Mechanisms in Organic Chemistry
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Lecture - 8
Curtin-Hammett Principle

So welcome to lecture 8 of reaction mechanisms. So as usual, we will first do a recap of the previous lecture.

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So in the last lecture we had looked at examples of the Hammond's postulate and we had looked at how when you do the free radical chlorination you have an early transition state whereas with the bromination reaction you have a late transition state because in one case the process is exothermic and in another case it is endothermic. And we also looked at the S_N1 reaction where you can see the Hammond postulate because the reaction is endothermic that is the formation of the carbocation and how with the stability of the carbocation the transition state keeps moving towards the left.

So it goes from a late transition state and slowly starts moving away from the product. We also looked at the concept of kinetic and thermodynamic control. This is a method used when you can form two products from one reactant and depending on whether the activation energy is low, the product formed is said to be under kinetic control, if the activation energy is high, the product A will be formed slower than B. The other thing is, the stability of the product. So, as you can see in this case A is more stable than B.

So, when you do the reaction under thermodynamic control, more of product A will be formed and we had looked at the specific example of enolization and how you can get it to go between the kinetic and thermodynamically controlled product by varying conditions such as temperature and nature of the base.

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So I had left you with a question in the previous class where if I take this particular ketone

there are two possible enolates, one of them is kinetically favored. So my question to you was which one is the kinetically favored enolate? So I had asked you to look at the conformation of this particular ketone. So, if I were to write the 3-dimensional structure in the most stable conformation, since this molecule is what is known as a trans decalin, I can write the structure where I have two chair forms and the two hydrogens one above and one below, are trans to each other.

Now the ketone is here at the 3 position with respect to the ring junction. Now when I consider the two positions, one is where I am looking at these hydrogens and the other is where I am looking at the hydrogens which are closer to the ring junction. So when you see, these hydrogens which are away from the ring junction are easier to deprotonate, especially this one because you have absolutely no steric hindrance at that point. So, when I do this reaction using a bulky base such as LDA; I had introduced you to LDA in the previous class.

LDA is a bulky base. So, if you have a situation like this where one, where one of the hydrogens is more easily accessible than the other set, it would prefer to go there at low temperature. So when you do this reaction at low temperature, what you would see is, you get a majority of the kinetically favored product which is this enolate. Now in the other cases what we had seen is that if you do the reaction under thermodynamic control, essentially what you are doing is letting the reaction go to equilibrium and one product is favored.

But in this case what you see is if I compare both of these enolates if I call this enolate A and enolate B, stability of both are almost comparable. So what you would see here is even when I heat this reaction, I do not see formation of one major enolate, what I see is almost a 50/50 mixture of both because what you are doing here is now making both these accessible. So, the kinetic control is lost and there is no thermodynamic control.

So this is an example where you can get kinetic control based on steric factors. In this case it is because of these hydrogens and other hydrogens which are at the axial orientation. So, this is the answer to the question in the last lecture. So let us do some more thinking.

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Here is another example where you can see kinetic and thermodynamic control. So the molecule here is 1, 3 butadiene and if you do addition of HBr to 1, 3 butadiene at low temperature, you get 1 bromo-substituted product, as you get one of the bromo products as the major product whereas in the other case you see the bromine at position 1. So if you look at it, it seems like what is called as a 1, 2 versus 1, 4 addition where the 1, 2 addition seems to be favored at low temperature.

So I would like you to press the pause button on your video and look at this example carefully and think about why this could be the case. So if you are still trying to figure out the answer to this, I will give you one hint. So when you start this reaction, write the mechanism of this reaction, the very first step would be addition of H^+. So when H^+ adds, what you generate is, so you would generate the more stable carbocation because here you have a carbocation which is in conjugation with a double bond. So, you generate the more stable carbocation.

So this would be the intermediate formed in either of these cases. Now once you form this intermediate, you have to think as to why in one case you have the kinetically controlled product whereas why in the other case you have the thermodynamically controlled product. So again, for those of you who do not know the answer, you can press the pause button on your video and think about this problem. So now let me ask you another question for those of you still trying to think about the solution for this problem.

When you compare both of these products, again I will call this product A and product B; which do you think is more stable? So most of you I think would have gotten the answer. This is more stable as you have greater substitution on your double bond. So now let us think of how you go from this intermediate I to the two products A and B. In the case of going to product A, you already have the stable intermediate and you have Br^-. The Br^- will come to this position to give you product A.

Now what you see is, if you do this under thermodynamic, I mean if you do this reaction

under kinetic control as soon as you form this intermediate, it is trapped by the Br^-. So you do not have enough time for it to form the other product which is more stable, which is product B. Now what happens when you do this reaction under thermodynamic control is that you can think of, again the same intermediate, so you have this intermediate. Some people talk about, you can think of the resonance structure of this which is actually less stable as compared to this, so this is more stable.

