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

Lecture - 21
Kinetic Isotope Effect

So welcome back. In the last class we were looking at solvent effects on reaction kinetics. In the previous lecture, we had looked at solvent effects on thermodynamics or equilibrium as well. So particularly we had looked at linear free energy relationships.

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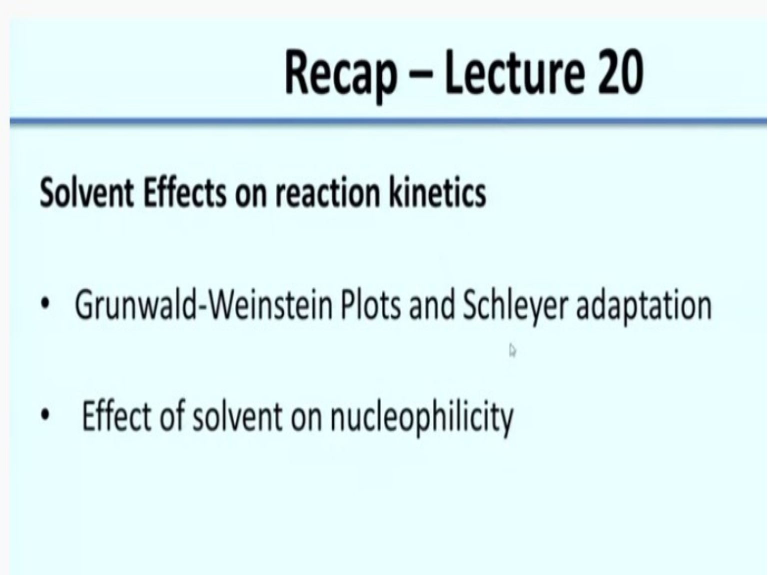

Recap – Lecture 20

Solvent Effects on reaction kinetics

- Grunwald-Weinstein Plots and Schleyer adaptation
- Effect of solvent on nucleophilicity

So we had looked at Grunwald-Weinstein plots and also the Schleyer adaptation, which helps us get an idea as to how solvents play an effect on the reaction. So reactions which typically involve a polar intermediate like an S_N1 reaction or an E1 will have a greater influence with a change in solvent from nonpolar to polar. So we had also looked at the effect of solvent or nucleophilicity.

There are certain solvents such as DMF and DMSO which can coordinate to cations making the nucleophiles more solvated and more reactive. So we had looked at these examples. We had also looked at how crown ethers can be used to improve solubility of salts in organic solvents. So in today's lecture, what we are going to look at is we are going to look at another experiment that is used very often to get an idea about the reaction mechanism. So this is called as the kinetic isotope effects.

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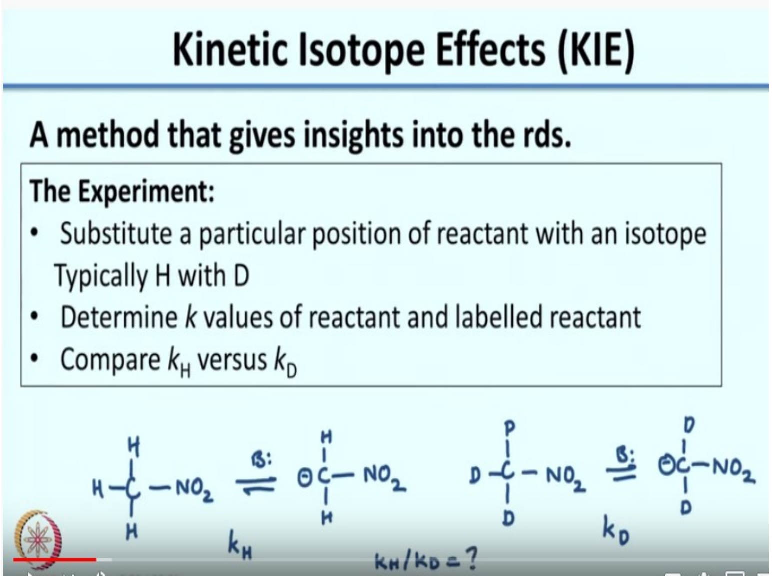

Kinetic Isotope Effects (KIE)

A method that gives insights into the rds.

