Mechanisms in Organic Chemistry

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Lecture - 11

Distinguishing Reaction Mechanisms Using Rate Laws

So welcome to the next lecture in reaction mechanisms. In the last class, we had looked at deriving rate laws.

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So what we had done is we had looked at the transformation of A+B going to P. This can happen by various pathways. One is the elementary reaction where you have A+B reacting where you have a single transition state giving the product. So this rate law can be given as k [A] [B]. So this reaction would be first order with respect to A and first order with respect to B.

The other option is where you form an intermediate I and this intermediate I reacts with B to give you the product P and we had derived the rate law for this particular mechanism as well. Another mechanism could be where A and B both react together to give an intermediate I first and then I gets converted to P and the rate constants for all of these are indicated and again the rate law for that was derived.

The last scenario we had done is where we had looked at a giving intermediate I and a side product P_1 and then the intermediate I reacting with B to give you the final product which is P_2 and we had derived the rate law for this as well. So now what you would see here is the first example is a simple rate law that you get from an elementary reaction whereas these are more complex. Now looking at these equations, I do not want you to feel overwhelmed or think that it is very difficult to use these to determine reaction mechanism.

So in today's lecture, what we will do is we look at how we can simplify these expressions further to determine reaction mechanisms. So now again I am going back to the same equations. When you look at all of these, I want you to carefully look at the numerator and the denominator in the cases of the complex reactions. Is there a common trend that you observe? You can press the pause button and think about it. So, what you would observe is normally what you have in the numerator leads to formation of product.

So everywhere you would see that the numerator talks about formation of the products. If you look at it the rate constant k_1 is going from A to I and in turn it goes and the rate constant k goes from I to P. So these are all related to formation, and if you see in all these cases you have the k_1 k_2 [A] [B] in the numerator whereas the denominator, the denominator represents all the processes that lead to consumption of the intermediate. So what you can see is in this case you have k_{-1} + k_2[B], so this essentially leads to, so this essentially comes from consumption of intermediate.

So, you can see the same in all cases. Now there is a difference because there are different mechanisms in all these scenarios for consumption of intermediate. So this is a very interesting fact that when you derive the rate law all the terms in the numerator would lead to formation of product and all the terms in the denominator would lead to consumption of I. So now that we have an idea of deriving rate laws, instead of A and B, you can imagine actual reactants. You can think of organic molecules and derive their rate laws. So now let us look at specific examples.

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So I had asked you this question in the previous class, can reaction kinetics be used to determine reaction mechanisms and what we had said is information from the kinetics can be used to arrive at mechanisms and also evaluate multiple mechanisms for a reaction and pick the most plausible one. So now that you know how to derive the rate laws, we will see how we can translate that into actually determining the mechanism.

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So, let us look at a simple example distinguishing between mechanisms. So when we had looked at different mechanisms in the first class, you had the option of if you have a substitution reaction, given by the example shown here, it can undergo the reaction via an S_N2 or an S_N1 mechanism. So the first thing you need to do is you need to write the S_N2 and S_N1 mechanism. So go ahead and write the mechanism for RX + Nu giving RNu going via the S_N2 two and the S_N1 mechanism in your notebooks.

You can press the pause button on the video. So the S_N2 mechanism if you remember the first week, is a bimolecular mechanism, so this is an elementary reaction and what you have here is in the mechanism you have, we are not going to push arrows here we are just going to simply write it. Let us say this goes by a rate constant of k, so what would be the rate law for the S_N1 process? Can you go ahead and write that in your notebook? Write next to where you wrote the mechanism.

So you can check your answer. This is analogous to the elementary reaction that you had seen in the generic example I had given you where you had A+B giving product. So based on the rate law, you can see that k is the rate constant for this particular transformation. So in the S_N1 mechanism, the first step you have R-X giving you $R^+ + X^-$. Now is this step reversible? Yes it is. So we will put a reversible arrow and you can call this process with the rate constant of k_1 and the reverse process with the rate constant of k_{-1}.

In the next step you have $Nu + R^+$, the rate constant of k_2 giving you are RNu. So now I want you to go ahead and derive the rate law, so this is very similar to the case we had seen earlier where you have A first forming an intermediate, in this case the intermediate is your carbocation. So go ahead and derive the Rate law, but instead of A and B, now you would write R^+ and X^- and RNu. So you can check your rate law. So what you would have is dP/dt = $k_1 \times k_2$ [RX] [Nu] concentration of nucleophile.