So, one might be confused as to how this would form the thermodynamically favored product; but if you think about the mechanism, the mechanism would go such that this would still be the major product but now you have Br^- coming in. So this would give you product B. And now product B being more stable would be the product that is formed when the reaction is done under thermodynamic control. So, as a homework assignment what you can do is you can draw the reaction coordinate diagram for this particular reaction which is bromination of 1, 3 butadiene.

So we have looked at kinetic and thermodynamic control where you can get two different products from a single reactant. Now we will look at another scenario where suppose you have conformers. So conformers are the molecules which are related to each other, the bonding is identical but the only difference is in the spatial arrangement of atoms. So you must have studied the various conformations of butane in your 11^{th} standard 12^{th} standard and also B.Sc.

You have what are called as various conformers of butane by rotation of the CC single bond. So you can generate several confirmations of a particular molecule. Some confirmations are more stable than other, others.

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So we will look at a scenario where suppose you have two conformations of the same molecules, so conformation A and conformation B, so it would be called conformer A and conformer B. So let us look at the scenario where conformer B is actually more stable than conformer A. So what I want you to do is, now again press the pause button on your video,

but before you do that I will tell you the question,

what you need to do is you need to draw a reaction coordinate diagram and in the reaction coordinate diagram just show the relationship between A and B. So you can go ahead and do that. So let us go ahead and draw the reaction coordinate diagram. So let us say this is the energy of A. So if you have 2 conformers, in this case we have said you have conformer A and conformer B, we have said conformer B is more stable than A. So with respect to A when I write B, it should be shown at a lower level than A.

Now let us look at the interconversion. Usually the energy difference between 2 conformations is not very high. So, I show a small hill going from A to B. Now if we were to decide as to which is the product form, so you can either form product P_A or you can form product P_B. So one scenario is both conformers react at the same rate. So can you show formation of P_A and P_B on this reaction coordinate diagram now that I have given you this information? Both conformers react at the same rate.

So again, go ahead, press the pause button on your video and try to draw the reaction coordinate for A going to P_A and B going to P_B on the same reaction coordinate that I have started for you. All right, so what you must have drawn is when you go from A to P_A, so let us not worry about the relative energies of P_A and P_B so let us call this as P_A, this as P_B. So when I say that both conformers react at the same rate, so let us say this is the energy of activation going from A to P_A.

So when I go from B to P_B, this value would be almost the same. So if I call this E1 and I call this E2, E1 would be almost equal to E2. So now if both conformers are reacting at the same rates what would decide which would be the major product? In this case, the major product ratio would depend mainly on the conformer ratio. So if B is more stable than A, so if B is more stable than A, that would indicate that the major product would be P_B as compared to P_A because the reaction rates for both of these are the same and here I have shown the energies being the same let us assume that this is a reaction which is going under kinetic control.

So this is the first scenario. The second scenario would be that the major conformer is the reactive conformer. So again, as I told you in the previous slide, we are assuming here that B conformer is more stable than A, with this information, I want you to draw a reaction coordinate diagram where you show this scenario where I am saying that major conformer is the reactive conformer. So again, press the pause button on your video and draw the reaction coordinate diagram for this particular scenario.

So in this particular scenario, again like before, we can start with drawing the relation between A and B. So this is your A, as I said B is more stable, so this would be B, this is A, a small hump. Now here what we are saying is B is the reactive conformer. Reactive means what? Smaller activation energy. So B would have a lower activation energy as compared to A. So now in this case what would decide which would be the major product? Now since the major conformer is the reactive conformer, the product from the major conformer prevails.

So the major product now would be P_B because B is lower in energy and also the activation energy for going from B to P_B is quite low. So now this is pretty straightforward. Let us look at the third scenario. The minor conformer is the reactive conformer. So again, we will start with our original assumption that B is more stable than A. So, with this assumption, I want you to draw the reaction coordinate diagram where you show this particular scenario that the minor conformer is the reactive conformer.

So again you can press, so you can press the pause button and work out the reaction coordinate diagram. So hopefully what you would have drawn would be, again let us start with E, reaction coordinate. I have A, B is more stable, so I will draw B lower than A, a small hump to show the interconversion. Now I am saying the minor conformer is the reactive. So between these two, the minor conformer would be the one in higher energy, the more stable conformer would be that that would be major.

So the minor conformer is the reactive one means, lower activation energy for P_A. So, if I put this as E1 and this as E2, E1 is less than E2 here. So, what is happening here is, the minor conformer is what is reacting faster. So how do you decide the product ratio in a situation like

this? And to understand this is what we have as the Curtin- Hammett principle.