The Experiment:

- Substitute a particular position of reactant with an isotope Typically H with D
- Determine *k* values of reactant and labelled reactant
- Compare k_H versus k_D

So in kinetic isotope effects, it is a method that gives you insights into the rate determining step for a particular reaction. So how the experiment works is you substitute a particular position of the reactant with an isotope. So typically what is done is you have hydrogen substituted with deuterium. So to make more sense of it you can imagine say this reaction.

So if you have say nitromethane and I am trying to look at how if I take a base I de-protonate it. So how the kinetic isotope effect would work is, first I will do the experiment where I have all hydrogens and I will get the k_H value which is the rate in the presence of only hydrogens. Then I will do another experiment. In this experiment I substitute the hydrogens with say deuterium.

And then I determine again the k value for this reaction. So once I have both of these k values, I compare the value of k_H versus k_D. And once you get that value, you can get a lot of information about the reaction. So now you would be curious as to how the k_H over k_D value gives you a lot of information about the reaction. So let us try to get a deeper look to understand what exactly is happening here.

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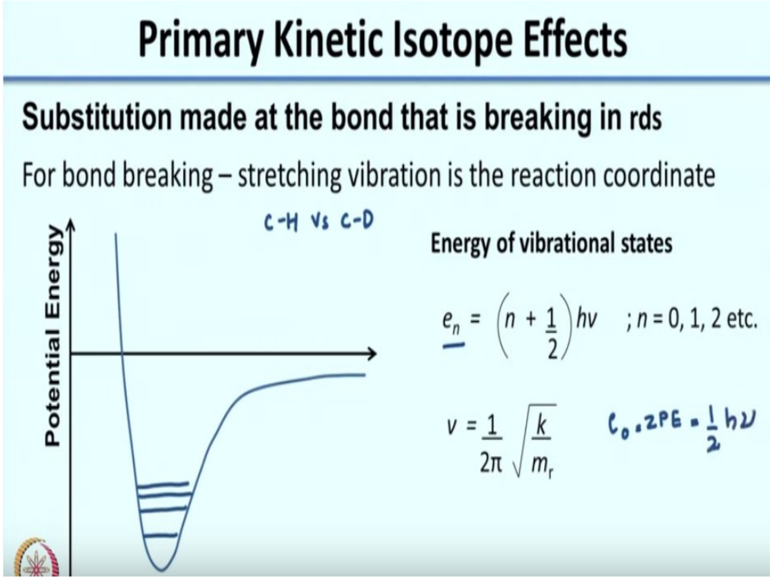

Primary Kinetic Isotope Effects

Substitution made at the bond that is breaking in rds

For bond breaking – stretching vibration is the reaction coordinate

C-H vs C-D

Energy of vibrational states

$\underline{e_n} = \left(n + \frac{1}{2}\right)hv$; $n = 0, 1, 2$ etc.

$v = \frac{1}{2\pi}\sqrt{\frac{k}{m_r}}$ $E_0 = ZPE = \frac{1}{2}h\nu$

So when we do a reaction like this, if we look at substitution at the bond that is breaking in the rate determining step, it is called a primary kinetic isotope effect. So again I repeat, if you have the bond that you have made the substitution at, if that is breaking in the rate determining step you have what is called as a primary kinetic isotope effect. So whenever you think of bond breaking bond making, we are essentially interested in the vibrations that are taking place.

We had looked at this concept when we were looking at reaction coordinate diagrams. So when you are looking at reactions, the vibration is what plays a very important role. So let us look at this case. So this is a potential energy diagram. So let us say we are looking at C-H bond breaking versus the C-D bond. Now what you will see is the potential energy diagram that you have here that will not change if you have C-H versus C-D.

So you will not have big change in the potential energy diagram. But what happens to the vibrations? Now each of the vibrational states if you see any potential energy diagram you must have studied this in physical chemistry and also when you have studied spectroscopy, there are several energy levels within this which are the vibrational energy levels. So you would see them as various levels here, alright?

So now each of these levels is given by an energy e_n which is $(n + \frac{1}{2})\,h\nu$. The value of n goes from zero to 1 to 2, etc. So now, we are interested in what is called as the zero point energy. So zero point energy corresponds to the energy when n is zero. That is given by 1/2 hν.

