Mechanisms in Organic Chemistry

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

Lecture - 19
Solvent Effects: Part A

So welcome back to this course on reaction mechanisms. So in the last class we had looked at how we can use LFER to determine the role of sterics in reaction. So before that we had looked at electronics using the Hammett equation. We looked at the Taft equation. The standard reaction for the Taft equation is ester hydrolysis.

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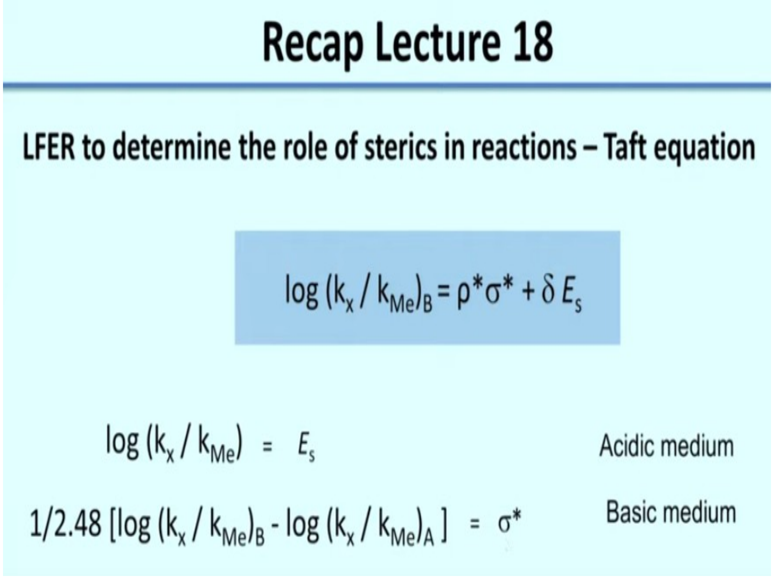

Recap Lecture 18

LFER to determine the role of sterics in reactions – Taft equation

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

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

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

And if you do the ester hydrolysis in a basic medium, essentially log (k_x/k_{Me}) in a basic medium is given by rho star σ^* + δ E_s. So here, δ is related to the effect of sterics on a particular reaction and to get the value of E_s, what was done was the ester hydrolysis was carried out in an acidic medium and in the acidic medium, the ester hydrolysis depends mainly on sterics.

And to decouple and get the electronic effect, the same reaction when carried out in a basic medium has both electronic as well as steric effect. So based on these two values, you can determine both the role of sterics as well as electronics for a reaction by comparing it with ester hydrolysis. And we had looked at an example where using the Taft equation you can say how sensitive the reaction is to change in sterics at a particular position.

So now when you think of organic reactions, they are mainly carried out in a solvent. So when you imagine it you would imagine a flask with some solution of your compounds. You do not just mix them as solids typically. Although there are some few reactions which are carried out now in solid state by rubbing or mixing the solids, but mainly solvents play a very important role in organic reactions.

So now, the question is, can the solvent actually play a very important role a) in the reaction kinetics, thermodynamics b) in determining what the mechanism of the reaction is. So before we move on to the different types of solvents, I would like you to think about this question. Now that you imagine a reaction being carried out in a flask do you think the solvent will play a role in the reaction kinetics?

b. Do you think we can use the solvent to determine the mechanism of the reaction? So I would like you to think about this by pressing the pause button on the video and writing it down in your notebooks.

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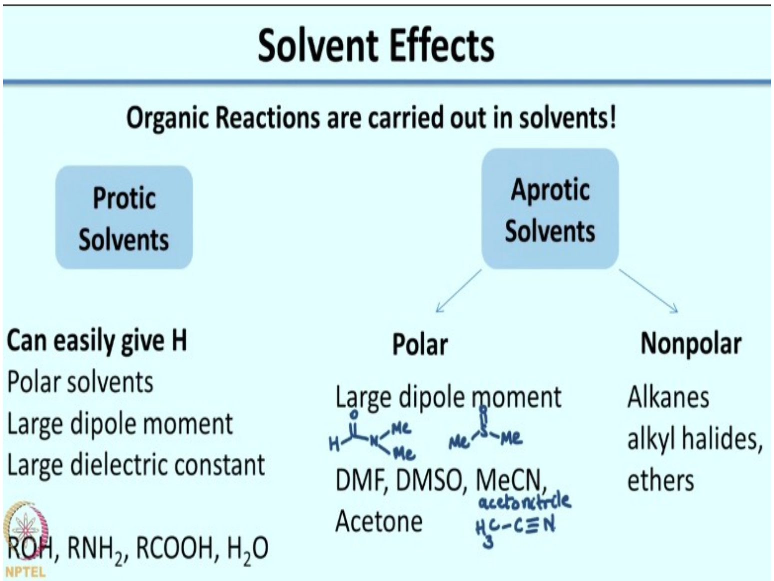

