Mechanisms in Organic Chemistry
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Lecture - 7
Kinetic versus Thermodynamic Control

Welcome to lecture 7 of reaction mechanisms. Just a recap of what we did in the last lecture.

(Refer Slide Time: 00:25)

So last lecture, we were looking at the information that can be obtained from reaction coordinate diagrams. If you look at reaction coordinate diagrams, on the Y-axis, you have potential energy. So what information do you get from that, we looked at in the last class. So one thing that you get from that is the stability. So if you see in this case if I look at the energy of R and the energy of P, since the energy of P is lower than the energy of R, we can say that P is more stable than R.

The other thing you can say is whether there is a possibility of equilibrium. and the third thing that we can say is which would be the rate determining step.

So whichever has higher activation energy in this case, it would be the second step which would be the rate determining step and this you can say based on the fact that you have a larger barrier going from, going to, going from I to P which is the second step. Now lot of information is also available from the X-axis. The X-axis as I told you gives you information regarding the geometry of the molecule.

So if you look at it we discussed the Hammond postulate in the last class and based on the Hammond postulate, if the transition state or the intermediates, so this is the transition state here; so if the transition state is close to energy to the reactant then it resembles the reactant whereas if the transition state is closer in energy to the product it resembles the product. So, based on that, the Hammond postulate was arrived which essentially tells that if you have an exothermic reaction, so a reaction which gives out heat,

what you would have is you would have the transition state being closer in energy to the reactant and what you have is called an early transition state because it comes closer to the reactant on the X-axis. So this is called an early transition state. If you have the transition state closer in energy to a product, this would happen in the case of an endothermic reaction, you would call it a late transition state and the transition state would resemble the product. So in the last class I had left you with a question.

(Refer Slide Time: 03:19)

The question was that for the reaction given here, so in this particular reaction what you see is this reaction is a free radical halogenation, and the relative rates are 5.2 is to 1 when X is chloride and 1640 is to 1 when X is bromide. I hope you had time to think about this question. Now let us try to reason why this is the case and I will give you a hint. The first thing that I would like you to do is write the mechanism for the reactions. So, you can press the pause button and write the reaction mechanism.

(Refer Slide Time: 04:14)

So the very first step of the reaction would be, so the very first step of the reaction would be, X_2, we had done this when we were looking at mechanisms of free radical reactions. Now this process takes place very quickly. So this would not be the rate determining step. Now the next step would be where you have your alkane reacting with $X^{\cdot}$. So you generate a radical, so you can either generate this radical, what would be the other possibility? I am sure you have the answer for that or it can generate.

So now if I were to look at both of these processes, in the case of Cl, I can have the alkane generate this radical and this radical and the same thing in the case of Br, I can have the alkane generate these two radiclas. So based on what you studied earlier which of these radicals is more stable? and I am sure you have got the answer correct. The tertiary radical is more stable, but now what is interesting is in one case you have a selectivity of 5.2 is to 1 for the tertiary radical whereas in the second case you have a much larger selectivity, we are talking about 1640.

So this is a huge difference in selectivity. Now why is that the case? Now I will ask you one more question. Between the chloride radical and the bromide radical which is more reactive? Now the chloride radical is known to be more reactive and let us look at the energetics to get more sense, to make more sense of this. So if I were to look at both of these processes which is the rate determining processes, what you would see is that the process is exothermic. So what you end up giving out is -9 kilo joules/mol in the case of the primary radical and -26 kilo joule/mol in case of the tertiary radical.

Again, why did you give out more energy for tertiary radical because in terms of stability if I were to compare the energies, the tertiary radical would be lower in energy than the primary radical. So obviously if you are coming from starting material what would you see is the energy difference would be more for the tertiary radical. So, this process is exothermic because you start with something highly reactive and end up forming the axial bond which is quite stable. So now let us look at the case of bromide.

What you see in the case of bromide is you see that the reaction is now endothermic. So this actually requires heat to be taken because you start with a relatively more stable bromide radical and then you form HBr which is not as stable as HCl.

(Refer Slide Time: 07:51)

So I put all the information here on the slide for you. These are the 2 processes which are exothermic and the relative rates are 1 is to 5.2 whereas for the bromide the relative rates are 1 to 1640. So on this reaction coordinate diagram, what I would like you to plot would be the energy of this process, the energetics of this process where you draw the energy of the alkane and theses 2 intermediates. Similarly you draw the reaction coordinate diagram for the process with bromide.