This is similar to the case of [A] x [B] and in the denominator you have the processes that lead to consumption of the intermediate. So you have k_{-1} where you have R^+ and X^- recombining and k_2 where you have R^+ actually going to the product. So those will come in the denominator. So this is similar to the generic example we had done earlier with P_1 and P_2. So in the denominator now you have both concentration of X^- and nucleophile.

Now one would look at this and think that this is quite complicated and how can one actually use this to differentiate between an S_N2 and S_N1 mechanism. Now let us simplify this expression further. Now what happens in reality is that between these 2 steps, the first step occurs much slowly because when you have to do a nucleophilic substitution reaction, you choose such a nucleophile which will react very quickly with the carbocation. So the nucleophile would be more reactive as compared to recombination, so this process,

so the nucleophile attacking would be much more efficient as compared to recombination of R^+ and X^-. So this is very logical, otherwise the reaction will not take place. You will go on regenerating your starting material. So if you want the nucleophilic substitution to actually take place, Nu^- should be more reactive than X_-. So in terms of rate constants what does that tell you about k_2 and k_{-1}? So which of these would be greater? I want you to think about this.

So logically if the nucleophile is very very reactive what you end up having is you have k_2 being much much greater than k_{-1}. So now what will that do to this equation here? So in this equation since k_2 is actually much larger than k_{-1}, this term also becomes much larger. So the effect of this term is negligible. So what I can now do is I can write this expression as $k_1k_2[RX][Nu]$ and in the denominator I have $k_2[Nu]$.

So now what happens is, what you end up getting is a rate law where you see no dependence on the nucleophile and that is because the first step is slower and the nucleophile addition which is the second step, is much faster. so we have called this as the rate determining step earlier. So the rate determining step is the first step, that is why you can translate this complex equation into a much similar one.

So now when you compare both these equations, what is the major difference that you see here? In the case of S_N2 you would notice that the rate of the reaction will vary with concentration of the nucleophile whereas in the S_N1 reaction you see that the concentration of nucleophile will have no effect on the reaction rate. So now if you were to design an experiment to figure out whether this reaction works via an S_N2 or S_N1 mechanism, it is quite simple because what you need to do is just look for the change of the rate in with respect to concentration of nucleophiles.

So now that you know the dependence of S_N2 and S_N1 with the concentration of nucleophile to experimentally determine this what you would need to do is you would just need to plot dP/dt with concentration of nucleophile. So if you see a linear dependence, you know that it is an S_N2 whereas if you get no dependence, you know that it is an S_N1 reaction. So this is such a simple experiment to distinguish between an S_N2 and an S_N1 reaction mechanism.

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Now can kinetics be used to distinguish between E2 and E1 elimination mechanisms? So like last time, what I would first like you to write the mechanism for E2 and E1 and then derive rate laws for each of these. So you can go ahead press the pause button on your video and derive the rate laws for E2 and E1. So let us look at the mechanism for the E2 elimination. So for the E2 elimination, you have a leaving group, and then in the presence of the base, in a single step you form the product.

Whereas in an E1 mechanism, what you have is, in the first step you would have formation of a carbocation and then in the next step you have the base abstracting the proton to give you your double bond. So now if I even write the mechanism based on whatever you have seen earlier, so you can now write rate constants and all if you want and derive the rate law, but something even simpler than that I can tell you. In the case of the E1 mechanism, the first step is the rate determining step.

So based on whatever you had seen with the S_N2 and S_N1 case, if I were to plot with concentration of base, what would you expect for an E2 and what would you expect for an E1 mechanism. So in an E2 mechanism what you would see is that you would see a linear dependence whereas for an E1 you would see no dependence. So, this would be a very quick way to distinguish between an E2 and an E1 mechanism.

So what you would essentially get would be, I am directly writing the simplified form, calling this R-LG whereas for an E1. We can use kinetics to distinguish between such contradicting mechanisms.

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Another very interesting example is when the nucleophilic substitution of thiamine, in biology you must have studied about thiamine. Now thiamine can undergo a nucleophilic substitution by sulfite and the process can be shown like this. So you have the thiamine and to simplify the reaction I am calling this as your leaving group LG. So what happens is you have the sulfite addition to give you this.

Now just looking at these molecules, one might assume that this could either go by the sulfite directly adding here via the S_N2 mechanism or an S_N1 like mechanism and what was known is that the proposed intermediate, so this usually works in an enzyme and the proposed intermediate for this was the protonated molecule shown here. So, what was found was that when a model substrate shown here was used to understand the mechanism of the reaction, it was found that the reaction is actually second order with respect to the sulfite ion.