Solvent Effects

Organic Reactions are carried out in solvents!

Protic Solvents

Aprotic Solvents

Polar

Nonpolar

Can easily give H
Polar solvents
Large dipole moment
Large dielectric constant
ROH, RNH_2, RCOOH, H_2O

Large dipole moment
DMF, DMSO, MeCN,
Acetone
acetonitrile
$H_3C-C\equiv N$

Alkanes
alkyl halides,
ethers

So now we will see what role the solvent plays. So there are different types of solvents if we were to classify them. They are protic solvents and aprotic solvents. So just like the name suggests protic meaning involving a proton. So protic solvents are those that can easily give protons. So now, when you think of protic solvents, typically they are polar.

Because if you have a non polar bond such as a CH bond, it will not be that easy for it to give your proton. Aprotic solvents can be polar or non polar. So aprotic solvents are those that cannot give protons, but you can have heteroatoms in the solvent which make them polar or if you do not have heteroatoms they are nonpolar. So let us look at the properties of each of these class of solvents.

So in the protic solvents as I said they can easily give protons; just by the name you can say that. They are usually polar. Now if they are polar, obviously, they will have a large dipole moment and they also have a large dielectric constant. So solvents in this class are ROH, RNH_2, carboxalic acid like acetic acid solvent, trifluoroacetic acid, water. So these are all examples of protic solvents.

And a lot of times people say polar protic solvents which is not technically correct because when you say protic, it is implied that the solvent is polar. Now coming to aprotic solvents as I said they can be polar or nonpolar. So can you think of some examples of polar aprotic solvents and examples of nonpolar aprotic solvents? You can try to list them out in your notebook.

So polar aprotic solvents have a large dipole moment. And examples are dimethylformamide, dimethyl sulphoxide, acetonitrile and acetone. So if you do not know the structure of DMF and DMSO I will write it for you. So DMF is N, N dimethylformamide and DMSO is dimethyl sulphoxide. And acetonitrile and of course you know the structure of acetone.

Nonpolar aprotic solvents are alkanes, alkyl halides, and ethers. So commonly used ethers are diethyl ether, you have tetrahydrofuran and alkyl halides like dichloromethane. So these are commonly used solvents for organic reactions. So the question I had asked you before we went into the classification is do they have an effect on the reaction? So let us first see what effect can they have on the thermodynamics.

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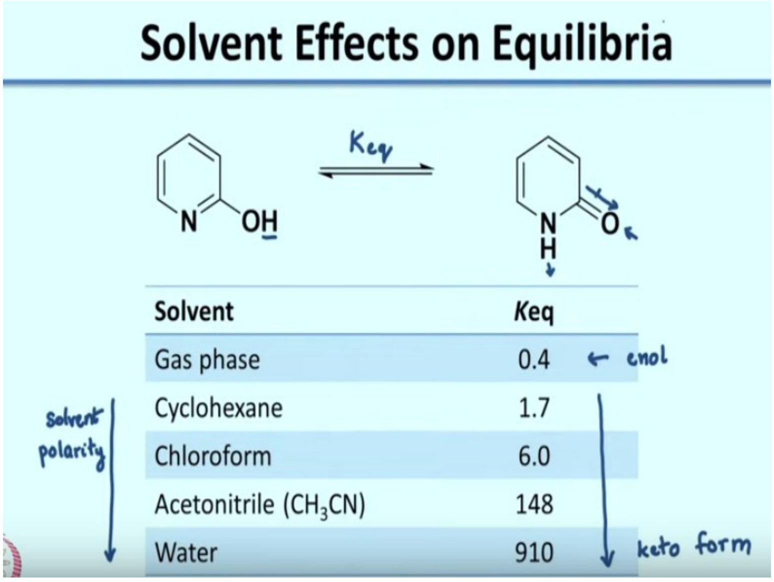