So you can press the pause button and go ahead and draw the reaction coordinate diagrams. So the first thing that you have to think of is, in terms of energies, if you were to look at the chloride radical since the process is exothermic, you would put the reactant higher in energy to both of these. So what you have is and we can call this A and we can call this B. So you have A here and you have B here.

Now since the reaction is endothermic, you can put the reactant here and the 2 products here and here. Again, I will call it A and B and B as I said since it is a tertiary radical it will be more stable. Now based on the Hammond postulate would you expect an early or a late transition state in the case of the chloride? You would expect an early transition state and the transition state would actually resemble the reactant. So in this case, the reactant is the same irrespective of whether you form R or A.

So since the transition state is early, and resembles the reactant, the energy difference between the transition state for A and B would be very less because essentially we are talking about a structure of the transition state which is very very very close to the reactant whereas in this case you have a late transition state. Now the transition state is resembling the product more and which is more stable? B. So what you end up getting would be you would end up getting a transition state which is, which has this energy difference, call it A prime, I mean A double dagger and B double dagger.

So now if I were to draw the energy profile, what I will get is, in one case that is what it will look like and in the second case it will look like this; whereas here, the energy profiles will look like this for A and this for B. So now we are looking at relative rates, so what would be important? What would be important would be the activation energies. So now let us compare the activation energies. So if I were to compare the activation energies, in this case, so this will be the E_{act} for B and then the E_{act} for A would be this barrier.

As you can see the energy for A is slightly higher than B, not a whole lot higher than B. In this case, this would be the activation energy barrier for B and for A as you can see the difference is much higher in the case of bromide. So you can clearly see that the energy difference in the case of bromide is much higher, which is why the relative rates you see a huge difference. So this is a very nice example of the Hammond postulate where depending on whether the process is exothermic or endothermic you get an early transition state or late transition state.

In the early transition state, since the transition state resembles a reactant which is the same for both products, what happens is the transition state energies are not too different and which is why the activation energies are not too different. Whereas in the case where you have a late transmission state, because now it resembles the product; so if one product is more stable, that transition state will be more stable. So for that case you have a much much higher reaction rate because of lesser activation energy. Another very nice illustration of Hammond postulate is the S_N1 reaction.

(Refer Slide Time: 13:31)

So the S_N1 reaction let us start with the generic case. So if you have R-X, so what is the mechanism of the S_N1 reaction? What would be the first step? So the first step of an S_N1 reaction is generation of a carbocation and this is the rate determining step. So this has an important role to play in deciding the kinetics of the reaction. Now let us look at multiple examples of the S_N1 reaction. So one example would be just the CH_3-X, the other example would be, then we can have and the last example would be.

In each of these cases, I want you to write the structure of the carbocation that you generate. Can you go ahead and quickly do that in your books? At the same time, I will also write it here. So in one case, you generate a methyl carbocation. In the other case, you generate an ethyl carbocation, you generate a propyl carbocation and then you generate a tertiary butyl carbocation and all of these plus X^-. So from whatever you have studied earlier what is the stability of this?

What you would see is the stability of the carbocation is increasing going from methyl to tertiary butyl carbocation. So you have, stability increases. So now if I were to write the reaction coordinate diagram for this, what is known is that in the case of this reaction, the step is endothermic. So what you would have is if you have your reactant here, each of these processes is endothermic. So let us look at the very first process. If I put this as formation of, so going down you would have since the ethyl is more stable, I will just put it as Et^+.

The isopropyl is next more stable so and then you have your t-butyl which is the most stable. So as the energy of each of these is decreasing, what you would see is the extent to which the reaction is endothermic is also decreasing because your reactant energies do not vary as much between all of these alkyl halides. So what you would see is, in one case because the reaction is more endothermic, you would have the transition state look more like the product.

In the second case now it is less endothermic, so you would see that the transition state shifts a little to the left and as you go what happens is the transition state going from alkyl to t-butyl would shift to the left because you start off with a late transition state and as you are moving down, the transition state keeps shifting to the left because the energy difference between your reactant and the intermediate is decreasing or it is becoming less endothermic.

So this is another nice example of the Hammond postulate whether depending on the energy difference between the reactant and intermediate or specifically whether it is exothermic or endothermic, you get an idea about the nature of the transition state; as in whether it is a late transition state or an early transition state or somewhere closer to the middle. So now we move on to another important concept when we look at reactions. It is not that always you have one reactant and you get one particular product.

