Mechanisms in Organic Chemistry
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Lecture - 12
Methods to Monitor a Reaction

So welcome to the 12th lecture on reaction mechanisms. So, we were looking at kinetics and how reaction kinetics can be used to determine the mechanisms.

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So initially we did some basic revision of kinetics and how you can write the mechanism and derive rate laws for different complex reactions. We then in the last lecture looked at how you can use reaction kinetics to arrive at mechanisms and also evaluate multiple mechanisms for a reaction and pick which is the most probable one based on the kinetic studies. So, the examples of reactions that we are done is we have looked at substitution, so we had looked at S_N2 versus S_N1, we had looked at elimination so we had looked at E2 versus E1.

We had also looked at addition reaction and I had given you an example of determining the mechanism of nucleophilic addition to thiamine to understand the applications of using reaction kinetics in understanding biology. The human body and the reactions that occur in the human body are very complex but what you see is they follow the basic principles of chemistry; so you can use model substrates to even understand complex reactions that happen in biology that are catalyzed by enzymes

So we looked at that with the example of thiamine. That was just to illustrate the applications of these kind of experiments to understand real life problems. So now the question is if I am doing the experiment, what I would need to do for any kind of kinetics analysis is I would like to measure the concentration of any one species, either the reactant or the product overtime. I say reactant or product because they are more stable as compared to intermediates.

There are also methods by which you can look at reactive intermediates, but then the reactive intermediates do not exist for a long time in solution, their lifetime is very small, so it becomes much more challenging for you to study intermediates. So later on during the course we will look at methods by which you can actually study the nature of the intermediates by what is called as trapping the intermediate. So now let us look at different scenarios for reactions. One is a reaction which can take minutes to hours or days. So this is the time scale of the reaction.

Now many of you might have done chemistry labs. So, one of the species, either the reactant or the product, should be such that you can measure it by using a simple titration. So, you may have done it by using acid-base titrations where you have one of the reactants as an acid or a base.

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So in our undergraduate lab, we used to do the reaction where we would look at hydrolysis of an ester to the acid and alcohol and the concentration of the acid was determined using titration. So this is a very basic lab experiment but many a times you have reactions that take place in minutes to within a few hours. So you need faster methods to determine the concentration of the reactants. So now, so some of the methods that are used are you can use NMR, fluorescence, UV visible spectroscopy, HPLC, IR to monitor the reactants or the products.

So to give you an example, in the same case, if I imagine the reaction where I have, now the product that I will get would be again the acid and paranitrophenol. Now this compound is UV active. So as you know, absorbance would be directly proportional to the concentration of the UV active species. So you can use absorbance to figure out how the product changes over time. Other methods as I said is you can use NMR spectroscopy. Now in NMR spectroscopy one has to ensure that sometimes NMR Spectra of a reaction mixture can be quite complicated.

So, if you have a reaction where you can easily follow the reactant or the product over time

with NMR, then NMR spectroscopy is also often used to determine the kinetics of the reaction. You can also use HPLC to monitor how the concentration of a particular species increases with time. Now a lot of times to actually get more quantitative information, people use what is called as an internal standard. So what the internal standard does is, so this is your reaction what you do is you will add an internal standard.

So this would be an organic molecule of known concentration, so you know exactly how much internal standard you have in your reaction flask. Now this is of known concentration and the internal standard should be such that it does not interfere with the reaction. So it is just almost as if it is sitting and watching the reaction without participating. So at every point of time what would happen is you know how much internal standard is there.

You can use either of these methods, you can use either UV visible spectroscopy or NMR spectroscopy to determine exactly how much quantity you have of your compound with respect to the internal standard. So you can quantify how much compound you have with respect to the internal standard.

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So just to give you an example of how you can use an internal standard, so say the method you are using is NMR spectroscopy. So typically in your NMR spectrum on your X-axis you have your chemical shift and you have the intensities on the Y-axis. Now suppose you use an internal standard, so this is 1, 1, 2, 2 tetrachloroethane, I call will this TCE, all right? So suppose you use an internal standard let us say this is 0 and this is somewhere around 7 and let us say your internal standard you have added a known amount; let us say you have added 2 mg.