Solvent Effects on Equilibria

Solvent	Keq
Gas phase	0.4
Cyclohexane	1.7
Chloroform	6.0
Acetonitrile (CH_3CN)	148
Water	910

← enol

Solvent polarity

keto form

And a classic example is shown here. So here you have the equilibrium leading to formation of 2-Pyridone. So here you have two forms, one is the aromatic 2-hydroxy form and the other is where you have a amide form. So when you look at the equilibrium constant for this transformation or this tautomerization, it is quite intriguing.

In the gas phase, what a seen is that you have the indole form, which is the major form. So the equilibrium constant is 0.4. It is the enol form. But as soon as you put it in a solvent, it seems to shift greater towards the keto form. And what you see is as you increase the solvent polarity, so when you go from cyclohexane to chloroform to acetonitrile to water, what is happening here is your solvent polarity is increasing.

And what you see is, you see a corresponding increase in the keto form. Now there are lot of research articles that talk about why there is this shift in equilibrium. Even as recently until a couple years ago, you would still see papers that try to understand the shift in equilibrium. On one side you have an aromatic molecule, whereas on the other side, you have the keto form.

Now what could be explanations for this and especially if you see in water, you would see a huge increase. One thing which could lead to a particular form being more favored, could be easier dissolution of this molecule in that particular solvent and stabilization of the molecule in that particular solvent. So what is seen here is that you have one hydrogen bond donor in the case of the enol form.

Whereas in the keto form, you have a hydrogen bond donor and you also have a hydrogen bond acceptor. So in water, probably the extent of hydrogen bonding is a lot more for the keto form as compared to the enol form. The other thing could be when you think of the dipole moment, right. So when you look at the keto form based on the enhanced directionality of the dipole moment in the keto form, polar solvents probably stabilize it more than the enol form.

And this you can see even in biology. So in biology, you can see that you would have a lot of the bases that you talk about in your nucleic acid prefer the non aromatic form as compared to the aromatic form. And this stabilization could be due to this dipole moment which is stabilized more in polar solvents because when you talk about nucleic acids, we are looking at water as the medium.

So what you see is you see that solvent can have a drastic effect on the equilibrium constant. So you are talking about a complete shift when you go from gas phase to solution phase and even in the solution phase, you are seeing a shift or an increase in the equilibrium constant as you increase the solvent polarity. So this is an example of how the solvent can shift an equilibrium for a particular transformation.

Now can it have an effect on the kinetics of a particular reaction? So now, whenever we think of kinetics and we have seen this in multiple examples earlier on, we are looking at the activation energy. Or if you remember at the very beginning, I had told you about climbing a hill. So if you have to climb a shorter hill, that indicates a lower activation energy.

If you have to climb a much larger hill, we are talking of a larger activation energy. So when we talk about the activation energy, we think of the reactant versus the transition state, correct? So now, whatever leads to decrease in this distance between the reactant and the transition state, would lead to a lower activation energy. So now what is important is the relative stabilization of transition state and reactant.

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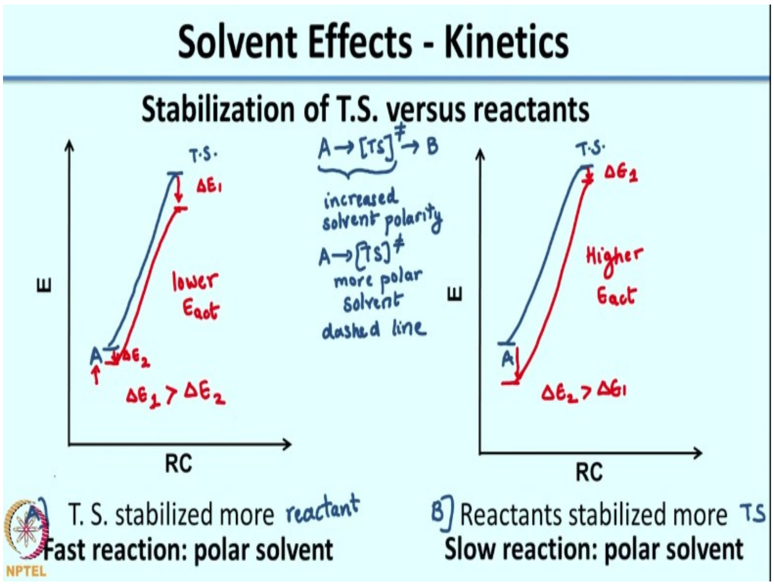