So we saw now where you have an alkane and its halogenation can lead to different products depending on the nature of the reaction and its energetics. So let us look at some other factors which govern which product is formed.

(Refer Slide Time: 19:41)

So let us take an example. So if you have a reactant R and suppose it can go one product A or a product B, the ratio of the products can be dictated again depending on the overall energetics of the process; so one is relative energy of transition states. So in this case the reaction is said to be under kinetic control. So just to show you what that means, so I have R it can go to A or it can go to B. So, let us say the transition state for formation of A is lower in energy, so basically E activation lower. So that means A would be formed faster than B.

So, such, if this is what decides what is formed, the reaction is called to be under kinetic control because here the major product is decided by which has a lower activation energy. So here speed is what is important. Right? So like I told you since A is formed faster, we are saying more of it will be formed. The other possibility is the relative energies of the products. So if I have R going to A and R going to B, now let us say that B is actually more stable than A. So in this case we are not looking at the energy of activation all we are looking at is the stability.

So where the stability decides which is the major product, we say that the reaction is under thermodynamic control. Now in this case, what is important is stability. Now, you might be wondering how does one decide whether speed is important or stability is important? So in the second case, both processes have their activation energies, similarly in the first case both products have their relatives energies. So how do we decide whether it is under kinetic control or under thermodynamic control. So let us look at this a little more deeply.

(Refer Slide Time: 22:28)

So let us consider these 2 reactions. So now in the first case, you have R going to A and B. I have shown you the reaction coordinate diagram for this. Similarly, in the second case also you have R going to A and B, but then here what you see is you have a different reaction coordinate diagram. So what I would like you to do is I would like you to look at both of these reaction coordinate diagrams and then point out in both of these cases which is the product corresponding to the faster reaction, which is kinetic control and which is the product corresponding to stability, which is thermodynamic control.

So for both of these reaction coordinate diagrams, I would like you to press the pause button and write in both cases what the kinetically controlled product is and what the thermodynamically controlled product is. So now let us considered the first reaction coordinate diagram. To figure out kinetic control what you need to see is, activation energies. So if I were to compare the activation energy in one case I have, so this is the E_{act} for A and this is E_{act} for B.

So just looking at this, which is higher, the energy of activation for B is higher. So which reacts faster? A reacts faster. So under kinetic control, we can call it as K.C. What would be the major product? A. Now which is more stable, in this case we compare the energy of A and the energy of B. Whatever is lower in energy is more stable. So here which is lower in energy? it is A. So under thermodynamic control, let us call it T.C. The major product will also be A.

So in this reaction, both kinetics as well as thermodynamics gives you the same product. Now let us look at the second case. Under kinetic control which would be the major product? As you can see if I were to look at the barriers, it is much smaller for formation of B, so under kinetic control major product would be B; and now if I were to consider thermodynamic control which is more stable? A is more stable. So under thermodynamics control, I actually get a different product which is A.

So now when you say in this case there is a possibility that you can actually tune which product you form by running the reaction under kinetic control or thermodynamic control. Because essentially when you are setting up these organic reactions, you are the one controlling what conditions you use. So why understanding this is important is that, you can design reactions so that you get one product more over the other. So let us now look at specific examples.

(Refer Slide Time: 26:05)

One of the classic examples for kinetic and thermodynamic control is deprotonation of the acidic α hydrogen next to a ketone to give you an enolate. So if you see this, there are 2 acidic hydrogens. So if you consider the ketone here, you have 2 similar protons, let us call them H_A, similarly here you just have one we can call it H_B. Now in presence of a base if you deprotonate H_A, what you end up getting is the enolate A. If you deprotonate H_B you end up getting the enolate B. Now B is a more substituted double bond, so it is more stable.

So as you can see the energy of B is less than A as it is more stable. But what you see is in the case of A, you do not have any crowding near those two hydrogens, here you have a methyl, so sterically it is more difficult to remove proton H_B as compared to the 2 protons H_A because of the methyl sitting right next to the hydrogen. So which is why if you compare the activation energy, the activation energy for formation of A is less than the activation energy for formation of B.

So activation energy for formation of A is less than formation of B means what is essentially the case here? A is formed under kinetic control and B is formed under thermodynamic control. Now how can we get the reaction to actually go under kinetic control or thermodynamic control? So for that one way to get the reaction to go under kinetic control is to set it up at a very low temperature. Now when you do a reaction under low temperature, the molecules have a much lower energy as compared to room temperature or higher temperature.