So if you remember when we had done the comparison of S_N2 versus S_N1, in S_N2 you would expect a first order relationship between the sulfite and the rate whereas in an S_N1 you would observe no relationship. But here it was very intriguing that a second order relationship was found. So, the reaction was second order with respect to the sulfite ion. Now how can we actually explain this mechanism? So maybe we can do this as a nice exercise for you, because in the first week we had also done how to write reaction mechanism.

So this would be a nice practice for arrow pushing. I am giving you a hint. The first step instead of the sulfite directly attacking at the carbon next to the leaving group, the sulfite actually attacks at the carbon next to this nitrogen. So this is a very electrophilic carbon because you have this positive charge on the nitrogen. So it is like an iminium ion and it is very electrophilic. This carbon centre is very electrophilic.

So based on this hint, I would like you to draw the mechanism for this reaction, you can press the pause button on your video and draw the mechanism. So let us draw the mechanism now. So the first step after sulfite addition would lead to the product. So there is no change in the rest of the molecule, so I am going to first copy that and by pushing the arrows, what I would get would be, so this would be the first intermediate that I get and as I as always I tell you should check the net charge.

So in this case the net charge is -1 as it is in the case of your model substrate and sulfite. Now the next step for this reaction would be because you have a lone pair on the nitrogen you can and it is in conjugation with this double bond, now that the aromaticity of this ring is lost, you can think of this participating. So then what you end up getting would be, so these parts are not part so these parts of the molecule are not participating, so I am going ahead and writing that. So here you have a double bond and then you have another double bond based on the arrow push.

So now what could be the next step of the reaction? Remember this is second order with respect to the sulfite ion. So, the next step would be, now you can imagine a 1, 4 addition, again you have an electrophilic center here. So, what you would end up getting would be, so this would be the next intermediate that you get. Now once you get this intermediate, you have the lone pair here which would kick out the sulfite molecule to give you the desired substitution reaction.

So now that you see here, you have 1 molecule of sulfite adding in initially and then you have another molecule of sulfite adding in later. So, this reaction then, is second order with respect to the sulfite ion. So here the kinetics was actually used to determine the mechanism. So it was not S_N1 not S_N2 but something completely different where it went through multiple addition reactions followed by elimination to give you the desired products.

So this is a very interesting example where a lot of times, mechanisms which seem very obvious might not be very obvious and the best way to find out what the mechanism is would be to actually do an experiment to determine this. So, in this case kinetics was very very valuable because by doing the kinetic analysis what was found was that it was neither S_N2 nor

S_N1 but went through a completely different pathway. So, this is also a very important tip for you. So, for those of you who want to do research, it is very important to have an open mind.

One might think by looking at a particular problem that this looks very straightforward and this is probably the only product that is possible, but with mechanisms, if you have interesting molecules, for example in this case you have a very interesting molecule where you have a highly electrophilic center generated in the intermediate, now this electrophilic center would actually react better with the nucleophile as opposed to the one you had initially thought would be the electrophilic center based on just looking at the starting material.

And another thing which I would like to point out is whenever you think of mechanisms, there is always a logic behind it. So, it is not randomly that you have now second order dependence on the sulfite. It is because of the fact that this molecule is getting protonated in the enzyme active site that you see this sort of mechanism and this was proven by using a model substrate.

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Another example would be addition of HCN to ketones. So now this is another classic textbook example. In an acidic medium, so in an acidic medium, you can imagine if you have, so this is a reaction that we are looking at. So imagine this is being done in an acidic medium. So in an acidic medium, what are the two mechanisms that you can write? One mechanism would be where you have the CN^- directly interacting with this electrophilic center to give you.

And then in the presence of, since you are doing this in an acidic medium, the other option could be where you have, so you can first have protonation followed by addition of the nucleophile to give you the product. Now again you can use kinetics to distinguish between 2 mechanisms. In one case you would see that there would be because this step is usually slower, so what you would see here is you would have no dependence, whereas in this case you would see.

So this is a very nice way where you can use kinetics to distinguish between two mechanisms/ So we have looked at substitution reactions, elimination reactions and now I have also shown you an example of an addition reaction where you can use kinetics to distinguish between the two mechanisms. So, we will stop here and in the next lecture, we will look at experimental methods for you to actually determine the kinetics. So thank you.