Solvent Effects - Kinetics

Stabilization of T.S. versus reactants

A) T. S. stabilized more reactant
Fast reaction: polar solvent

B) Reactants stabilized more TS
Slow reaction: polar solvent

So I want you to sketch on these two reaction coordinate diagrams that you see on your screen. What I want you to do is in your notebook, think of two different scenarios. In one case, the transition state is stabilized more than the reactant for a particular reaction when you increase the solvent polarity. So let us assume like we saw in the earlier case, we are increasing solvent polarity.

So when you increase solvent polarity, in case A transition state stabilized more than reactant. In case B reactant is stabilized more than transition state. So on each of these graphs, I want you to draw two reaction coordinate diagrams on the same graph. One for say a reaction of A going to B. So in both these cases, let us say A is going via a transition state to a product B. Now, so this would be one reaction coordinate.

So here you need not draw B. You can only stop at the transition state because we are trying to figure out kinetics. So as I said, the distance to the peak is what is more important. So this would be one thing you plot. Then you imagine that you have increased solvent polarity for this reaction. So when you increase the solvent polarity, you would get a new reaction coordinate; again more polar solvent.

You can show this with a dashed line. So I have now given you two scenarios. In scenario A your transition state is stabilized more than the reactant with a greater solvent polarity. In case B the reactants are stabilized more than the transition state. So you go ahead and do this exercise in your notebooks. You can press the pause button on the video now.

So let us compare whether your answers are correct. So first case is where you have just A going to B. So you have A. Let us say this is the transition state. As I said, I am not going to bother about, so this is simple. We are not bothering about B. Same thing here. It is the same reaction let us say. Okay? So in one case, this is hypothetical. If it were the same reaction, it would behave identically. I am just keeping it simple.

So in one case, let us say the transition state is stabilized more than the reactant. So stabilization means energy is lowered. So you can use the dashed line, I will use a separate colored ink. You can also do that if you wish. So now the transition state is stabilized more means this drop in energy let us say is ΔE_1 and this is stabilized less. So when you say transition state is stabilized more, what you essentially need to draw is ΔE_1 greater than ΔE_2.

In the other case the reactant is stabilized more. So in this case ΔE_2 will be greater than ΔE_1. So this is a smaller drop. So now the reaction coordinate will look like this in one case and then like this in the other case. So what has happened in case one? Is the reaction going faster or slower here? Look at the reaction coordinate carefully.

So again, when you are thinking of mountain climbing, if you are standing at point A, right? If there is something which just leads to a small drop in your position from point A, right? You can think of it even as steps. So imagine that you are climbing just one step down from point A. But when you look at the goal, which is the top of the hill, there if you have come down by say six steps.

So you have to travel a shorter distance. So that means lower activation energy. So that means the reaction will go faster. Whereas in this case, you have a higher activation energy and so reaction will go slower. So, fast reaction in a polar solvent and slow reaction in a polar solvent for these two scenarios. So now that you have an idea of the general picture, let us look at two specific examples.

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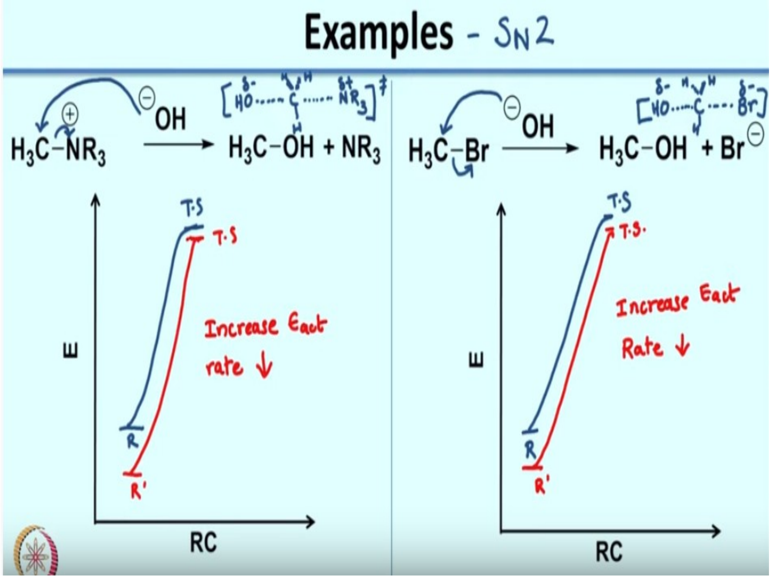