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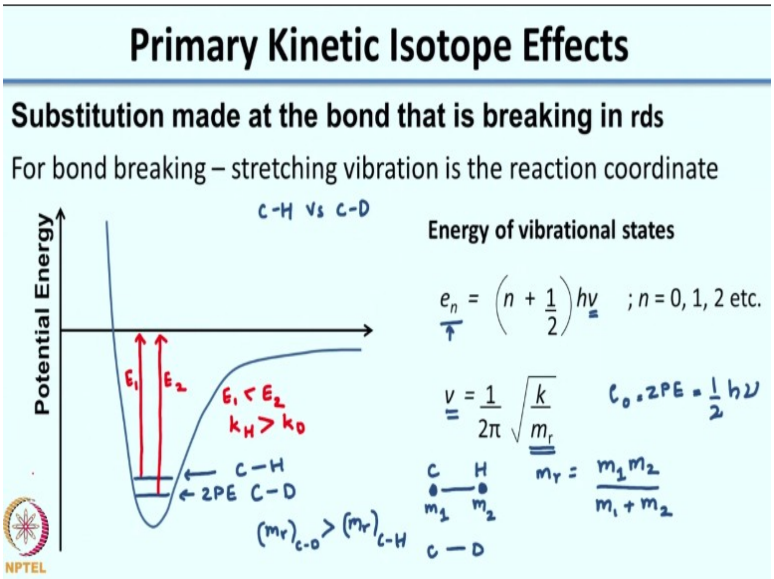

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$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{m_r}} \qquad E_0 = ZPE = \frac{1}{2}h\nu$$

C — H, m_1 m_2

$$m_r = \frac{m_1 m_2}{m_1 + m_2}$$

C — D

So essentially I am going to erase now all the other energy levels here. We are only looking at this, which is the zero point energy. Now here what happens is there is a difference between C-H and C-D. And why is that? The ν is given by $1/ 2 \Pi(\sqrt{k}/ m_r)$. This is just imagining as if this is a spring that you are looking at. So imagining that these two atoms say C and H and we are looking at the vibration.

So if we imagine this to behave like a spring, the frequency would be given by $1/ 2 \Pi(\sqrt{k}/ m_r)$ where m is the reduced mass. So m_r is given by so let us say this is the mass of C and this is the mass of hydrogen. It is given by m_1 $m_2/(m_1 + m_2)$. So this is your reduced mass. Now if you were to compare C-H versus C-D. So in the case of C-H versus C-D, what you would see is C-D will have a greater reduced mass or m_r value.

And because this value is greater for C-D, what you would see is that the new value would be lower for C-D. So if this is the zero point energy for C-D, the zero point energy for C-H would be higher. And this is because m_r for C-D is greater than m_r for C-H. And if you substitute that and substitute it in the e_n, what you would see is the ν would be inversely proportional to the reduced mass, which is why you would see that energy for C-D would be less than C-H.

So now let us imagine that once you have the C- H C-D bond, and we are looking at a primary kinetic isotope effect, so essentially we are trying to break this bond. So C-H C-D bond we are trying to break. So essentially where we are going is we are going to the dissociation point. This is for C-H the energy that would be required and this is for C-D.

Now when you compare both these energies, let us call this E_1 and let us call this E_2, what you would observe is that E_1 is less than E_2. Remember I told you earlier also the example of the mountain peak, if you start from a position, which is higher up, you have a smaller distance to travel. The same thing here, the C-H zero point energy is higher, which is why the energy required for dissociation of the C-H bond is less than the C-D bond.

So in other terms, if you were to look at the rates, k_H would be greater than k_D. Now the question is, how much will be the difference between k_H and k_D? So now to understand this we need to look at the reaction.

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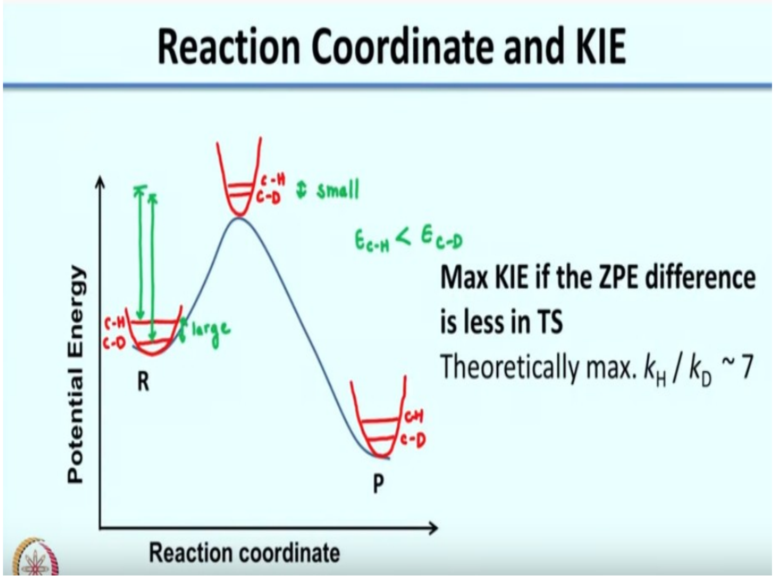
Reaction Coordinate and KIE