So you can figure out how many millimoles that corresponds to. So if this is the peak of your internal standard, let us say it will come around 6, now the area under the curve corresponds to concentration or integration. So based on the integration value, say I get an integration I set the integration of this to be around, so this corresponds to 2 protons. So 2 protons corresponding to an integration of 2.

Now suppose in the same flask I have my reactant and say we are looking at the reactant protons and the rest of the reactant, so typically your NMR spectrum would be pretty complicated. So you can imagine that you would have peaks here in this region, you will also have other peaks in this region, and let us say these protons show up independently around this region. Now these also correspond to 2 protons, but when I integrate this, since I have set the integration of TCE to 2 and let us say this value comes out to be 1.

So now 2 protons of TCE corresponds to an integration of 2, so 1 proton corresponds to an integration of 1 for TCE. Now for your compound, what you see is the integration is 1 and that corresponds to 2 protons, so which implies for 1 proton you have an integration of 0.5. So that means if I take the ratio of TCE is to compound, let us call this A, it would be 1/0.5. So what that means is if I have put x millimoles of TCE, it implies I have x/2 millimoles of A. So using this method at every point of time, so I start with t = 0, obviously at t = 0, I will have none of the product that is being formed.

If this is the product, let us say A is the product, if A is a reactant that is when you will have maximum amount of the reactant and then you take NMR Spectra at t is equal to different time intervals. So you take Spectra at t = 0, then say 1 minute, depending on how quickly the reaction is 1 minute, 5 minutes, all the way up to t minutes and at each point you do this integration to see how the concentration of A changes.

This is fixed because TCE is as I said is just a silent spectator for this reaction so it is not doing anything, that concentration will remain the same, only the concentration of your product will increase over time or reactant will decrease over time and then once you know the millimoles you can plot it versus the time just like we had done in the earlier examples. So you can plot the concentration versus time and then do the kinetic analysis.

So you can figure out whether its first order, second order or zeroth order by doing a systematic kinetic analysis. Now what would you do when your reaction lifetime is a few seconds or lesser? Because usually when you do any of these techniques UV visible

spectroscopy, NMR, what happens is it takes at least a minute for you to get the data from the reaction mixture, but then if the reaction is done in seconds, then by the time you actually mix everything and get some information, the reaction is already done.

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So in these cases, what is done is flow techniques are used. So in the flow techniques, I will give you a simple example. Let us consider a reaction A+B going to the product. So what you do is you use a reactor. So let us say the reactor will have 2 inputs A and B, so A will flow through this pipe, B will flow through this pipe, and then you mix A and B. So what happens is at this point no reaction, at this point also no reaction. Now when you mix the two together that is when your reaction takes place along this pipe.

So at this point, you have A coming here and meeting B. so this is when your reaction starts and this corresponds to t = 0. Now what is done is along the path of the reaction what you have is, you have different time points because this is where the mixing is taking place; this is t = 0. At different points if you are able to analyze what is happening here, you can study the kinetics even within seconds. So here what happens is usually in a flask you mix everything together and then try to collect the data.

Here because it is a flow based reaction at different distances along the pipe, as the distance increases, the reaction time also increases and different methods are used to study the kinetics. So it is coupled with detectors, you can use IR, you can use fluorescence which are very quick. Either many a times the tubes are designed such that you can get information real time or what is done is a stopped-flow method is used where at each of these distances you can actually stop the flow and get information regarding concentration of the reactant and product, reactant or product.

Now this is a commercially available you can even buy what is called a stopped flow kit and attach it to an instrument such as a fluorescence instrument to study how a reaction progresses. So this will tell you information about reactions where the reaction happens very quickly and the data can actually be obtained within one-tenth of a millisecond. So this shows

you how much technology has progressed.

So in your lab when you did your titrations, you were talking about hour, hour scale reactions where each of these titrations in itself would take you 2 to 3 minutes to get the endpoint and get the concentration whereas here you can obtain the data in the timescale of one-tenth of a millisecond. Now what do you do for reactions that are even faster than that? Especially many photoreactions. When you do a photochemical reaction, you generate radicals, they react very quickly or you generate a radical anion radical cation.