Examples - S_N2

So I have given you two reactions on your screen and what I want you to do is, I want you to sketch the reaction coordinate diagram for each of these examples and tell me what will happen to the reaction rate upon increasing solvent polarity. So the question is, again, I will repeat. What happens to each of these reactions on increasing solvent polarity. I want you to explain this by showing on the reaction coordinate diagrams.

So you can go ahead and do this exercise. So let us check. So in the first case your reactants are two charged species, right? So I have a charged amine and a hydroxide. And what is the mechanism here? So the mechanism is that you have the hydroxide coming here, and then the amine going. So it is an S_N2 like mechanism. Here, you again have a hydroxide.

It is not a charged species coming here and the Br^- leaving. So both of these are first of all classifying S_N2 mechanisms. So when you think of this one step S_N2 mechanism, let us again draw the starting materials here. So let us say this corresponds to the reaction mixture R and then you have your transition state. Now what will happen when you increase the solvent polarity?

You must have heard this like dissolves like before in textbooks. So when you increase solvent polarity, polar molecules will be stabilized more than nonpolar molecules. We saw that in the case of the equilibrium also earlier. Correct? So when you have charged species such as these two reactants both the hydroxides as well as the charged amine species, what you would see is, that would be stabilized much more, and what will your transition state look like?

See your transition state here would be now if you look at the charge in your transition state and you compare that with your reactant, the charge is more dispersed in your transition state as compared to your reactant. So now what will happen is when you increase the solvent polarity, what would be stabilized more? Will it be the reactant or the transition state? Think about it.

I am sure you must have gotten the answer. So in this case, the reactant is actually stabilized more than the transition state. So you have a greater stabilization for the reactant as compared to the transition state. So what would that do? So that would increase the activation energy and the reaction rate will decrease. Now what about the second example?

Now even in the second example, you have one reactant which is charged. Again, if I were to write the transition state so here again in the transition state the charge is more diffused as compared to the reactant. So this would look very similar to the example that we had just seen. So when you increase the solvent polarity the increase in reactant energy might not be as much as the earlier case, because only one of your reactants is charged.

But it would still be more than what is seen in the transition state. So you will have again increase in the activation energy and the rate will decrease. So if you have understood this concept, then we can generalize it.

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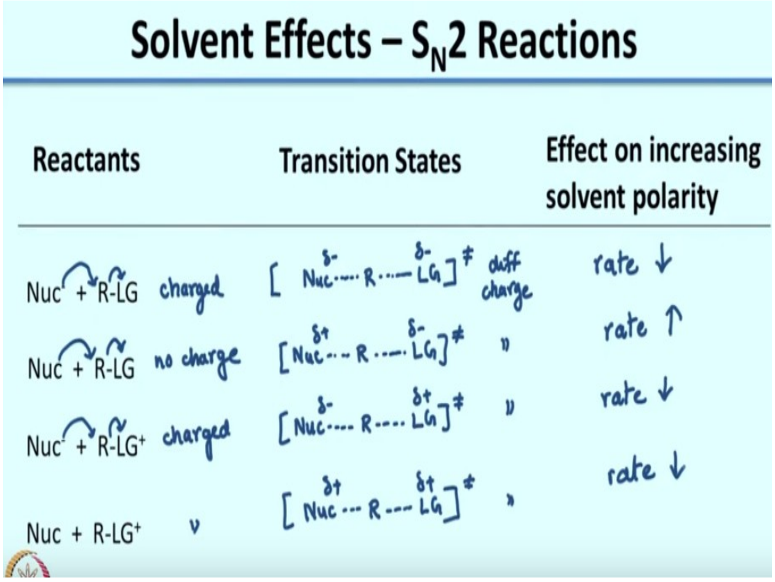