Max KIE if the ZPE difference is less in TS

Theoretically max. $k_H / k_D \sim 7$

So again, let us look at the reaction coordinate and kinetic isotope effect. So when we look at the reaction coordinate diagram, as I told you earlier, where we looked at the dissociation of a bond, even for a reaction the reaction coordinate will not change when you move from C-H to C-D. So now to understand the change that actually takes place at each of these levels you can imagine vibrational levels.

So you have your C-H and C-D. So even here at this point you can imagine and again at the product you can imagine vibrations that correspond to C-H and C-D. Now just like we had seen in all the other effects it is the relative energy difference that is very important. So if I look at the scenario which I have drawn, in this case what is happening is the difference here in the case of the reactant is large.

The difference here is small. So what that means is if I were to look at the energy difference between C-H and C-D, $E_{C\text{-}H}$ would be still less than, so the activation energy for C-H will be still less than C-D, because in this case what we have seen is, the difference is more in the reactant and less in the transition state. So when this is the case, you still have an activation energy, which is lower for C-H as compared to C-D.

So again the same example, as I told you earlier, imagine a mountain peak. If the final destination difference is not much, how quickly you reach depends on your starting point. So in this case, because the reactant has a large C-H C-D difference, you would see that the reaction goes much faster than in the case of C-D. So in general, for any reaction, you would observe maximum kinetic isotope effect, in which case? When the zero point energy difference is very less than the transition state.

So if the zero point energy difference is very very less in the transition state, you will observe maximum kinetic isotope effect. Theoretically, if you put in the values of the masses of hydrogen and deuterium and determine the v for each of these, what you would figure out is that the maximum k_H over k_D value is approximately 7. So this is assuming that very less difference in transition state and a big difference in your reactant.

So now let us see what causes a small difference in your transition state and what causes a large difference in your transition state. So clear so far? So, so far what we have studied is that the reaction coordinate diagram does not change when you make a replacement of C-H versus C-D. What makes, what changes is the vibrations that you are talking about.

So the zero point energy for C-H is larger than C-D because C-D has a greater reduced mass. Now for reactions which involve a very small difference in zero point energy in the transition state, but a large difference in the reactant will show a maximum difference in activation energy between C-H and C-D, which means it will show you a maximum kinetic isotope effect.

So now we are trying to understand what are the cases where the transition state zero point energy difference is small and what are the cases where it is comparable to the reactant.

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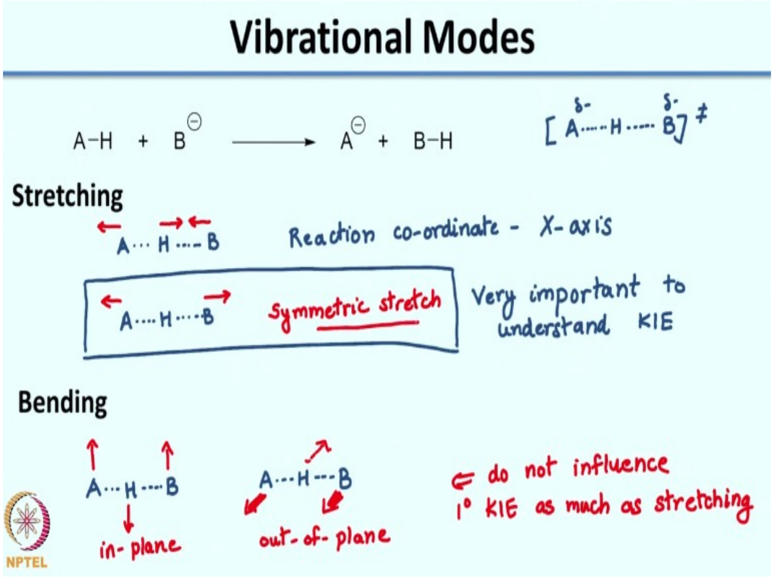