So are there methods to study these? One method what is called is a flash photolysis method. So this involves a pump and a probe. I will try to walk you through this method. What is done is initially a flash of light is shown to your flask to initiate the photochemical reaction. So with this flash of light, what happens is you generate your reactive intermediate. So what is very important to understand about this flash of light is that the duration of the light pulse, so when I say pulse you must get an idea that it is a quick thing that we are talking about.

So the duration of this pulse must be shorter than the lifetime of the intermediate. Otherwise if you put a light pulse which is very long by the time you shine light your reaction is also done. So it has to be a quick pulse with the advent of lasers, now that you have lasers, you can actually get this quick pulse very nicely. So you put this quick pulse and what the quick pulse does is, it generates a lot of your reaction intermediate. Then what is done is the pulse is gone and the intermediate converts to the product.

So if I were to plot, so if I were to plot the absorbance versus time, what would be, what you would see is, initially, with the big pulse, there is a huge increase in the absorbance because you are generating, I mean, a lot of your intermediate. Now that the pump is gone, so this initial flash of light is your pump which initiates the photochemical reaction. Now once the reactive intermediate is produced, it will slowly decay to give you your product. So now essentially what you get is you get graph, you get a graph similar to what we had shown earlier where you can study the kinetics of decay of the intermediate.

So as you see, initially the energy of the light pulse is enough to generate a lot of the intermediate. Otherwise you will not be able to observe it using spectroscopic methods and then slowly you let it decay and the probe is what is used to actually study the decay of the intermediate. Currently with sophisticated techniques, these instruments are equipped with mathematical programs which allow you to fit these curves.

So you can fit these curves to equations that are already there for reaction kinetics and whichever fits the best would tell you the nature of this intermediate and it would give you an idea of what would be the kind of rate law that is being observed for the particular reaction and this could give you information for reactions in the femtosecond scale. And if you want to know more about these techniques, you can also look at the Nobel Prize in 1999 which was given to Professor Ahmed Zewail for development of these kind of techniques which could help you monitor reactions at the femtosecond scale.

So now what I thought was that, now that we have done lot of theory of understanding kinetics, I would also show you, give you a flavor of how in research labs these methods are actually used to understand chemical reactions. So, you can study more about these methods using appropriate text books which talk about methods to study reaction kinetics. In this course, we would like to focus on the understanding the theory behind this, but I thought it would be a good idea to also give you a flavor of how practically this is done in research laboratories. So with this, we end the part where we looked at reaction kinetics.

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So, if you remember at the very beginning of the class, I told you that whenever you want to propose a reaction mechanism, the first thing you should be able to do is you should be able to write reaction mechanisms. So, in the first week and a half, we looked at methods to write reaction mechanisms.

So we looked at arrow pushing and based on your assignment and practice problems that we did during the lectures, I hope by now you have some confidence in pushing arrows, one advice that I have for you is now people are always very hesitant in pushing arrows, please

don’t be because a reaction can potentially have multiple pathways, so as long as you follow basic principles of chemistry, you should not be afraid to push arrows. Just follow the guidelines that were given to you, show the arrows going from the source to the sink.

So, we looked at arrow pushing. Then we looked at representing reactions. So we looked at reaction coordinate diagrams and then we looked at how looking at reaction and we saw that looking at reaction coordinate diagrams, we get idea about what could be the major product that is formed in a reaction. You get idea about intermediates that are present and you also get an idea about the nature of the transition state and we looked at various theories like the Hammond postulate, Curtin-Hammett principle and kinetic and thermodynamic control to understand many of these principles.

So, this came to writing mechanisms and representing reactions. So, we started with checking hypothesis with experiment by looking at kinetics. So kinetics experiments could be used to propose mechanisms and distinguish between different mechanisms. So in the coming lectures what we would be doing is, we would be looking at more such experiments along with the theory to understand how you can develop clever experiments to understand reaction mechanisms. So thank you and I will see you in the next lecture.