Solvent Effects – S_N2 Reactions

Reactants		Transition States		Effect on increasing solvent polarity
$\text{Nuc}^- + \text{R-LG}$	charged	$[\overset{\delta-}{\text{Nuc}}\cdots\text{R}\cdots\overset{\delta-}{\text{LG}}]^{\ddagger}$	diff charge	rate ↓
$\text{Nuc} + \text{R-LG}$	no charge	$[\overset{\delta+}{\text{Nuc}}\cdots\text{R}\cdots\overset{\delta-}{\text{LG}}]^{\ddagger}$	"	rate ↑
$\text{Nuc}^- + \text{R-LG}^+$	charged	$[\overset{\delta-}{\text{Nuc}}\cdots\text{R}\cdots\overset{\delta+}{\text{LG}}]^{\ddagger}$	"	rate ↓
$\text{Nuc} + \text{R-LG}^+$	"	$[\overset{\delta+}{\text{Nuc}}\cdots\text{R}\cdots\overset{\delta+}{\text{LG}}]^{\ddagger}$	"	rate ↓

So if I look at S_N2 reactions, I have shown you four different scenarios. What I want you to do is on your sheet of paper, write the transition state for each of these scenarios and see how this has an effect upon increasing the solvent polarity. So you can quickly go ahead and do this exercise. Press the pause button on the video and write the answers. So I will quickly walk you through this.

In the first case, your transition state will look like this. So you have a charged nucleophilic species. So these are all S_N2 reactions. The nucleophile is negatively charged and your leaving group will leave taking the electrons from the nucleophile. So you have a δ^- there. In this case, your nucleophile has no charge. So when it comes in here, there will be a positive charge.

This will leave with a negative charge. So your transition state will look as I have shown you here. In the third case, your nucleophile is again charged like in the first case. In this case, both your reactants have charge associated with it, δ^-, this will come here. In the last case your nucleophile is not charged but your leaving group is charged.

So now to determine what happens to the rates in each of these cases, let us look at the first case. You are starting with charged reactants. Right? One of the reactants is charged. Transition state diffused charge, so less stabilized. So rate decreases. In the first case, reactants no charge, transition state diffused charge. So reactant will not be stabilized much, but your transition state will be stabilized relatively more.

So the rate will increase slightly. In the third case, reactants both are charged. Transition state diffused charge. Again, the reactant will be stabilized more. So rate will decrease. And in the last case again reactant is charged, transition state has diffused charge, so the rate will decrease. So now this gives you the general overview of how the solvent polarity can have an effect on an S_N2 reaction.

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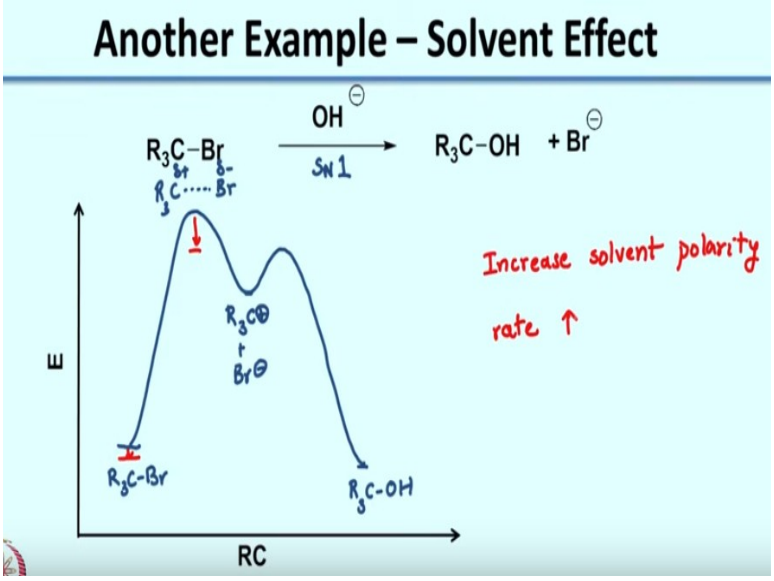

Another Example – Solvent Effect

$R_3C-Br \xrightarrow[S_N1]{OH^{\ominus}} R_3C-OH + Br^{\ominus}$

Now let us look at this reaction, I would like you to draw the reaction coordinate for this reaction. And for the first step, you show how the reaction rate is affected by increase in solvent polarity. So you can go ahead and work this out, press the pause button on the video. So now what is happening in this case? This is an S_N1 mechanism.