So when they have a lower energy, what happens is they would only be able to cross the lower barrier here. Alright? So just think as I told you earlier you can think of climbing mountains again. If you have less energy, it is easier for you to climb a mountain which has a shorter or lesser peak as compared to a mountain which is very tall. So it is the same thing with molecules. When the temperature is lower and they have lower energy, it is very difficult for them to go through the higher barrier.

So a low temperature ensures that the reaction is under kinetic control. The other thing is a bulky base. Now what will a bulky base do? As I told you, in this case the major difference is. because of this methyl, it is very difficult to, I mean, it is more difficult to remove H_B compared to H_A. So what happens is if you use a bulky base which is a large base, you make this process even more difficult. So what you end up doing is you end up raising the barrier for this process even higher. So with the bulky base, the second peak activation energy because even higher, so the reaction goes under kinetic control.

The third thing is to use a very strong base. So, in the presence of a strong base what happens is the reaction will go very quickly and it will do whatever forms easier first or whatever forms faster first. So you do not let this use a strong base and let the reaction go for a very long time, use a strong base and let the reaction go for a very short time, then you have it under kinetic control because the strong base works quickly and gives you the product that is formed faster.

Now to get the reaction to go under thermodynamic control what you do is you would increase the temperature. So now similar to what I told you earlier, the molecules have enough energy to actually cross both these barriers. So because of the higher energy, the molecule can actually either go to A and either go to or go to B. And typically when you do the reaction, so typically when you do the reaction under thermodynamic control, there is always, it only works when you have an equilibrium that can be established between A and B through R.

So what happens is at high temperature if you let the reaction go for a long time, it keeps going back and forth between A and B, but what happens is, since B is more stable, once it forms B, there is a lesser chance of it to come back to R and form A. So over time what happens is the concentration of B will increase and you get the more stable or the thermodynamically controlled product and the second case is where you use a weak base.

Now with the weak base, the process is so slow that you have a situation like this where you have A going to R and all this is in equilibrium. So when you have this system in equilibrium letting it go for a long amount of time, it will end up forming the more stable product which is B. So remember whenever you want thermodynamic control, what you need to have is a condition which would lead to equilibrium where you end up forming the more stable product. Whereas for kinetic control you do not want to attain the equilibrium,

you want the reaction to happen quickly such that you form only the product that is formed faster. So you do not give it time to equilibrate back to R and then form the more stable product B or what you do is you will use such a low temperature that it cannot actually cross the barrier to form the product B.

(Refer Slide Time: 32:51)

So this, this is a specific example of kinetic and thermodynamic control. So in this case I am using a bulky base, this bulky base is called LDA. Now in the case of LDA, the base is bulky because you have these large isopropyl groups next to the amine. Okay? So now because the base is bulky, it becomes more difficult to deprotonate from here. If you do this reaction under kinetic control which is -78 degree, the major product to get is the one corresponding to the kinetically controlled product. So you get 99% of the kinetically controlled product.

Whereas with the same base now if I heat the reaction, I am letting it equilibrate and allowing the molecules to also go through the higher energy barrier, what I end up getting is, I end up getting more of the thermodynamically controlled products. So by cleverly choosing the reaction conditions, I can get either the thermodynamically controlled product or the kinetically controlled product. So before we stop this lecture, I would like you to think about this problem.

Now in this case I am looking at a ketone, so there are 2 positions from which you can remove the protons. None of them have a methyl, but what I want you to think about is there are 2 different enolates that are possible, which of these would be kinetically favored? And to understand this what would be important is, I suggest that you try to draw the most stable conformation for this molecule. You can look it up, you can look up stable conformation of trans decalin. I hope you all know to write the chair form of cyclohexane. So this is the chair form of cyclohexane.

So based on the chair from of cyclohexane, draw the most stable conformation of trans decalin and then you will get an idea of which would be the product under kinetic control. In this case what you would see is since both the double bonds are equally substituted, there is not added stability for either of these products. So thermodynamic control might be difficult in this case, but there is still kinetic

I am giving you a hint that there is still kinetic control that is possible in this case, and to understand why I suggest that you draw the confirmation of trans decalin. So we will stop this lecture here and take up this problem in the next class where we will draw the confirmation of trans decalin and figure out which is the kinetically controlled product.