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So, what we had drawn in the previous slide is essentially what this potential energy diagram looks like. You have A and B, B is the more stable conformer, but it also has a higher activation energy going to P_B whereas A which is the higher energy conformer so minor conformer has a lower activation energy to form P_A. So then the questions that would come up is what dictates the major product?

Is it the relative stability of A and B? Is it the activation energy barrier for P_A and P_B or is it the relative stability of P_A and P_B? So what Curtin-Hammett principle says is when you have a scenario like this, the product ratio that is $P_B/P_A = K \times k_B/k_A$ where k_B and k_A are the rate constants corresponding to formation of P_B from B and P_A from A. So let us understand how you actually get this ratio.

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So let us try to derive the Curtin-Hammett principle. So if I were to look at formation of P_B, so the rate for formation of P_B, so the rate for formation of $P_B = k$ [B] because P_B is being formed from B. The rate for formation of P_A would be given by k_A [A]. So now if you were to determine which is the major product that is being formed, let us take the ratio of rate of P_B/rate of PA, so that, because concentration of P_B would be directly proportional to the rate and concentration of P_A again be directly proportional to the rate.

So what you get would be concentration of $[P_B]/ [P_A] = k_B$ [B] / $k_A \times$ [A]. So now based on your understanding of basic thermodynamics, if you look at the interconversion of B which is in equilibrium, interconversion of A which is in equilibrium going to B, the K equilibrium constant would be equal to concentration of B over concentration of A. So in this case, this equation reduces to $k_B/k_A \times K_{equilibrium}$. Remember always that capital K stands for the equilibrium constant whereas a small ks stand for the rate constants.

So this is how the Curtin-Hammett principle is arrived at. So based on the Curtin-Hammett

principle if you have rapidly interconverting conformers, so essentially you have a small hump going from A to B, the major product would be determined based on the activation energies. So, in this case this is the activation energy going from A to P_A, this is the activation energy going from B to P_B. So, this is the difference in activation energies that we are talking about.

So greater the difference in these activation energies, better would be the selectivity. So, in this case the major product would be the one which has the smaller activation energy, so P_A will be major product. So, this is the basic essence of Curtin-Hammett principle where it says that if the difference in activation energy is much larger, then you would get a greater selectivity for formation of one product over the other. So, we will look at some examples to understand the Curtin-Hammett principle

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So, let us first try to understand what is the epoxidation reaction before we look at how Curtin-Hammett principle can be seen in a specific example of epoxidation. So what, how the epoxidation reaction works is here you have a base, again to understand this you would need to draw the chair form. So organic chemistry students, I would strongly recommend you practice drawing the chair form because it is very useful for you to explain several mechanistic observations and also conformations of molecules.

So here I have to show OH coming up and Br coming down. So this is one conformation. I can also have another conformation, here this is flipped, so I have the OH here and the Br down. Now for the epoxidation reaction to take place, the first thing that you would have is, you would have generation of the O^-. So let us go ahead and generate the O^-. Now once you generate the O^-, for the Br to go, it is very important to have what is called as an antiperiplanar orientation, which is a 180 degree dihedral angle, which is possible in this conformation.

With this conformation, you do not have the proper orientation. So, in this case, the product actually goes via this particular conformation. Now if I were to look at the energies of these

two conformations, this conformation is actually more preferred because you have the two groups in the diequatorial positions. However, the product is actually formed from the diaxial conformer because the energy of the transition state in this antiperiplanar orientation is much lower than the energy of the transition state in, from the major conformer.

So now let us look at this extended slightly further. So you can have an example. Now that we have practiced drawing trans decalin, here is another example of trans decalin. Now in this case, I am specifying the position whether it is axial or equatorial. So here I have Me going up and then hydrogen coming down and at the 3 position with respect to Me, I have the Br coming up, so coming up means it has to be axial and the OH coming down; which also has to be axial.

So now in this case once I deprotonate it, let us again erase the proton. So once I deprotonate it, it has a very nice antiperiplanar orientation to give you the epoxide

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So now I want to leave you with a question, now that you understand the epoxidation reaction, we have looked at an example of the epoxidation reaction, here is another molecule, the only difference here is I have Br coming down instead of going up and OH coming up. When I treat this in the presence of a base, the time taken is 72 hours at room temperature. I don't know how many of you noticed in the previous slide how long it took for the reaction to take place, but in case you have forgotten, I will show it to you again.

For this particular molecule, it took only 1 minute to form the epoxide whereas for this particular molecule, it takes 72 hours. So why is this reaction much slower than reaction on previous slide? Think about this question. I will leave you with this and in the next lecture, we would look at the explanation for this particular problem.