improves drastically by using such solvents which can coordinate.

Actually a similar effect is seen by crown ethers. Crown ethers are known to coordinate to cations. So the structure of one crown ether is, so this is 18 crown 6, this is known to coordinate to potassium. So what is seen is if you do a reaction where you have R-X plus potassium fluoride and you are trying to generate in an organic solvent, it is very difficult to dissolve potassium fluoride in an organic solvent.

But if you add crown ether, what it does is it coordinates to potassium and makes F minus available for the reaction. So essentially, it solvates KF very nicely in the organic solvent. So these are some of the solvent effects that are seen. So before I stop, I will just summarize the linear free energy relationships that we have seen so far.

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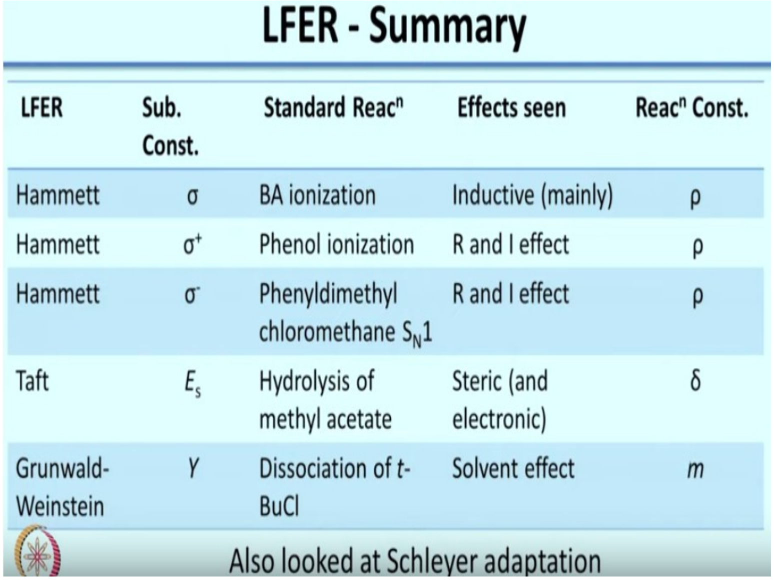

LFER - Summary

LFER	Sub. Const.	Standard Reac^n	Effects seen	Reac^n Const.
Hammett	σ	BA ionization	Inductive (mainly)	ρ
Hammett	σ^+	Phenol ionization	R and I effect	ρ
Hammett	σ^-	Phenyldimethyl chloromethane S_N1	R and I effect	ρ
Taft	E_s	Hydrolysis of methyl acetate	Steric (and electronic)	δ
Grunwald-Weinstein	Y	Dissociation of *t*-BuCl	Solvent effect	m

Also looked at Schleyer adaptation

So we have looked at the Hammett equation and the substituent constants we have seen are σ, σ^+, and σ^-. And these give you an idea about how electronic effects play a role in a particular reaction. So each of these have their standard reactions which we have seen already. The reaction constant is rho in all these cases.

So here what is typically done is the substituent on the aromatic ring is varied. We have looked at the Taft equation, which looks at steric effects and the substituent constant is Es. So what the Taft equation tells you is that how sterics effect a particular reaction and here you get a reaction constant which is δ. And in this class we looked at the Grunwald-Weinstein equation, where what you get is how the solvent affects a particular reaction.

So based on the constant m, you can tell how sensitive a reaction is to the solvent. In other words, it will tell you whether the reaction is forming some sort of a polar intermediate in its reaction mechanism. We also looked at the Schleyer adaptation to look at how solely the solvents stabilize the ionized intermediate and do not look at nucleophilic assistance. So we will stop with this. So thank you and see you in the next lecture.