I hope you got that because now you have a tertiary carbocation that would be generated. So when I write the reaction mechanism, I will have the first step which is the rate determining step followed by second step. So this will be R_3CBr. This will be your tertiary carbocation that is generated plus Br^- and then you have your product.

Now when I increase the solvent polarity, remember your transition state here is, so you have the bond breaking here. So the transition state is a lot more stabilized here as compared to your reactant. So what you will see here is you will see greater stabilization for your transition state. So increase in solvent polarity will show you an increase in the reaction rate.

So and the extent of increase would be greater than the cases earlier where you saw where you started with a slight increase, okay for the S_N2 case. So this way, one can also use the solvent effect to distinguish between and an S_N2 and S_N1 mechanism. So if you consider all the scenarios we had seen in the earlier slide, what you saw was that in most cases the rate was decreasing. Whereas here you see an increase in rate.

So you can use this to distinguish between an S_N2 and an S_N1 mechanism. So before I leave you, there is one problem that I would like you to think about.

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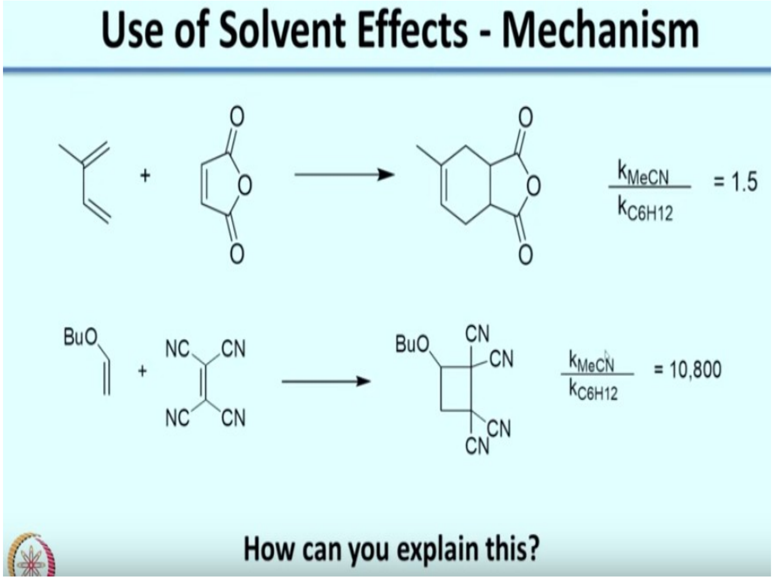

Use of Solvent Effects - Mechanism

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

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

How can you explain this?

So this is an example of where the solvent effects were used to determine the reaction mechanism. Not one example, actually two examples. So in the first case, what is seen is when you do the reaction shown here, this is an example of a Diels-Alder reaction. So it is a [4+2] cycloaddition reaction to give the cyclohexene molecule.

When you do the reaction in acetonitrile, so if you remember the very first slide we had on solvent effects where we classified the solvents, acetonitrile is a polar, aprotic solvent. So it is a polar solvent and I do the reaction in cyclohexane, which is a nonpolar solvent. The difference in the reaction rates is not much. Now this is another reaction. This is also an addition reaction.

So I have two pi bonds coming together to form cyclobutane. Here when I decrease the solvent polarity, I see a drop in the reaction rate. So in acetonitrile which is the more polar solvent, the reaction rate is 10,800 times more than cyclohexane. So this is a huge difference compared to the tiny 1.5 that we see in the Diels-Alder reaction. So obviously it has something to do with the nature of the transition state or the intermediate in each of these reactions.

So what I want you to think about is what could be a mechanism that would explain this solvent effect for both of these reactions. So we will come back to this problem in the next lecture. So I want you to work this out. So thank you and I will see you in the next class.