Vibrational Modes

$A{-}H + B^{\ominus} \longrightarrow A^{\ominus} + B{-}H$ $[\overset{\delta-}{A}\cdots H\cdots\overset{\delta-}{B}]^{\ddagger}$

Stretching

A··· H ···· B Reaction co-ordinate - X-axis

A····H····B Symmetric stretch Very important to understand KIE

Bending

A···H···B in-plane

A···H···B out-of-plane

⇐ do not influence 1° KIE as much as stretching

So to understand that, we need to take a deeper look into all the vibrations we are talking about. So let us look at a generic reaction. So we have A-H with a base. So you can imagine the base abstracting the proton to give you B-H and giving you A -. So now let us look at the different modes of vibration. So one mode of vibration is the stretching mode. So let us first write the transition state.

So you have A-H-B. So bond partially broken partially formed and you have a small charge on A and a small charge on B. So the first type of stretching vibration is I will write the atoms A-H-B. So we are looking at the transition state. And you can imagine this atom moving away, this atom moving away, this atom coming closer, alright? This is called an antisymmetric stretch.

So it is like the A-H bond is moving in the, stretching like this, while the B-H bond is stretching like this, alright? So this is one type of mode of stretching. The other mode of stretching is I have A. So you can imagine A and B both being pulled away from H. Like a tug of war you can imagine H being in the middle and A and B both pulling on the opposite sides. So this is a symmetric stretch.

Now when you consider both these stretches, in the first case, essentially you have A and H going away from each other and B and H coming closer to each other, which is very similar to what is happening in your reaction. So this is your reaction coordinate. That is your X axis. So now what becomes very important to understand the kinetic isotope effect is this symmetric stretch.

So this is very important to understand kinetic isotope effects. Now let us look at the other modes, the other modes are what are called as bending modes. So if I have, so I can have a bending mode which is in plane. So these are my three atoms, it can be either what is called as a scissoring mode or you can also have it bending in the plane, okay? My fingers are not moving that well, but you can imagine them.

Imagine it not moving out of the plane. Maybe I will try like this. So it is like this or you can see like this, okay? Imagine these are the three atoms. The other option is where you have, so you can have these coming out of the plane. So you can also have what are called as out of plane bending vibrations. So these could be again, if you are looking at, if this is the plane these could be going in and out of the plane.

Now what is seen with these, so this is in-plane and this is out-of-plane. So if you have studied spectroscopy, IR spectroscopy, what do you remember in terms of the stretching vibration and the bending vibrations? Which have a higher energy? Yes. So the stretching vibrations have a higher energy. So which is why the bending vibrations do not influence the primary kinetic isotope effect as much as the stretching.

So which is why it is very very important to understand the symmetric stretch. So based on analysis of all the vibrational modes, one is the reaction coordinate. So we are not worried about that. What we are worried about is the symmetric stretch. Now we will see how the symmetric stretch can affect the zero point energy difference in the transition state. So if you remember our discussion of the Hammond's postulate, we had looked at how you can have an early transition state, a symmetric transition state, and a late transition state depending on the type of the reaction.

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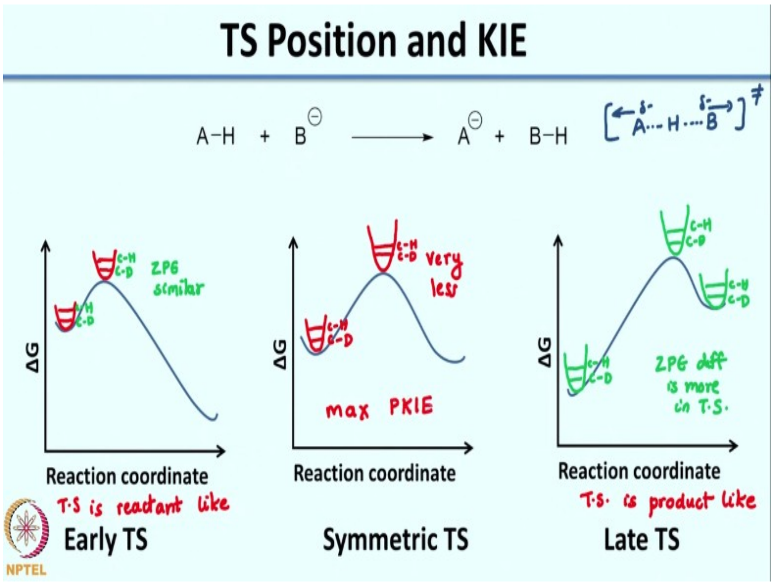

TS Position and KIE

$A\text{–}H + B^{\ominus} \longrightarrow A^{\ominus} + B\text{–}H \quad [A^{\delta-}\cdots H \cdots B^{\delta-}]^{\ddagger}$

So if you consider an early transition state or a late transition state, so in this case the transition state is reactant like and in this case the transition state is product like. And we had looked at it in terms of exothermic and endothermic reactions. The same logic is applicable here. So if you have an early transition state, which is very reactant like what you would see is if you have, so if you compare the zero point energies they will be very similar.

That is because now your transition state behaves a lot like your reactant. And if you remember from the previous slide, what we are essentially looking at is this transition state and we are looking at the symmetric stretch, right? We are looking at this symmetric stretch. So if you have the reaction, the transition state very close to the reactant, so the C-H over C-D here and in the transition state will be very similar.

So the difference will not be much. The same thing will also be true for a late transition state. Because here itself you have a case where you have it is like product. So it would be a case very similar to the C-H and C-D bond dissociation that we had seen earlier. So the transition state will be very similar to that of the reactant or the product. So even in the product as I said you will have C-H higher than C-D.

So this would be very similar to product. So zero point energy difference is more in transition state. Now what happens in the case of a very symmetric transition state? So when you have a symmetric transition state, so what you imagine is you have your hydrogen and you have A and B pulling it away like a tug of war. So when you have almost, so when it is highly symmetric, you can imagine that the force constant you are talking about between A-H and B-H is very similar.

So it is almost like a tug of war, you imagine both the teams are equal in energy. So at the center point, you essentially have no movement. So if you have a hydrogen atom sitting in the center, being pulled on either side by A and B in the opposite direction, because it is symmetric, essentially the atom in the middle is hardly moving. So then its mass, whether it is hydrogen or deuterium will not matter.

So imagine a tug of war. If the forces on both sides are similar, you can have an elephant standing in the middle or a small human being, the movement will not be much. The person will be stationary because you are talking about equal forces on both side. So that is why whether you have hydrogen or deuterium, so there is not a big difference.

So what that means is if you were to compare the vibrational levels here, the difference between C-H and C-D will be very less. Here it is more. So essentially, if you have a symmetric transition state you have maximum primary, I will write it as PKIE primary kinetic isotope effect. So now hopefully you have a feel for when you have the maximum kinetic isotope effect.

It is when you have the more symmetric transition state. So the position of the transition state is in the middle of your reactant and product which essentially means that you have partial bond formation and partial bond breaking, okay? So just to give you an illustration of this concept, this reaction was studied.

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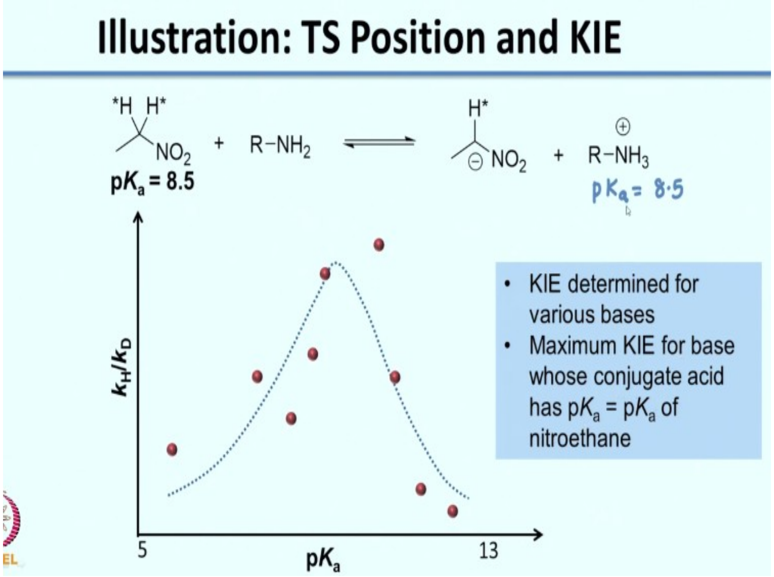

Illustration: TS Position and KIE

- KIE determined for various bases
- Maximum KIE for base whose conjugate acid has $pK_a = pK_a$ of nitroethane

So this is deprotonation of nitroethane with different amines. So you can imagine using different amines and deprotonating nitroethane and you can do the reaction. So is shown here are these two hydrogens in star. What it means is that the same reaction when repeated with deuterium, you will get a k_D value. So you can get different k_H over k_D values depending on which amine you use, correct?

So if you use one particular amine you will get a particular k_H over k_D value. If you change it to another amine, you will get a different k_H over k_D value. So this study was done where several different amines were used to deprotonate nitroethane. And then the k_H over k_D that was obtained was plotted versus the pKa of the protonated amine which is this, alright?

So again to repeat all these red dots that you see in front of you on the screen, so how many are there? You have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. These correspond to 10 different amines, all right? And what was done was for each amine the k_H over k_D was determined because each amine would be a separate equilibrium, a separate reaction, okay?

So now you determine the k_H over k_D value you can imagine a curve like this, alright? It is the average curve where you have some points on the left of the curve and some points to the right of the curve. So if you imagine an average curve like this, what is interesting is the maximum that you see in the curve corresponds to the pKa of around 8.5 which is the pKa of nitroethane. Now what does that mean?

We are looking on the X axis the pKa of this amine. So if you have the case where the pKa of this amine is equal to or this ammonium salt is equal to, so what does that tell you? So since both of these have similar pKa's, what that tells you is that the rate of the forward and backward reaction is similar. So essentially what does that mean? That means, a very symmetric transition state.

So when you have a very symmetric transition state, you see the maximum kinetic isotope effect. So this is just summarizing what I told you, kinetic isotope effect was determined for various bases and it was observed that the maximum kinetic isotope effect for the base whose conjugate acid had a pKa, which was equal to the pKa of nitroethane. And this is because you got the most symmetric transition state.

In all the other cases, you would get an early or late transition state because in some cases, this would be such a good base or rather this will not be a great acid. So this would be quickly deprotonated. Whereas, in other case, because this would have a lower pKa, this would not be deprotonated very easily, right? So in one case you will have reactant like transition state, in another case you will have product like transition state.

But when they are both equal, you have a symmetric transition state and you get maximum k_H over k_D. So this is an experimental evidence for what we were talking about in the previous slide. So now before we end this lecture, I want you to think about these two reactions.

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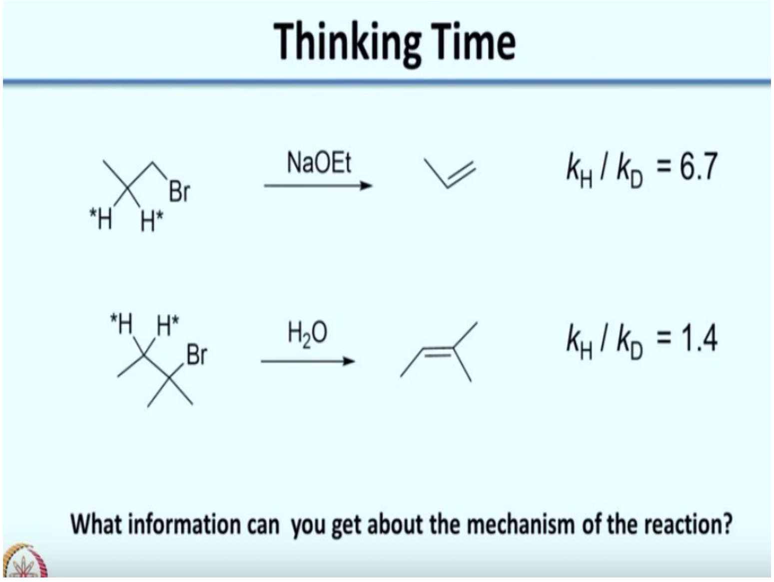

Thinking Time

$k_H / k_D = 6.7$

$k_H / k_D = 1.4$

What information can you get about the mechanism of the reaction?

So shown here are two reactions on the screen in front of you. And you have also been given the k_H over k_D value for these reactions. So what I would like you to do is I would like you to first write the mechanism for these reactions and then see based on the k_H over k_D value, is your mechanism correct, alright?

So I repeat the question, I want you to write the mechanism for both these reactions and then based on the k_H over k_D value, you need to tell me whether the mechanism is correct. So thank you and I will see you again in the next lecture where we will discuss little more about kinetic isotope effects. Thank you.